Determination of Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) Cut-off Level for Early Detection of Acute Kidney Injury in Thai Adult Patients Undergoing Open Cardiac Surgery

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Background: *Acute kidney injury (AKI) is a common complication in patients undergoing open cardiac surgery. Urinary neutrophil gelatinase-associated lipocalin (UNGAL) is an early marker of AKI, however, its predictive value in adult patients undergoing open cardiac surgery has never been investigated in Thailand.*

Objective: *The present study aimed to determine the cut-off level of UNGAL for predicting AKI in adult patients undergoing open cardiac surgery and also to determine the risk factors for AKI development.*

Material and Method: *In all, 130 patients at Rajavithi Hospital were prospectively enrolled during a six-month period. UNGAL was obtained at baseline before surgery, and at 0, 3, and 6 hours after surgery and assessed by ARCHITECT NGAL assay. Serum creatinine levels were measured at baseline before surgery simultaneously for the collection of UNGAL and then daily after surgery. AKI was defined as an increment in serum creatinine of ≥0.3 mg/dl within 48 hours according to the Acute Kidney Injury network (AKIN) criteria.*

Results: *Forty-six patients (35.4%) developed AKI, and 80.4% of these patients had the onset of AKI within the first 6 hours after surgery. In this group, UNGAL increased significantly at 0, 3, and 6 hours after surgery compared with patients without AKI. UNGAL at 3 hours after surgery was the best time-point for predicting AKI. The cut-off value was >11.3 ng/ml with the sensitivity and specificity of 72% and 60%, respectively. By univariate analysis, older age, lower ejection fraction, impaired baseline renal function and longer cardiopulmonary bypass (CPB) time were clinical factors associated with AKI. However, by multivariate analysis, only lower ejection fraction and longer CPB time were associated with AKI.*

Conclusion: *UNGAL level may be a useful marker for predicting AKI in Thai adult patients undergoing open cardiac surgery. Lower ejection fraction and longer CPB time were two major risk factors for AKI development.*

Keywords: *Neutrophil gelatinase-associated lipocalin (NGAL), Cardiac surgery, Acute Kidney injury*

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Acute kidney injury (AKI) is a major postoperative complication and may occur in up to 30% of patients undergoing open cardiac surgery[1] and 1-5% of patients who develop severe AKI require dialysis. The prognosis of these patients is particularly poor because the mortality risk in these patients increases by approximately 40%, compared with the overall mortality after cardiac surgery, which ranges between 2-8%[2]. It is commonly reported that the routine use of serum creatinine elevation for monitoring the renal function change is a late indicator of renal dysfunction, because of a delay of serum creatinine rising up to 48-72 hours behind the decrement of glomerular filtration rate after the surgery[3]. Recently, newer biomarkers appear to be promising for the early diagnosis of AKI, including cystatin C, interleukin-18, kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). Human NGAL is a protein covalently bound to gelatinase from neutrophils. This protein is rapidly upregulated and expressed in response to ischemic or nephrotoxic injury[4]. These properties of NGAL explain the increasing enthusiasm to establish it as an early biomarker of AKI and it has been shown to be one of

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the most promising markers across a range of different clinical settings of AKI. A study in patients undergoing heart surgery to compare the role of plasma NGAL (PNGAL) and urinary NGAL (UNGAL) on early detection of AKI found that UNGAL was superior to PNGAL[5]. In addition, due to its origin from renal tubules, UNGAL might be of a higher predictive value compared with PNGAL originating mostly from neutrophils, liver and renal epithelial cells[6]. As a result, UNGAL is more widely used for the diagnosis of AKI. However, conflicting observations have been reported concerning the cut-off level of UNGAL level to predict AKI development. A clear cut-off concentration to detect AKI has not yet been reported. Therefore, the purpose of the present study was to determine the cut-off point of UNGAL to predict AKI in Thai patients undergoing open cardiac surgery, and additionally, to evaluate the risk factors that influence the development of AKI.

Material and Method

Patients

A prospective, diagnostic test study was conducted over a period of 6 months (June to November 2010) in adult patients undergoing open cardiac surgery at Rajavithi Hospital (Bangkok, Thailand). Adult cardiac surgical patients were consecutively recruited into the study using the following inclusion criteria: (1) age $\geq$18 years; (2) patients who underwent cardiac surgery necessitating the use of cardiopulmonary bypass (CPB). Patients were excluded when any of the following criteria was met (1) preexisting renal dysfunction with baseline serum creatinine >3 mg/dl; (2) kidney transplant patients (3) history of using potential nephrotoxic agents, e.g., aminoglycoside, nonsteroidal anti-inflammatory agent, radiocontrast agent within two weeks before surgery (3) patients with sepsis and (4) patients undergoing emergency operation (<24 hours after admission).

Written informed consent was obtained from all patients. They received verbal and written descriptions of the study protocol. The present study protocol was reviewed and approved by the Ethics Committee of Rajavithi Hospital.

Methods

The clinical data were obtained from the patients' history and medical records. Physical examination was also taken in all patients. The baseline blood and urine samples were collected one day before operation for complete blood count, blood urea nitrogen (BUN), serum creatinine, electrolytes and urinary NGAL (UNGAL). The UNGAL was measured with the ARCHITECT NGAL assay (Abbott Diagnostics, USA) on urine sample[3]. All patients received an open cardiac surgery with CPB. Thereafter, the urine samples for UNGAL were collected consecutively at 0, 3, and 6 hours after surgery. The blood samples were also collected for serum creatinine at 0, 3 and 6 hours; twice daily during the first two postoperative days; then once daily during days 3 to 7 postoperative.

Acute kidney injury (AKI) was defined as an increment of serum creatinine of higher than or equal to 0.3 mg/dl within 48 hours, according to the Acute Kidney Injury Network (AKIN) criteria[7] compared with the baseline level.

Statistical analysis

Sample size estimation[8] was calculated based on sensitivity of UNGAL reported by Parikh et al[9] and the reported prevalence of AKI (up to 30%) in patients undergoing open cardiac surgery[1]. With the estimated sensitivity of 90% and 95% CI of 90$\pm$10%, a sample of 130 subjects was required in the present study.

Continuous variables with normal and non-normal distribution were reported as mean $\pm$ SD or median (P_{25}, P_{75}) respectively. Unpaired t-test or Mann-Whitney U test was employed to test the difference in quantitative variables between patients with and without AKI whereas Chi-squared test or Fisher's exact test was used for qualitative variables. The diagnostic value of UNGAL to predict AKI after cardiac surgery was analyzed using receiver-operating characteristic (ROC) curve, area under ROC (AUC-ROC), sensitivity and specificity. Logistic regression was employed to determine factors associated with AKI development.

A *p*-value of less than or equal to 0.05 was considered statistical significance. SPSS 17 was used for all statistical analyses.

Results

Patient characteristics

During the six-month prospective study, 130 patients undergoing open cardiac surgery with cardiopulmonary bypass at the Division of Cardio-vascular-thoracic Surgery, Rajavithi Hospital (Bangkok, Thailand) with a mean age of 51.0$\pm$15.6 years (58.5% male) met the enrollment criteria and agreed to participate in the present study. The demographic characteristics of cardiac patients are presented in Table 1. The body mass index (BMI) was 22.5$\pm$4.2 kg/m^2, and a majority of

Table 1. Baseline characteristics of patients undergoing open-cardiac surgery (n = 130)

Characteristic	n (%) or mean ± SD
Male: female	76:54 (58.5:41.5)
Age (years), mean ± SD	51.1±15.6
BMI (kg/m^2), mean ± SD	22.50±4.20
Diabetes mellitus	21 (16.2)
Dyslipidemia	9 (6.9)
Hypertension	43 (33.1)
Coronary heart disease	38 (29.2)
Valvular heart disease	82 (63.1)
Ejection fraction (%), mean ± SD	57.2±13.0
Previous myocardial infarction	40 (30.8)
Hx congestive heart failure	54 (35.8)
Hx previous cardiac surgery	6 (4.62)
Systolic blood pressure (mmHg), mean ± SD	115.5±18.0
Diastolic blood pressure (mmHg), mean ± SD	68.7±17.2
Plasma BUN (mg/dl), mean ± SD	15.3±5.3
Plasma Cr (mg/dl), mean ± SD	1.0±0.3
Estimate GFR (ml/min/1.732), mean ± SD	74.1±25.9
NYHA classification	
Class 1	5 (3.8)
Class 2	73 (56.2)
Class 3	48 (36.9)
Class 4	4 (3.1)
Hematocrit (%), mean ± SD	39.5±5.4
Hemoglobin (g/dl), mean ± SD	12.9±1.9

patients (55.4%) were within normal range. The most common comorbid disease was hypertension (33.1%) followed by diabetes (16.2%) and dyslipidemia (6.9%). The most common cause of heart disease was valvular heart disease (63.1%) followed by coronary heart disease (29.2%). The average ejection fraction (EF) was 57.23±12.96%. Most patients (56.2%) had cardiac status in NYHA class 2. The estimated glomerular filtration rate (eGFR) before surgery was 74.1±25.9 ml/min/1.73 m^2. The baseline BUN and serum creatinine levels were 15.3±5.3 and 1.0±0.3 mg/dl, respectively. The most common surgical procedure was valve surgery 56.9% followed by coronary artery bypass grafting (CABG) surgery, 28.5%, combined CABG and valve surgery, 1.5% and the remaining for other surgeries.

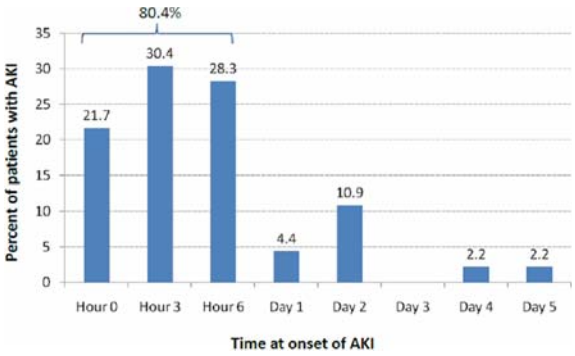

Fig. 1 Onset of AKI in 46 patients who developed inhospital AKI.

Predictive value of UNGAL for AKI

In all, 46 patients (35.4%) developed in hospital AKI according to the AKIN criteria (Fig. 1). Of these 46 patients, 37 patients (80.4%) had onset of AKI within the first 6 hours as the following: 21.7%, 30.4%, 28.3% at 0, 3, 6 hours postoperative, respectively. The serum creatinine in patients with and without AKI immediately postoperative were 1.13±0.25 and 0.86±0.24 mg/dl, respectively (p<0.001) and reached their peak levels at 6 hours in both groups (1.35±0.43 vs. 0.97±0.26 mg/dl, p<0.001), then decreased to 1.15±0.74 and 0.81±0.29 mg/dl, respectively (p = 0.005) on day 7.

Fig. 2 compares the UNGAL levels between patients with and without AKI. No significant difference was found in baseline UNGAL levels between both groups (11.4 [IQR 25.4-3.0] vs. 10.0 [IQR 20.7-3.9] ng/ml). However, the median postoperative UNGAL levels

were significantly different at 0 hours (11.0 [IQR 26.6-4.9] vs. 4.1 [IQR 11.4-2.1] ng/ml, $p = 0.022$), 3 hours (19.3 [IQR 46.3-9.7] vs. 8.6 [IQR 21.8-4.4] ng/ml, $p<0.001$) and 6 hours (20.8 [IQR 84.6-9.8] vs. 15 [IQR 40.1-6.7] ng/ml, $p<0.001$).

On the basis of receiver-operating characteristic (ROC) analysis, the area under the curve for ROC (AUC-ROC) of UNGAL (Table 2) at 0, 3, and 6 hours postoperative were 0.68, 0.69 and 0.62, respectively. Fig. 3 displays the ROC curve showing the optimal UNGAL cut-off at 3 hours postoperative was >11.3 ng/ml, with AUC of 0.69 (95% CI 0.60-0.79, $p<0.001$) and with a sensitivity of 72% and specificity of 60%.

Risk factors for AKI

The result of univariate analysis (Table 3) by comparing variables considered likely to be significantly

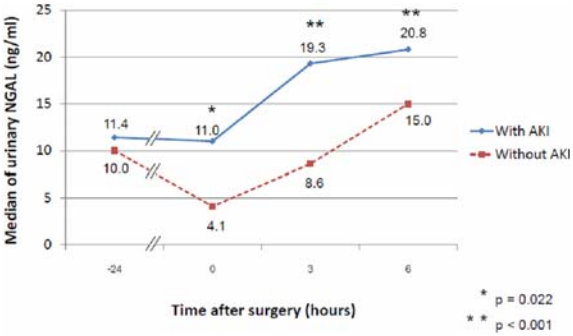

Fig. 2 Comparison of UNGAL between patients with and without AKI.

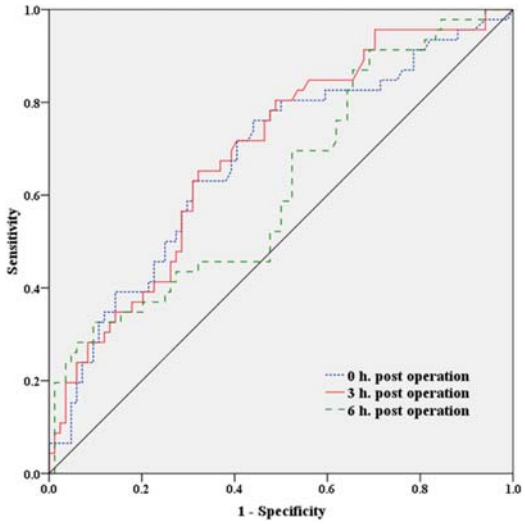

Fig. 3 Receiver-operating characteristic (ROC) curve for prediction of AKI by UNGAL.

Table 2. Area under the curve (AUC) of UNGAL at 0, 3, and 6 hours postoperative

Postoperative (hours)	Area under ROC curve		Cut-off level (ng/ml)	Sensitivity (%)	Specificity (%)
	Area (95% CI)	*p*-value			
0	0.68 (0.58, 0.77)	0.001	>6.4	63	63
3	0.69 (0.60, 0.79)	<0.001	>11.3	72	60
6	0.62 (0.52, 0.72)	0.022	>18.2	59	50

Table 3. Univariate analysis of vatiables associated with AKI development

Variable	Mean ± SD or n (%)		Crude OR (95% CI)	*p*-value
	With AKI (n = 46)	Without AKI (n = 84)		
Age (years)	55.3±15.0	48.8±15.5		0.020
Ejection fraction (%)	52.97±12.3	59.56±12.8		0.005
Baseline serum creatinine (mg/dl)	1.0±0.3	0.9±0.3		0.043
Cardiopulmonary bypass time (min)				
<60	6 (31.6)	13 (68.4)	1	
60-119	21 (30.9)	47 (59.1)	0.97 (0.32, 2.90)	0.954
120-179	15 (42.9)	20 (57.1)	1.62 (0.50, 5.27)	0.419
≥180	4 (50.0)	4 (50.0)	2.17 (0.40, 11.74)	0.370

associated with the risk of developing AKI between patients with and without AKI, showed four significant factors: older age, low pre-operative ejection fraction, pre-existing renal dysfunction and long CPB time. By multivariate analysis (Table 4), only two variables remained significant: ejection fraction ($p = 0.011$) and CPB time ($p = 0.047$). A 10% decrease in ejection fraction was related to odd ratio (OR) of 1.50 and 10 minutes increase in the CPB time was related to OR of 1.06 for risk of AKI development.

Subanalysis of CPB time on AKI development categoried the CPB time into four groups: <60 min (n = 19), 60-119 min (n = 68), 120-179 min (n = 35), and ≥180 min (n = 8), the numbers of patients who developed AKI in each group were 6 (31.6%, OR = 1), 21 (30.9%, OR = 0.97, $p = 0.954$), 15 (42.9%, OR = 1.62, $p = 0.419$) and 4 (50.0%, OR = 2.17, $p = 0.370$), respectively (Table 3).

Discussion

Rajavithi Hospital is one of the medical school hospitals in Thailand that perform a large number of open cardiac surgeries each year. Regarding the previous study of this institute in 1999, 9.3% of patients developed acute kidney injury from 207 patients who received open cardiac surgery in four months[10]. In the present study, using AKIN criteria, the incidence of AKI in patients undergoing open cardiac surgery was 35.4% apparently much higher than previously reported. One of the reasons is possibly due to the different diagnostic criteria that were used. The acute rising of serum creatinine ≥0.3 mg/dl by the AKIN criteria is widely used to diagnose AKI nowadays, and may be more sensitive with an influence on the higher incidence. However, the incidence of AKI in the present study is still close to the reported incidence that varies from 20% to 50% depending on the definition of AKI[11]. It appears that pre-operative, intra-operative and postoperative factors are critically related to the development of AKI[2]. The important pre-operative factors include advanced age, pre-existing renal dysfunction (eGFR <50 ml/min), high body mass index (BMI >40 kg/m^2), history of recent myocardial infarction, severe valvular disease, cardiogenic shock and inotropic support. Patients with diabetes and wide pulse pressure hypertension are also significant predictors of AKI. In the present study, although a significant numbers of patients had a history of previous myocardial infarction and congestive heart failure, most patients (56.2%) were classified in NYHA class 2 and had a fair average ejection fraction of 57.2±13.0%. Peri-operative and intra-operative factors that have important impact on renal function include the use of a CPB machine and hemodilution. The kidneys are very susceptible to injury during CPB because up to 30% of patients undergoing CPB develop acute kidney injury[12]. The nature of nonpulsatile flow during CPB is thought to be an important etiologic factor, resulting in renal vasoconstriction and ischemic renal injury. The duration of CPB use is strictly associated with the onset and the severity of systemic inflammatory response syndrome. CPB activates the complement cascade, increases several cytokines and induces the production of oxygen free radicals. These inflammatory mediators lead to leukocyte extravasation and edema, and finally causing renal injury[2].

Some of the mentioned risk factors for AKI development were confirmed by the present study. By univariate analysis, variables found to be significantly associated with risk of developing AKI included older age, low pre-operative ejection fraction, pre-existing renal dysfunction and long CPB time. However, the only two variables that remained significant, by multivariate analysis were ejection fraction and CPB time. The duration of CPB time also had a trend to be positively correlated with the percentage of patients who developed AKI.

AKI is a frequent postoperative complication in patients undergoing open cardiac surgery and possibly associated with substantial morbidity and mortality. Because of the limited usefulness of serum creatinine change for the early diagnosis of AKI,

Table 4. Multivariate analysis of risk factors for development of AKI

Factor	b	SE(b)	Adjusted OR (95% CI)	*p*-value
Age (years)	0.023	0.014	1.02 (1.00, 1.05)	0.090
Ejection fraction (%)	-0.040	0.016	0.96 (0.93, 0.99)	0.011
Serum creatinine (mg/dl)	0.805	0.727	2.24 (0.54, 9.30)	0.269
Cardiopulmonary bypass time (min)	0.009	0.005	1.01 (1.00, 1.02)	0.047

SE = standard error

UNGAL has been investigated extensively and appears to be one of the most promising early biomarkers of AKI. In spite of this, with accumulating evidence, a wide range of predictive values of UNGAL for AKI vary from 50 to 550 ng/ml[3,13-15]. Bennett et al[3] reported a significant increase of UNGAL within two hours and reaching its peak within four to six hours; hence the authors decided to collect UNGAL only during the first six hours after surgery. Although the UNGAL levels in the present study were lower than those previously reported; however, the baseline levels of UNGAL in patients with/without AKI were found to be comparable. The UNGAL levels in patients with AKI were significantly higher than in those patients without AKI from immediately postoperative to six hours after surgery. Interestingly, the UNGAL levels at hour 0 postoperative were lower than their baseline levels in both groups. This may be explained by the hemodilution effect during the surgical procedure. Mild elevation of UNGAL at six hours in patients without AKI might indicate renal stress and also represents a response to systemic inflammation[16] without subsequent creatinine increase.

On the basis of the AUC-ROC analysis, representing the diagnostic value of UNGAL to predict AKI after cardiac surgery, the highest AUC was 0.69 at 3 hours after surgery, which gave a cut-off value for AKI prediction of >11.3 ng/ml, with sensitivity of 72% and specificity of 60%. Nonetheless, a wide range of results in predictive performance for UNGAL have currently been reported. NGAL has been reported to represent an early and highly specific biomarker for AKI in several studies in pediatric cardiac surgery with an AUC-ROC >0.9[3,15]. Conversely, more recent prospective clinical studies found a low predictive value of early NGAL for AKI after adult cardiac surgery, with an AUC-ROC $\leq$0.7[13,17]. The cut-off value of UNGAL in the present study might be relatively low compared with previous reports; however, the AUC value still represented a fair predictive performance. Therefore, UNGAL may be a useful marker to predict AKI in patients undergoing cardiac surgery.

The present study had some limitations. The authors wished to collect more urine samples for UNGAL during the 48 hours after surgery; it might give a more promising result for the predictive value of AKI.

Conclusion

UNGAL may be a useful marker to predict AKI in patients undergoing cardiac surgery. Using the AUC-ROC analysis, representing the diagnostic value of UNGAL to predict AKI after cardiac surgery, the highest AUC was 0.69 at 3 hours after surgery, which gave a cut-off value for AKI prediction of >11.3 ng/ml with a sensitivity of 72% and specificity of 60%. Lower ejection fraction and longer CPB time were two major risk factors for AKI development.

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Potential conflicts of interest

None.

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การประเมินเกณฑ์ตัดสินของระดับ urinary neutrophil gelatinase-associated lipocalin (UNGAL) ในการวินิจฉัยโรคไตวายเฉียบพลันในผู้ป่วยไทยที่ได้รับการผ่าตัดหัวใจแบบเปิด

ประเสริฐ ธนกิจจารุ, บุญธรรม จิระจันทร์

ภูมิหลัง: ไตวายเฉียบพลันเป็นภาวะแทรกซ้อนที่พบได้บ่อยในผู้ป่วยที่ได้รับการผ่าตัดหัวใจแบบเปิดการตรวจ urinary neutrophil gelatinase-associated lipocalin (UNGAL) นับว่าเป็นดัชนีบ่งชี้ถึงภาวะไตวายเฉียบพลันได้เร็วขึ้น อย่างไรก็ตามยังไม่เคยมีการศึกษาถึงระดับของ UNGAL ที่ช่วยทำนายถึงการเกิดไตวายเฉียบพลันในผู้ป่วยที่ได้รับการผ่าตัดหัวใจแบบเปิดในประเทศไทย

วัตถุประสงค์: เพื่อศึกษาระดับของ UNGAL ที่เป็นเกณฑ์ตัดสินเพื่อทำนายการเกิดไตวายเฉียบพลันในผู้ป่วยที่ได้รับการผ่าตัดหัวใจแบบเปิดและวิเคราะห์ปัจจัยเสี่ยงต่อการเกิดไตวายเฉียบพลัน

วัสดุและวิธีการ: เป็นการศึกษาไปข้างหน้าในผู้ป่วยโรคหัวใจที่เข้ารับการผ่าตัดหัวใจแบบเปิดที่โรงพยาบาลราชวิถี จำนวน 130 ราย ในเวลา 6 เดือน มีการเก็บปัสสาวะเพื่อหาระดับ UNGAL ก่อนผ่าตัดและชั่วโมงที่ 0, 3, 6 หลังการผ่าตัดพร้อมกับการตรวจเลือด serum creatinine ในเวลาเดียวกับ UNGAL และต่อไปทุกวัน โดยกำหนดเกณฑ์การวินิจฉัยภาวะไตวายเฉียบพลันเมื่อมีระดับเพิ่มขึ้น ≥0.3 มก./ดล. ภายในเวลา 48 ชั่วโมง ตามเกณฑ์การวินิจฉัยของ AKIN criteria

ผลการศึกษา: ผู้ป่วยที่เกิดไตวายเฉียบพลันมีจำนวน 46 ราย (35.4%) และ 80.4% ของผู้ป่วยจำนวนนี้ตรวจพบได้ภายใน 6 ชั่วโมงแรกหลังผ่าตัด พบว่าระดับ UNGAL ที่ชั่วโมง 0, 3, 6 หลังการผ่าตัดในผู้ป่วยที่เกิดไตวายเฉียบพลัน มีระดับสูงกว่าผู้ป่วยที่ไม่เกิดไตวายเฉียบพลันอย่างมีนัยสำคัญทางสถิติ ระดับ UNGAL ที่ 3 ชั่วโมง หลังการผ่าตัดซึ่งมีค่า ≥11.3 นก./มล. มีความน่าเชื่อถือมากที่สุดและใช้เป็นเกณฑ์ตัดสินเพื่อทำนายการเกิดไตวายเฉียบพลันได้ดีที่สุดโดยมี sensitivity 72% และ specificity 60% การวิเคราะห์ด้วย univariate analysis พบว่าปัจจัยเสี่ยงที่มีผลต่อการเกิดไตวายเฉียบพลันได้แก่ สูงอายุ ejection fraction ที่ต่ำ การทำงานของไตผิดปกติและ cardiopulmonary bypass (CPB) time มีระยะเวลานาน แต่เมื่อวิเคราะห์ด้วย multivariate analysis พบว่ามีเพียง ejection fraction ที่ต่ำ และ CPB time ที่นานเท่านั้นที่มีความสำคัญ

สรุป: การตรวจ UNGAL สามารถใช้เป็นดัชนีบ่งชี้ที่อาจช่วยทำนายการเกิดไตวายเฉียบพลันได้ในผู้ป่วยไทยที่ได้รับการผ่าตัดหัวใจแบบเปิด การมี ejection fraction และ CPB time นานเป็นปัจจัยเสี่ยงสำคัญในการเกิดไตวายเฉียบพลัน