Effects of Metabolic Syndrome on Renal Function After Radical Nephrectomy in Patients with Renal Cell Carcinoma

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Research

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Abstract

Background: Nephrectomy, partial or radical, remains the standard treatment for renal cell carcinoma (RCC). However, increased risk of chronic kidney disease (CKD) must still be considered. This study aimed to evaluate the effects of concomitant metabolic syndrome (MetS) on renal function in patients with RCC after radical nephrectomy.

Methods: Medical records of 310 patients who underwent radical nephrectomy for clear-cell RCC at 900th Hospital of the Joint Logistics Support Force, PLA from December 2012 to January 2017 were reviewed retrospectively. Estimated glomerular filtration rate (eGFR) and CKD stages were calculated at one week preoperative as baseline and then at postoperative 1 week, 3 months, 12 months and 24 months. MetS patients were identified and enrolled in the MetS group (n=31), and a non-MetS group was selected by propensity score matching (n=31). Non-neoplastic renal parenchyma specimens taken at least 2 cm from edge of tumor were evaluated.

Results: Baseline characteristics between the two groups were comparable. At 24 months postoperative, mean eGFR levels of the MetS group were significantly lower than those in the non-MetS group (62.7 vs. 73.3 ml/min/1.73m^2; p=0.004). CKD stages were still more severe in the MetS group than those in the non-MetS group (p = 0.006). The proportions of global sclerosis, tubular atrophy and interstitial fibrosis were all significantly more prevalent in MetS patients, compared to non-MetS patients (all p<0.05).

Conclusion: In RCC patients with MetS, the possibility of declining eGFR and CKD progression must be considered after radical nephrectomy. Routine monitoring of renal function must be emphasized.

Background

Renal cell carcinoma (RCC) is one of the most common urologic tumors and accounts for 5% and 3% of all malignancies in men and women, respectively.[1] Nearly 62,700 new-onset cases and at least 14,000 related deaths yearly have been reported in the United States.[1] In China, the estimated new cases are about 68,300 with around 25,600 deaths per year.[2] Diagnosis and management of RCC have both improved in recent decades, however RCC is still an aggressive and often fatal disease.[3] Clear-cell RCC is a histological subtype of RCC and at least one-third of clear-cell RCC patients experience metastasis and recurrence, leading to unsatisfactory outcomes.[4]

The standard treatment for RCC is nephrectomy, either partial or radical.[5] Radical nephrectomy could achieve optimal oncological outcome, however because of the loss of functional renal parenchyma and sequential renal function impairment, results in the increased risk of chronic kidney disease (CKD).[6] Clinically significant CKD after nephrectomy and the increased morbidity and mortality of RCC due to CKD has been intensively discussed and evaluated recently. Older age, smoking, male sex, obesity, hypertension, diabetes mellitus, tumor size, cancer severity, types of nephrectomy and surgical procedures have been reported as risk factors of the development or progression of CKD after surgical management of RCC[7-11].However, a consensus of how to use so many patient and surgical factors to

identify the patients with higher risk of CKD is still not achieved since the diversity of the results still high, some parameters, for example, the role of obesity presented by body mass index (BMI) is controversial in different studies[11-13].

Metabolic syndrome (MetS) is a cluster of chronic conditions, including abdominal obesity, hyperlipidemia, hypertension, cardiovascular disease and diabetes mellitus that is associated with organ injury. MetS may affect the kidneys, resulting in microvascular renal injury, diabetic nephropathy, CKD or end-stage renal disease (ESRD).[14-18] In addition, in a large number of studies, MetS has been found to be associated with RCC. However, the etiology of RCC still remains unclear, although some MetS components have been confirmed as etiological factors of RCC as listed in several guidelines published by well known international organizations such as the European Association of Urology, the American Urological Association, and the Chinese Urological Association.[19] Furthermore, MetS has been used as predictor for RCC outcomes .[12] The progression-free survival (PFS) of RCC was shorter in patients with MetS, compared to those without MetS.[12] The correlation of MS and RCC and the effects on each other complicate the evaluation of the mechanism of CKD caused by surgical management of RCC.

To clarify the impact of MetS on patients with RCC and, more specifically, the incidence and progression of CKD following radical nephrectomy for RCC, this retrospective study aimed to clarify the role of concomitant MetS on renal function in patients with RCC after undergoing radical nephrectomy for clear-cell renal carcinoma.

Patients And Methods

Patients

Patients with clear-cell RCC who underwent radical nephrectomy at the 900th Hospital of the Joint Logistics Support Force, PLA, from December 2012 to January 2017 were included, and their medical records were reviewed retrospectively. Patients with eGFR less than 60ml/min/1.73m^2, with advanced CKD or with severe infection, heart disease, liver disease, hematopoietic disease before the surgery were all excluded. Patients with MetS were identified and enrolled in the MetS group. Propensity scoring matching was conducted, matching patients without MetS by age, gender, tumor diameter, and the surgical approach of patients in the MetS group and were included in the non-MetS group.

Ethical considerations

The protocol for this study was reviewed and approved by the Institutional Review Board of the 900th Hospital of the Joint Logistics Support Force, PLA. Informed consent of patients was waived because of the retrospective design of this study in which patients remained anonymous.

Main measures

Patients' eGFR levels were calculated at baseline (1 week preoperative) and 1 week, 3 months, 12 months and 24 months postoperative using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI)[20] as follows:

$141\times\min(SCr/\kappa, 1)^{\alpha}\times\max(SCr/\kappa, 1)^{-1.209}\times0.993^{Age}$ [×1.018 if female][×1.159if black],

where SCr is serum creatinine (in mg/dl), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum SCr/κ or 1, and max indicates the maximum SCr/κ or 1. Stages of chronic kidney disease were defined according to the KDOQI Chronic Kidney Disease Guidelines 2012.[21]

MetS was defined based on the presence of any three of the following criteria: 1) Body Mass Index (BMI) ≥25kg/m^2; 2) hyperglycemia (fasting blood glucose [FBG] ≥6.1mmol/L and/or 2-hour postprandial blood glucose≥7.8mmol/L), and/or confirmed diabetes with treatment; 3) hypertension (≥14090mmHg) and/or confirmed hypertension with treatment; 4) dyslipidemia (triglycerides≥1.7mmol/lL and/or high density lipoprotein cholesterol (HDL-C)<0.9mmol/L for males, <1.0mmol/L for females).[22]

Clinical and biochemical values were collected from patients' medical records, all of which were performed in our hospital using standard procedures. Age, gender, body weight, height, blood pressure (BP), FBG, lipid profile, serum creatine (SCr), serum uric acid, hemoglobin (HB) within 30 days before radical nephrectomy were recorded for further statistical analysis.

Pathological evaluation

Non-neoplastic renal parenchyma specimens collected at least 2 cm from the edge of the clear-cell renal carcinoma were evaluated by two experienced pathologists after hematoxylin and periodic acid-silver methenamine staining using light microscope. The pathologists were blinded to the clinical information of the patients. Glomerular, tubular, interstitial, and vascular features and the percentage of globally or segmentally sclerosed glomeruli were determined. Grade of tubular atrophy, interstitial fibrosis, and vascular sclerosis were scored according to the Banff pathological classification.[23] Within the selected MetS and non-MetS patients, specimens of 21 patients were missing and 7 were less than 2 cm from the edge of tumor, therefore these were not included in the pathological examination.

Statistical analyses

Categorical data are presented as count and percentage, and their associations with MetS were identified using Fisher's exact test. Normally distributed continuous data are displayed as mean with standard deviation (mean ± SD), and comparisons between the two patient groups were performed using the independent two samples t-test. Changes in eGFR levels at difference time points within groups were performed using the paired t-test. Bonfferroni correction was applied for multiple comparisons, including the eGFR levels between groups and the eGFR levels within groups at various time points. Other continuous or ordinal data are displayed as median with interquartile range (IQR), and comparisons

between the two patient groups were performed using the non-parametric Mann-Whitney test. Linear mixed models were performed to show the time effect (from preoperative 1 week to postoperative 24 months) and group effect (MetS vs. non-MetS) of the repeat measures. Associations between MetS components and CKD stages at 24 months after radical nephrectomy were performed as odds ratios (ORs) with 95% confidence intervals (CIs) using binary logistic regression models. All statistical analyses were performed using IBM SPSS version 22.0 (IBM Corp. Armonk, NY, USA). A two-tailed p-value less than 0.05 indicates statistical significance.

Results

Clinical characteristics

During the study period of this matched case-control study, 310 patients who underwent radical nephrectomy for clear-cell renal carcinoma were screened for demographic and clinical information. Thirty-one patients were diagnosed with MetS and included in the MetS group. Based on propensity score matching, another 31 patients without MetS were matched by age, gender, tumor diameter, surgical approach and included in the non-MetS group for further analysis. The clinical characteristics of the two groups are presented in **Table 1**. Significant differences were found between the two groups, including BMI, triglyceride (TG), FBG, systolic blood pressure (BP), diastolic BP, and mean arterial pressure (MAP), which were significantly higher in patients of the MetS group compared to those in the non-MetS group; while high density lipoprotein cholesterol (HDL-C) of the MetS group was significantly lower than that of the non-MetS group. The proportions of obesity, hyperlipidemia, hypertension in the MetS group were significantly larger than those in the non-MetS group.

Effects of MetS on eGFR levels after radical nephrectomy

Figure 1 shows the changes in trends of eGFR levels from preoperative 1 week to postoperative 24 months between the two groups. Significant time effects and group effects on eGFR levels from preoperative 1 week to postoperative 24 months were observed in the linear mixed model ($p<0.001$, data not shown). No significant differences were found between the two groups in preoperative eGFR levels. At 1 week after radical nephrectomy, the mean eGFR level of both groups decreased significantly from 107.2 to 69.3 ml/min/1.73m^2 in the non-MetS group and from 96.7 to 62.7ml/min/1.73m^2 in the MetS group. From 1 week to 24 months postoperatively, the mean eGFR levels of the non-MetS group (69.3, 71.2, 72.7 and 73.3ml/min/1.73m^2 for postoperative 1 week, 3, 12 and 24 months) kept increasing slightly; while the mean eGFR of the MetS group remained stable (62.7, 62.5, 61.4 and 62.7ml/min/1.73m^2 for postoperative 1 week, 3, 12 and 24 months). At the 12- and 24-month time points postoperatively, the mean eGFR levels of the MetS group were significantly lower than those of the non-MetS group, with 61.4 vs. 72.7ml/min/1.73m^2 ($p=0.003$) and 62.7 vs. 73.3ml/min/1.73m^2($p=0.004$), respectively.

Effects of MetS on CKD stages after radical nephrectomy

Preoperative and postoperative CKD stages are shown in **Figure 2**. Pre-operative CKD stages of the two groups ranged from normal to mild (Stages 1-2, eGFR>60ml/min/1.73m^2). Postoperative 1-week CKD stage of the two groups were both mainly mild to moderate (Stages 2-3a, eGFR 45 to 89ml/min/1.73m^2). At 3 months after radical nephrectomy, the CKD stages of patients in the MetS group were significantly more severe than those in the non-MetS group (p=0.005); 5 (16.1%) patients were Stage 1, 19 (61.3%) were Stage 2, and 7 (22.6%) were Stage 3a in the non-MetS group. In the MetS group, 1 (3.2%) patient was Stage 1, 14 (45.2%) were Stage 2, 12 (38.7%) were Stage 3a and 4 (12.9%) were Stage 3b. At 12 months postoperatively, differences in CKD stages between the two groups were not statistically significant. At 24 months after radical nephrectomy, the CKD stages became more severe in MetS group patients compared to those in the non-MS group (p = 0.006); 4 (12.9%) patients were Stage 1, 22 (71.0%) were Stage 2, and 5 (16.1%) were Stage 3a in the non-MetS group; while, in the MetS group, 1 (3.2%) patient was Stage 1, 16 (51.6%) were Stage 2, 10 (32.3%) were Stage 3a, and 4 (12.9%) were Stage 3b. No severe CKD or kidney failure (Stage 4-5, eGFR<30ml/min/1.73m^2) was found in any patients.

Renal pathological findings

Renal pathological findings in patients with and without MetS are listed in **Table 2,** n=18 in each group. The proportion of global sclerosis was significantly larger in patients with MetS (median 3.60% vs. 1.73%, p=0.028) than in those without MetS. However, the difference in segmental glomerulosclerosis between the two groups did not reach statistical significance. Notably, tubular atrophy (p=0.023) and interstitial fibrosis (p=0.010) were more prevalent in patients with MetS.

Factors associated with moderate to severe CKD at 24 months after radical nephrectomy

As shown in **Table 3**, baseline eGFR level, hypertension, and diabetes mellitus were associated with moderate to severe CKD at 24 months after radical nephrectomy (p<0.05). The risk of moderate to severe CKD was decreased by each 1 unit of increase in baseline eGFR level, with a crude OR of 0.95 (p=0.003). Patients with hypertension and diabetes mellitus were more likely to have moderate to severe CKD at 24 months after radical nephrectomy, with crude ORs of 9.69 (p=0.001) and 4.50 (p=0.037), respectively. After adjusting for baseline eGFR, only hypertension still showed a significant association with moderate to severe CKD at 24 months after radical nephrectomy (adjusted OR = 6.11, p = 0.009).

Discussion

In the present study, the trend of eGFR levels increased from preoperative to over 2 years after radical nephrectomy, representing that CKD is a chronic condition. Both MetS and non-MetS groups showed recovery of eGFR postoperatively, however MetS patients demonstrated a significantly lower recovery rate. Also, at 24 months after radical nephrectomy, the severity of CKD in patients with MetS was higher than the severity in patients without MetS. Baseline eGFR level, hypertension and diabetes mellitus appear to be risk factors for moderate to severe CKD. Differences in renal pathological features between the two groups, including global sclerosis, tubular atrophy and interstitial fibrosis, which were all more

prevalent in patients with MetS at the time of radical nephrectomy, indicating that MetS may cause more severe kidney injury. Overall, results of the present study confirm that patients with MetS need a longer time for renal function recovery after radical nephrectomy than those without MetS. It is also clear that MetS patients who underwent radical nephrectomy had greater risk of progression of renal insufficiency.

CKD following nephrectomy due to RCC will lead to ESKD or cardiovascular events, which is associated with potential cardiovascular and overall survival, also has a heavy impact on patients' quality of life.[24] Thus, predicting the risk of CKD before surgical management of RCC may be invaluable in helping patients and surgeons to determine the necessity of surgical treatment, and improve both the surgery and follow-up plans to balance the risk of oncological and renal function progression and achieve maximum benefit for the patients. For example, early referral to a nephrologist and initial regular eEGF monitoring and appropriate, timely management is essential.[25] The patient population in the present study had all undergone radical nephrectomy, which is typical for those who have advanced RCC and are more likely to have preoperative CKD, and preservation of renal function is both more necessary and more difficult.[26] The data of patients' baseline characteristics also confirmed these factors.

CKD, regardless of the causes, and RCC share many risk factors, including age, gender, smoking, hypertension and diabetes mellitus, and these are also related to MetS components.[27] In a large cohort study with nearly 1,200, 000 adults with eGFR< 30 ml/min/1.73 m^2 and a two-fold risk of RCC compared to those with 60-89ml/min/1.73 m,[28] CKD itself was reported to be an independent risk factor for RCC. In order to clarify the effects of MetS and simplify the study design, we controlled for age and gender. Also, because associations between the tumor size and surgical approach have been studied as well as the development of CKD after nephrectomy,[26, 28] we also adjusted for these factors in our analysis. However, this strategy limited the generalization of our results and is a limitation of the present study.

MetS is a combination of metabolic disorders. Even the MetS-related abnormalities such as hypertension and diabetes mellitus are shown to increase the risk of CKD after nephrectomy.[27] Therefore, MS may reflect a more comprehensive presentation of individuals with CKD risk than each individual component of MS. When Kriegmair et al.[12] evaluated the impact of MetS and each of the single components of MetS on outcomes of patients with RCC, the results of Kaplan-Meier and log-rank analysis revealed that MetS was significantly associated with a shorter PFS (p=0.018), whereas no significant differences were found in the effects of diabetes mellitus, BMI, hypertension and hypertriglyceridemia on the outcomes. Another study of the outcomes of patients with RCC had controversial results. Diabetes mellitus and hypertriglyceridemia were shown to be associated with worse PFS in RCC patients, [29, 30] but obesity had a positive impact on RCC outcomes.[31] No consensus has yet been reached in previously published studies. The pathogenetic mechanisms of MetS for inducing diseases or influencing disease outcomes, including insulin resistance, inflammation, endothelial dysfunction, oxidative stress, or all of above, may lead to nephron injury and further renal function impairment.[27] Thus, using MetS as a relatively comprehensive marker for CKD risk can probably identify CKD risk before it actually occurs.

In the present study, global sclerosis, tubular atrophy and interstitial fibrosis were seem more frequently in patients with MetS. Histopathological abnormalities identified in the non-neoplastic parenchyma of the kidney are associated with renal function decline after radical nephrectomy.[32] These findings are consistent with the results reported by Alexander et al.[33] In addition, obesity has been shown to induce glomerulosclerosis in an animal model, resulting in ESRD.[34] Interstitial fibrosis and tubular atrophy are both related to hyperlipidemia-induced oxidative stress, the increased reactive oxygen species (ROS), vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β), which together increase the level of matrix synthesis and reduce matrix degradation, resulting in glomerular, tubular and vascular damage.[35, 36]

This study has several limitations, including its retrospective nature, which limits generalizations to other populations and precludes inferences of causation. It also had a small sample size from a single hospital. Further prospective study with a large multicenter cohort study would help to confirm results of the present study.

In conclusion, clinicians treating RCC patients with concomitant MetS should be aware of the possibility of decreasing eGFR and CKD progression more than in RCC patients without MetS after radical nephrectomy, and routine monitoring of renal function should be emphasized in the post-nephrectomy follow-up plan. A large prospective cohort study should be conducted to further support the findings of the present study.

Abbreviations

renal cell carcinoma (RCC)

chronic kidney disease (CKD)

metabolic syndrome (MetS)

Estimated glomerular filtration rate (eGFR)

body mass index (BMI)

end-stage renal disease (ESRD)

progression-free survival (PFS)

Declarations

Ethics approval

The protocol for this study was reviewed and approved by the Institutional Review Board of the 900th Hospital of the Joint Logistics Support Force, PLA. Informed consent of patients was waived because of

the retrospective design of this study in which patients remained anonymous.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YZ: clinical studies、data acquisition、statistical analysis、literature research, manuscript preparation

TKW: clinical studies、data acquisition、statistical analysis、literature research, manuscript preparation

JJX: clinical studies、data acquisition, statistical analysis

LQY: clinical studies、data acquisition, literature research、 statistical analysis

XLG: clinical studies、data acquisition、literature research

WJX: data acquisition, literature research

LPW: guarantor of integrity of the entire study、study concepts、definition of intellectual content ,study design、manuscript editing、manuscript review

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None

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Figures

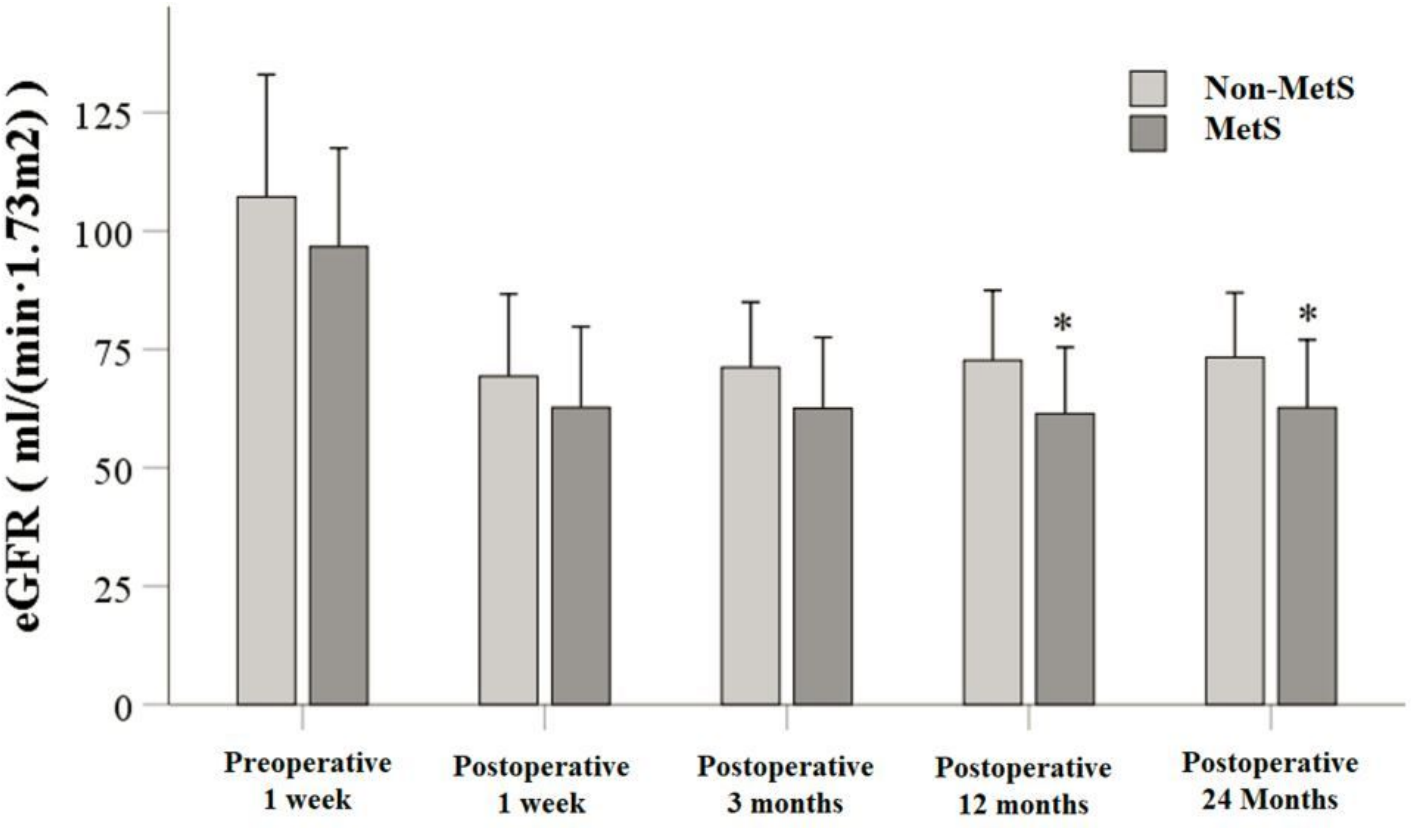

Figure 1

The change trends of perioperative eGFR levels for the patients with MetS and without MetS. *Indicates a statistically significant difference observed in the patients with MetS compared to those without MetS (p=0.003 & 0.004).

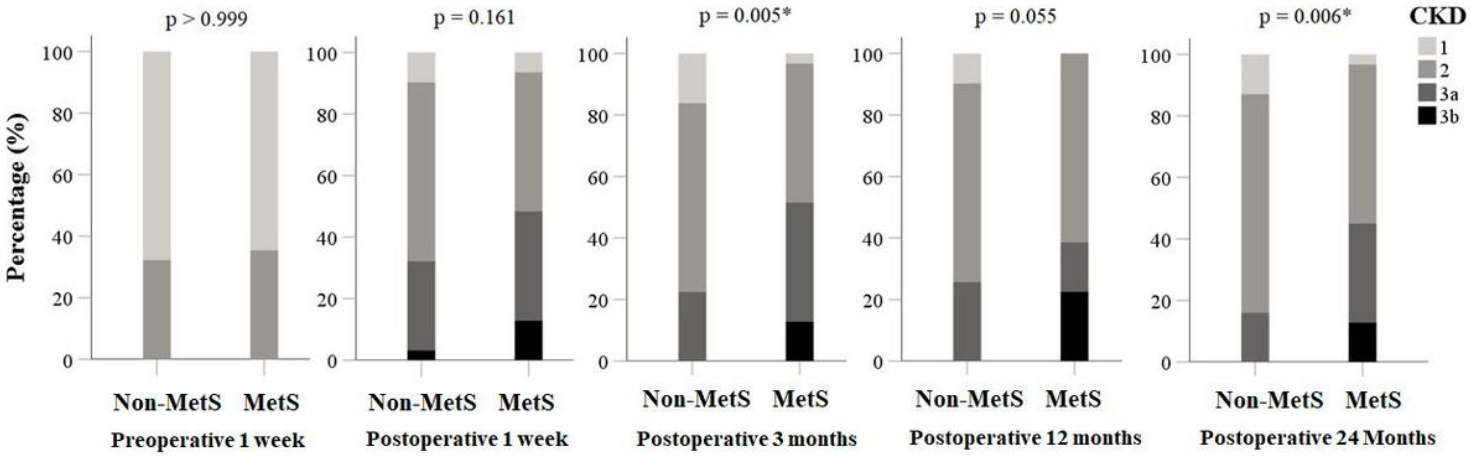

Figure 2

The CKD staging among the two groups from preoperative 1 week to postoperative 2 months. *p <0.05 indicates a significant difference exists between the two groups. (Analyzed with the Mann-Whitney test)