Original Article

A Retrospective Comparison of Preoperative Estimated Glomerular Filtration Rate as a Predictor of Postoperative Cardiac Surgery Associated Acute Kidney Injury

Abstract

Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) remains common with distressingly high mortality. Over time, risk scorings systems have been developed to predict it and preoperative low estimated glomerular filtration rate (eGFR) has been regarded as one of the predicting risk factors. **Objectives:** The present study is aimed at assessing the relation of different ranges of preoperative eGFR with an incidence of CSA-AKI defined by the AKI network (AKIN) criteria. **Materials and Methods:** Files of 134 patients with eGFR of >40 cc/min/1.73 m^2 body surface area (BSA) who underwent cardiac surgeries on cardiopulmonary bypass were screened for data collection. Occurrences of CSA-AKI were evaluated as per the AKIN criteria over the course of 3 postoperative days. The relationships of different ranges of preoperative eGFR with CSA-AKI were analyzed by appropriate statistical tests using Instat software and $P < 0.05$ was considered statistically significant. **Results:** A total of 60 males and 74 females with a mean + standard deviation (SD) age of 37.98 ± 12.50 years and mean + SD preoperative eGFR of 70.20 ± 20.89 cc/min/1.73 m^2 were analyzed in this study. About 49.25% of patients suffered from CSA-AKI by the 3rd postoperative day. The crude risk of CSA-AKI in patients with eGFR 40–60 cc/min/1.73 m^2 was not higher (odds ratio 0.29) as compared to patients in patients with eGFR >100 cc/min/1.73 m^2. The CSA-AKI trend with different eGFR was also statistically insignificant ($P > 0.05$). **Conclusion:** In patients with preoperative eGFR >40 cc/min/1.73 m^2 BSA, a lower preoperative eGFR (40–60 cc/min/1.73 m^2) does not predict higher incidence of CSA-AKI as defined by AKIN criteria as compared to higher preoperative eGFR (>100 cc/min/1.73 m^2). Lower height is independently associated with higher incidence of CSA-AKI in such patients.

Keywords: *Acute kidney injury, cardiac surgery, cardiopulmonary bypass, renal function, urine*

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Introduction

Cardiac surgery-associated acute kidney injury (CSA-AKI) is still a common and serious problem which is independently associated with in-hospital mortality and long-term morbidity, even after adjustment for co-morbid diseases.[1] Therefore, renal risk stratification in cardiac surgeries has become the very necessary strategy for the informed perioperative care of such patients. Predicting CSA-AKI also has potential applications of clinical, therapeutic, and research.[2] Increased serum creatinine has been recognized as a strong risk factor of AKI after cardiac surgery and long-term survival.[3] However, there is limited knowledge and research in the context of preoperative estimated glomerular filtration rate (eGFR) in predicting the incidence of nondialysis requiring CSA-AKI in patients having preoperative eGFR >40 cc/min/1.73 m^2 body surface area (BSA) as defined by AKI network (AKIN) criteria.

Materials and Methods

The present retrospective evaluation of prospectively collected data was conducted after the Institute's Research Board approval. A total of 134 patients who underwent cardiac surgeries on cardiopulmonary bypass (CPB) with aortic cross clamp during January 2012–July 2016 were included in the study. Demographic parameters, diagnosis, preoperative serum creatinine, and blood urea (baseline) were noted. Patients having preoperative serum creatinine >2 mg/dl, known cases of chronic renal failure and/or on hemodialysis were excluded from the present study. Those patients who had serum creatinine <2 mg%,

Submitted: 04-Aug-2018
Revised: 07-Oct-2018
Accepted: 26-Oct-2018
Published: 07-Jan-2020

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Access this article online

Website: www.annals.in

DOI: 10.4103/aca.ACA_156_18

Quick Response Code:

How to cite this article: Karim HM, Yunus M, Dey S. A retrospective comparison of preoperative estimated glomerular filtration rate as a predictor of postoperative cardiac surgery-associated acute kidney injury. Ann Card Anaesth 2020;23:53-8.

but eGFR <40 cc/min/1.73 m^2 were also excluded from the study. Patients who required intra-aortic balloon pump and extracorporeal membrane oxygenators, redo surgery were also excluded. EGFR was calculated using the Cockcroft–Gault equation.[4]

The perioperative care was given by the same team. All patients received 0.1 mg/kg morphine and timed to approximately 7–10 min before intubation. General anesthesia was induced with titrated doses of propofol and rocuronium or vecuronium to facilitate tracheal intubation. Rocuronium infusion was started soon after. Intraoperatively, additional 50 mcg fentanyl was administered before sternotomy. Injection paracetamol 20 mg/kg (maximum 1 g) was also administered. Hemodynamic management included a targeted mean arterial pressure (MAP) of + 20% from basal during pre-bypass. The MAP of 50–65 mmHg and a flow of 2.4 L/min/m^2 BSA were maintained during nonpulsatile CPB. Cardiac output monitoring was done in a few patients using EV1000 clinical platform from Edwards Lifesciences and a cardiac index of 2.4 L/min/m^2 BSA was targeted. However, these data were not included for analysis as the monitoring was not done in the majority of the cases. Vasopressor, vasodilator, and/or ionotropic support were administered as needed while coming out of bypass and postoperatively to maintain a minimum of 65–70 mm Hg MAP and effective left ventricular contraction. Serum creatinine, blood urea, and urine output were noted till the 3rd postoperative day (POD). All patients received postoperative care till POD 3 in the same ICU with the same staffs as per prevailing protocol.

Urine output was noted in the chart hourly in the ICU. However, for calculation of CSA-AKI as per AKIN criteria [Table 1],[5] four hourly urine output was considered from the chart and for statistical analysis and comparison of urine output, 24 h total amount is taken.

The sample size for this retrospective study was calculated for a prevalence (proportion) of 40% ± 10% (absolute precision) of the CSA-AKI as per previous studies discussed in this study. A design effect of 1.4 was applied to compensate the retrospective nature of the study. Online tool OpenEpi (Open Source Epidemiologic Statistics for Public Health; http://www.openepi.com/SampleSize/SSPropor.htm) was used for calculating the sample applicable for a large population which gave a sample size of 130 for 95% confidence interval.

CSA-AKI occurrence was determined using the AKIN criteria and expressed in absolute number and percentage scale. The cohort was stratified based on the different range of preoperative eGFR (i.e., 40–60, >60–80, >80–100 and >100 cc/min/1.73 m^2 BSA). The relationships with occurrences of CSA-AKI were evaluated by Chi-squared test for independence and odds ratio calculated by Fisher's exact test and other parameters were analyzed by appropriate statistical tests. INSTAT software from Graphpad software, Inc., La Jolla, CA, USA, was used and a $P < 0.05$ was considered as statistically significant. Multinomial logistic regression was done using MedCalc statistical software version 18.10 (MedCalc, Seoul, Republic of Korea) using values for binomial parameters such as sex (female = 1; male = 0) and outcome of "CSA-AKI positive = 1;" "CSA-AKI negative = 0."

Results

Data from 134 patients (44.78% of males and 55.22% of females) in the age group of 15–74 years and eGFR between 40 and 135.76 cc/min/1.73 m^2 BSA, who underwent open heart surgeries under CPB and aortic cross-clamp were analyzed. The demographic and mean preoperative kidney function parameters of the entire cohort are shown in Table 2. There were one infective endocarditis, 5 diabetes mellitus, 21 atrial fibrillations, 56 preoperative anemia, and 68 hypertensive/on antihypertensive medications (most of them were receiving calcium channel blockers as well) patients among the cohort.

A total of 66 (49.25%) cases met the diagnosis of CSA-AKI till the 3rd POD as defined by the AKIN criteria. Nearly two-thirds of the patients who underwent aortic valve and double valve replacement surgeries developed CSA-AKI. The names and numbers of surgical procedures performed along with the CSA-AKI are shown in Table 3.

Out of the 66 CSA-AKI cases, 34 (51.52%) patients were female and female gender was not associated with development of CSA-AKI (odds ratio: 0.743%, 95% confidence: 0.37–1.44, $P = 0.4873$). Patients who developed CSA-AKI had higher mean + standard deviation (SD) preoperative eGFR values than the patients who did not develop CSA-AKI (74.12 + 22.57 versus 66.40 + 18.49 cc/min/1.73 m2 BSA; $P = 0.03$). The postoperative urine output of the patients (POD 1–3) who developed CSA-AKI was not different than the patients who did not develop

Table 1: Acute kidney injury network staging/classification of acute kidney injury[5]

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥26.4 μmol/L) or increase to more than or equal to 150%-200% (1.5-fold-2-fold) from baseline	<0.5 ml/kg per hour for more than 6 h
2	Increase in serum creatinine to more than 200%-300% (>2-fold-3-fold) from baseline	<0.5 ml/kg per hour for more than 12 h
3	Increase in serum creatinine to more than 300% (>3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl [≥354 μmol/L] with an acute increase of at least 0.5 mg/dl [44 μmol/L])	<0.3 ml/kg per hour for 24 h or anuria for 12 h

CSA-AKI [Table 4]. However, the patients who developed CSA-AKI had lower mean + SD heights than the patients who did not develop CSA-AKI $P = 0.02$ [Table 4].

Multinomial logistic regression of the preoperative variables again confirmed that the patients who developed CSA-AKI had significantly higher mean + SD preoperative eGFR values than the patients who did not develop CSA-AKI and lower height was independently associated with higher incidence of CSA-AKI [Table 5].

Nine (69.23%) of the patients whose preoperative eGFR was >100 cc/min/1.73 m^2 BSA developed CSA-AKI as compared to 39.62% of the patients whose preoperative eGFR was 40–60 cc/min/1.73 m^2 BSA (odds ratio: 0.29, $P > 0.05$). The CSA-AKI occurrences trends over the different strata of preoperative eGFR were also not statistically significant [Table 6].

Discussion

It is well established that CSA-AKI is very common after cardiac surgery and associated with significant impact on mortality and morbidity.[1,6,7] Although it is known for a few decades, limited effective therapeutic intervention exists till date to either ameliorate renal injury or improve survival. However, experimental studies suggest that if therapeutic interventions are started within 24–48 h of inducing CSA-AKI, promising results probably can be obtained.[8,9] Establishing the predictors of CSA-AKI will help healthcare providers in risk stratification as well as in decision-making for initiation of early intervention postoperatively.

Prognostic risk stratification methods to predict renal dysfunction and identify patients who are at a greater risk for developing AKI after cardiac surgery has been described and the Cleveland clinical score is one of them.[3] External validation has shown that Cleveland clinical score is not only effective in predicting AKI requiring dialysis but also in predicting severe AKI.[10] In this scoring system, preoperative creatinine of >1.2 mg% has been found as a risk factor and >2 mg% as a very strong risk factor with a good area under the curve.

On the other hand, kidney function is better represented by eGFR then absolute serum creatinine level and Kidney Disease Foundation classifies chronic kidney disease (CKD) based on it.[11] As the absolute value of 1.2 mg% of serum creatinine may indicate renal failure in a 70-year-old female weighing 50 kg (stage 3), whereas the same value may be of normal kidney function in a 20-year-old male weighing 65 kg (stage 1), there is a possibility that eGFR will help better in predicting postoperative CSA-AKI.

Sixty-six (49.25%) of the patients met the definition of CSA-AKI during the postoperative 3 days. This is relatively higher as compared to the findings of other studies and reviews.[6,12] This is probably and partly because of the criteria used (i.e., AKIN) in the present study, which categorizes even 0.3 mg% absolute rise of serum creatinine as Class I AKI. A study conducted in northern New England medical center using the AKIN criteria found that 39% of the patients underwent cardiac surgeries suffered from CSA-AKI.[13] The AKIN criteria have shown to diagnose significantly more patients as having AKI as compared to RIFLE (risk, injury, failure, loss of kidney function, and end-stage renal failure).[14] However, a recent study using RIFLE criteria found 49.9% AKI, which is similar to the present study finding (49.25%).[15] Although the AKIN criterion considers both the creatinine and urine output as criteria, urine output is often not low, even in patients with progressing CSA-AKI in immediate few postoperative days due to fluid resuscitation, diuretics.[16] Oliguria was not very prevalent in the present study cohort of CSA-AKI also.

Table 2: Demographic and baseline kidney function parameters of entire cohort

Parameters	Mean (SD)/*n* (%)	95% CI
Age (years)	37.98 (12.50)	35.86-40.10
Male	60 (44.78)	
Female	74 (55.22)	
Weight (kg)	49.86 (8.29)	48.46-51.27
Height (cm)	158.18 (8.44)	156.76-159.62
eGFR (ml/min/1.73m^2)	70.20 (20.89)	66.66-73.74
Serum creatinine (mg %)	0.967 (0.22)	0.929-1.006
Blood urea (mg %)	30.06 (16.21)	27.32-32.81

eGFR: Estimated glomerular filtration rate, SD: Standard deviation, CI: Confidence interval

Table 3: Distribution of cardiac surgeries performed and their respective number of cardiac surgery associated acute kidney injury

Name of the surgery performed	Number of cases (*n*=134), *n* (%)	Number of CSA-AKI, *n* (%)
ASD closure±TAP	23 (17.16)	5 (21.74)
VSD closure±patent ductus arteriosus closure	8 (5.97)	3 (37.5)
Aortic valve replacement±TAP	26 (19.40)	17 (65.38)
Mitral valve replacement±TAP/± ASD/± LA clot removal	47 (35.07)	23 (48.94)
Double valve replacement+LA clot removal	14 (10.45)	9 (64.29)
CABG/CABG+valve replacement	7 (5.22)	3 (42.86)
Others (DORV/rupture aneurysm/LA myxoma/tetrology of fallot)	9 (6.72)	6 (66.67)

CSA-AKI: Cardiac surgery associated acute kidney injury, DORV: Double outlet right ventricle, ASD: Atrial septal defect, TAP: Tricuspid annuloplasty, VSD: Ventricular Septal Defect, LA: Left atrial, CABG: Coronary artery bypass graft

Table 4: Comparisons of cardiac surgery associated acute kidney injury positive and negative cases statistically tested by unpaired *t*-test

Parameters	CSA-AKI positive (*n*=66)		CSA-AKI negative (*n*=68)		*P*
	Mean (SD)/*n* (%)[#]	95% CI of mean	Mean (SD)/*n* (%)[#]	95% CI of mean	
Male[#]	32 (48.48)		28 (41.18)		0.4873
Female[#]	34 (51.52)		40 (58.82)		0.4873
Age (years)	39.66 (13.15)	36.43-42.90	36.35 (11.71)	33.51-39.19	0.1256
Weight (kg)	50.95 (7.81)	49.03-52.87	48.80 (8.66)	46.71-50.90	0.1349
Height (cm)	159.80 (7.90)	157.86-161.75	156.61 (8.70)	154.51-158.73	0.0284
eGFR (ml/min/1.73m^2)	74.12 (22.57)	68.57-79.67	66.40 (18.49)	61.92-70.88	0.0319
Preoperative creatinine (mg %)	0.91 (0.22)	0.85-0.96	1.02 (0.22)	0.96-1.07	0.0047
Preoperative blood urea (mg %)	29.75 (14.70)	26.14-33.37	30.36 (17.66)	26.08-34.64	0.8286
CPB time (min)	103.71 (40.50)	93.74-113.68	89.30 (43.38)	78.79-99.82	0.0492
X-clamp (min)	79.62 (34.53)	71.12-88.11	66.76 (37.30)	57.72-75.80	0.0405
POD 1 urine output	1.15 (0.28)	1.08-1.28	1.25 (0.41)	1.15-1.35	0.1208
POD 2 urine output	1.17 (0.37)	1.08-1.27	1.21 (0.37)	1.12-1.30	0.5596
POD 3 urine output	1.21 (0.41)	1.11-1.31	1.20 (0.28)	1.14-1.27	0.9644
Serum creatinine (mg %)					
POD 1	1.27 (0.37)	1.18-1.36	1.03 (0.24)	0.97-1.09	<0.0001
POD 2	1.36 (0.41)	1.26-1.47	1.00 (0.23)	0.95-1.06	<0.0001
POD 3	1.31 (0.47)	1.19-1.43	0.94 (0.23)	0.89-1.00	<0.0001
Blood urea (mg %)					
POD 1	41.15 (14.59)	37.56-44.74	36.10 (13.17)	32.91-39.29	0.0374
POD 2	46.86 (14.99)	43.17-50.55	37.41 (13.71)	34.09-40.73	0.0002
POD 3	48.10 (16.42)	44.03-52.18	34.52 (13.76)	31.16-37.88	<0.0001

[#]Fisher's exact test, CSA-AKI: Cardiac surgery associated acute kidney injury, eGFR: Estimated glomerular filtration rate, SD: Standard deviation, CI: Confidence interval, CPB: Cardiopulmonary bypass, X-clamp: Aortic cross clamp, POD: Postoperative day

Table 5: Results of multinomial logistic regression for analyzing independent preoperative variables as a predictor of postoperative cardiac surgery associated acute kidney injury

Independent variables	Coefficient	SE	*t*	*P*	$r_{partial}$	$r_{semipartial}$
Constant	−1.2371					
Age (years)	0.00519	0.0044	1.172	0.2436	0.1046	0.0953
Blood urea (mg %)	0.00075	0.0028	0.261	0.7949	0.02339	0.0212
CPB time (min)	0.00025	0.0039	0.0649	0.9483	0.00583	0.0052
eGFR (cc/min/1.73m^2)	−0.00061	0.0041	−0.146	0.8841	−0.01312	0.0118
Height (cm)	0.01395	0.0062	2.220	0.0283	0.1955	0.1806
Preoperative creatinine	−0.7453	0.3292	−2.264	0.0253	−0.1992	0.1842
Weight (kg)	−0.00126	0.0084	−0.150	0.8810	−0.01347	0.0122
Sex	−0.03983	0.0963	−0.414	0.6799	−0.03711	0.0336
Cross clamp time (min)	0.00175	0.0047	0.370	0.7124	0.03317	0.03006

CPB: Cardiopulmonary bypass, eGFR: Estimated glomerular filtration rate, SE: Standard error

The other reason for such high incidence is probably that more than 70% of patients in the present study underwent complex cardiac/valve replacement surgeries. Valve replacement itself has been shown as a risk factor for CSA-AKI.[17] The predominant (65.67%) surgical procedures were valve replacements in the present study. Diagnosis wise, the present study cohort is also different as usually ventricular septal defects (VSD) are more common than atrial septal defects (ASD). Although we do not have population-based data from this region (region where the study was conducted), data from another part of the country found that the most common congenital cardiac defect was VSD (33%), followed by ASD (19%) and tetralogy of Fallot (16%) in children.[18] However, as the majority of the congenital cardiac defect patients do not makeup to adulthood without corrective surgery; the scenario changes. The same study found that the most frequent congenital cardiac defect in adult was ASD (44.5%).[18] Rheumatic heart disease and rheumatic valvular heart disease are very prevalent in developing countries. Therefore, the present discrepancy in diagnosis may be because that, the patient population was adult and adolescents from a developing country. Moreover, the study is carried out in a referral center and simple congenital cardiac surgeries are done in

Table 6: Clinical parameters and cardiac surgery associated acute kidney injury trend with estimated glomerular filtration rate analyzed by Chi-square test of independence and Fisher's exact test

Parameters	Preoperative eGFR (ml/min/1.73m² BSA), mean (SD)				*P*
	>100 (*n*=13)	>80-100 (*n*=30)	>60-80 (*n*=38)	40-60 (*n*=53)	
Age (years)	34.0 (9.66)	36.83 (13.54)	35.15 (10.98)	41.64 (12.89)	0.0431
Weight (kg)	56.0 (9.87)	54.06 (9.93)	48.10 (6.36)	47.24 (6.38)	<0.0001
Height (cm)	161.46 (8.63)	160.10 (12.05)	158.50 (7.46)	156.07 (5.89)	0.0745
Base serum creatinine (mg %)	0.73 (0.20)	0.83 (0.16)	0.94 (0.17)	1.12 (0.19)	<0.0001
Preoperative eGFR (ml/min/1.73 m²)	113.22 (8.75)	87.85 (6.03)	68.61 (4.92)	50.81 (5.80)	<0.0001
Baseline blood urea (mg %)	22.76 (8.89)	27.03 (18.63)	29.76 (12.57)	33.79 (17.76)	0.0885
CPB time (min)	84.00 (46.67)	95.7 (53.57)	95.78 (34.81)	100.28 (39.87)	0.6712
Aortic clamp time (min)	56.07 (32.73)	73.56 (45.17)	73.26 (32.06)	76.88 (34.43)	0.3339
CSA-AKI, *n* (%)	9 (69.23)	17 (56.67)	19 (50.00)	21 (39.62)	0.1943*
OR$ (P)$	Control	0.58 (0.51)	0.44 (0.33)	0.29 (0.06)	
95% CI of OR$		0.14-2.31	0.11-1.69	0.07-1.07	

*Chi-square test of independence, $Fisher's exact test. CSA-AKI: Cardiac surgery associated acute kidney injury, eGFR: Estimated glomerular filtration rate, SD: Standard deviation, CI: Confidence interval, CPB: Cardiopulmonary bypass, OR: Odds ratio, BSA: Body surface area

other centers nearby. Healthcare seeking behavior and poor socioeconomic status is also likely to play a role.

A high number (41.79%) of anemic (hemoglobin <12.5 g%) patients in the study cohort can also contribute to the high incidence of CSA-AKI. Anemia leads to increased blood transfusion and both anemia and increased red blood cell transfusion has been shown to be associated with postoperative increased AKI.[19,20] This is probably because of the free iron load which works as a free radical.

The present retrospective evaluation of prospectively collected data was aimed to evaluate the relationship of preoperative eGFR with the occurrences of CSA-AKI. As it is well established that CKD and patients with serum creatinine of >2 mg% are unequivocally associated with postoperative renal failure, it was aimed to evaluate the relation of eGFR with CSA-AKI in patients whose preoperative serum creatinine was <2 mg% with eGFR >40 cc/min/1.73 m² BSA in the present study. The eGFR >100 cc/min/1.73 m² BSA was taken as reference and other strata of eGFR were compared with regard to the occurrences of CSA-AKI. However, the present study failed to find a relation of increasing CSA-AKI with the decreasing trend of eGFR as defined by AKIN criteria. This finding probably does not indicate that the absolute value of serum creatinine >1.2 mg% is not a risk factor and for this further evaluation will be required. However, this finding does indicate that revalidation of prognostic risk scores for predicting CSA-AKI as defined by AKIN is required to give a new weighted/score for this risk factor if required.

With median 2 years follow-up after valve replacement surgeries, a study found that preoperative eGFR <60 cc/min/1.73 m² was a powerful predictor of all-cause mortality.[21] In the present study, mortality analysis was not an objective, but the finding of less CSA-AKI in patients with preoperative eGFR 40–60 cc/min/1.73 m² as compared to more eGFR (>100 cc/min/1.73 m²) indicates that the mortality contribution will unlikely be statistically insignificant. The present study excluded patients with eGFR <40 cc/min/1.73 m² (more severe cases) and this may be a contributing factor for the difference. To some extent, the finding of the present study; however, resembles some extent to the findings of the study evaluating renal dysfunction and outcome after coronary artery bypass grafting by analyzing the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies[22] The study found that severe, but not moderate; renal dysfunction was independently associated with an increased risk of long-term cardiovascular events and death.[22]

The present finding and conclusion are, however, is limited by the fact that it is a single center study. Although the study was conducted with calculated samples a relatively larger sample size would have been better. Being retrospective study, a few relevant data (vasopressor support, blood transfusion, etc.,) were not possible to analyze due to the relatively incomplete nature of the data.

Conclusion

In patients with preoperative eGFR >40 cc/min/1.73 m² BSA, a lower preoperative eGFR (40–60 cc/min/1.73 m²) does not predict higher incidence of CSA-AKI as defined by AKIN criteria as compared to higher preoperative eGFR (>100 cc/min/1.73 m²). Lower height is independently associated with a higher incidence of CSA-AKI in such patients. This finding, however, requires validation by further prospective, multicenter study with a larger sample.

Acknowledgment

We would like to acknowledge the help provided by the Department of CTVS, NEIGRIHMS, Shillong.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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