Turkish Journal of Health Science and Life

Is preoperative vitamin D level a risk factor for acute kidney injury developing after cardiopulmonary bypass?

Ersin Çelik[a], Ahmet Rıfkı Çora[b], Kadir Burhan Karadem[c]

[a,b]*Department of Cardiovascular Surgery, Isparta City Hospital/ Isparta/Türkiye*

[c]*Department of Cardiovascular Surgery, Suleyman Demirel University/Isparta/Türkiye*

ARTICLE INFO

RESEARCH ARTICLE

Article history:

Received: 29 November 2022

Accepted: 21 December 2022

Available : 30 December 2022

[a]https://orcid.org/0000-0002-0015-3280

[b]https://orcid.org/0000-0002-4892-9463

[c]https://orcid.org/0000-0003-2410-8318

*Correspondence: Ersin Çelik

Isparta City Hospital Cardiovascular Surgery Clinic Sanayi Mahallesi Atatük Bulvarı NO:51 Isparta, 32200, Türkiye

e-mail: dr.ersincelik@gmail.com

Turkish Journal of Health Science and Life

2022, Vol.5, No.3, 247-254.

DOI: https://10.56150/tjhsl.1211890

ABSTRACT

Objective: In this study, the relationship between acute kidney injury (AKI) that developed in the early postoperative period in the patients that underwent open heart surgery with cardiopulmonary bypass (CPB) and their preoperative 25-Hydroxy Vitamin D (25-OHD) levels was investigated.

Method: 285 patients who underwent open heart surgery with CPB between February 2018 and December 2020 were retrospectively analyzed. Ninety seven patients (71 men, 26 women) who met the criteria were included in the study. The patients were divided into 3 groups according to their preoperative 25-OHD levels as deficiency (group I, n=28), insufficiency (group II, n=42) and normal (group III, n=27).Demographic and clinical characteristics, AKI, and CPB time were compared between the groups. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were used to define postoperative AKI.

Results: According to the KDIGO guidelines, the incidence of postoperative AKI decreased to 19% at the end of 48 hours and to 6.2% at discharge whereas it was 21% in the first 24 hours. The decrease in KDIGO AKI stages was found to be statistically significant (p=0.002). The rate of DM was found to be significantly higher in Group I (p=0.001). No statistical difference was found between AKI and 25-OHD levels at 24 hours, 48 hours and discharge. CPB time was found to be significantly higher in Group I (p=0.006). In the univariate logistic regression model created after 25-OHD groups were taken as low (group I+group II) and normal (group III), low 25-OHD levels were found to have a significant effect on the development of DM (p=0.001, OR:8.474, 95%CI 2.336 -30.303).

Conclusion: Although we could not find a statistical relationship between AKI and preoperative 25-OHD levels in the patients that underwent open heart surgery with CPB, we believe that 25-OHD deficiency might have effects on postoperative morbidity and mortality by affecting the renocardiovascular system.

Keywords:25- Hydroxy Vitamin D, acute kidney injury, cardiopulmonary bypass, renin–angiotensin system, diabetes mellitus

Introduction

Acute kidney injury (AKI) is defined as abrupt reduction in kidney function within 48 hours of the triggering event [1] and it exerts an independent effect on the mortality risk [2]. Kidney Disease: Improving Global Outcomes (KDIGO) criteria were established in 2012 for the detection of AKI, and three stages were defined according to serum creatinine level or hourly urine output [3]. AKI can be seen with a rate of 18-30% as an important cause of morbidity and mortality after open heart surgeries that were performed with cardiopulmonary bypass (CPB) [4,5]. It is known that there are many risk factors in the development of AKI such as anemia, need for inotropic support, low ejection fraction (EF), blood transfusion volume, age, and diabetes mellitus (DM).

Vitamin D is a steroid vitamin that has two forms: D2 taken in the diet and D3 synthesized in the skin after exposure to sunlight. These inactivated forms of vitamin D transforms to 25-Hydroxy Vitamin D (25-OHD) by being hydroxylated in the liver, and then transforms to the active form, 1,25 dihydroxyvitamin D (1,25(OH)2D3) by being hydroxylatedin the kidneys with 1 α-hydroxylase. 25-OHD is the major circulating form of vitamin D. It is currently the best marker of vitamin D status and is used by clinicians to

determine a patient's vitamin D status [6].

25-OHD has effects on many organ systems such as skeletal system, nervous system, immune system, and cardiovascular system. Despite the increasing research in recent years, the protective effect of 25-OHD for cardiovascular diseases has not been fully understood, but it is known that it has effects on the regulation of calcium accumulation in the vascular wall due to the effects of the renin-angiotensin system (RAS), glycemic control, inflammatory cytokine release, serum calcium level and parathormone level [7-9]. Although 25-OHD receptors have been shown on the renal system and its effects on RAS and blood pressure regulation, there has not been enough research in the literature examining postoperative AKI and 25-OHD levels after CPB.

In our study, we aimed to examine the relationship between AKI that developed in the early postoperative period and preoperative 25-OHD levels in patients who underwent open heart surgery with CPB.

Material and Method

After permission with the number 03.02.2021/61 was obtained from Süleyman Demirel University Ethics Committee, the data of 285 patients that underwent open heart surgery in our hospital between February 2018 and December 2020 were reviewed retrospectively. Patients whose 25-OHD level was not measured within one month before the operation, patients that received vitamin D therapy in the last three months, patients that underwent off-pump open heart surgery, patients that underwent combined surgery such as aortic surgery, valve and coronary artery bypass graft surgery, and patients that underwent emergency surgery were excluded from the study. A total of 97 patients who underwent single procedure open heart surgery with cardiopulmonary bypass and whose 25-OHD level was measured for any reason within 1 month before the operation were included in the study.

Detailed medical history, physical examination, routine blood tests, echocardiogram, electrocardiogram, chest radiograms and respiratory function tests, body measurement index (BMI), and European System for Cardiac Operative Risk Evaluation (EuroSCORE) were performed on all patients that were planned to undergo an open heart surgery. Patients that were smoking on the date of coronary angiography were evaluated as smokers. Internal medicine consultation was requested from the patients who had a previous diagnosis of DM and patients who did not have a diagnosis of DM but whose fasting blood glucose was >126 mg/dl and thus, the diagnosis of DM was confirmed. Patients who had previously received antihypertensive treatment and those who had >130/85 mm/Hg blood pressure during clinical follow-up were considered hypertensive patients. All patients that had Chronic Obstructive Pulmonary Disease (COPD) were evaluated by a chest physician with pulmonary function test or by arterial blood gas examination and those who could not perform pulmonary function tests were evaluated with physical examination.

Biochemical and Hematological Parameters

Hemoglobin values were obtained by using the automated blood counter Mindray BC-6800 (Mindray, China). Creatinine values were measured by theADVIA 2400 Clinical Chemistry System (Siemens corp., Japan) and 25-OHD values were obtained by using the ADVIA Centaur XPT Immunoassay System (Siemens Corp., Ireland). Glomerular filtration rate was estimated by using Cockcroft-Gault formula. For the plasma 25-OHD level, the patients were divided into 3 groups by considering Group I: <10 ng/dl as deficiency, Group II: ≥10-20 ng/dl as insufficiency, and Group III: ≥20-80 ng/dl as normal.

Acute Kidney Injury

According to the serum creatinine levels specified in the 2012 KDIGO guidelines, AKI in the patients were determined as stage I: 1.5-1.9-fold or ≥0.3 mg/dl increase from the basal value, stage II: 2.0-2.9-fold increase from the basal value, and stage III: ≥3 times from the basal value, or serum creatinine >4.0 mg/dl or initiation of renal replacement therapy.

Operative Technique

Median sternotomy was applied to all the patientswith general anesthesia. CPB was performed by using aortocaval cannulation technique in all patients following systemic heparin administration (300 IU/kg). Cardiac arrest was achieved by using hypothermic hyperkalemic blood cardioplegia and topical hypothermia. Surgery was performed with moderate systemic hypothermia (32˚C). Cardiopulmonary bypass flow was maintained at 2.2 –2.5 L/min/m2, mean perfusion pressure was maintained between 50 and 80 mm Hg, and hematocrit level was maintained at 20–25% during CPB. Cardiac arrest was maintained by using intermittent antegrade cold blood cardioplegia infusions. In the patients that had low EF, multivessel disease and poor ventricular function, continuous retrograde cold blood cardioplegia infusion was performed in addition to intermittent antegrade cold blood cardioplegia. Warm blood cardioplegia was given in all patients just before removing the crossclamp. All early postoperative patient follow-ups were done in the third-degree cardiovascular

Table 1. Categorical measurements according to vitamin D levels

		Group I	Group II	Group III	Total	
		N(%)				p
Type of operation	CABG	25 (89.3)	37 (88.1)	21 (77.8)	83 (85.6)	0.067
	AVR	2 (7.1)	2 (4.8)	1 (3.7)	5 (5.2)	
	MVR	1 (3.6)	3 (7.1)	3 (11.1)	7 (7.2)	
	ASD	0 (0.0)	0 (0.0)	2 (7.4)	2 (2.1)	
Sex	M	17 (60.7)	34 (81.0)	20 (74.1)	71 (73.2)	0.258
	F	11 (39.3)	8 (19.0)	7 (25.9)	26 (26.8)	
DM	none	12 (42.9)	22 (52.4)	24 (88.9)	58 (59.8)	0.001*
	Yes	16 (57.1)	20 (47.6)	3 (11.1)	39 (40.2)	
Hypertension	none	18 (64.3)	24 (57.1)	21 (77.8)	63 (64.9)	0.305
	Yes	10 (35.7)	18 (42.9)	6 (22.2)	34 (35.1)	
COPD	none	21 (75.0)	34 (81.0)	23 (85.2)	78 (80.4)	0.343
	Yes	7 (25.0)	8 (19.0)	4 (14.8)	19 (19.6)	
Smoker	none	26 (92.9)	33 (78.6)	23 (85.2)	82 (84.5)	0.424
	Yes	2 (7.1)	9 (21.4)	4 (14.8)	15 (15.5)	
KDIGO 24.hour	No damage	22 (78.6)	32 (76.2)	22 (81.5)	76 (78.4)	0.591
	Stage1	5 (17.9)	10 (23.8)	5 (18.5)	20 (20.6)	
	Stage2	1 (3.6)	0 (0.0)	0 (0.0)	1 (1.0)	
KDIGO 48.hour	No damage	21 (75.0)	36 (85.7)	21 (77.8)	78 (80.4)	0.952
	Stage1	7 (25.0)	3 (7.1)	5 (18.5)	15 (15.5)	
	Stage2	0 (0.0)	2 (4.8)	1 (3.7)	3 (3.1)	
	Stage3	0 (0.0)	1 (2.4)	0 (0.0)	1 (1.0)	
KDIGO Discharge	No damage	27 (96.4)	40 (95.2)	24 (88.9)	91 (93.8)	0.451
	Stage1	1 (3.6)	1 (2.4)	3 (11.1)	5 (5.2)	
	Stage3	0 (0.0)	1 (2.4)	0 (0.0)	1 (1.0)	

CABG: Coronary artery bypass grafting, AVR: aortic valve replacement, MVR: mitrale valve replacement, ASD: atrial septal defect, DM: diabetes mellitus, COPD: cronic obstructive pulmonary disease KDIGO: Kidney Disease Improving Global Outcomes

Group I: patients with preoperative serum 25-OHD levels <10 ng/dl

Group II: patients with preoperative serum 25-OHD levels ≥10-20 ng/dl

Group III: patients with preoperative serum 25-OHD levels ≥20-80 ng/dl

**Significant at the 0.05 level according to the chi-square test*

surgery intensive care unit.

Statistical Analysis

Statistical analyses of the study were performed with SPSS 20.0 (IBM Inc, Chicago, IL, USA) program. Descriptive measures were presented as median Q1-Q3 and frequency (percentage). Normality of the continuous variables was tested with the Kolmogorov-Smirnov test. Since it was found out that the distributions were not normal, group comparisons were performed with the Kruskal-Wallis test.Chi-square analysis was used to determine the relationships between categorical variables. The Friedman test was used to test the variation between KDIGO stages. A multinomial logistic regression model was established according to 25-OHD levels.A $p<0.05$ value was considered statistically significant by taking the typeI error rate as 5% throughout the study.

The power analysis of the study was performed with the GPower 9.1.2 (Universitaet Kiel, Germany) program.KDIGO stage scoring and hypothetical relationships between the 25-OHD groups were used to determine the sample size. Chi-square was chosen as the test family, and cross-tabulation goodness of fit was chosen as the test analysis.The effect size was calculated as 0.547.The sample size determined accordingly was 80 patients in total. The margin of error was taken as 5% and the power value was taken as 95%.

Results

A total of 97 patients who met the criteria were included in the study.The proportion of male patients was higher (73.2%), and the median age was calculated as 63 years. The operation type of the patients was mostly coronary artery bypass grafting (CABG) (85.6%), and aortic valve replacement, mitral valve replacement and atrial septal defect operations were performed at lower rates. Categorical measurements based on 25-OHD levels are given in Table 1. One patient was lost due to low

Table 2. Surgical and clinical features according to vitamin D levels

	Group I	**Group II**	**Group III**	
	(Median; Q1-Q3)			***p***
Age	68; 59.25-76.75	62; 54-71.5	61; 51-70	0.137
BMI (kg/m²)	28; 25.85-32.85	29.11; 26.61-33.45	26.75; 23.51-30.38	0.126
Weight (kg)	74; 62.75-86	84; 71.5-91.25	74; 68-85	0.092
EF (%)	57.5; 50-60	55; 44-60	55; 45-60	0.421
Post-contrast time (day)	12.5; 8.25-20	10.5; 7-17	13; 9.5-20.5	0.387
Euroscore	1.96; 1.17-2.53	1.36; 0.78-2.53	1.65; 0.98-2.62	0.379
Preop Hemoglobin (g/dL)	12.75; 11.33-14.55	14.1; 12.28-15	12.9; 11-14.6	0.296
CPB time (min.)	123; 90.5-140.5[a]	101; 75-121.5	86; 61-103[a]	0.006*
Pre-op creatine (mg/dL)	0.86; 0.71-1.05	0.9; 0.8-1.03	0.99; 0.73-1.17	0.323
Pre-op GFR	85.75; 58.67-99.42	93.04; 71.11-118.27	81.51; 66.01-110.89	0.253
Post-op creatine (mg/dL)	0.86; 0.65-0.99	0.87; 0.7-1.02	0.84; 0.74-1.18	0.578
Creatine 24.hour	0.97; 0.73-1.15	1.08; 0.83-1.27	1.04; 0.84-1.5	0.407
Creatin 48.hour	0.86; 0.7-1.16	0.89; 0.75-1.15	0.99; 0.8-1.37	0.524
GFR 48.hour	72.45; 52.23-102.61	90.08; 63.28-122.51	75.76; 61.36-129.17	0.310
Creatine Discharge (mg/dL)	0.93; 0.7-1.11	0.91; 0.71-1.09	0.98; 0.71-1.09	0.757
GFR Discharge	80.03; 67.23-100.61	91.74; 79.24-121.8	80.61; 69.53-116.48	0.129
ICU time(day)	2; 2-3	2; 2-3	2; 2-2	0.128
Hospital stay (day)	7; 6-8	7; 6-9	7; 6-8	0.664

BMI: body mass index. EF: ejection fraction. 25-OHD: 25-hydroxyvitamin D. CPB: Cardiopulmonary bypass. ES: erythrocyte suspension. GFR: glomerular filtration rate. ICU:intensive care unit

Group I: patients with preoperative serum 25-OHD levels <10 ng/dl

Group II: patients with preoperative serum 25-OHD levels ≥10-20 ng/dl

Group III: patients with preoperative serum 25-OHD levels ≥20-80 ng/dl

**: Significant at the 0.05 level according to the Kruskal-Wallis test*

[a]: The difference between categories with the same exponential letters is significant at the 0.05 level

cardiac output on the 3rd postoperative day and another patient who had an ischemic stroke on the 1st postoperative day was lost on the 13th day due to the development of multiorgan failure. According to the KDIGO criteria, the incidence of AKI was 21% in the first 24 hours, and it decreased to 19% at the end of 48 hours and to 6.2% at discharge. The decrease in AKI in the time period until discharge was found to be statistically significant (p=0.002) (Table 1).

The 25-OHD levels and all demographic, surgical, clinical and biochemical measurements of the patients that were divided into three groups were compared. While the number of patients in groups I and II was close to each other (~28%), it was approximately 44% in group III. The rate of DM was found significantly higher in group I (p=0.001). There was no statistical difference between AKI and 25-OHD levels at 24 hours, 48 hours and discharge (Table 1). No significant difference was detected between 25-OHD levels as a result of the demographic data and biochemistry measurements (Table 2). CPB time was found to be significantly higher only in group I (p=0.006).

In the univariate logistic regression model created after taking the 25-OHD groups as low (group I+group II) and normal (group III), it was found that low 25-OHD levels have a significant effect on the development of DM (p=0.001, OR:8.474, 95%CI 2.336 - 30,303) (Table 4). In the analysis performed between the group I and group II, it was found that the risk of DM development increased as 25-OHD levels decreased (Table 5).

Table 3. Factors affecting vitamin D level

Model	-2LL=93.44	$R^2_{Nagelkerke}$=0.284	Hosmer-Lemeshow X^2=3.826; p=0.872	
	Beta	**p**	**OR**	**95% CI**
DM	-2.050	0.002*	7.751	2.079-29.411
Age	1.292	0.256		
Sex	0.441	0.507		
HT	0.132	0.716		
COPD	0.534	0.216		
BMI (kg/m²)	0.326	0.568		

DM: diabetes mellitus. HT: hypertension. COPD: chronic obstructive pulmonary disease. BMI: body mass index

**: Significant at the 0.05 level according to the Univariate logistic regression model*

Table 4. The effect of vitamin D levels on the development of diabetes mellitus

Model	-2LL=115.82	$R^2_{Nagelkerke}$=0.192		
	Beta	**p**	**OR**	**95% CI**
25-OHD < 20 ng/dl	-2.137	0.001	8.474	2.336-30.303

25-OHD: 25 hydroxyvitamin D3

**Significant at the 0.05 level according to the chi-square test*

Table 5. Risk of developing diabetes mellitus based on vitamin D levels

Model	-2LL=115.20	$R^2_{Nagelkerke}$=0.210		
	Beta	**p**	**OR**	**95% CI**
Grup I	2.367	0.001	10.667	2.593-43.886
Group II	1.984	0.004	7.273	1.896-27-895

Group I: patients with preoperative serum 25-OHD levels <10 ng/dl

Group II: patients with preoperative serum 25-OHD levels ≥10-20 ng/dl

**: Significant at the 0.05 level according to the Univariate logistic regression model*

Discussion

In this study, the relationship between the 25-OHD levels and AKI in the patients that underwent open heart surgery with CPB was investigated. No statistical difference was detected between the preoperative 25-OHD levels and postoperative AKI. The 25-OHD level was found lower in diabetic patients (p=0.001). In the patients with preoperative 25-OHD deficiency, CPB time was found longer and the risk of developing DM was found higher (p=0.006),(p=0.001, OR:8.474, 95%CI 2.336-30.303).

Depending on the criteria used to define AKI, the incidence of AKI after CPB varies between 0.7-31% [10,11]. Makado et al found the rate of postoperative AKI as 42% based on the KDIGO criteria [12]. The reason behind the different rates of postoperative AKI in many studies is the difference in the criteria used. In our study, using the KDIGO criteria, AKI was detected as 21% in the first 24 hours, 19% in the 48 hour, and 6.2% at discharge. Intravascular hemolysis [13], release of inflammatory cytokines [14], hemodilator and decreased blood viscosity, hypothermia, and hypoperfusion seen during CPB cause a decrease in renal artery flow velocities and renal tubular injury [5,14,15]. Hemodynamic unstable processes, anemia, use of high blood products, and the need for inotropic agents in the early postoperative period are also important causes of AKI [5,15]. We think that the gradual decrease in AKI rates in our study is related to the following conditions seen after the early postoperative period: themaintenance of hemodynamic stabilityin most patients, the decrease in inflammation and cytokine release due to CPB, and the disappearance of inotropic needs.

RAS is traditionally known for its role in regulation of blood pressure, fluid and electrolyte balance [16]. 1,25(OH)2D3 also functions as a negative endocrine regulator of the RAS and thus plays an important role in the regulation of the renocardiovascular functions [17,18]. Additionally, 1,25(OH)2D3 regulates inflammatory responses and upregulates the expression of anti-inflammatory cytokines, such as interleukin (IL)-10, according to in vitro experiments [19]. It has been shown in a few experimental models that 1,25(OH)2D3 can ameliorate renal injury in various conditions [17,20]. Shen et al. investigated the renal injury caused by angiotensin II (Ang II) in rats in their experimental study. After Ang II infusion, glomerular injury and glomerular filtration membrane injury occurred, mitochondrial morphology deteriorated, and proinflammatory cytokine IL-1B and transforming growth factor B (TGF-B) levels increased. All this histopathological deterioration was not observed in the 1,25(OH)2D3 administered rat group, and IL-1B and TGF-B levels decreased (18). In our study, however, no statistically significant difference was found between 25-OHD levels and AKI. The reason for this may be that 1,25 (OH)2D3 acts on these mechanisms mostly over long processes. However, it should not be ignored that there may be acute effects, especially in situations that trigger inflammatory processes such as CPB.The fact that our study was retrospective and conducted with a relatively small number of patients may be a reason of not detecting a statistically significant difference.

It has been shown that CPB is associated with increased inflammatory response [14,21], and increased morbidity and mortality following the adult and pediatric cardiac surgery [22]. During acute inflammation, a complex mediator cascade is triggered to bring about the recruitment of neutrophils to the site of tissue injury. Tissue residential macrophage populations respond by producing pro-inflammatory mediators such as tumor necrosis factor alpha (TNFa), IL-1 and IL-6 [14, 21]. On the other hand, an increase is observed in anti -inflammatory cytokines such as IL-2, IL-10, IL-13, and inflammatory processes are tried to be suppressed [21]. Wen et al. showed that Ang II directly affects inflammation and triggers IL-1B maturation [23]. Again, in the study of Shen et al., TGF -B and IL-1B levels increased significantly in the Ang II-induced experimental group (p<0.005) (18). 1,25 (OH)2D3 also functions as a negative endocrine regulator of the RAS [17]. In addition, it has been

shown that 1,25(OH)2D3 administration has led to increase in IL-10 levels, one of the anti-inflammatory cytokines [19], and decrease in the levels of IL-1B, one of the pro-inflammatory cytokines [18]. In our study, the CPB time was found higher in the group with deficient 25-OHD levels (p=0.006). We think that the reason for the prolongation in CPB time might be related to endothelial dysfunction developing as a result of increased inflammatory response due to insufficient balancing of inflammation, myocardium developing due to increased permeability, and end organ dysfunction such as damage in lung and kidney. Yet, it is rather difficult to discern the isolated, negative impact and use of CPB from the patient's individual operative risk, intraoperative technical difficulties, and the surgeon's and anesthetist's skills and experience, and, last but not least, the quality of postoperative care.

Pancreatic tissue, like the kidney, plays a role in vitamin D metabolism and hydroxylates 25-OHD to 1,25(OH)2D3 [24]. In a longitudinal study of Finnish men and women, a 40% reduction in the risk of developing type 2 diabetes was observed in those with 25(OH)D levels >28 ng/mL at baseline after 17 years of follow-up [25]. Zhang et al showed that vitamin D supplementation to people with prediabetes reduces the risk of developing type 2 DM [26]. Similarly, in our study, the risk of developing DM was found to be higher in patients with 25-OHD <20ng/dl (p=0.001, OR:8.474, 95%CI 2.336-30.303).

The major limitation of this study is its retrospective design with relatively small size of the 25-OHD groups. Also, the patients reflect a single center experience.

Conclusion

Although we could not find a statistical relationship between AKI and preoperative 25-OHD levels in the patients that underwent open heart surgery with CPB, we believe that 25-OHD deficiency might have effects on postoperative morbidity and mortality by affecting the renocardiovascular system, glucose regulation and insulin resistance. Multicenter randomized controlled studies are needed to better understand these effects of 25-OHD.

Conflicting Interests Statement

The authors declared no conflicts of interest with respect to the authorship or publication of this article.

Funding

The authors received no financial support for the research or the authorship of this article.

Statement of Ethics

This research project was reviewed and approved by the Süleyman Demirel University Ethics Committee with number 03.02.2021/61. No informed consent applicable as this is a retrospective database review.

Information

The article was presented as an oral presentation at the 17th Turkish Society of Cardiovascular Surgery Congress held on 17-20 November 2022.

REFERENCES

1. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Wornock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Critical Care 2007; 11(2):R31
2. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 2009; 53(6): 961-73
3. Kellum JA, Lameire N, and the KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Critical Care 2013; 17(1): p204
4. Pickering JW, James MT, Palmer SC. Acute kidney injury and prognosis after cardiopulmonary bypass: A meta-analysis of cohort studies. Am J Kidney Dis 2015; 65(2):283-93
5. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol 2015; 1:19-32
6. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. Mayo Clinic Proceeding 2010; 85(8):pp 752-8
7. Judd S, Tangpricha V. Vitamin D deficiency and risk for cardiovascular disease. Am J Med Sci 2009; 338: 40-4
8. Wang TJ, Pencina MJ, Booth SL, Jacques PF,

Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008; 117 (4):503-11

9. Turin A, Bax JJ, Doukas D, Joyce C, Lopez JJ, Mathew V, et all. Interactions among vitamin D, atrial fibrillation, and the renin-angiotensin-aldosterone system. Am J Cardiol 2018; 122(5):780-4
10. Landoni G, Zangrillo A, Franco A, Aletti G, Roberti A, Calabrò MG, Slaviero G,Bignami E, Marino G. Long-term outcome of patients who require renalreplacement therapy after cardiac surgery. Eur J Anaesthesiol. 2006;23(1):17–22
11. Wittlinger T, Maus M, Kutschkal I, Baraki H, Friedrich MG. Risk assesment of acute kidney injury following cardiopulmonary bypass. Journal of Cardiothoracic Surgery 2021;16:p1
12. Machado MN, Nakazone MA, Maia LN. Prognostic value of acute kidneyinjury after cardiac surgery according to kidney disease: improving globaloutcomes definition and staging (KDIGO) criteria. PLoS One. 2014;9:e98028
13. Vercaemst L: Hemolysis in cardiac surgery patients undergoing cardiopulmonary bypass: a review in search of a treatment algorithm. J Extra Corpor Technol 2008;40:257–67.
14. Boehne M, Sasse M, Karch A, Dziuba F, Horke A, Kaussen T, et al. Systemic inflammatory response syndrome after pediatric congenital heart surgery: incidence, risk factors, and clinical outcome. J Card Surg. 2017;32:116–25
15. Liu D, Liu B, Liang Z, Yang Z, Ma F, Yang Y, et al. Acute kidney injury following cardiopulmonary bypass: A challenging Picture. Oxidative Medicine and Cellular Longevity 2021 doi.org/10.1155/2021/8873581
16. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM. Renin-angiotensin system and cardiovascular risk. Lancet 2007;369:1208-19
17. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-DihydroxyvitaminD(3) is a negative endocrine regulator of the renin–angiotensin system, J. Clin. Invest. 2002;110:229–38
18. Shen Q, Bi X, Ling L, Ding W. 1,25- Dihydroxyvitamin D3 attenuates angiotensin II- induced renal injury by inhibiting mitochondrial dysfunction and autophagy. Cell PhysiolBiochem2018;51:1751-62
19. Canning MO, Grotenhuis K, de Wit H, Ruwhof C, Drexhage HA. 1-alpha,25-Dihydroxyvitamin D3 (1,25 (OH)(2)d(3)) hampers the maturation of fully active immature dendritic cell from monocytes. Eur J Endocrinol 2001;145:351-7
20. Mizobuchi M, Morrissey J, Finch JL, Martin DR, Liapis H, Akizawa T, et al. Combination therapy with an angiotensin-converting enzyme inhibitor and a vitamin D analog suppresses the progression of renal insufficiency in uremic rats. J Am Soc Nephrol 2007;18:1796-806
21. Natanov R, Gueler F, Falk CS, Kühn C, Maus U, Boyle EC, et al. Blood cytokine expression correlates with early multi-organ damage in a mause model of moderate hypothermia with circulatory arrest using cardiopulmonary bypass. PLoS ONE 2018;13 (10):e0205437
22. Salis S, Mazzanti VV, Merli G, Salvi L, Tedesco CC, Veglia F, et al. Cardiopulmonary bypass duration is an independent predictor of morbidity and mortality after cardiac surgery. J CardiothoracVascAnesth 2008; 22: 814–22
23. Wen Y, Liu Y, Tang T, Lv L, Liu H, Ma K, Liu B: NLRP3 inflammasome activation is involved in Ang II-induced kidney damage via mitochondrial dysfunction. Oncotarget 2016;7:54290-302
24. Judd S, Tangpricha V. Vitamin D deficiency and risk for cardiovascular disease. Circulation 2008;117(4):503-11
25. Matilla C, Knekt P, Männistö S, Rissanen H, Laaksonen MA, Montonen J, et al. Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. Diabetes Care 2007;103(35):2569-70
26. Zhang Y, Tan H, Tang J, Li J, Chong W, Hai Y, et al. Effects of vitamin D supplementation on prevention of type 2 diabetes in patients with prediabetes: a systematic review and meta-analysis. Diabetes Care 2020;43(7):1650-8