High-density Lipoprotein Cholesterol Concentration and acute kidney injury after noncardiac surgery

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Research article

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Abstract

Background: Abnormal High-density Lipoprotein Cholesterol Concentration is closely related to postoperative acute kidney injury (AKI) after cardiac surgeries. The purpose of this study was to analyze the relationship between High-density Lipoprotein Cholesterol Concentration and acute kidney injury after non-cardiac surgeries.

Method: This was a single-center cohort study for elective non-cardiac non-kidney surgery from January 1, 2012, to December 31, 2017. The endpoint was the occurrence of acute kidney injury (AKI) 30 days postoperatively in hospital. Preoperative serum High-density Lipoprotein Cholesterol Concentration was examined by multivariate logistic regression models before and after propensity score weighting analysis.

Results: Of the 74284 surgeries, 4.2% (3159 cases) suffered acute kidney injury. Preoperative serum HDL was associated with postoperative AKI, with odds ratio (0.96-1.14 as reference, <0.96, 1.14-1.35, >1.35 mmol/L, Quartile) 1.27 (1.15~1.39), P <.001; 0.90 (0.80~1.01), P= .086; 0.75 (0.65~0.85), P <.001, respectively. Preoperative serum HDL <1.03 mmol/L was associated with increased risk of postoperative AKI, with odds ratio 1.32 (1.21~1.46), P<0.001 before propensity score weighting, and 1.32 (1.18~1.48), P<0.001 after propensity score weighting. Sensitivity analysis with other cut values of HDL showed similar results.

Conclusions: Postoperative acute kidney injury occurred in 4.2 % of patients undergoing elective non-cardiac non-kidney surgery. This study found that low HDL cholesterol levels were independent risk factors for AKI after non-cardiac surgery.

Introduction

Acute kidney injury (AKI) is a common complication after both cardiac and non-cardiac surgery. The prevalence varies greatly, from 1.1% in the minimally invasive procedure to 17.9% in major surgery. [1–9] Patients' mortality rate increase significantly with the occurrence of AKI.[3–5] There are many risk factors associated with AKI, including factors that are difficult to modify, such as gender, BMI, age, time and complexity of the surgery, and also factors that can be intervened, such as preoperative albumin levels, duration of hypotension, colloid and dexmedetomidine use etc.[1–7]

Recent studies found High-density Lipoprotein Cholesterol Concentration was associated with acute kidney injury after major cardiac surgery. However, no report was found regarding AKI after non-cardiac surgery. The research aimed to illustrate the relationship between High-density Lipoprotein Cholesterol Concentration and acute kidney injury after non-cardiac surgery.

Methods

Study design

This study was approved by the Peking University First Hospital Ethics Committee, and the requirement for written informed consent was waived. The trial was registered at clinicaltrials.gov (NCT03954353; Principal investigator: Yan Zhou; Date of registration: May 16, 2019).

Data source and Study Patients

This study used the perioperative database of Peking University First Hospital, which integrates the perioperative information of inpatients after 2012. The analysis set of this study was adults (age ≥ 18 years old) who underwent elective non-cardiac surgery from January 1, 2012, to December 31, 2017. Non-cardiac non-nephrotic surgery was identified by the International Classification of diseases and procedures, Ninth Revision Clinical Revision volume 3 (ICD−9-v3). All operations other than the ICD codes listed were defined as "other." (Table S1 in the Supplementary Appendix)

Exclusion criteria: cardiac surgeries, kidney surgeries, obstetric surgeries, local infiltration anesthesia, and perioperative data missing. Also, patients with more than one operation within a year (including reopening of surgical causes) was excluded.

Preoperative serum cholesterol was originally obtained by laboratory database and connected into the perioperative database. Results were categorized according to patients' operative day. For patient with more than one results preoperatively, the mean value was calculated.

Study ENDPOINTS

The endpoint was acute kidney injury within 30 days in the hospital. Which was defined by patient's postoperative serum creatine increase no less than 26.5 μmol/l within 48 hours, or 1.5 times from baseline within the 7 days after surgery or initializing blood dialysis. As the serum creatine fluctuates much postoperatively and could cause inaccurate of Estimated Glomerular Filtration Rate (eGFR), and oliguria in clinical practice is always followed by serum creatine lab test, this study did not define AKI based on GFR value or urine output.

Statistical analysis

According to previous studies, the incidence of postoperative acute kidney injury would be 1.1−17.9% in elective patients.[1−9] We expect the patients with abnormal serum cholesterol have an OR 1.20 compared with patients' intraoperative hypotension within the threshold. With significance set at 0.05 and the power set at 90%, the calculated sample size needed to compare two proportions was 3206 patients in each group.

For comparative analysis, patients were divided into two groups according to the occurrence of postoperative acute kidney injury. Continuous variables with normal distribution were compared with one-way analysis of variance; those with non-normal distribution were compared with the Kruskal–Wallis H test. Kolmogorov–Smirnov test was used for testing normality. Categorical variables were compared with the Chi-Square test or continuity correction Chi-Square test. Rank variables were compared with the Kruskal–Wallis H test.

Association detection by logistic regression between High-density Lipoprotein Cholesterol Concentration and AKI

A logistic regression model was constructed as the following formula:

AKI = HDL + confounder

Confounders (covariates) were the same in both logistic regression and generalized additive models except preoperative serum albumin. Confounders were assessed based on a priori knowledge and literature.[1–10] The following covariates were considered: sex, age, body mass index, revised cardiac risk index grade, surgery duration, anesthesia type, cancer surgery, intraoperative blood transfusion, surgical complexity (Modified John Hopkins hospital criteria, MJHSC [11], Table-S5 in Appendix supplement 1), preoperative serum albumin and serum creatine, anesthesiologist experience, intraoperative dexmedetomidine and colloid use.

Propensity score weighting analysis

The analysis set was divided into two new cohorts based on the high and low High-density Lipoprotein Cholesterol Concentration. Propensity scores were estimated for each surgery by gradient boosted regression model. The covariates used to generate the propensity scores was age, gender, body mass index, revised cardiac risk index, surgery duration, anesthesia type, cancer surgery, intraoperative blood transfusion, surgical complexity, type of surgery classified by site, anesthesiologist experience, severe intraoperative hypotension, preoperative coronary heart disease, arrhythmia, cerebral infarction, diabetes, chronic kidney disease, preoperative creatine, cholesterol components, intraoperative dexmedetomidine and colloid use.

Statistical Packages

All data management and statistical analysis were performed using the R programming language (v.3.5.2).

Results

Study Population

This study identified 74284 non-cardiac non-nephrotic non-obstetric elective surgeries in 57983 unique patients between Jan 1, 2012, and Dec 31, 2017 (Figure-S1 in the supplement appendix). 3159 (4.2%) cases had postoperative acute kidney injury. Of which, 2587 grade 1 cases, 193 grade 2 cases, 379 grade 3 cases. As compared with patients without postoperative acute kidney injury, those with postoperative acute kidney injury were older, were more likely to be male, were more likely to be low body mass index, were more likely to have Co-existing disease, more likely to be high in blood pressure, and more likely to be in lengthy surgery (Table 1, 2). (Table S2 in the Supplementary Appendix)

Association detection by logistic regression between High-density Lipoprotein Cholesterol Concentration and AKI

Multivariate logistic regression results showed an association between low HDL with postoperative AKI. The odds ratio for HDL (0.96–1.14 as reference, <0.96, 1.14–1.35,>1.35) was 1.27 (1.15~1.39), P<0.001; 0.90 (0.80~1.01), P = 0.086; 0.75 (0.65~0.85), P<0.001, respectively. (Table 3)

Propensity score weighting analysis

After propensity score weighting, data set was regrouped by HDL cholesterol predetermined cut point of previous literature (HDL:1.03). Moreover, logistic odds ratio was calculated. The odds ratio for HDL (<1.03 as reference) was 1.32 (1.18~1.48), P<0.001. (Table 3) (Table S2, S3 in the Supplementary Appendix)

Sensitivity analysis

Different cutting points were used to re-analysis the association between High-density Lipoprotein Cholesterol Concentration and AKI, and similar results were found. (Table S4 in the Supplementary Appendix)

Discussion

This study showed that the incidence of postoperative acute kidney injury was 4.2% in adult patients undergoing elective non-cardiac surgery. Low High-density Lipoprotein Cholesterol Concentration was strongly associated with AKI after non-cardiac surgery, by multi-variable adjustment before or after propensity score weighting.

Although low HDL is an independent risk factor for cardiovascular disease after adjusting for other risk factors.[12–17] However, simply increasing HDL does not reduce cardiovascular events, and there is no causal relationship between them.[18–21] The MESA cohort study found that HDL particles were more predictive of cardiovascular events than HDL cholesterol, suggesting that certain structures and features of HDL are the key roles.[16] The causal relationship is not accepted between HDL cholesterol level and cardiovascular disease.

This study found that preoperative HDL levels were associated with AKI after non-cardiac surgery, as an independent risk factors for postoperative AKI. After propensity score weighting balancing as much as possible of confounding factors and other cholesterol and triglycerides levels, the results still showed that HDL was closely related to postoperative AKI.

The protective mechanism of HDL from postoperative AKI is not clear. The mechanisms related to HDL and cardiovascular events which may also be possible for AKI, which included macrophage cholesterol efflux; [19,22] Promoting maintenance of endothelial function;[23,24] Protecting against oxidation of LDL;[25,26] Protecting against inflammation; [27] Immunomodulation;[28] and finally, via a variety of actions, interfering with the thrombotic component of atherosclerosis.[29–32] These mechanisms may also play a role in the prevention of AKI. There may be other mechanisms specific to the kidney currently not found needing further research. Studies have reported that dysfunction of HDL's anti-inflammation, anti-oxidation, and endothelial protection are associated with increased risk of chronic renal disease.[33–35]

Our study found that preoperative statin use did not reduce postoperative AKI. This is consistent with previous multiple high-quality studies.[36–38] Recently, one study suggested that long-term use of statin can enhance the protection of HDL. [39] These contradictory results suggest that the protective effect of statins on the kidney is not direct and requires further research.

Although the authors tried their best to implement better research methods and improve the quality of the database, various shortcomings and errors were still inevitable, which include: 1. This study was a retrospective cohort study, which may cause inaccuracy. 2. Postoperative lab tests and exams were not performed in every patient but were based on clinical observations when symptoms and signs were suspected, which may result in an underestimation of the primary outcome rate. Many patients were discharged from the hospital within 30 days without following up after discharge. There may be a small number of patients with primary outcome events not detected.

Conclusion

Using multivariate regression analysis before and after propensity score weighting in addition to multiple sensitivity analysis methods, this study found that low HDL cholesterol levels were independent risk factors for AKI after non-cardiac surgery.

Glossary Of Terms

AKI: acute kidney injury

LDL: low-density lipoprotein cholesterol

HDL: high-density lipoprotein cholesterol

TG: triglycerides

ICD−9-v3: International Classification of diseases and procedures, Ninth Revision Clinical Revision volume 3

ICD: International Classification of diseases and procedures

eGFR: Estimated Glomerular Filtration Rate

MJHSC: Modified John Hopkins hospital criteria

Declarations

Ethics approval and consent to participate: This study was approved by the Peking University First Hospital Ethics Committee Review Board and written informed consent was exempt due to its retrospective nature. The trial was registered before patient enrollment at clinicaltrials.gov (NCT03954353, Principal investigator: Yan Zhou, Date of registration: May 16, 2019). IRB Contact Information: Peking University First Hospital Ethics Committee. Tel: 010–82805563

Consent for publication: Yes.

Availability of data and material: yes.

Competing interests

Funding: None.

Authors' contributions:

Yan Zhou, MD, Ph.D.: This author conceived and designed the study, performed data collection and analysis, drafted and critically revised the manuscript.

Hong-Yun Yang, MD.: This author helped data collection.

Hui-Li Zhang, M.S: This author helped in collecting data in the research database and gave some advice.

Xiao-Jin Zhu, M.S: This author helped in collecting data in the research database and gave some advice in programming.

Acknowledgment: None

Conflict of interest: None

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Tables

Table 1. Demographic characteristics and preoperative comorbidities

characteristic	ALL (n=74284)	No AKI (n=71125)	AKI (n=3159)	P value
ge	56.1±15.9	55.9±15.9	62.5±14.6	<0.001
ender, female	37226(49.2%)	36120(49.8%)	1106(35.0%)	<0.001
ody mass index, kg/m^2	24.5±3.7	24.5±3.7	24.5±4.0	0.373
o-existing disease				
hypertension	21236(28.0%)	19889(27.4%)	1347(42.6%)	<0.001
oronary artery disease	3938(5.2%)	3588(4.9%)	350(11.1%)	<0.001
Heart failure	704(0.9%)	575(0.8%)	129(4.1%)	<0.001
Stroke	3092(4.1%)	2833(3.9%)	259(8.2%)	<0.001
diabetes mellitus	9184(12.1%)	8516(11.7%)	668(21.1%)	<0.001
Renal insufficiency	1009(1.3%)	561(0.8%)	448(14.2%)	<0.001
{egular statin therapy[a]	900(0.8%)	822(0.8%)	78(1.6%)	<0.001
SA				<0.001
I	18472(24.4%)	18181(25.1%)	291(9.2%)	
II	51065(67.6%)	49093(67.8%)	1972(62.6%)	
III	5900(7.8%)	5057(7.0%)	843(26.8%)	
IV	138(0.2%)	95(0.1%)	43(1.4%)	

Results reported as mean ± SD or n (%)

a: Only regular statin therapy with more than 3 months was count.

Table 2. perioperative parameters

characteristic	ALL (n=74284)	No AKI (n=71125)	AKI (n=3159)	P value
Anesthesia duration, min	189.0±122.2	186.6±120.3	246.0±149.3	<0.001
Anesthesia type				<0.001
General anesthesia	59918(79.1%)	57328(79.0%)	2590(82.0%)	
General anesthesia + epidural/nerve block	4511(6.0%)	4239(5.8%)	272(8.6%)	
Neuraxial or nerve block	11289(14.9%)	10992(15.1%)	297(9.4%)	
Infusion volume, ml	1100(750-1750)	1100(700-1700)	1600(1100-2600)	<0.001
Crystal, ml	1100(600-1600)	1100(600-1600)	1400(1000-2100)	<0.001
Colloid, ml	0(0-500)	0(0-500)	0(0-500)	<0.001
Estimated blood loss, ml	0(0-50)	0(0-50)	30(0-200)	<0.001
Intraoperative blood infusion	6669(8.8%)	6133(8.5%)	536(17.0%)	<0.001
Urine, ml	0(0-300)	0(0-300)	130(0-450)	<0.001
Surgery time, min	117.1±122.8	115.5±120.4	156.2±164.0	<0.001
Surgery type				<0.001
Eye/ear/throat	3728(4.9%)	3687(5.1%)	41(1.3%)	
Integumentary	2723(3.6%)	2675(3.7%)	48(1.5%)	
Genital/urinary	20066(26.5%)	18791(25.9%)	1275(40.4%)	
Musculoskeletal	9215(12.2%)	8924(12.3%)	291(9.2%)	
Nervous	4217(5.6%)	4057(5.6%)	160(5.1%)	
Vascular	2703(3.6%)	2618(3.6%)	85(2.7%)	
Digestive	25380(33.5%)	24347(33.6%)	1033(32.7%)	
Respiratory	4303(5.7%)	4142(5.7%)	161(5.1%)	
Other	3383(4.5%)	3318(4.6%)	65(2.1%)	
Intraoperative mean HR, bpm	65.5±9.7	65.4±9.7	67.3±10.8	<0.001
Baseline SBP, mmHg	128.3±17.8	128.1±17.7	132.2±18.7	<0.001
Baseline DBP, mmHg	76.6±10.9	76.5±10.9	77.3±11.9	<0.001
KDIGO AKI grade				
I	2587(5.6%)	-	2587(81.9%)	<0.001
II	193(0.4%)	-	193(6.1%)	<0.001
III	379(0.8%)	-	379(12.0%)	<0.001

Table 3. Association detection with logistic regression models and causal inference after propensity score weighting analysis

	Cut value (mmol/l)	Odds ratio by multivariate logistic regression	P value	Before or after propensity score weighting
Model 1[a]	0.96-1.14	reference		before
	<0.96	1.33 (1.22~1.43)	<.001	
	1.14-1.35	0.91 (0.82~1.00)	0.049	
	>1.35	0.79 (0.70~0.87)	<.001	
Model 2[b]	< 1.03 vs ≥ 1.03	1.32 (1.21~1.46)	<.001	before
Model 3[c]	< 1.03 vs ≥ 1.03	1.32 (1.18~1.48)	<.001	after

a: multivariate logistic regression model without propensity score weighting, the HDL was cut by quantile.

b: multivariate logistic regression model without propensity score weighting, the HDL was cut by 1.03 mmol/l.

c: multivariate logistic regression model after propensity score weighting, the HDL was cut by 1.03 mmol/l.

Supplementary Files

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