Pre-operative Proteinuria and Post-operative Acute Kidney Injury in Non-cardiac Surgery: The NARA-AKI Cohort Study

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Abstract

Background

Little is known about the association between pre-operative proteinuria and post-operative acute kidney injury (AKI) in non-cardiac surgery.

Methods

This is a retrospective cohort study. Adults who underwent non-cardiac surgery under general anesthesia from 2007 to 2011 at Nara Medical University Hospital were included. Those with obstetric or urological surgery, missing data for analyses, or pre-operative dialysis were excluded. Exposure of interest was pre-operative proteinuria, defined as ≥(+) by dipstick test. Outcome variable was post-operative AKI, defined by KDIGO criteria, within 1 week after surgery. Multivariable logistic regression analyses were performed.

Results

Among 5,168 subjects, 309 (6.0%) developed AKI. Pre-operative proteinuria was independently associated with post-operative AKI, with odds ratio (OR) [95% confidence interval (CI)] of 1.80 [1.30–2.51]. A sensitivity analysis restricted to elective surgery yielded a similar result. As proteinuria increased, the association with AKI became stronger (OR [95% CI]: 1.14 [0.75–1.73], 1.24 [0.79–1.95], 2.75 [1.74–4.35], and 3.95

[1.62–9.62] for urinary protein (+/−), (+), (2+), and (3+), respectively). Subgroup analyses showed proteinuria was especially associated with post-operative AKI among subjects with renin-angiotensin-system inhibitors, other anti-hypertensives, hypoalbuminemia, or impaired renal function (p for interaction = 0.05, 0.003, 0.09, or 0.02, respectively).

Conclusions

In non-cardiac surgery, pre-operative proteinuria was independently associated with post-operative AKI. Subjects with proteinuria should be managed with caution to avoid AKI peri-operatively.

Key Words: proteinuria, post-operative, acute kidney injury, non-cardiac surgery

Introduction

Post-operative acute kidney injury (AKI) is a serious complication of surgical procedures that is associated not only with short-term increase in mortality[1-3] but also with long-term mortality.[4-6] Currently, there are no effective treatments for AKI, therefore it is important to identify high-risk subjects pre-operatively and manage them with caution to prevent AKI.

Proteinuria has been reported to be associated with AKI in various clinical settings. Some studies indicate that baseline proteinuria is a predictor for contrast-induced AKI.[7,8] In cardiac surgery, pre-operative proteinuria has been shown to be associated with post-operative AKI regardless of baseline renal function.[9,10] A meta-analysis demonstrates that there is monotonous increase in adjusted hazard ratio of AKI associated with increase in albuminuria across age, sex, and race.[11]

In contrast, there are only a few studies which demonstrated the association between proteinuria and post-operative AKI in non-cardiac surgery, and furthermore, these studies were done under specific population or situation,[12,13] and whether these association is generalizable to patients at standard risk undergoing non-cardiac surgery is unknown. The aim of this study was to examine the association between pre-operative proteinuria and post-operative AKI in non-cardiac surgery in general medical practice.

Materials and Methods

Study design and subjects

The NARA-AKI Cohort Study is a single center, retrospective cohort study. The study is aimed at investigating not only predictors of AKI but also long-term outcomes of AKI. Inclusion criteria were subjects being 18 years or older, who underwent non-cardiac surgery under general anesthesia from April 2007, when electronic medical records started at our hospital, to December 2011 at Nara Medical University Hospital. Exclusion criteria were those who underwent obstetric surgery (as serum creatinine levels decrease during pregnancy due to hemodilution and criteria for AKI is not validated in pregnant women), or urological surgery (as increase in creatinine due to nephrectomy or ureteral manipulation could be of different mechanisms from other post-operative AKI), pre-operative dialysis, or those with missing data for analyses, including serum creatinine within 1 month before and 1 week after surgery. If subjects underwent multiple surgeries during the study period, only first eligible surgery was considered.

The study protocol and waiver of consent were approved by Nara Medical University Ethics Committee (Approval No. 1208 and No. 1208-2 for amendment). This study waived the requirement for written informed consent due to the retrospective nature

of this study. Rather, research content has been included on the web page of our department (http://nephrology.naramed-u.ac.jp/research/clinical.html). The study was conducted in accordance with Declaration of Helsinki. The study was registered in the University hospital Medical Information Network (UMIN000037141).

Exposure of interest and outcomes

The exposure of interest was pre-operative proteinuria. The outcome variable was post-operative AKI within 7 days after surgery.

Data acquisition and Definition

The list of subjects who underwent non-cardiac surgery under general anesthesia, age, sex, date of surgery, and laboratory data were automatically abstracted from electronic medical records. Comorbidities, use of medications, and outcomes were hand-searched from electronic medical records by investigators.

Pre-operative proteinuria was regarded as positive when dipstick test indicated (+) or more. AKI was defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria (increase in serum creatinine $\geq$0.3 mg/dL or 150% compared to pre-operative baseline value, or urine output <0.5 mL/kg/hour for $\geq$6 hours).[14] Baseline laboratory data

including serum creatinine and urinary protein were defined as values within 1 month before surgery and the closest to the date of surgery. Cerebrovascular diseases were defined as either ischemic or hemorrhagic stroke. The presence of cardiovascular diseases indicated more than one of followings; coronary artery disease, congestive heart failure, peripheral artery disease, or atrial fibrillation. Non-cardiac surgeries were classified into 4 categories; intra-thoracic surgery, intra-abdominal surgery, pelvic and major joint surgery, and others. Estimated glomerular filtration rate (eGFR) was calculated using the equation developed for Japanese populations by the Japanese Society of Nephrology, based on the baseline serum creatinine value.[15] Pre-operative use of non-steroidal anti-inflammatory drugs (NSAIDs) or contrast agents was defined as the use of these agents within 48 hours before surgery. Vasopressors included phenylephrine, ephedrine, dopamine, and norepinephrine. Intra-operative lowest blood pressure was defined as the lowest systolic blood pressure (SBP) during surgery. Delta SBP was defined as the difference between SBP at the beginning of surgery and lowest intra-operative SBP. Intra-operative fluid balance was defined as the difference between total amount of fluid administration and sum of amount of urine output and bleeding divided by body weight.

Statistical methods

The data were expressed as median with interquartile range or number with percentage. Logistic regression models were used to examine the association between pre-operative proteinuria and post-operative AKI. The data were adjusted for the following potential confounders including those previously reported to be predictors of post-operative AKI;[12,16-19] age, sex, body mass index, the presence of hypertension, diabetes mellitus (DM), cerebrovascular diseases, cardiovascular diseases, types of surgeries (intra-thoracic, intra-abdominal, pelvic or major joint surgeries, and others), emergent surgery, surgery for malignancy (surgery not for malignancy and curative or palliative resection of malignancy), regular use of angiotensin-converting-enzyme inhibitors (ACE-Is) or angiotensin II receptor blockers (ARBs), other anti-hypertensive agents, diuretics, statins, pre-operative use of NSAIDs, contrast agents, baseline eGFR, hematocrit, serum albumin, and log-transformed C-reactive protein (CRP) in model 1. Furthermore, in model 2, the data were adjusted for variables in model 1 plus intra-operative potential confounders, including intra-operative lowest SBP, intra-operative delta SBP, intra-operative use of diuretics, intra-operative use of vasopressors, and intra-operative fluid balance. All subgroup analyses and sensitivity analyses were adjusted for the same variables in model 2. Values of $p < 0.05$ were considered statistically significant except for interactions where $p < 0.10$ was considered statistically significant.[20] Statistical analyses were performed

using the STATA version 15 (STATA Corp., College Station, TX).

Results

During the study period, 12,771 subjects underwent non-cardiac surgeries under general anesthesia at Nara Medical University Hospital. After the exclusion of data by exclusion criteria, data for 5,168 subjects were available for analyses (Figure 1). Among them, 482 (9.3%) had positive proteinuria (Table 1). Subjects with positive proteinuria were significantly older, had lower eGFR, hematocrit, serum albumin, and higher CRP. The proportion of subjects with comorbidities, the regular use of ACE-Is or ARBs, other anti-hypertensive agents, or subjects who underwent emergent surgery were significantly higher among those with positive proteinuria. Those with proteinuria also had significantly higher intra-operative delta SBP or intra-operative fluid balance compared with those without proteinuria.

Among those included in this study, 309 (6.0%) developed post-operative AKI. Pre-operative proteinuria was associated with post-operative AKI (unadjusted odds ratio [OR] [95% confidence interval (CI)]: 3.44 [2.60–4.55]). In multivariable logistic regression, adjusted OR [95% CI] for AKI among those with positive proteinuria was 1.92 [1.39–2.65] compared to those with negative proteinuria after adjustment for

baseline characteristics in model 1, and 1.80 [1.30–2.51] after additional adjustment for intra-operative hemodynamics and the use of medications in model 2, respectively (Table 2).

Subgroup analyses showed that the association between pre-operative proteinuria and AKI was similar across age, sex, the presence or absence of DM, cerebrovascular or cardiovascular disease, or regular use of statins. In contrast, proteinuria was especially associated with AKI among those with regular use of ACE-Is or ARBs, other anti-hypertensives, hypoalbuminemia, or impaired baseline renal function (p for interaction = 0.05, 0.003, 0.09, or 0.02, respectively) (Figure 2). There is a possibility that proteinuria is a reflection of infection or acute inflammation. However, analysis limited to elective surgeries yielded similar results (the adjusted OR [95% CI]: 1.70 [1.19–2.42]). The association between proteinuria and AKI became stronger as the severity of proteinuria increased (Table 3).

Discussion

This cohort study demonstrated that pre-operative proteinuria was independently associated with post-operative AKI after adjustment for potential confounders, including the presence of DM, baseline eGFR, serum albumin, and CRP. Analysis restricted to

elective surgeries yielded the same result. These results suggested that the association between proteinuria and AKI was not through DM, renal function, infection, or acute inflammation. Subgroup analyses indicated that proteinuria was especially associated with AKI among those with regular use of ACE-Is or ARBs, other anti-hypertensives, hypoalbuminemia, or impaired renal function. As the severity of proteinuria increased, the association between proteinuria and the incidence of AKI became stronger.

Proteinuria has been reported to be associated with AKI in various clinical settings including contrast-induced AKI[7,8] and cardiac sugery.[9,10] There has been less data in non-cardiac surgery. One retrospective cohort study reported the association between pre-operative proteinuria and increased incidence of AKI after robotic partial nephrectomy among those with normal baseline renal function.[13] In this study, only 947 subjects were included, and the number of AKI was only 47. Their logistic regression model was over-adjusted. Also, increase in serum creatinine level after nephrectomy is at least partially from the loss of renal mass and different from post-operative AKI in other non-cardiac surgery. In our study, we excluded those who underwent urological surgery to eliminate the increase in creatinine from nephrectomy and ureteral manipulation from the diagnosis of AKI. Another large cohort study including 153,767 subjects who underwent non-cardiac surgery at Veterans Affairs facilities showed that proteinuria was

independently associated with AKI.[12] This study also showed that the association between proteinuria and AKI became stronger as the severity of proteinuria increased. Their findings were consistent with our findings. However, the targeted subjects in their study were predominantly male (93.2%), and they had especially high prevalence of comorbidities. For example, the prevalence of DM requiring any medications was 27.1% and hypertension requiring medications was 70.4% of all subjects. As a result, the incidence of AKI was 11.2% and it was much higher than reported incidence of 5.0–7.5% in other studies on non-cardiac surgery.[16-18,21,22] In contrast, in the NARA-AKI cohort study, the incidence of AKI was 6.0%, which was similar to other studies on non-cardiac surgery. Our study expanded the generalizability of association between pre-operative proteinuria and post-operative AKI among standard risk patients undergoing non-cardiac surgery.

Despite several studies showing association between proteinuria and AKI, the pathophysiologic explanations for the association have been unknown. It has been shown that the association was independent of baseline eGFR, the presence of hypertension, or DM.[8-10,12,13] We considered the possibility that proteinuria was a reflection of acute infection or inflammation. However, even after adjustment for baseline CRP and albumin levels, proteinuria was independently associated with AKI. Also, the analysis restricted

to elective surgery did not change the results. We also considered the possibility that proteinuria led to hypoalbuminemia, and that decreased oncotic pressure from hypoalbuminemia led to intravascular volume contraction and susceptibility for AKI. However, proteinuria was independently associated with AKI after adjustment for serum albumin levels, intra-operative hemodynamic change, intra-operative fluid balance, and the use of intra-operative diuretics and vasopressors. One possibility is that the presence of pre-operative proteinuria is a sign of unrecognized glomerulonephritis. Another possible mechanism that explains the association between proteinuria and AKI is endothelial dysfunction. The luminal surface of the glomerular endothelium is covered with a hydrogel called the glycocalyx, which acts as a barrier against protein filtration across the endothelium.[23] Sustained glomerular endothelial activation, caused by chronic inflammation, changes the properties of glycocalyx,[24] or increases activity of enzymes that degrade the glycocalyx.[25] Impaired glycocalyx leads to increase the rate of passage of albumin,[26,27] extensive uptake of albumin into the podocytes, and results in secondary podocyte injury.[23] Under physical stress of operation, these potential damages might reveal as a form of AKI.

In subgroup analyses, the association between proteinuria and AKI was stronger among those with regular use of ACE-Is or ARBs or other antihypertensives,

hypoalbuminemia, or impaired renal function. What is common among these subgroups is impaired renal autoregulation. Among those with chronic hypertension, renal autoregulation curve shifts to right and they require higher blood pressure for maintaining renal perfusion. Among those with hypoalbuminemia, lower oncotic pressure leads to intravascular volume contraction. For those with chronic kidney disease, persistent activation of renin-angiotensin-aldosterone system leads to impaired additional vasoconstrictive capacity in the setting of surgical stress. To maintain blood pressure to higher levels for those with proteinuria and impaired renal autoregulation might help to prevent AKI, although this remains speculative.

There are several clinical implications of the results of this study. First, there are multiple prediction models for AKI after cardiac surgery[28] and two for AKI after non-cardiac surgery.[17,19] Most of the prediction models do not include proteinuria as a predictor except for one.[17] As proteinuria is an independent, strong predictor of AKI, it should be included in the prediction model for AKI developed from now on. Second, the presence of proteinuria can be used to risk stratify and identify those at high risk for developing AKI for clinical trials on prevention or treatment of AKI. Third, as the presence of pre-operative proteinuria might be a sign of unrecognized glomerular diseases, it is important not only to recognize it as a predictor of AKI, but also to follow through

proteinuria post-operatively.

There are several strengths of our study. First, large number of subjects were included, and the data were vigorously adjusted for potential confounders including intra-operative hemodynamics and fluid balance. As long as we know, there are no studies which take intra-operative hemodynamics into account except for one study.[12] We expanded the generalizability of association between proteinuria and AKI among standard risk patients undergoing non-cardiac surgery. We also showed that association between proteinuria and AKI is stronger possibly among those with impaired renal autoregulation. This might help to elucidate the mechanism between proteinuria and higher incidence of AKI, although we still do not have clear explanations for the association.

There are also a few limitations in our study. First, as this was an observational study, there is a possibility of residual unknown confounders. There were significant differences in the background of patients with and without proteinuria, including the prevalence of comorbidity, use of medications, and intra-operative hemodynamics and fluid balance. Although maximum effort was made to adjust for these confounders, it was uncertain we could completely adjust for the severity of comorbidities or invasiveness of the surgeries. In fact, one study suggested that pre-admission proteinuria was associated with non-recovery after dialysis-requiring AKI, after adjusting for baseline eGFR and

comorbidity.[29] This suggests that the presence of proteinuria might be associated with worse background and suggests the difficulty of completely adjusting for confounders in an observational study. Second, histological findings associated with proteinuria was unknown as very few subjects underwent renal biopsy. However, the number of subjects with (3+) of urinary protein was only 32 (0.6%), which would suggest there were few subjects with severe glomerulonephritis or nephrotic syndrome. Third, proteinuria was measured with a dipstick, and hence semi-quantitative. Although accuracy of the amount of urinary protein might be concerned, dipstick test would be one of the most useful tools for stratifying the risk of AKI in terms of cost-effectiveness. Fourth, the data were from 2007 and 2011. The possibility that some changes in the care of surgical patients might have affected the association between pre-operative proteinuria and post-operative AKI cannot be excluded. Fifth, as this is a single center study, external validation is necessary for our results.

In conclusion, pre-operative proteinuria was independently associated with post-operative AKI. It is important to recognize that those with proteinuria are prone to develop AKI irrespective of baseline renal function and that those with positive proteinuria should be managed more carefully in peri-operative period to prevent AKI.

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Conflict of Interest Statement

None declared. The results presented in this paper have not been published previously in whole or part, except in abstract form.

Authors' Contributions

Research idea and study design: MN, MT; data acquisition: MT, MN, MK; supervision or mentorship: MM, ME, KS, YA, KT. All authors provided intellectual content of critical importance to the work described and approved the final version.

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Table 1. Characteristics of subjects

	Pre-operative Proteinuria		p value
	Negative (n = 4,686)	Positive (n = 482)	
Dipstick test	(−) 4,291 (83.0) (+/−) 395 (7.6)	(+) 287 (5.6) (2+) 163 (3.2) (3+) 32 (0.6)	–
Age	63 (49–72)	67 (56–75)	<0.001
Male sex	2,156 (46.0)	258 (53.5)	0.002
BMI	22.4 (20.3–24.8)	22.5 (20.2–25.4)	0.81
Hypertension	1,589 (33.9)	239 (49.6)	<0.001
Diabetes mellitus	668 (14.3)	141 (29.3)	<0.001
Cerebral infarction	243 (5.2)	43 (8.9)	0.02
Intra-cranial hemorrhage	129 (2.8)	30 (6.2)	<0.001
Ischemic heart disease	210 (4.5)	34 (7.1)	0.02
Congestive heart failure	62 (1.3)	15 (3.1)	0.005
Peripheral artery disease	41 (0.9)	16 (3.3)	<0.001
Atrial fibrillation	110 (2.3)	25 (5.2)	0.001
Intra-thoracic surgery	445 (9.5)	42 (8.7)	
Intra-abdominal surgery	848 (18.1)	150 (31.1)	<0.001
Pelvic or major joint surgery	740 (15.8)	68 (14.1)	
Other types of surgery	2,653 (56.6)	222 (46.1)	
Emergent surgery	210 (4.5)	88 (18.3)	<0.001
Surgery for malignancy	1,570 (33.5)	173 (35.9)	0.29
ACE-Is or ARBs	828 (17.7)	149 (30.9)	<0.001
Other anti-hypertensive agents	1,065 (22.7)	187 (38.8)	<0.001
Diuretics	348 (7.4)	70 (14.5)	<0.001
Statins	511 (10.9)	64 (13.3)	0.13
NSAIDs	742 (15.8)	82 (17.0)	0.51
Contrast agents	245 (5.2)	68 (14.1)	<0.001
eGFR, mL/min/1.73 m^2	78.9 (66.9–92.7)	65.9 (44.9–85.6)	<0.001
Hematocrit, %	38.2 (34.8–41.6)	36.0 (31.5–40.2)	<0.001
Serum albumin, g/dL	4.3 (4.0–4.5)	4.0 (3.4–4.3)	<0.001
CRP, mg/dL	0.1 (0.1–0.3)	0.3 (0.1–2.3)	<0.001
Intra-operative lowest SBP, mmHg	80 (70–85)	80 (70–85)	0.68
Intra-operative delta SBP, mmHg	60 (45–80)	70 (50–85)	<0.001
Intra-operative diuretics	461 (9.8)	79 (16.4)	<0.001

Intra-operative vasopressors	3,826 (81.6)	402 (83.4)	0.39
Intra-operative fluid balance, mL/kg	20.8 (13.9–31.2)	24.5 (16.1–37.3)	<0.001

Data were shown as median (interquartile range) or number (%). P values were determined using Mann-Whitney U test, Chi-square test, or Fisher's exact test.

Positive proteinuria was defined as ≥(+) or more, and negative proteinuria was defined as (+/−) or (−) by dipstick test.

BMI: body mass index, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, ACE-Is: angiotensin-converting-enzyme inhibitors, ARBs: angiotensin II receptor blockers, NSAIDs: non-steroidal anti-inflammatory drugs, SBP: systolic blood pressure.

Table 2. Odds ratios for post-operative acute kidney injury among those with positive proteinuria.

	OR [95% CI]
Unadjusted	3.44 [2.60–4.55]
Model 1	1.92 [1.39–2.65]
Model 2	1.80 [1.30–2.51]

In model 1, the data were adjusted for age, sex, BMI, hypertension, diabetes mellitus, cerebrovascular diseases, cardiovascular diseases, types of surgery, emergent surgery, surgery for malignancy, regular use of ACE-Is or ARBs, other anti-hypertensive agents, diuretics, statins, pre-operative use of NSAIDs, contrast agents, baseline eGFR, hematocrit, serum albumin, and lnCRP. In model 2, the data were adjusted for variables in model 1 plus intra-operative lowest SBP, intra-operative delta SBP, intra-operative fluid balance, and intra-operative use of diuretics, and vasopressors.

OR: odds ratio, CI: confidence interval, BMI: body mass index, ACE-Is: angiotensin-converting-enzyme inhibitors, ARBs: angiotensin II receptor blockers, NSAIDs: non-steroidal anti-inflammatory drugs, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, SBP: systolic blood pressure.

Table 3. Adjusted odds ratios for post-operative acute kidney injury stratified by the severity of pre-operative proteinuria.

	Urinary protein	OR [95% CI]
Model 2	(−)	1.0 [reference]
	(+/−)	1.14 [0.75–1.73]
	(+)	1.24 [0.79–1.95]
	(2+)	2.75 [1.74–4.35]
	(3+)	3.95 [1.62–9.62]

The data were also adjusted for the same variables in model 2.
OR: odds ratio, CI: confidence interval.

Figure Legends

Figure 1. Flow of subjects.

Figure 2. Subgroup analyses for association between positive proteinuria and post-operative acute kidney injury. Data were adjusted for the same variables as in model 2. DM: diabetes mellitus, CVD: cardiovascular disease or cerebrovascular disease, ACE-Is: angiotensin-converting-enzyme inhibitors, ARBs: angiotensin II receptor blockers, eGFR: estimated glomerular filtration rate.

Figure 1.

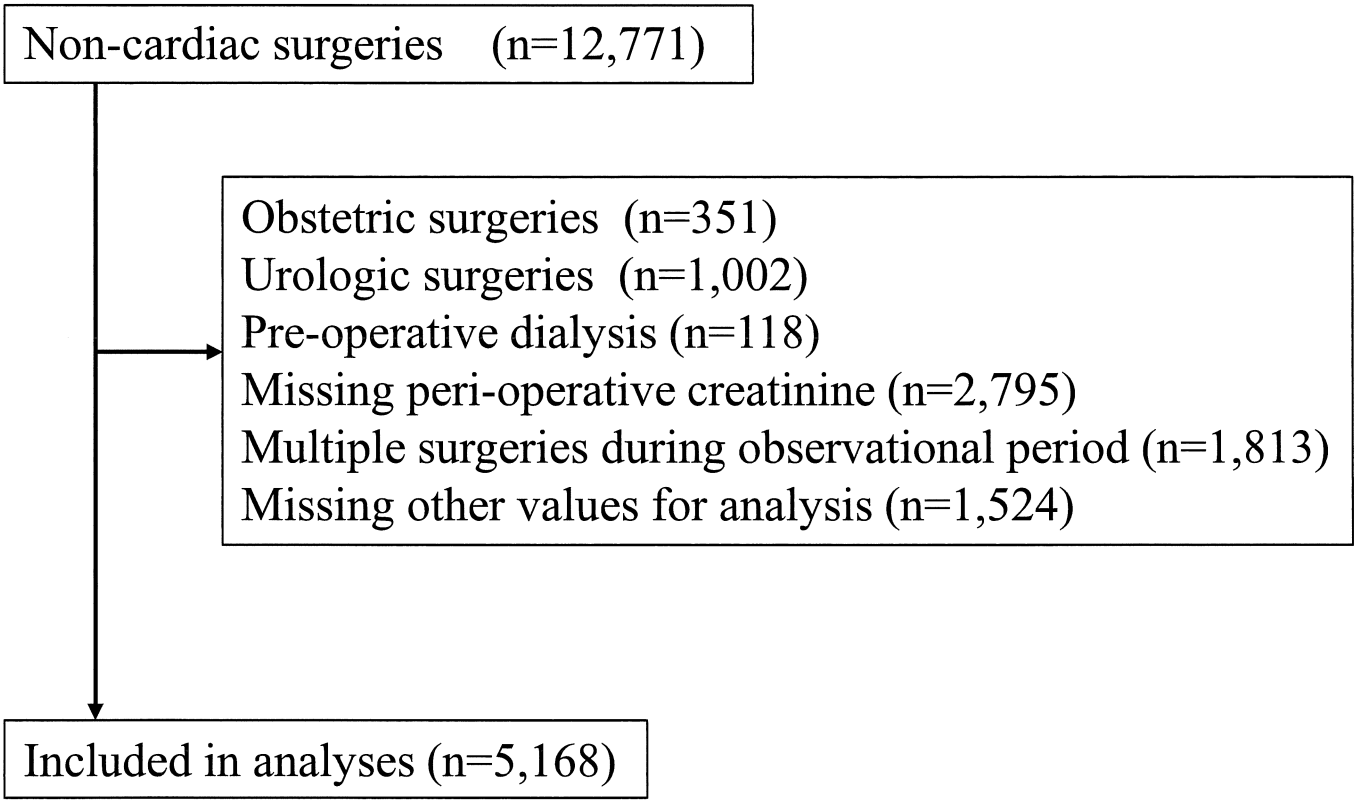
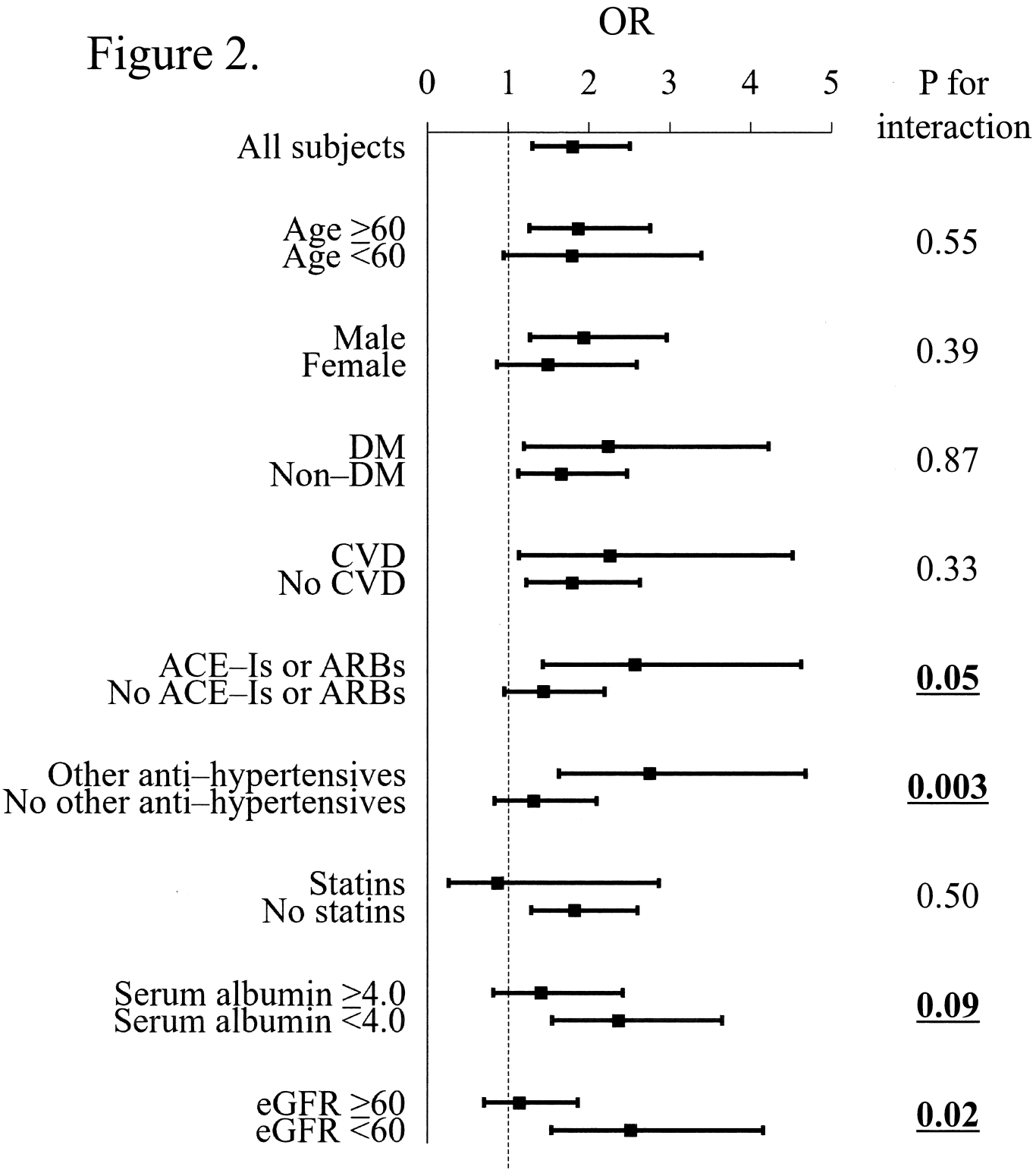

Non-cardiac surgeries (n=12,771)
Obstetric surgeries (n=351)
Urologic surgeries (n=1,002)
Pre-operative dialysis (n=118)
Missing peri-operative creatinine (n=2,795)
Multiple surgeries during observational period (n=1,813)
Missing other values for analysis (n=1,524)
Included in analyses (n=5,168)

Figure 2.


OR
0
1
2
3
4
5
P for interaction
All subjects
Age ≥60
Age <60
0.55
Male
Female
0.39
DM
Non–DM
0.87
CVD
No CVD
0.33
ACE–Is or ARBs
No ACE–Is or ARBs
0.05
Other anti–hypertensives
No other anti–hypertensives
0.003
Statins
No statins
0.50
Serum albumin ≥4.0
Serum albumin <4.0
0.09
eGFR ≥60
eGFR <60
0.02