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Development and Standardization of a Furosemide Stress Test to Predict the Severity of Acute Kidney Injury

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Abstract

Background: Rehab patients continue to have difficulties obtaining an accurate diagnosis and assessing their risk. The furosemide stress test has been recommended as an easy, safe, affordable, and efficient method of tubular integrity assessment; this is especially true when compared to recently discovered markers for urine and plasma. This study's goal is to investigate the creation and the development of a “furosemide stress test” standard to gauge the degree of “acute kidney injury”.

Method: An observational study that was prospective and multicenter was carried out with patients who had AKI stages 1 and 2. AKI-KDIGO stage 1 or stage 2 diagnosis in 80 individuals were subjected to furosemide stress testing (FST). In the FST, patients who had not previously been exposed to furosemide were dosed at 1 mg/kg, whereas those who had received it in the week before were dosed at 1.5 milligram to kilogram ratio. Urine output was observed for 2 hours, and volume replacement was provided as needed. Within fourteen days of FST, the key result—the advancement to 3 stages of AKI-KDIGO—was examined. The secondary result was the composite end target, which was defined as either achieving AKI-KDIGO 3 stage or dying within fourteen days of furosemide stress test.

Result: Of the overall count of patients (80), 28 (35% success rate) and 34 (42.5%) achieved the secondary composite result. Beyond the existence or absence of CKD at baseline, there were no statistically significant variations in the demographics between the progressing and stable CKD groups (p=0.018). The sensitivity of predicting advancement to level 3 AK I was 80.14%, The precision was 81.67%, and the area under the curve was 0.87 when a cumulative urine output of 300 mL was measured 2 hours after the FST.

Conclusion: The findings of the FST demonstrate potential as a novel tubular biomarker for accurately detecting the development of severe acute kidney injury (AKI), exhibiting strong predictive capabilities.

Keywords: Acute Kidney Injury, Critical care, Functional assessment, Furosemide stress test, Renal biomarkers.

1. Introduction

"Acute kidney injury" is a condition that is typified by an abrupt onset of decreased excretory function; nevertheless, there is a lack of accuracy in its definition. Acute kidney injury is a condition with a noteworthy and increasing incidence that also has a high death rate, especially in critically ill patients [1,2]. In addition, it has serious long- and medium-term consequences, including increased cardiovascular morbidity and mortality and the onset of chronic renal disease. It has been shown that the severity of AKI is linked to less successful outcomes. Given the fast evolution of AKI and the limited range of interventions available, which mostly include addressing the aetiology and ensuring proper hydration, it is crucial to get an early diagnosis for optimal therapeutic care. Due to these rationales, an optimal diagnosis need to include prognosis assessments. Nevertheless, there is a lack of unambiguous associations between outcome and other characteristics other than severity [3]. In addition, the existing diagnostic criteria, including the internationally recognised grading scales based on creatinine levels, such as AKIN,KDIGO, and RIFLE, just provide a delayed categorization of the severity of the condition. The perspective that focuses only on creatinine levels in the context of AKI fails to consider the necessary level of detail about the underlying causes and mechanisms, which is essential for individualised diagnostic approaches. The inherent limitation of diagnostic approaches relying on a single metric or biomarker arises from the variability of acute kidney injury and the intricate nature of the underlying biological processes [4].

In recent years, a number of novel biomarkers, mostly related to urine function, have been identified. These biomarkers have the ability to provide valuable pathophysiological insights that are not captured by traditional creatinine testing. Moreover, they have shown the potential to enhance diagnostic capabilities by enabling earlier detection and improving sensitivity [5,6].Nonetheless, the uncertainty surrounding their biological and pathophysiological importance poses a major barrier to their utilization in conventional diagnostic procedures and classifications. The precise mechanisms behind the emergence of these indicators in different biological specimens remain incompletely elucidated. Therefore, the therapeutic usefulness of these biomarkers is limited to the statistical correlations observed between their levels and the

outcomes of acute kidney injury (AKI) at a population level. One possible explanation for the continued use of creatinine as a gold standard for assessing renal function in the field of nephrology is its longstanding heritage. Despite its inadequate specificity, creatinine is widely recognised as a proxy marker for glomerular filtration rate (GFR) [7]. A closely related problem is the historical emphasis on measuring glomerular filtration rate (GFR) alone for assessing renal function. The furosemide stress test (FST) has garnered increasing attention in recent decades as a practical means of evaluating tube functioning [8].

The FST has a high sensitivity but a limited resolution capability for detecting subclinical tubular changes that are reflected in the aberrant diuretic response to a single dose of furosemide. In reality, undamaged tubules are required for a proper diuretic response to furosemide, therefore changes to practically all nephron segments have the potential to affect the outcome of the FST. As a result, the FST has high multivalence at the price of poor specificity, making it a double-edged sword [9,10]. Extension and confirmation of the results of Chawla et al. (2013) were conducted by Pon et al. (2021) on a population in an Indian critical care setting. In both studies, there was a decent degree of accuracy in the FST results for persons with early-stage AKI (KDIGO 1 and 2) in terms of their development to KDIGO stage 3 [11,12].In 2015, Koyner et al. assessed the accuracy of FST vs a number of biomarkers in predicting the severity of AKI. It was demonstrated that biomarkers could not predict mortality, the need for RRT, or the development to stage III AKI with any more accuracy than the FST. The risk prediction for all outcomes, however, significantly enhanced when FST was used in conjunction with the other AKI biomarkers [13].

In a more recent investigation, Rewa et al., 2019 conducted a prospective, and multicenter, observational analysis including patients diagnosed with stage I or II acute kidney injury (AKI). Upon conducting a fractional sodium excretion test (FST), the researchers made the observation that the rate of urine flow during the first two-hour period exhibited the highest level of predictability for the development to stage III acute kidney injury (AKI), as shown by a region beneath the value of the receiver operating characteristic curve 0.87. The optimal threshold for this predictor was determined to be less than 200 milliliter, yielding a sensitivity of 73.9 percent and a specificity of 90.0 percent [14].

In general, the FST (Functional Scoring Tool) offers a potential diagnostic metric that incorporates established pathophysiological understanding and additional information that is not influenced by creatinine levels. However, it requires further comprehensive contextualization to enhance its usefulness. Moreover, the FST serves as an effective stress test that aligns well with the theoretical framework of an acquired susceptibility to acute kidney injury (AKI) resulting from a diminished functional reserve. In accordance with the reductionist paradigm of renal function, prior to the introduction of the Functional Stress Test, a diminished functional reserve specifically denoted the reserve of glomerular filtration rate, often referred to as renal functional reserve [15]. Hence, the aim of this research to investigate the growth and standardisation of a "furosemide stress test" for the purpose of predicting the severity of "acute kidney injury".

2. Methodology

2.1 Study area

This study was a prospective study conducted at the Government medical college, India, between ……. to …… 2018 after approval by the Institutional Ethics Committee of the hospital.

2.2 Study Design

A total of 80 patients were taken. Informed consent was obtained from each participant. The basic demographic data of the patients and their clinical history were recorded. The presence of diabetes, hypertension, or other co-morbidities and the treatment they pursue for these ailments were noted. Basic laboratory investigations were also done.

2.3 Patient Selection

Patients over the age of 18 who were admitted to an intensive care unit with either AKI-KDIGO stage 1 (an increase in creatinine of less than 0.3 mg/dL within the previous 48 hours, an increase from baseline of 1.5–1.9 times, or a decrease in urine output of less than 0.5 mL/kg/hr for six to twelve hours) or stage 2 (an increase in creatinine of more than 2.0–2.9 times from baseline, or a decrease in urine output of less than Patients with previous renal transplant, obstructive nephropathy, acute glomerulonephritis, volume depletion, non-oliguria, active bleeding, pregnancy, and history of allergy to frusemide were excluded from the trial. Baseline severe chronic kidney disease (CKD) was defined as having an eGFR 30 mL/min/1.73 m^2.

2.4 Study procedures

At each study location, the research ethics commission granted approval for the study. Prior to the enrolment of participants, informed consent was acquired. Upon enrollment, a total of 7 millilitres of whole blood and 50 millilitres of urine were collected in order to establish a baseline biochemical profile. Subsequently, a solitary bolus of furosemide was delivered. Prior exposure to furosemide was ascertained by assessing whether the patient had been administered furosemide during the preceding 7-day period. In cases where the patient had no prior exposure to loop diuretics (i.e., furosemide naïve), an intravenous dosage of 1.0 miligram/kilogram of furosemide was delivered. However, if the patient had previous exposure to loop diuretics, a higher dose of 1.5 miligram/kilogram of furosemide was administered. The urine production of the patient was thereafter documented on an hourly basis throughout the subsequent 24-hour period. The clinical team was provided with the opportunity to implement a pre-established methodology for replacing either the whole or a portion of the urine output generated by furosemide.

2.5 Outcomes

The key outcome was the development of AKIN 3 stage within 30 days post-FST (defined as the need for RRT, a rise in sCr to 3x baseline, or an u/o b 0.3 ml/kg/h 24 h). Hospital mortality and the combination of hospitalization and death were considered secondary outcomes. We also recorded FST-related adverse events, including as hypokalemia, hypomagnesemia, furosemide allergies, and clinically severe hypotension.

2.6 Statistical analysis

Descriptive statistics were used to characterize the data for categorical variables. The mean, standard error of mean,standard deviation, and percentage analysis were utilized for continuous variables. Versions 23.0 and 19.1.3 of the SPSS and MedCalc statistical software were used for the statistical analysis.

3. Result

3.1 Baseline Characteristics

Eighty individuals were selected and had FST out of the 112 patients that were assessed for eligibility. The participants' average age was 50±1.62 years, with 42 (52.5%) of the group being male. Out of the 80 patients, 27 (33%) achieved the AKI-KDIGO stage 3 main outcome, and 34 (42.5%) achieved the secondary composite outcome of either

AKI-KDIGO stage 3 or passing away within 14 days after FST. Patients who advanced did not vary substantially from those who did not in terms of baseline variables such as gender (p=0.424), diabetes mellitus (p=0.12), hypertension (p=0.102), cardiac failure (p=1.0), albumin (p=0.12), alcohol (p=0.467), and smoking status (p=0.867).

The complete cohort included six patients with baseline CKD, and baseline CKD status was substantially related with the progressors group when comparing the two groups. The majority cause of 81.3% of patients in the whole cohort was sepsis, and there was no discernible correlation (p=0.215) between the two groups in terms of etiology. In all groups, there were comparable numbers of patients with AKI-KDIGO stages 1 and 2, 57.1 vs. 53.8% and 42.9 vs. 46.2%, p=0.78). Comparing the progressors group to the non-progressors, there was a statistically significant difference in the mean pre-FST creatinine (p=0.05). Eight progressor patients required RRT. 16 (20%) of the 80 patients passed away throughout the research period. In contrast to the non-progressors' 11.5% mortality, the progressors' group experienced 35.7% (p=0.01). An overview of the patient characteristics and outcomes is given in Table 1.

Table 1. Patient outcomes and characteristics				
Charactersticks	**Combined (n=80)**	**Progressors (n=28)**	**Non-progressors (n=52)**	**P**
Age (years, mean ± SE)	50±1.62	51.46±2.72	50.46±1.04	0.607
Gender (male), n (%)	41(52.5%)	12(46.0%)	27(53.7%)	0.424
Comorbidities, n (%)				
Diabetes mellitus	30(36.8%)	12(50%)	15(30.6%)	0.12
Hypertension	19(25%)	11(33.5%)	10(19.2%)	0.102
Cardiac failure	8(10.3%)	5(11.7%)	7(11.3%)	1
CKD	5(7.5%)	7(15.9%)	1(1.8%)	0.017
Albumin (g/dL, mean ± SD	-	3.52±0.31	2.73±0.3	0.12
Smoking, n (%)	15(20.3%)	5(21.4%)	10(20.2%)	0.867
Alcohol intake, n (%)	21(26.8%)	6(25%	15(27.8%)	0.467
Sepsis, n (%)	62(82.3%)	22(87.3%)	39(72.9%)	0.215
Clinical data				
Pre-FST creatinine (mg/dL	-	2.06±0.09	1.72±0.05	0.03
Frusemide (1.5miligram per kilogram), n (%)	13(18.8%)	7(24.6%)	8(12.5%)	0.085
2-hour post-FST urine output (mililiter, mean ± SE)	-	209.83±17.98	520.71±30.03	<0.001
AKI-KDIGO 1, n (%)	42(55%)	13(55.1%)	26(51.8%)	0.775
AKI-KDIGO 2, n (%)				
Outcomes, n (%)				
AKI-KDIGO 3	27(33%)	28(100%)	-	-
Death	15(22%)	11(35.7%)	6(10.2%)	0.02
RRT	7(12%)	8(10%)	-	-

3.2 Frusemide StressTest

Patients did not experience any negative test-related reactions, and they handled the test process well. The individuals who were administered an increased dosage of frusemide at a rate of 1.5 mg/kg did not show a statistically significant distinction (p=0.09). With a p-value of less than 0.0001, urine production was significantly lower in those who moved to stage 3 (212.86±18.98 mL) cumulatively 2-hour post-FST than in those who did not (524.81±30.03 mL) (Table 2). AUC of 0.89±0.03 (p<0.001) was found in the cumulative urine production after FST for two hours, as per ROC curve analysis for the primary outcome.

Table 2. Furosemide stress test effect on urine flow				
Measurement time point	**Combined**	**Progressed to AKIN III**	**Non-progressors**	**p**
Hour1	250 (33.2)	88 (33.0)	88 (33.0)	0.001
Hour 2	295 (33.8)	94 (46.6)	390 (40.2)	0.001
Hour 3	243 (24.6)	106 (33.4)	309 (33.7)	0.001
Hour 4	205 (22.1)	84 (23.4)	262 (31.1)	262 (31.1)
Hour 5	173(16.6)	82 (23.7)	217 (21.8)	0.001
Hour 6	153 (18.4)	72 (15.4)	72 (15.4)	0.001

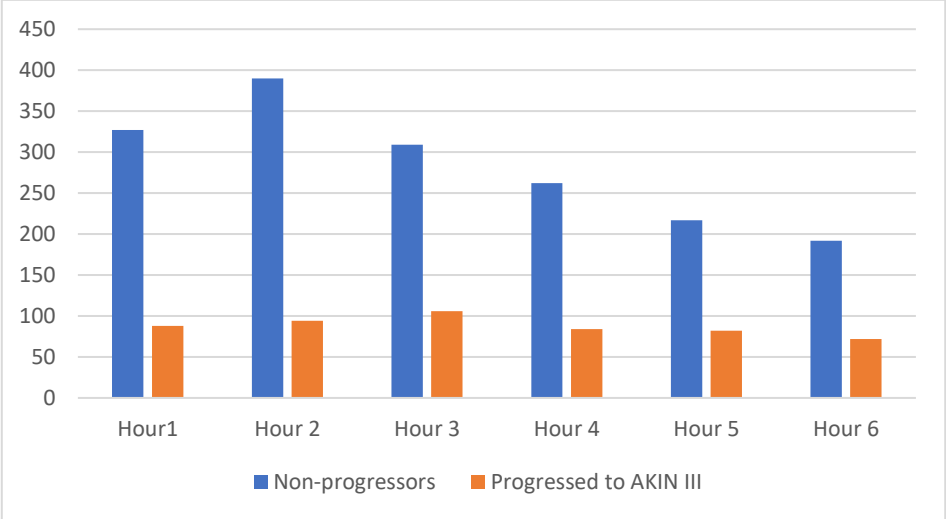

Figure 1. Urinary output in response to furosemide stress test

Furthermore, the ability of several 2-hour post-FST urine production cut-offs to predict progression was evaluated based on their sensitivity and specificity. When used to predict the progression of urine output of less than 300 mL cumulatively two hours after the FST, the Youden index demonstrated 82.14% sensitivity and 82.69% specificity. After two hours of FST, the cumulative urine output showed an AUC of 0.86±0.04 ($p<0.001$) for the secondary composite outcome of AKI-KDIGO stage 3 or death (Table 3).

Table 3. Sensitivity and specificity of cumulative 2-hour post-FST urine output thresholds for progression to AKI-KDIGO stage 3

Cumulative 2-hour urine output	Specificity	Sensitivity
≤ 100 milliliters	96.15	14.29
≤ 200 milliliters	96.15	46.43
≤ 300 milliliters	82.69	82.14
≤ 400 milliliters	61.54	96.43
≤ 500 milliliters	50	100

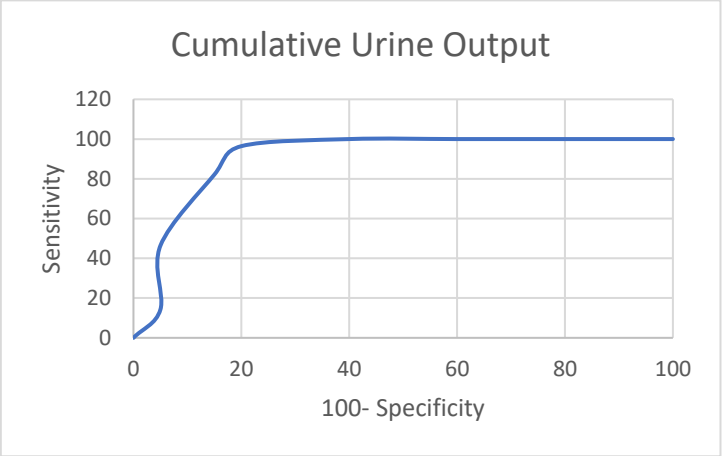

Figure 2. The ROC curve for cumulative urine output was utilized two hours after the FST to predict the main result of moving to stage 3 of the AKI-KDIGO.

Utilizing a total urine output of less than 300 milliliters yielded a 76.47% sensitivity and an 86.96% specificity as a urine volume cut-off among the various FST criteria (Table 4).

Table 4. Sensitivity and specificity of cumulative 2-hour post-FST urine output thresholds for progression to AKI-KDIGO stage 3/death

Cumulative 2-hour urine output	Specificity	Sensitivity
≤ 100 milliliters	97.83	14.71
≤ 200 milliliters	97.83	41.18
≤ 300 milliliters	86.96	76.47
≤ 400 milliliters	63.04	88.24
≤ 500 milliliters	52.17	94.12

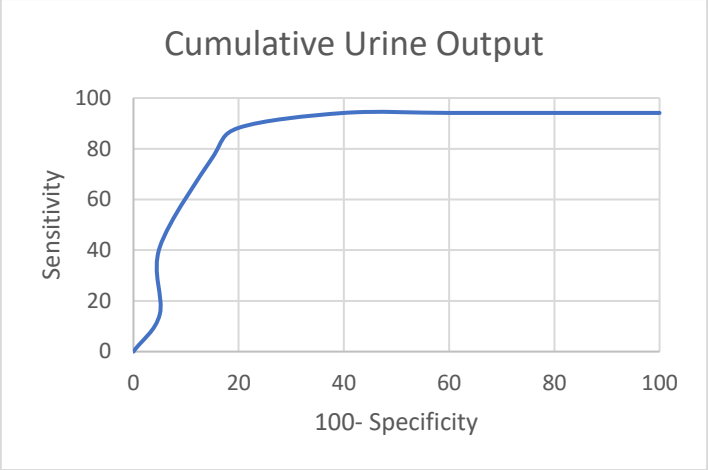

Figure 3.ROC curve of cumulative 2-hour post-FST urine output to predict the secondary composite outcome of AKI-KDIGO stage 3/ death.

Table 5. Optimal urine output cut-off characteristics for primary and secondary outcomes

Outcome	Urine output cut-off	Sensitivity	Specificity	Youden index J	Area Under Curve	p value
Primary outcome	≤300 milliliters	80.14	81.67	0.6243	0.84(0.04)	<0.001
Secondary outcome	≤300 milliliters	72.47	84.95	0.6274	0.87(0.03)	<0.001

4. Discussion

Adrenal kidney injury (AKI) does not always show clear symptoms right after an insult, and by the time indications of decreased kidney function appear, significant damage has already happened, reducing the window of opportunity for treatment. AKI prognosis that occurs early enough to enhance results is therefore unfulfilled. Biomarkers of tubular integrity have been proposed as a better predictor of the likelihood of AKI development since the majority of AKI types include acute tubular damage. Measuring tubular creatinine secretion served as a stand-in for tubular functional evaluation in the first investigations. Its usefulness in evaluating tubular functional capacity in AKI is called into doubt, in addition to its intrinsic drawbacks, due to unstable creatinine kinetics. Frusemide, a loop diuretic, has potential since its action requires the functional integrity of many nephron tubule domains in order to produce an increase in urine production. Frusemide cannot readily pass through the glomerular barrier because it is an organic anion that circulates in proximity to albumin [16]. The drug enters the tubular lumen through the proximal convoluted tubule's human organic anion transporter. Urine flow is

then dependent on the As it obstructs the luminal “Na+ K+ 2Cl-cotransporter” in the thick ascending loop of Henle, the distal tubular lumen remains patent. Frusemide has long been used as a tubal integrity test. With a sensitivity of 82.14% and specificity of 82.69%, A total 2-hrs post-furosemide stress test urine output of 300 miligram or less was found to be predictive of the development to AKI-KDIGO 3 stage (AUC 0.89). As for the composite outcome of mortality following two hours of post-FST urine output or AKI-KDIGO stage 3, the results showed an 86.96 percent specificity, 76.47 percent sensitivity, and an area under the curve of 0.86. 92 critically sick patients participated in a multicentric study conducted by Rewa et al. prospectively evaluated the cumulative 200 mL urine production threshold and found that it was 73.9% sensitive, 90.0% specific, and had an area under the curve of 0.87 [17].

Facing a furosemide challenge, Baek et al. (1973) examined the free water clearance (CH2O) of fifteen individuals who at the time did not display clinically noticeable AKI. Researchers discovered that "acute renal failure was imminent" when CH2O was close to zero and there was a poor response to furosemide. The study didn't say whether the individuals had early-stage acute kidney injury or any indication of acute kidney injury at all, and the small-scale study's furosemide dose was not standardized. Still, the results of that first study are supported by ours. Our functional test for predicting progressive AKI in this investigation was the FST. The use of urine biomarkers to forecast AKI worsening has been done before. Based on other recent biomarker research, the FST's predictive value compares well. The effectiveness of kidney injury molecule-1 , urine neutrophil gelatinase associated lipocalin (NGAL), and IL-18 as predictors of increasing AKI was established by Hall and colleagues [18]. The uncorrected AUC values for these three variables were 0.71, 0.64, and 0.63. AUC of 0.86 was observed by Koyner and colleagues in a different research pertaining to the forecast of stage advancement III AKI by π- glutathione S-transferase (GST). Angiotensinogen levels in the urine have been reported to have an AUC of 0.70 in predicting worsening AKI [19].An FST standard version was created in 2013 by Chawla. The specialists looked at two groups of critically ill individuals, numbering 23 and 54, respectively. The Acute Kidney Injury Network classified all enrolled patients as having stage I or II AKI. Furosemide was administered intravenously at a standardized dose of 1 miligram/kilogram for those who had never taken a loop diuretic before and 1.5 miligram/kilogram for those who had. Ringers

lactate or saline were added to the urine output in a 1:1 ratio six hours after furosemide was administered.

The study's principal finding was that, after fourteen days of furosemide therapy, patients progressed to AKIN 3 stage. There were no negative effects or hypotensive episodes linked to the FST, indicating that it was a rather safe procedure. An indication of progression to AKIN 3 stage, a 2-hour urine output threshold of 200 cc demonstrated the greatest combination of sensitivity (80.1%) and specificity (81.1%). To predict the primary result, the total amount of urine generated in the first two hours after the FST was measured, and the area under the receiver operator characteristic curves was found to be 0.87. However, the authors point out that in order for the test to be performed, the patient has to be euvolemic and any blockage to the flow of urine needs to be cleared up before the FST is given.In another study Voort et al. [20] used a different method to assess the FST's predictive ability.In this investigation, urine output was assessed in a sampling of individuals in critical condition with AKI four hours after continuous renal replacement therapy (CRRT) was stopped. After this period, some patients received a placebo or furosemide at a dosage of 0.5 miligram/kilogram/hrs, with a 24-hrs urine output evaluation conducted afterward. In this investigation, patients with quick recovery of renal function produced considerably more urine both spontaneously after stopping CRRT and as a result of furosemide infusion.

In a retrospective analysis of 95 ICU patients, Matsuura et al. showed that plasma NGAL was a worse predictor of stage 3 AKI development than frusemide responsiveness (FR) at different doses. For every two-hour dose of frusemide, the factor that could distinguish between severe AKI and normal urine production the best was the FR of 3.9 milliliters. Additionally, FR demonstrated significant effectiveness to predict progression in individuals with increased plasma NGAL levels. In addition to identifying early AKI, there is much discussion on the best time to begin RRT. There are advantages and disadvantages to both early and late commencement, and extensive research on the subject has yielded conflicting findings. Lumlertgul et al. used a cohort of 162 patients using FST as a screening method to determine if the patients needed RRT [21]. Just six (13.6%) of the 44 patients who had a positive FST reaction required RRT. Randomization was used to compare early vs conventional (indication driven) RRT start

among the 118 FST non-responsive individuals. RRT18 was administered to 45 individuals (or 75%) in the standard arm.

Sakhuja et al. investigated whether AKI stage 3 patients who may need RRT could be identified by FST. The research was retrospective in nature, therefore the amount of furosemide was not standardized. However, inclusion was restricted to subjects who received an equivalent dosage of bumetanide or an intravenous bolus of furosemide at least 1 mg/kg. This research did not include patients who had received loop diuretics prior to the furosemide stress test. One of the two main categories outcomes mentioned by Sakhuja et al. was the requirement for emergency dialysis within 24 or 72 hrs following the FST. 687 patients in all comprised the sample. In the first 24 hours after FST, 162 patients (23.6%) required dialysis. The 6-hour urine production following FST, according to the authors, demonstrated only a limited ability to distinguish between patients who needed dialysis within the next 24 hours, but it might be useful in determining whether critically ill AKI stage 3 patients needed dialysis [22].

For AKI risk classification, the FST has shown to be a very good functional biomarker. The biomarker's performance will decline and there will be a large number of false positives if it is used on a larger population. The group at risk of renal damage must be identified in order to improve biomarker performance. To enhance patient outcomes, a novel AKI algorithm may be developed based on these data. Patients who are at risk for acute kidney injury (AKI) must first be identified [23]. These patients may include the elderly, those with diabetes mellitus, those with chronic kidney disease, those who have organ failure, etc. Additionally, early indicators of damage such as slight increases in creatinine, fluid overload, and reduced urine output must be monitored. The "renal angina index" has been developed with good negative predictive value for use in the adult and pediatric population by taking into account the risk factors and symptoms of renal angina. Testing for a structural damage biomarker should come after this evaluation, and FST may be used to further enhance risk classification in individuals whose biomarker test results are positive. Early AKI patients will have improved risk classification thanks to this serial testing approach, which uses biomarkers with a greater positive predictive value after tests with a strong negative predictive value.

Conclusion

FST exhibits a significant degree of predictive possibility of future risk classification of early “Acute Kidney Injury” as a tubular integrity biomarker. Furosemide Stress Test, It is necessary to include a new dynamic biomarker that is about to be developed into decision-making systems to detect acute kidney injury early enough to assess experimental treatments and lessen the negative effects of this worldwide health issue. Multicenter prospective trials with a high enough sample size, accurate time and dose of furosemide, and a comparison of the furosemide stress test with other novel urine and plasma Biomarkers are requiredfor adequate data validation and the defining of the test's possible clinical applications.

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