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LABORATORY STUDY

Apolipoprotein E genotype, TNF-α 308G/A and risk for cardiac surgery associated-acute kidney injury in Caucasians

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Abstract

Objectives: Acute kidney injury following cardiac surgery depicts a severe clinical problem that is strongly associated with adverse short- and long-term outcome. We analyzed two common genetic polymorphisms that have previously been linked to renal failure and inflammation, and have been supposed to be associated with cardiac surgery associated-acute kidney injury (CSA-AKI). *Methods*: A total of 1415 consecutive patients who underwent elective cardiac surgery with CPB at our institution were prospectively enrolled. Patients were genotyped for Apolipoprotein E (ApoE E2,E3,E4) (rs429358 and rs7412) and TNF-α-308 G > A (rs1800629). *Results*: Demographic characteristics and procedural data revealed no significant differences between genotypes. No association between ApoE (E2,E3,E4) and TNF-α-308 G > A genotypes and the RIFLE criteria could be detected. Several multiple linear regression analyses for postoperative creatinine increase revealed highly significant associations for aortic cross clamp time ($p < 0.001$), CPB-time ($p < 0.001$), norepinephrine ($p < 0.001$), left ventricular function ($p = 0.004$) and blood transfusion ($p < 0.001$). No associations were found for ApoE (E2,E3,E4) and TNF-α-308 G > A genotypes or baseline creatinine. When the sample size is 1415, the multiple linear regression test of $R^2 = 0$ for seven covariates assuming normal distribution will have at least 99% power with significance level 0.05 to detect an R^2 of 0.108 or 0.107 as observed in the data. *Conclusions*: ApoE (E2,E3,E4) polymorphism and the TNF-α-308 G > A polymorphism are not associated with renal injury after CPB.

Keywords

Acute kidney injury, apolipoprotein E (E2,E3,E4), cardiac surgery, genetics, TNF-α-308 G > A

History

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Introduction

Cardiac surgery associated-acute kidney injury (CSA-AKI) represents an important clinical issue,[1] because even slight changes in the postoperative renal function are associated with an increase in morbidity, mortality and costs.[2,3] Novel biomarkers for acute renal failure are on the horizon.[4] Nevertheless, the variability in the clinical outcome makes it difficult to predict the risk for an individual patient. Former research suggests that genetic diversity contributes to CSA-AKI.[5–13] Perioperative genetics have become an emerging field in recent years as clinicians could be enabled to strengthen existing clinical scores by also considering genetic risk factors predisposing to CSA-AKI.

The inflammatory response to CPB generates cytokines that may affect renal microcirculation and lead to tubular injury.[6] The inflammatory response after CPB on one hand and the ischemia–reperfusion injury of the kidney on the other hand are generally thought to be responsible for CSA-AKI. Associations between genetic variants and CSA-AKI have been made with several genes encoding inflammation[7,14] and Apolipoprotein E (ApoE).[5,9]

ApoE plays a key role in various biological functions like lipid metabolism, tissue repair, and immune response. The gene locus for the three major ApoE alleles (E2,E3,E4) is located on chromosome 19q13.2 and the E4 allele has been validated as a strong predictor for Alzheimer's disease.[15] Furthermore, ApoE variants increase cardiovascular disease risks by altering vascular inflammation,[16] and patients carrying the E4 allele are more likely to require CABG at a younger age.[17] In chronic renal failure, Arikan et al. showed an association between ApoE genotypes an atherogenic lipid levels in dialysis patients.[18] Furthermore, Reis et al. observed an association between ApoE and diabetic nephropathy.[19] ApoE variants influence the outcome of severe sepsis in surgical patients.[20] In the context of cardiac surgery, former studies have linked ApoE genotypes with renal failure,[5,9,21] postoperative changes in neurobehavioral status[22–24] and inflammation.[22,25–28]

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As a pro-inflammatory cytokine, TNF plays a key role in the inflammatory response after CPB.[29] TNF-α level peaks shortly after surgery and is rapidly degraded afterwards. Excessive production of TNF-α may lead to organ dysfunction or death.[30,31] There is increasing evidence that inter-individual differences in TNF- α productions are caused by genetic variability.[8,14,27,29,32–34] Nevertheless, the clinical impact of those genetic variants needs validation in large cohorts. This study investigates in a large, prospectively enrolled patient cohort whether the individual variability in the ApoE (E2,E3,E4) genotype or TNF-α-308 G > A has an influence on the development of postoperative CSA-AKI.

Methods

The study protocol was approved by the ethical committee of the Technical University of Munich. Written informed consent was obtained from each patient. We prospectively enrolled a total number of 1415 consecutive adult patients who underwent cardiac surgery with cardiopulmonary bypass (CPB) at our institution. All patients were Caucasians.

Patient management

Perioperative management and anesthesia were conducted according to standard institutional practice. Surgical procedures were distributed into ''CABG'' (coronary artery bypass grafting), ''valve'', ''CABG + valve'' and others. A total of 1415 consecutive adult patients underwent elective cardiac surgery with CPB at our institution. Emergency cases, patients with endocarditis, aortic aneurysms, patients after renal transplantation, nephrectomy and preoperative requirement of dialysis were excluded. All patients received antifibrinolytic therapy.

Genotyping

Patients were tested for the following polymorphisms: TNF-α 308 G/A and ApoE (E2,E3,E4). Preoperatively, a sample of peripheral venous blood was taken. Genomic DNA was isolated using the ''E.Z.N.A.® Blood DNA II Kit'' (PEQLAB Biotechnologie GmbH, Erlangen, Germany) according to the manufacturer's recommendation.

Genotyping of the ApoE polymorphisms was performed on a LightCycler 1.5 System (Roche Diagnostics, Mannheim, Germany) using a fluorescent melting-curve analysis approach with hybridization probes. Primers and probes (TIBMOLBIOL, Berlin, Germany) were used as follows. For both ApoE polymorphisms identical primers which amplify a 462 bp fragment were used: ApoE CA1 primer forward 5′ TTG AAG GCC TAC AAA TCG GAA CTG 3′, ApoE CA2 primer reverse 5′ CCG GCT GCC CAT CTC CTC CAT CCG 3′. Hybridization probes for ApoE Cys112Arg were as follows: ApoE4-112 A anchor probe 5′ CTG CAG GCG GCG CAG GCC CGG CTG GGC GC-fluorescein 3′, ApoE4-112 M sensor 5′ LCRed640-ACA TGG AGG ACG TGC GCG G-p 3′, for ApoE Arg158Cys: ApoE2-158 A anchor probe 5′ GCT GCG TAA GCG GCT CCT CCG CGA TGC CG-fluorescein 3′; ApoE2-158 M sensor 5′ LCRed640-GAC CTG CAG AAG CGC CTG GC-p 3′.

For the detection of the SNP in the TNF-α 5′ UTR (−308 G > A, rs1800629) a 241 bp fragment was amplified using the following primers: forward 5′ AAG GAA ACA GAC CAC AGA CCT G 3′, reverse 5′ CTG CAC CTT CTG TCT CGG TTT 3′, sensor AAC CCC GTC CCC ATG CCC C-Fluorescein 3′, anchor 5′ LCRed640-CAA AAC CTA TTG CCT CCA TTT CTT TTG GGG AC 3′.

Genomic DNA was amplified by FastStart Taq Polymerase (0.4 U) (Roche Diagnostics) in the presence of 1 × PCR buffer (50 mM Tris/HCl, 10 mM KCl, 5 mM $(NH_4)_2SO_4$), 3.25 mM $MgCl_2$, dNTPs (200 μM each), BSA (0.5 mg/mL), forward and reverse primer (0.25 μM each), anchor and sensor (0.2 μM each) in a final volume of 10 μL. The amplification protocol was as follows: activation of Taq polymerase at 95 °C for 10 min followed by 40 cycles of 95 °C for 0 sec, 60 °C for 10 sec and 72 °C for 15 sec. Thereafter, melting curves were created: the reaction was cooled to 40 °C for 30 sec and the reaction mix was slowly heated to 80 °C (0.2 °C/sec). By plotting the fluorescence signal against temperature-specific melting points (Tm) are generated: for ApoE Cys112 (e3 allele) 64–65 °C, for ApoE Cys112Arg (e2 allele) 55–56 °C, for ApoE Arg158 (e3 allele) 53–55 °C for ApoE Arg158Cys (e4 allele) 62–63 °C, for TNF-α G allele 60 °C and for TNF-α A allele 65 °C.

Renal failure

Creatinine was taken preoperatively, immediately after surgery upon arrival on the Intensive Care Unit (ICU), on the first postoperative day and before discharge. Additional measurements were performed in case of renal impairment and whenever the clinicians felt it necessary.

These groups were analyzed for an association of genotype with an overall increase of postoperative creatinine and the frequency of acute postoperative kidney injury according to RIFLE-criteria.[35] RIFLE-groups were classified according to postoperative creatinine levels ''risk'': increased creatinine × 1.5–2.0; ''injury'': increased creatinine × 2–3; ''loss'': complete loss of kidney function >4 weeks; due to length of hospital stay the groups ''loss'' and ''ESRD'' (*end stage renal disease* complete loss of kidney function >3 months) could not be evaluated.

Statistics

Statistical tests were run with IBM SPSS Statistics (version 20; IBM, Armonk, NY), the power analysis was performed with StatPages.org. For continuous variables mean values, standard deviation, for ordinal scaled variables numbers and corresponding percentages were listed. For comparison of group mean values, an analysis of variance (ANOVA) was used. For comparative analyses of categorical variables, a χ^2 test was run. Pearson correlation coefficients were calculated for the evaluation of bivariate correlations. A multiple linear regression analysis evaluated the influence of age, norepinephrine, left ventricular ejection fraction (LVEF) cardiopulmonary bypass-time, aortic crossclamp-time, creatinine at baseline and genotype on postoperative creatinine increase. An explorative, two-sided *p*-value of less the 0.05 was considered significant for all results. There is no correction for the issue of multiple testing due to the screening nature of

the study. In addition, this is a conservative interpretation for no-association results.

Results

Genotyping revealed for ApoE: 189 patients were carriers of the e2 allele (13.4%), 913 patients of the e3 allele (64.5%), 313 patients of the e4 allele (22.1%), respectively (Table 1). Baseline demographics did not differ between the genotypes (Table 1). For TNF-α 308 G/A, 1007 patients were carriers of the GA allele (71.2%), 338 patients AA (23.9%), and 70 patients GG (4.9%) (Table 2). Baseline characteristics were also equally distributed across genotype groups (Table 2).

In total, 688 patients (48.6%) underwent CABG. Aortic valve replacement (AVR) was performed on 244 patients (16.1%). One-hundred forty-four patients (9.8%) needed AVR and CABG. Mitral valve surgery was done on 124 patients (8.6%) and 290 patients (20.0%) underwent combinations. Bypass time was 103 ± 41 min, and LV-function was $59 \pm 14\%$. The perioperative treatment revealed no differences between genotype groups. Detailed data are given for ApoE (Table 3) and TNF-α 308 G/A genotypes (Table 4).

Baseline creatinine in ApoE2 was 1.12 ± 0.32 mg/dL, in ApoE3 1.11 ± 0.32 mg/dL, in ApoE4 1.1 ± 0.28 mg/d (Table 1). Peak postoperative creatinine during hospital stay in ApoE2 was 1.31 ± 0.8 mg/dL, in ApoE2 1.27 ± 0.66 mg/dL, in ApoE4 1.21 ± 0.51 mg/dL (Table 3, Figure 1). Baseline creatinine in TNF AA was 1.11 ± 0.27 mg/dL, in TNF GA 1.1 ± 0.32 mg/dL, in TNF GG 1.14 ± 0.36 mg/dL (Table 2). Peak postoperative creatinine during hospital stay in TNF AA was 1.29 ± 0.71 mg/dL, in TNF GA 1.26 ± 0.64 mg/dL, in TNF GG 1.22 ± 0.54 mg/dL (Table 4, Figure 1). Differences between baseline and peak creatinine levels between groups were not significant (Tables 5(a–c) and 6(a–c)). According to RIFLE criteria, renal failure occurred as follows: 209 patients developed renal failure in the ''risk'' classification, 41 in the ''injury'' category (Figure 2). Sixty-eight patients required postoperative dialysis (4.8%).

The genotype groups were tested for the occurrence of acute renal failure according to the RIFLE-classification. The analysis revealed no significant differences in the incidence of acute kidney injury. Statistical analyses revealed no differences for ''Risk'' and ''Injury'' between the groups ($p = 0.567$ for ApoE and $p = 0.766$), respectively. $p = 0.215$ for ''Risk'' and $p = 0.901$ for ''Injury'' (TNF-α 308 G/A) (Figure 2).

In multivariate analyses, every genetic variant was tested on possible associations with postoperative creatinine increase. The following parameters consistently showed significant linear correlations with postoperative increase of creatinine across all the multivariate analyses: aortic clamp time, CPB time, transfusion receiver, left ventricular function and application of norepinephrine (Tables 5(a–c) and 6(a–c)). Observed power of the every single analysis was >99%.

Discussion

Preoperative renal risk stratification provides an opportunity to develop strategies for early diagnosis and intervention for CSA-AKI. Existing clinical scores for renal risk stratification could be strengthened by considering the variability in genetic risk factors predisposing to postoperative CSA-AKI. In the future, studies involving genetic polymorphisms may help to elucidate the pathogenesis of CSA-AKI, discover potential markers of susceptibility, severity and clinical outcomes; identify markers for responders and non-responders in therapeutic trials, and recognize targets for therapeutic intervention.[8]

ApoE

Ischemia–reperfusion injury of the kidney and the generation of inflammatory response after CPB are generally believed to be responsible for the development of CSA-AKI. While the

Table 1. Demographics ApoE.

	Apo E2 189 (13.4%)	Apo E3 913 (64.5%)	Apo E4 313 (22.1%)	*p*
Age (years)	66.58 ± 10.03	66.22 ± 11.04	66.49 ± 10.60	0.876
Male	68 (36%)	282 (30.9%)	90 (28.8%)	0.229
Weight (kg)	79.04 ± 14.66	77.94 ± 14.32	77.69 ± 13.50	0.569
Height (cm)	169.6 ± 8.9	170.2 ± 9	170.2 ± 9.1	0.743
LVEF	58.6 ± 14.4	59.7 ± 14.4	59.2 ± 16.2	0.612
PMI	37 (19.7%)	152 (16.7%)	70 (22.4%)	0.070
Atrial fibrillation	42 (22.3%)	160 (17.5%)	48 (15.3%)	0.360
EuroSCORE	4.3 ± 2.5	4.4 ± 2.7	4.5 ± 2.7	0.712
Cardiovascular risk factors				
Arterial hypertension	122 (64.6%)	647 (70.9%)	224 (71.6%)	0.285
Diabetes	40 (21.2%)	215 (23.6%)	72 (23%)	0.375
Hyperlipidaemia	94 (49.7%)	523 (57.3%)	174 (55.6%)	0.112
Preoperative medication				
Beta-blockers	114 (60.6%)	558 (61.2%)	201 (64.2%)	0.599
Diuretics	79 (42%)	360 (39.5%)	144 (46%)	0.125
ACE-inhibitor	93 (49.5%)	431 (47.3%)	144 (46%)	0.754
Nitrates oral	38 (20.2%)	168 (18.4%)	61 (19.5%)	0.811
Preoperative laboratory findings				
Hemoglobin (g/dL)	13.80 ± 1.58	13.76 ± 1.58	13.89 ± 1.61	0.454
Urea (mg/dL)	44.04 ± 20.62	42.36 ± 18.88	43.13 ± 21.80	0.534
Creatinine (mg/dL)	1.12 ± 0.32	1.11 ± 0.32	1.10 ± 0.28	0.856

Notes: LVEF, left ventricular ejection fraction; PMI, previous myocardial infarction; ACE, angiotensin-converting enzyme.

Table 2. Demographics TNF-α-308 G > A.

	TNF 308 A/A 338 (23.9%)	TNF 308 G/A 1007 (71.2%)	TNF 308 G/G 70 (4.9%)	*p*
Age (years)	65.95 ± 10.60	66.57 ± 10.87	64.63 ± 10.82	0.266
Male	229 (67.8%)	692 (68.7%)	54 (77.1%)	0.309
Weight (kg)	78.91 ± 14.34	77.55 ± 14.06	80.61 ± 14.93	0.098
Height (cm)	170.5 ± 9.3	169.9 ± 9	170.9 ± 7.4	0.518
LVEF	58.9 ± 15.5	59.5 ± 14.7	59.9 ± 13.4	0.750
PMI	59 (17.4%)	187 (18.6%)	13 (18.6%)	0.893
Atrial fibrillation	57 (16.9%)	187 (18.6%)	6 (8.6%)	0.523
EuroSCORE	4.5 ± 2.6	4.4 ± 2.7	3.9 ± 2.7	0.275
Cardiovascular risk factors				
Arterial hypertension	232 (68.6%)	710 (70.6%)	51 (72.9%)	0.783
Diabetes	90 (26.6%)	216 (21.5%)	21 (30%)	0.172
Hyperlipidaemia	191 (56.5%)	562 (55.9%)	39 (55.7%)	0.889
Preoperative medication				
Beta-blockers	222 (65.7%)	607 (60.4%)	44 (62.9%)	0.221
Diuretics	140 (41.4%)	417 (41.5%)	26 (37.1%)	0.773
ACE-inhibitor	156 (46.2%)	482 (48%)	30 (42.9%)	0.636
Nitrates oral	58 (17.2%)	192 (19.1%)	17 (24.3%)	0.365
Preoperative laboratory findings				
Hemoglobin (g/dL)	13.76 ± 1.58	13.81 ± 1.59	13.80 ± 1.66	0.895
Urea (mg/dL)	44.23 ± 22.45	42.20 ± 18.80	42.76 ± 20.04	0.253
Creatinine (mg/dL)	1.11 ± 0.27	1.10 ± 0.32	1.14 ± 0.36	0.658

Notes: LVEF, left ventricular ejection fraction; PMI, previous myocardial infarction; ACE, angiotensin converting enzyme.

Table 3. Procedural and perioperative data for Apo E.

	Apo E2 189 (13.4%)	Apo E3 913 (64.5%)	Apo E4 313 (22.1%)	*p*
CABG	80 (42.3%)	454 (49.7%)	154 (49.2%)	0.175
Valve	64 (33.9%)	260 (28.5%)	102 (32.6%)	0.189
CABG + valve	27 (14.3%)	134 (14.7%)	38 (12.1%)	0.535
Others	18 (9.5%)	65 (7 a.1%)	19 (6%)	0.404
AoX time (min)	71 ± 30.1	68 ± 28.3	68.3 ± 27.2	0.413
CPB-time (min)	105 ± 41.2	103.6 ± 41.8	103.1 ± 38	0.877
Blood loss (mL)	673 ± 511	661 ± 543	665 ± 499	0.961
Transfused blood (mL)	439 ± 2086	335 ± 864	295 ± 759	0.350
Transfusion receiver	63 (33.3%)	335 (36.7%)	112 (35.8%)	0.678
Postop. ventilation time (h)	20.3 ± 70.8	18.9 ± 83.6	23.4 ± 97.9	0.726
Duration of norepinephrine (d)	1.9 ± 3.5	1.5 ± 2.8	1.7 ± 4.5	0.177
Peak creatinine (mg/dL)	1.31 ± 0.80	1.27 ± 0.66	1.21 ± 0.51	0.246

Notes: CABG, coronary artery bypass grafting; AoX time, aortic cross clamp time; CPB-time, cardiopulmonary bypass time.

Table 4. Procedural and perioperative data for TNF-α-308 G > A.

	TNF 308 A/A 338 (23.9%)	TNF 308 G/A 1007 (71.2%)	TNF 308 G/G 70 (4.9%)	*p*
CABG[a]	158 (46.7%)	489 (48.6%)	41 (58.6%)	0.197
Valve	102 (30.2%)	304 (30.2%)	20 (28.6%)	0.960
CABG + valve	52 (15.4%)	141 (14%)	6 (8.6%)	0.327
Others	27 (7.7%)	73 (7.2%)	3 (4.3%)	0.554
AoX-time (min)	68.1 ± 26.9	69.6 ± 28.1	64.5 ± 28.7	0.267
CPB-time (min)	102.2 ± 37.3	105.5 ± 42	98.7 ± 41.7	0.387
Blood loss (mL)	634 ± 552	673 ± 523	683 ± 487	0.496
Transfusion (mL)	338 ± 851	346 ± 1186	259 ± 574	0.810
Transfusion receiver	123 (36.4%)	368 (36.5%)	19 (27.1%)	0.282
Postop. ventilation time (h)	20.9 ± 82.3	20.5 ± 89.2	9.7 ± 8.5	0.579
Duration of norepinephrine (d)	1.7 ± 4.4	1.5 ± 3.0	1.3 ± 2.5	0.584
Peak creatinine (mg/dL)	1.29 ± 0.71	1.26 ± 0.64	1.22 ± 0.54	0.643

Notes: CABG, coronary artery bypass grafting; AoX time, aortic cross clamp time; CPB-time, cardiopulmonary bypass time.

Apo E4 allele represents a strong predictor for Alzheimer's disease, numerous studies analyzed effects of ApoE genotypes on renal failure,[5,9,21] postoperative changes in neurobehavioral status[22–24] and inflammation.[22,25–28]

Grocott et al. analyzed 338 patients undergoing cardiac surgery and found that carriers of the Apo E4 allele had significantly lower level of Interleukin 1 receptor antagonist after surgery than patients with a non-Apo E4 genetic background.[27] In a cohort of 343 patients of mainly Caucasian ethnicity (83.1%), who underwent elective major non-cardiac surgery, Moretti et al. found a protective effect of the Apo E3 allele with a lower incidence of severe sepsis after

Figure 1. Maximum creatinine values.

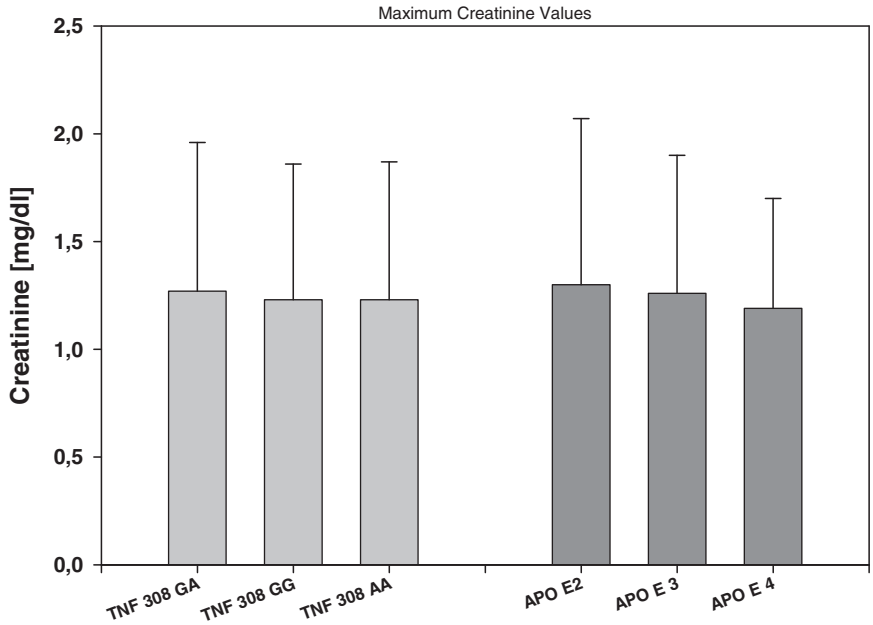

Table 5. Linear regression analysis for postoperative creatinine increase for ApoE.

	Regression coefficient	Standard error	*p*
a: Apo E2			
(Constant)	−0.235	0.090	0.674
AoX-time	−0.004	0.001	<0.001
CPB-time (min)	0.004	0.001	<0.001
LVEF[c]	−0.003	0.001	0.004
Baseline creatinine	0.071	0.045	0.117
Transfusion receiver	0.182	0.029	<0.001
Norepinephrine	0.090	0.033	0.007
Apo E2	0.054	0.039	0.169
b: Apo E3			
(Constant)	0.037	0.092	0.685
AoX-time[a]	−0.004	0.001	<0.001
CPB-time (min)	0.004	0.001	<0.001
LVEF	−0.003	0.001	0.003
Baseline creatinine	0.071	0.045	0.114
Transfusion receiver	0.180	0.029	<0.001
Norepinephrine	0.092	0.033	0.006
Apo E3	0.014	0.028	0.685
c: Apo E4			
(Constant)	0.057	0.090	0.530
AoX-time (min)	−0.006	0.001	<0.001
CPB-time (min)	0.004	0.001	<0.001
LVEF	−0.001	0.001	0.003
Baseline creatinine	0.071	0.045	0.116
Transfusion receiver	0.181	0.029	<0.001
Norepinephrine	0.092	0.033	0.006
Apo E4	−0.050	0.032	0.113

Notes: Observed $R^2 = 0.108$, statistical power >99%. Observed $R^2 = 0.107$, statistical power >99%. Observed $R^2 = 0.108$, statistical power >99%. AoX time, aortic cross clamp time; CPB time, cardiopulmonary bypass time; LVEF, left ventricular ejection fraction.

Table 6. Linear regression analysis for postoperative creatinine increase: TNF-α-308 G > A.

	Regression coefficient	Standard error	*p*
a: TNF AA.			
(Constant)	0.046	0.090	0.612
AoX-time	−0.004	0.001	<0.001
CPB-time (min)	0.004	0.001	<0.001
LVEF	0.003	0.001	0.004
Baseline creatinine	0.072	0.045	0.110
Transfusion receiver	0.180	0.029	<0.001
Norepinephrine	0.091	0.033	0.007
TNF 308 AA	−0.034	0.062	0.583
b: TNF GA			
(Constant)	0.033	0.090	0.716
AoX-time	−0.004	0.001	<0.001
CPB-time (min)	0.004	0.001	<0.001
LVEF	0.003	0.001	0.004
Baseline creatinine	0.072	0.045	0.112
Transfusion receiver	0.180	0.029	<0.001
Norepinephrine	0.090	0.033	0.007
TNF 308 GA	0.040	0.031	0.208
c: TNF GG			
(Constant)	0.046	0.092	0.497
AoX-time	−0.004	0.001	<0.001
CPB-time (min)	0.004	0.001	<0.001
LVEF	−0.003	0.001	0.004
Baseline creatinine	0.071	0.045	0.117
Transfusion receiver	0.181	0.029	<0.001
Norepinephrine	0.090	0.033	0.007
TNF 308 GG	−0.027	0.030	0.357

Notes: Observed $R^2 = 0.107$, statistical power >99%. Observed $R^2 = 0.108$, statistical power >99%. Observed $R^2 = 0.107$, statistical power >99%. AoX time, aortic cross clamp time; CPB time, cardiopulmonary bypass time; LVEF, left ventricular ejection fraction.

surgery.[20] Those links between ApoE genotypes and inflammation has led to studies that analyzed associations between ApoE genotypes with postoperative CSA-AKI.

In an initial study, Chew et al. observed an association between ApoE variants and postoperative creatinine peaks, with a protective effect of the Apo E4 allele.[5] They showed reduced postoperative creatinine increases and lower peak creatinine levels after cardiac surgery in patients with the E4 allele compared to the Apo E2. MacKensen et al. found an interaction of the Apo E4 allele and aortic atheroma, with a significant higher peak in postoperative serum creatinine and with increasing atheroma of the ascending

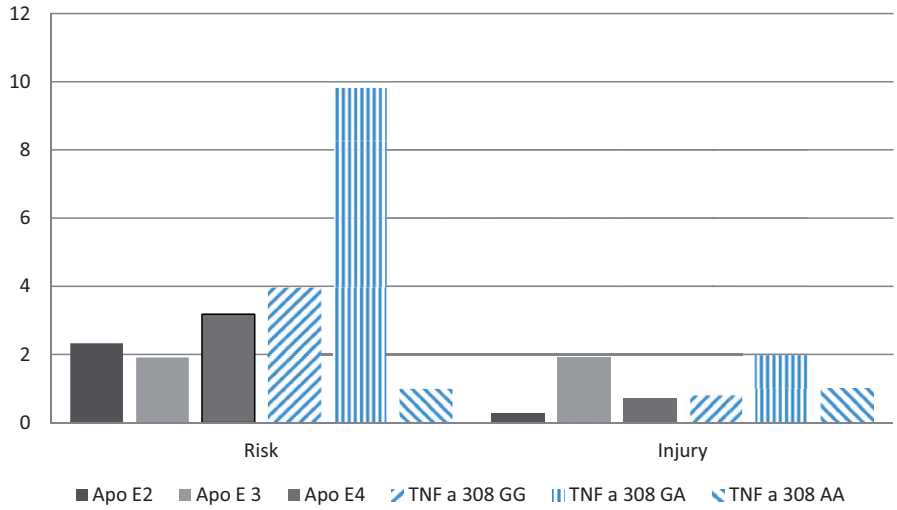

Figure 2. Incidence of perioperative acute kidney injury according to RIFLE criteria (%).

aorta in patients with a non-Apo E4 genetic background.[9] They speculated, that ApoE may influence renal outcome by embolic damage.

TNF-α

The findings of genetic triggers of the inflammatory response after CPB lead to the question, if those genetic factors are associated with clinical outcome. Bittar et al. found associations between different carriers of the TNF-α-308 G > A polymorphism and the postoperative inflammatory response.[29] In 96 patients undergoing cardiac surgery, the AA allele turned out to be associated with elevated TNF-α level after surgery, prolonged intensive care unit stay, and increased mortality risk, and diabetes. This finding was supported by Yoon et al., who also observed elevated TNF-α levels after cardiac surgery in patients carrying the TNF-α-308 G > A GA or AA allele in a Korean population.[36] Although we could not validate those findings for the TNF-α-308 G > A polymorphism in a Caucasian population,[32] we found another genetic variant in the promoter region of the TNF-α gene associated with postoperative TNF-α levels underscoring the genetic status of the promoter region of the TNF-α gene. Furthermore, Yende et al. found in 400 patients undergoing cardiac surgery, that the haplotypes of the Lymphotoxin-α-250 G/TNF-α308 G carry a higher risk for prolonged mechanical ventilation after surgery.[37] In this study, 66.3% of all patients were Caucasians.

Cardiac surgery-associated acute kidney injury

The tested genetic polymorphisms were not associated with peak creatinine levels (Figure 1) and renal failure as defined by the RIFLE criteria (Figure 2) and, also not with the course of creatinine changes during the perioperative period (Tables 5(a–c) and 6(a–c)). The latter findings turned out to be particularly significant as several studies describe even subclinical changes in serum creatinine as an independent risk factor for all cause 30-day mortality after cardiac surgery.[2,3] A recent multicenter study revealed that perioperative creatinine levels are superior in detection of CSA-AKI in comparison with cystatin C.[38] Therefore, we chose the perioperative creatinine increase as the primary endpoint for multiple regression analyses and the subsequent power analyses. The additional analyses of the RIFLE criteria revealed also no significant genetic influence. Nevertheless, a limitation of the current study remains its Caucasian background, and the results of the current study are not necessarily applicable to other ethnicities.

In conclusion, we did not find any associations between the described genetic polymorphisms and renal failure. Given the statistical power >99% of the current study, we can rule out deleterious effects of the ApoE (E2,E3,E4) and TNF-α-308 G > A polymorphism on CSA-AKI. Further, genome-wide studies are necessary to evaluate genetic risk factor for renal failure.

Summary

Apolipoprotein E (rs429358 and rs7412) and TNF-α-308 G > A (rs1800629) have been linked with inflammation and acute kidney injury after cardiac surgery using cardiopulmonary bypass. We analyzed 1415 consecutive patients undergoing elective cardiac surgery. Several multiple linear regression analyses for postoperative creatinine increase revealed highly significant associations for aortic cross clamp time ($p < 0.001$), CPB-time ($p < 0.001$), norepinephrine ($p < 0.001$), left ventricular function ($p = 0.004$) and blood transfusion ($p < 0.001$). No associations were found for ApoE (E2,E3,E4) and TNF-α-308 G > A genotypes. Multiple linear regression testing revealed a statistical power of least 99% (R^2 of 0.108 or 0.107).

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Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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