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Acute kidney injury and its impact on renal prognosis after robot-assisted laparoscopic radical prostatectomy

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Abstract

Background: This study assessed the incidence and impact of acute kidney injury (AKI) on renal prognosis in patients who underwent robot-assisted laparoscopic radical prostatectomy (RARP).

Methods: Medical records of 305 patients treated with RARP were retrospectively reviewed. The patients with postoperative AKIs were dichotomized into early AKI (immediately after surgery) and late AKI (1-7 days after surgery). The impact of AKIs and their risk factors were statistically assessed.

Results: Early and late AKI were observed in 143 (46.9%) and 12 (3.9%) patients, respectively. Hypertension and console time were independent risk factors for early AKI. Among the patients with preoperative eGFR ≥60 mL/min, the eGFR decline 12 months after surgery was significantly greater in patients with early AKI than that without early AKI (−6.8 vs −3.2 mL/min, $P = .02$).

Conclusions: Approximately half of patients developed early AKI after RARP. The patients with early AKI had reduced renal function 12 months after surgery.

KEYWORDS

acute kidney injury, prostate cancer, robot-assisted laparoscopic radical prostatectomy

1 | INTRODUCTION

Prostate cancer is the second leading cause of cancer-related death in men worldwide.[1] Radical prostatectomy is one of the standard modalities for localized prostate cancer.[2] Robotic surgery has been accepted to improve surgical quality[3] in urological surgery, and robot-assisted laparoscopic radical prostatectomy (RARP) has become one of the most widely used procedures due to its minimal invasiveness and comparable outcomes with conventional procedures.[4,5] Therefore, it is important to achieve satisfactory surgical outcomes of RARP without peri- and postoperative complications. Acute kidney injury (AKI) is a postoperative complication of prostatectomy that is associated with chronic kidney disease (CKD) and death.[6,7] There are several potential causes of postoperative AKI, including patient and surgical factors.[7] RARP can impair renal function due to high pneumoperitoneum pressure and an extremely steep head-down position of the patient.[8,9] Several studies report the incidence of AKI after RARP compared with that after conventional open surgery.[7,10] However, the frequency and clinical significance of AKI after RARP remains unclear. In this study, we assessed the incidence, risk factors and impact on renal prognosis of AKI observed during the very early period after surgery in patients with prostate cancer who underwent RARP.

2 | PATIENTS AND METHODS

2.1 | Patients and study design

We retrospectively reviewed the medical records of 305 consecutive patients with localized prostate cancer patients who underwent

RARP at Akita University Hospital between December 2012 and December 2017. Data on baseline characteristics, including age, body mass index (BMI), presence of hypertension, presence of diabetes mellitus, presence of preoperative proteinuria, and prostate volume were collected from the medical records. Data on cancer status included prostate-specific antigen (PSA) level, Gleason biopsy score, and the risk classification reported by D'Amico et al.[11] Data on intraoperative outcomes, including operative time, console time, estimated blood loss, volume of intraoperative fluid replacement, presence of nerve sparing, and presence of lymph node dissection, were also collected. Operative time was defined as the interval between the first incision and the end of the operation. Console time was defined as the duration of surgery using a da Vinci surgical system. Estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease (MDRD) equation.[12] AKI was defined and staged based on Kidney Disease Improving Global Outcomes (KDIGO) creatinine criteria (Table S1).[13] The KDIGO urinary output criteria are not used in the definition of AKI because accurate measurement of urinary output is difficult. Patients with AKI were dichotomized into a group with early AKI (immediately after surgery) and a group with late AKI (1-7 days after surgery). Biochemical recurrence was defined as PSA level >0.2 ng/mL. The study was approved by the Ethical committee of our institution (number 1517). An opt-out method for consent was adopted, in which patients were informed of their inclusion in the study and were provided information on the institution's website.

2.2 | Surgical technique

Eight urologists who were certified surgeons on the da Vinci surgical system performed RARP according to the standard protocols of our institution, as reported previously.[5] We used a da Vinci S or Si unit, placed six transabdominal ports, and applied an antegrade approach to dissect the prostate. Bladder neck-sparing technique was performed in all patients. A pneumoperitoneum was created by CO_2 insufflation (10-15 mmHg), and the patients are placed in the Trendelenburg position (25°). Continuous sutures were used for the urethrovesical anastomosis. Nerve sparing and lymph node dissection were selectively performed based on the patient's clinical status and preference. Anesthesia was induced with propofol (1-1.5 mg/kg), remifentanil (0.2-0.3 μg/kg), and rocuronium (0.6-1.0 mg/kg) and maintained with volatile anesthetics (sevoflurane 1.5% or desflurane 4%) and remifentanil (0.02-0.5 μg/kg/min). Fluids were administered using crystalloid and colloid to maintain systolic arterial blood pressure at 90 mmHg during surgery and were manually changed based on the surgeon's directions. Vasoactive drugs were administered based on routine monitoring during anesthesia according to the anesthesiologist's discretion. Rocuronium was administered by continuous infusion (5 μg/kg/min) during surgery. Anticoagulants were withdrawn before surgery, and perioperative antibiotics were routinely administered to all patients. Before surgical incision, antibiotics were administered within 30 minutes and continued every 4 hours during surgery and 12 hours after surgery until postoperative day 2.

2.3 | Statistical analysis

Continuous variables were presented as means ± standard deviation or medians with interquartile range (IQR), and categorical variables were presented as counts and percentages. Differences between the two groups were evaluated using the χ^2 or the Fisher exact test for categorical variables and the *t*-test or the Mann-Whitney*U* test for continuous variables. Odds ratios (ORs) for the presence of AKIs were estimated using univariate and multiple logistic regression analyses. Preoperative or intraoperative variables that could be confounding factors based on previous reports and clinical experience, such as age, BMI, presence of hypertension and/or diabetes mellitus, preoperative serum creatinine (sCr), console time, estimated blood loss, and intraoperative fluid replacement, were included in multivariate analyses. All reported *P* values are two-sided, with $P < .05$ considered to indicate statistical significance. All statistical analyses were conducted using the SPSS software package for Windows, version 24.0 (SPSS, Chicago, Illinois).

3 | RESULTS

3.1 | Patients

Patient characteristics and surgical parameters are shown in Table 1. The median age was 66 years (IQR, 63-70 years). The median preoperative eGFR was 73.7 mL/min/1.73 m^2(IQR, 64-83.6 mL/min/1.73 m^2). Forty-six (15.1%), 211 (69.1%), and 45 (14.8%) patients were classified as CKD grade G1, G2, and ≥G3a, respectively. According to the D'Amico risk classification, 56 (18.4%), 160 (52.5%), and 89 (29.2%) patients were classified in the low, intermediate, and high-risk group, respectively. The median operative time was 225 minutes (IQR, 196-263 minutes), and the median estimated blood loss was 82 mL (IQR, 34-182 mL). No patient required conversion to open surgery. Postoperative complications were noted in 29 cases (9.5%), including 14 (4.6%) with Clavien-Dindo classification[14] ≥3 (nine inguinal hernia, three port site hernia, one intestinal injury, and one ureteral stricture).

In all patients, the mean sCr level immediately after surgery was significantly higher than at baseline (1.16 vs 0.82 mg/dL, $P < .01$). The mean sCr levels on postoperative days 1 to 7 were not significantly different from those at baseline (0.82 vs 0.82 mg/dL, $P = .596$), and those at 1 month, 3 months, 6 months, and 1 year after RARP were also not significantly different from those at baseline (Figure S1). There were no statistically significant differences in renal function between presence and absence of AKI at 6 and 12 months after RARP (Figure 1).

During a median follow-up period of 13 months, 22 patients (7.2%) experienced a biochemical recurrence. Two patients (0.7%) died, one from cancer and one from an accident, whereas no patients died of prostate cancer progression.

TABLE 1 Patient characteristics

		n = 305
Age, median (IQR)		66 (63-70)
Body mass index, kg/m^2, median (IQR)		24.2 (22.7-26)
Baseline sCr, mg/dL, (IQR)		0.8 (0.72-0.93)
Baseline eGFR, mL/min/1.73 m^2, median (IQR)		73.7 (64-83.6)
Baseline CKD grade, No. (%)		
	Grade1	46 (15.1)
	Grade2	211 (69.1)
	Grade3a	45 (14.8)
	Grade3b, 4	3 (1)
Comorbidity, No. (%)		
	Hypertension	153 (50.2)
	Diabetes mellitus	28 (9.2)
Baseline PSA, ng/ml, median (IQR)		6.2 (5.1-9.1)
D'Amico risk group, No. (%)		
	Low	56 (18.4)
	Intermediate	160 (52.4)
	High	89 (29.2)
Neoadjuvant therapy, No. (%)		
	ADT	29 (9.5)
	Chemotherapy + ADT	5 (1.6)
Operative time, min, median (IQR)		225 (196-263)
Console time, min, median (IQR)		174 (147-212)
Estimated blood loss, mL, median (IQR)		82 (34-182)
Nerve sparling		
	Unilateral	94 (30.8)
	Bilateral	7 (2.3)
Lymph node dissection		
	Limited	114 (37.4)
	Extended	2 (0.7)

Abbreviations: ADT, androgen deprivation therapy; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; iPSA, initial prostate-specific antigen; sCr, serum creatinine.

3.2 | Incidence and risk factors of AKI after RARP

Early and late AKIs were observed in 46.9% (143/303) and 3.9% (12/303) patients, respectively. All AKIs were stage 1 or 2, with no stage 3 or higher AKIs (Table 2). Univariate analyses showed that patients in the early AKI group had a significantly higher proportion of hypertension and a higher BMI than those in the non-early AKI groups (57.4% vs 42.0%, $P < .01$; 24.5 vs 23.9 kg/m^2, $P < .01$, respectively; Table 3). On the other hand, patients in the late AKI group had a significantly higher proportion of diabetes mellitus than those in the non-late AKI group (41.7% vs 7.9%, $P < .01$; Table 4). Regarding operative outcomes, the console time was significantly longer in patients in the early AKI group than in patients in the non-early AKI group (187 vs 166 minutes, $P < .01$), and intraoperative fluid replacement was significantly lower in patients in the early AKI group than in patients in the non-early AKI group (5.2 vs 6.0 mL/kg/h, $P < .01$; Table 3). On the other hand, perioperative outcomes were not significantly associated with late AKI (Table 4).

The risk factors which associated with early or late AKI after RARP listed in Table 3. Hypertension and console time were independent risk factors for early AKI, whereas diabetes mellitus was an independent risk factor for late AKI.

3.3 | Changes in renal function at 6 and 12 months in patients with or without AKI after RARP

Finally, we evaluated the impact of AKI after RARP on renal function at 6 and 12 months. In all patients, eGFR at 6 and 12 months was 75.1 and 72.4 mL/min/1.73 m^2, respectively. eGFR was significantly decreased at 12 months after RARP (75.3 vs 72.4 mL/min/1.73 m^2, $P < .01$). There was no significant difference in eGFR decline at 6 months after RARP in the early AKI groups compared with those in the non-early AKI groups (Figure 2). On the other hand, the decline in eGFR at 12 months in patients with early AKI tended to be greater than that in patients without early AKI (−5.2 vs −2.8 mL/min/1.73 m^2, $P = .084$; Figure 2). In particular, among 172 patients with normal preoperative eGFR (≥60 mL/min/1.73 m^2), the decline in eGFR at 6 and 12 months after RARP was significantly greater in patients with early AKI than in patients without early AKI (6 months, −0.14 vs −3.1 mL/min/1.73 m^2, $P = .033$; 12 months, −3.2 vs −6.8 mL/min/1.73 m^2, $P = .022$; Figure 2).

The decline in eGFR at 6 months was greater in patients with late AKI than in patients without late AKI (−0.5 vs −7.7 mL/min/1.73 m^2, $P = .049$, Figure 2), but there was no significant difference between the groups in the decline in eGFR at 12 months after RARP. The tendency toward decline in eGFR was similar in patients with normal preoperative eGFR.

In patients with early AKI, 9 (6.3%) experienced late AKI and 134 (93.7%) did not. There was no significant difference in postoperative renal function between the two groups at 1 to 12 months after RARP (Figure S2).

4 | DISCUSSION

The impact of postoperative AKI has been mainly assessed in the fields of cardiovascular surgery and liver transplantation,[15,16] and there are few reports on its impact after urological surgery. This is the first study to assess the incidence, risk factors, and impact on survival of AKIs that includes very early assessment of AKI after RARP. Early AKI (immediately after surgery) was observed in 46.9% of patients

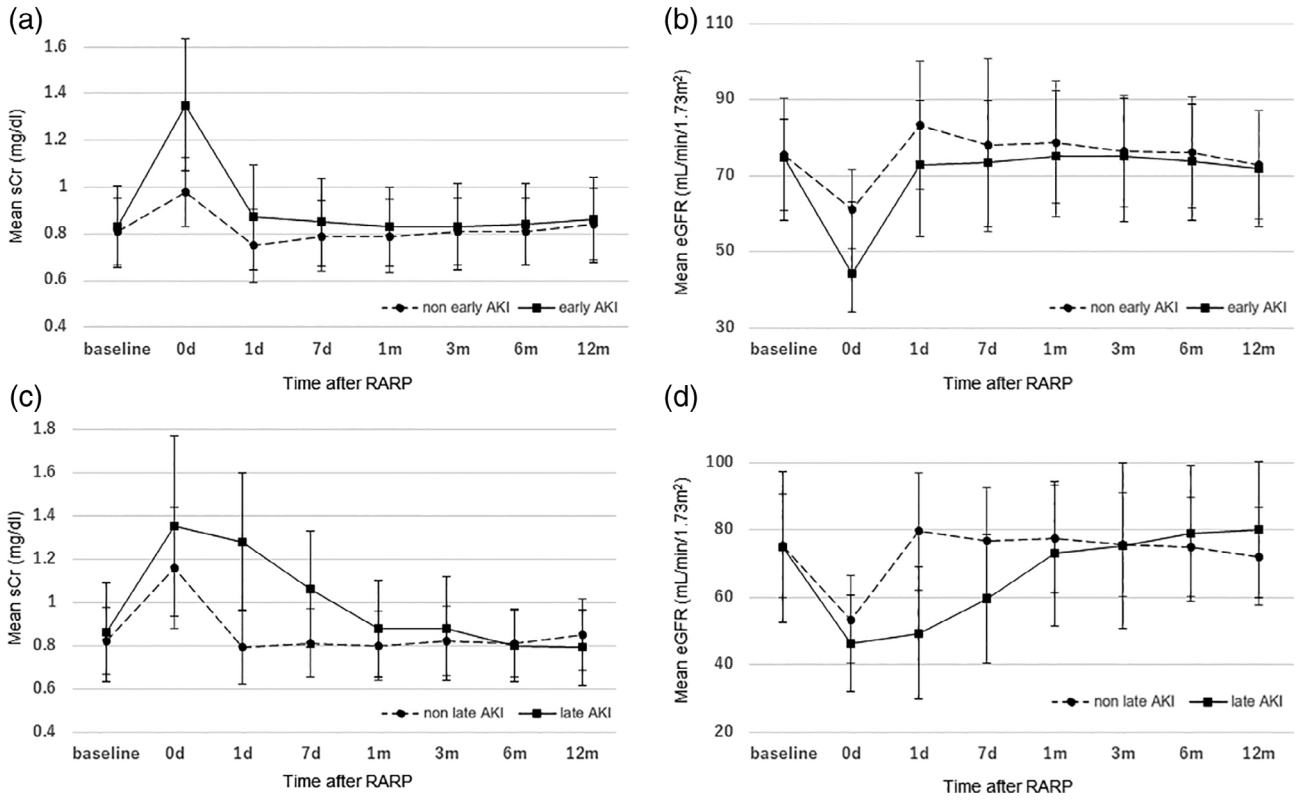

FIGURE 1 Longitudinal changes in renal function after robot-assisted laparoscopic radical prostatectomy (RARP) in patients with and without acute kidney injury (AKI). A, Comparison of mean serum creatinine (sCr) levels between the early AKI and the non-early AKI groups. B, Comparison of mean estimated glomerular filtration rate (eGFR) between the early AKI and the non-early AKI groups. C, Comparison of mean sCr levels between the late AKI and the non-late AKI groups. D, Comparison of mean eGFR levels between the late AKI and the non-late AKI groups

TABLE 2 Incidence of postoperative early and late AKIs

	Early AKI n (%)	Late AKI n (%)
Total	143 (46.9)	12 (3.9)
Stage 1	131 (43.0)	11 (3.6)
Stage 2	12 (3.9)	1 (0.3)
Stage 3	0 (0)	0 (0)

Abbreviation: AKI, acute kidney injury.

who underwent RARP, whereas late AKI (1-7 days after surgery) was observed in only 3.9%. Joo et al tried to evaluate the difference in AKI incidence between open radical prostatectomy and RARP using the KDIGO criteria that were applied in the current study.[7] That study found that the incidence of AKI after RARP was significantly lower than that after open surgery (5.5% vs 10.4%, $P = .044$). To define the presence of AKI, it is important to determine how soon laboratory data are evaluated after RARP. In the study by Joo et al, there was no information on the time to measurement of serum creatinine levels. However, the rate of AKI (5.5%) was similar to the rate of late AKI (3.9%) in the current study, which suggests that the previous study assessed serum creatinine levels on postoperative days 1 to 7. These results, in addition to those of our study, suggest that the incidence of AKI after RARP according to the KDIGO criteria in 1 to 7 days may be around 5%, and the incidence might be higher if laboratory data were obtained immediately after surgery. Further validation with a larger number of patients in other cohorts is needed to confirm the incidence of early AKI in RARP.

We showed that the presence of early AKI was significantly associated with deterioration of eGFR 12 months after RARP in patients with normal renal function. However, the difference in eGFR was minimal (3.54 mL/min/1.73 m^2) at 12 months post RARP, which may not be clinically relevant. A study to determine the risk factors predictive of long-term graft outcome in renal transplantation showed that serum creatinine at 12 months was the most significant predictor of graft survival.[17] This finding suggests that real outcome 1 year after surgery has a potential to be associated with long-term renal function. Because, renal function at 12 months after RARP may be associated with long-term renal function, further studies are needed to assess the impact of minimal differences at 12 months on long-term renal functions in patients who underwent RARP.

Regarding the risk factors for the development of postoperative AKI, previous studies of the outcomes of cardiovascular surgery and liver transplantation demonstrated that advanced age, obesity, hypertension, diabetes mellitus, and intraoperative blood transfusion were common risk factors for the development of AKI.[18-20] A recent large population-based retrospective study showed that patients with CKD had five times greater risk of postoperative AKI after radical

TABLE 3 Univariate and multivariable logistic regression analyses for presence of early AKI after RARP

	Early AKI							
			Univariate			Multivariable		
Variables	Early AKI n = 143 n (%)	Non-early AKI n = 162 n (%)	OR	95% CI	*P* value	OR	95% CI	*P* value
Age, y	66	66	0.99	0.96 to 1.03	.76	1.00	0.95 to 1.05	.88
BMI, kg/m^2	24.5	23.9	1.11	1.02 to 1.20	**.01**	1.05	0.96 to 1.16	.29
Hypertension (+)	93 (57.4)	60 (42.0)	3.16	1.98 to 5.05	**<.01**	3.52	2.09 to 5.91	**<.01**
Diabetes mellitus (+)	15 (9.3)	13 (9.1)	1.34	0.62 to 2.93	.46	1.38	0.57 to 3.34	.47
Preoperative proteinuria (+)	8 (4.9)	5 (3.5)	1.86	0.60 to 5.82	.27	2.03	0.51 to 8.17	.32
Preoperative sCr, mg/dL	0.82	0.80	1.87	0.45 to 7.82	.39	0.70	0.13 to 3.76	.68
PSA, ng/mL	6.5	6.0	1.02	0.97 to 1.07	.40	1.00	0.95 to 1.06	.98
Prostate volume, mL	41.4	43.3	1.01	0.99 to 1.02	.57	1.01	0.99 to 1.03	.40
Console time, min	187	166	1.01	1.01 to 1.02	**<.01**	1.01	1.00 to 1.02	**<.01**
Blood loss, mL	90	71	1.00	0.99 to 1.00	.87	1.00	0.99 to 1.00	.09
Intraoperative fluid replacement, mL/kg/h	5.2	6.0	0.83	0.75 to 0.92	**<.01**	0.91	0.80 to 1.04	.15
Nerve sparling (+)	49 (30.2)	52 (36.4)	1.10	0.68 to 1.78	.69	1.30	0.71 to 2.40	.40
Lymph node dissection (+)	59 (36.4)	57 (39.9)	1.29	0.81 to 2.06	.28	1.19	0.65 to 2.19	.57

Note: Significant values are indicated in bold.
Abbreviations: 95% CI, 95% confidence interval; AKI, acute kidney injury; BMI, body mass index; HR, hazard ratio; PSA, prostate-specific antigen; sCr, serum creatinine.

TABLE 4 Univariate and multivariable logistic regression analyses for presence of late AKI after RARP

	Late AKI							
			Univariate			Multivariable		
Variables	Late AKI n = 12 n (%)	Non-late AKI n = 293 n (%)	OR	95% CI	*P* value	OR	95% CI	*P* value
Age, y	64.5	66	0.94	0.85 to 1.03	.165	0.873	0.77 to 0.99	**.034**
BMI, kg/m^2	23.7	24.2	0.96	0.78 to 1.17	.655	0.774	0.59 to 1.03	.075
Hypertension (+)	7 (58.3)	146 (49.8)	1.41	0.44 to 4.54	.565	0.781	0.20 to 3.08	.724
Diabetes mellitus (+)	5 (41.7)	23 (7.9)	8.39	2.47 to 27.52	**.001**	21.889	4.27 to 112.20	**<.001**
Preoperative proteinuria (+)	2 (16.7)	11 (3.8)	5.13	1.00 to 26.26	.050	1.359	0.07 to 24.91	.836
Preoperative sCr, mg/dL	0.82	0.80	3.71	0.16 to 87.54	.417	11.923	0.17 to 857.67	.256
PSA, ng/mL	7.1	6.1	1.01	0.91 to 1.13	.848	0.989	0.85 to 1.15	.884
Prostate volume, mL	45.0	42.1	1.02	0.98 to 1.05	.385	1.039	0.99 to 1.09	.147
Console time, min	201	174	1.01	0.99 to 1.02	.421	1.008	0.99 to 1.02	.289
Blood loss, mL	150	80	1.00	0.99 to 1.00	.829	1.00	0.99 to 1.01	.704
Intraoperative fluid replacement, ml/kg/h	5.3	5.6	0.90	0.69 to 1.18	.446	0.884	0.61 to 1.27	.506
Nerve sparling (+)	3 (25)	98 (33.4)	0.66	0.18 to 2.51	.545	0.571	0.11 to 2.90	.499
Lymph node dissection (+)	5 (41.7)	111 (37.9)	1.17	0.36 to 3.78	.792	2.062	0.42 to 10.10	.372

Note: Significant values are indicated in bold.
Abbreviations: 95% CI, 95% confidence interval; AKI, acute kidney injury; BMI, body mass index; HR, hazard ratio; PSA, prostate-specific antigen; sCr, serum creatinine.

prostatectomy than patients in the non-CKD group.[21] In our study, hypertension was a preoperative risk factor for early AKI, and diabetes mellitus was a preoperative risk factor for late AKI. Because prostate surgery is usually performed on elderly patients, we must carefully monitor for the presence of AKIs and take appropriate prophylaxis.

Maintaining renal perfusion and blood pressure is an effective prophylaxis to avoid postoperative AKIs.[22] Therefore, we should

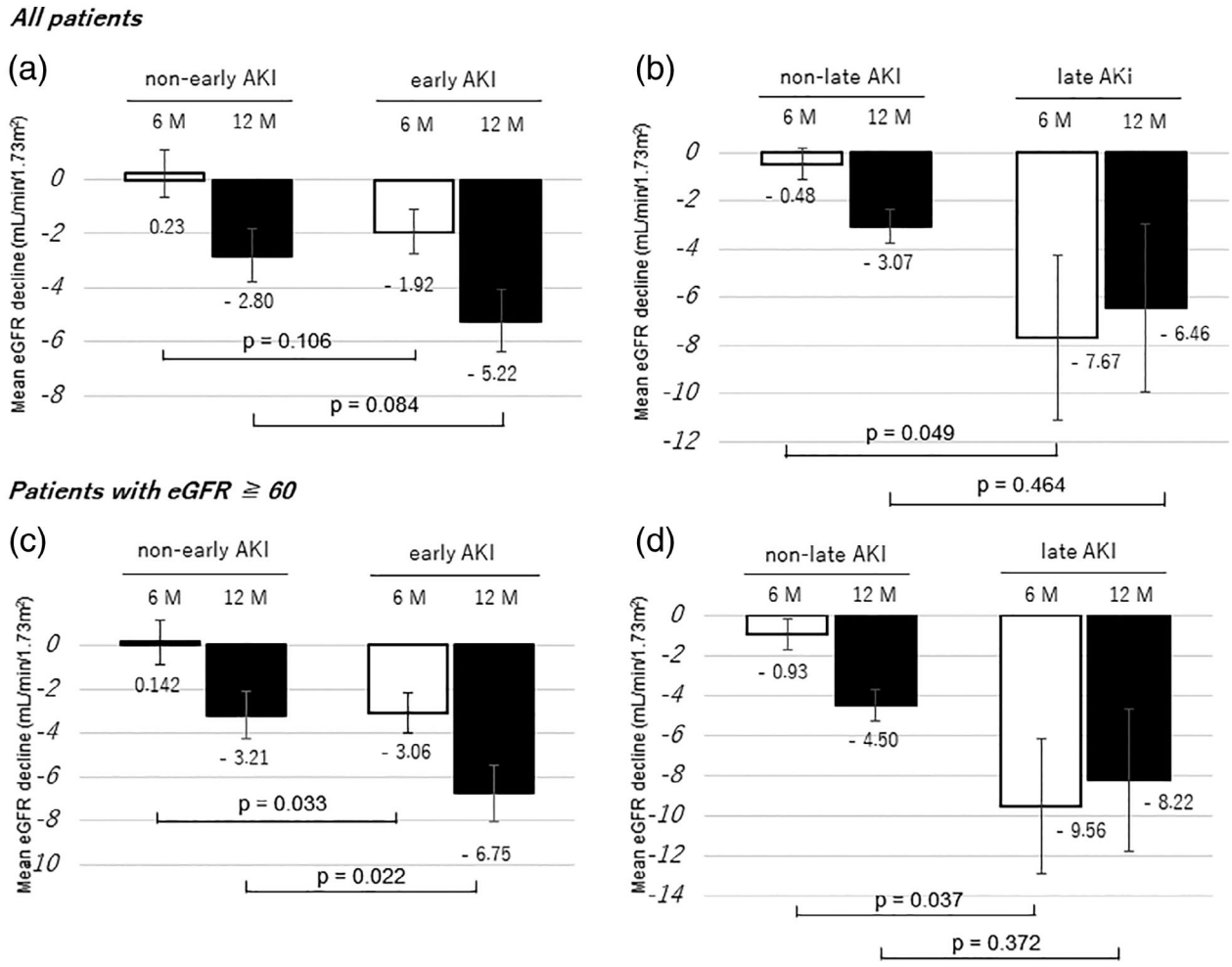

FIGURE 2 Decline in estimated glomerular filtration rate (eGFR) from baseline at 6 and 12 months after robot-assisted laparoscopic radical prostatectomy (RARP) in patients with or without acute kidney injury (AKI). A, Mean eGFR decline with or without early AKI in all patients. B, Mean eGFR decline with or without late AKI in all patients. C, Mean eGFR decline with or without early AKI in patients with eGFR ≥60. D, Mean eGFR decline with or without late AKI in patients with eGFR ≥60

focus on adjusting fluid volume and blood pressure in patients at high-risk for AKIs during surgery. Cho et al conducted a randomized trial to assess the impact of continuous infusion of low-dose nicardipine in patients undergoing RARP.[23] The study showed that more patients in the control group than in the group receiving nicardipine developed renal insufficiency on postoperative day 1. Although results with a longer follow-up are expected, perioperative intervention is a potential option to preserve renal function after RARP.

In this study, operative outcomes such as prolonged console time and decreased intraoperative fluid replacement were associated with development of early AKI. A longer console time results in a decline in renal blood flow due to a low head-down position and a decrease in circulating plasma volume.[24] In addition, high pneumoperitoneum pressure, which decreases cardiac output and a renal blood flow, is considered a specific risk factor for AKI.[25]

To show the causal relationship between these influential factors and renal function, it might be interesting to compare our findings with the results of other studies of prostatectomies and general surgeries performed with open and laparoscopic approaches.

This study has several limitations. First, it was conducted retrospectively at a single center with a relatively short follow-up period. Second, assessment of renal function at 6 and 12 months is not sufficient to show the clinical significance of early AKI for long-term renal function. Finally, we did not consider the impact of other risk factors such as the absorption of creatinine from the peritoneum because of urine leakage into the intraperitoneal or extraperitoneal space during surgery and perioperative antibiotic administration. The impact of these variables should be investigated in future studies.

5 | CONCLUSION

Approximately half of patients developed early AKI after RARP. Hypertension and console time were risk factors for postoperative early AKI, and diabetes mellitus was a risk factor for postoperative late

AKI. Early AKI after RARP may be associated with a decrease in renal function at 12 months after surgery, particularly in patients with normal renal function before RARP. Further studies are needed to clarify the impact of AKI on long-term renal outcomes.

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CONFLICT OF INTEREST

No competing financial interests exist.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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