Ph.D. Dissertation of Medicine

Comparative analysis of mortality and progression to end-stage renal disease between surgically induced-chronic kidney disease (CKD) versus medical CKD

– CKD-S versus CKD-M –

수술 후 발생한 만성신부전과 내과적 만성신부전의 사망과 말기신부전 진행에 대한 비교 연구

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Abstract

Purpose: To analyze whether there is a difference in progression to end-stage renal disease (ESRD) and survival rate between surgically-induced chronic kidney disease (CKD-S) and medically-induced chronic kidney disease (CKD-M).

Methods: Two different cohort studies were conducted. The first study was a multicenter hospital-based cohort, and patients who underwent partial or radical nephrectomy for renal cell carcinoma (RCC) without preoperative CKD were included in the CKD-S group. Patients enrolled in the Korean cohort study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD) were included in the CKD-M group. The second study was a population-based cohort study using medical records, and estimated glomerular filtration rates in health checkups were extracted from the Korean National Health Insurance Service database. The primary outcome was progression to ESRD, defined as dialysis or kidney transplantation. The secondary outcome was all-cause mortality.

Results: In the first study, patients with CKD-M were at higher risk of progression to ESRD (hazard ratio [HR]: 9.89, 95% confidence interval [CI]: 4.67–20.92, p<0.001) and overall death (HR: 1.32, 95% CI: 0.79–2.19, p=0.288). In the Kaplan-Meier analysis, the incidence of ESRD was significantly higher in the CKD-M group. In a subgroup analysis of those who were followed up for >5 years after adjusting for age, sex, body mass index, hypertension, and diabetes, the odds ratio of progression to ESRD or a 50% decrease in GFR within 5 years was significantly higher in the CKD-M group. In the second study, in the whole matched cohort without cardiovascular disease (CVD) history, patients with CKD-M were at higher risk of progression to ESRD (HR: 1.895, 95% CI: 1.044–3.442, p=0.0357) and CVD (HR: 1.167, 95% CI: 1.057–1.289, p=0.0023) than those with CKD-S. Patients with CKD-M were at lower risk of overall death; however, this observation was not statistically significant (HR: 0.922, 95% CI: 0.718–1.185, p=0.5268). Among patients with CKD grade ≥3 in the whole cohort, including CVD history, the CKD-M group was at significantly higher risk of progression to ESRD (HR: 2.208, 95% CI: 1.474–3.306, p=0.0001), CVD (HR: 1.318, 95% CI: 1.198–1.451, p<0.0001), and overall mortality (HR: 1.497, 95% CI: 1.208–1.856, p=0.0002).

Conclusion: Patients with CKD-S appear to have a lower risk of developing ESRD than those with CKD-M in this study. Regarding mortality and progression to ESRD, it might not be accurate to conceive CKD-S and CKD-M as being on the same CKD spectrum.

Keyword: Surgical CKD, Medical CKD, ESRD, Survival
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Introduction

The kidneys are paired ovoid, reddish-brown retroperitoneal organs in the posterior part of the abdomen on each side of the vertebral column and lie on the psoas muscles. [1] They are crucial for maintaining homeostasis through physiological fluid volume control, electrolytes and acid-base balance regulation, elimination of waste products and foreign substances, and secretion of hormones. [2] Renal function can be impaired for various reasons, and it is classified as acute kidney injury (AKI) or chronic kidney disease (CKD), depending on the clinical course. AKI means that renal function rapidly decreases in a short time, and this definition also depends on the treatment process for the cause. Renal function may recover from AKI or may progress to chronic kidney disease. [3]

CKD is a renal disease in which structural or functional damage to the kidneys occurring for >3 months due to various mechanisms causes an irreversible decrease in nephrons and a detectable loss of clinical renal function. [4] Glomerular filtration rate (GFR), which measures the total volume of fluid filtered through all functioning nephrons within a specified time frame, is the best indicator known commonly as overall kidney function. [5] Although the classification and definition of CKD have changed over time, the first international guideline, which was demonstrated in the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guideline in 2002 (Table 1) [6], defines CKD as decreased kidney function indicated by a GFR of <60 mL/min/7.3m^2 or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause. The notion of CKD was broadened to include chronic kidney failure by including early renal disease in the conventional definition.

Population aging and the rise in chronic diseases contribute to increased CKD prevalence and mortality. The worldwide prevalence of CKD in adults ranges from 10.8% to 13.1% and has increased by 29.3% since 1990. [7] Approximately 8.7% of males and 8.1% of females had moderate-to-severe renal dysfunction (estimated GFR [eGFR] <60 mL/min/1.73m^2), with a notably high prevalence of 26.5% among those over the age of 70

in 2021. [8] As patients age, those with a history of diabetes mellitus (DM), hypertension (HTN), or obesity are at a higher risk of developing CKD [9]. Approximately 3.2–5.6% of the population had stage III CKD (30–59 mL/min/1.73m^2), which was greater than the prevalence of DM. In addition, patients with CKD have a higher risk of cardiovascular complications and a higher mortality rate than healthy individuals. [10] In a large population-based study, even after adjusting for confounding variables, reduced eGFR was associated with an elevated risk of cardiovascular events and all-cause death. [11] In this study, as the stage of CKD increased, mortality and cardiovascular events increased compared to healthy individuals; patients with CKD stage 4 had a mortality rate of 3.2 times and a cardiovascular disease rate of 2.8 times compared to healthy individuals. Loss of kidney function is a feature of end-stage renal disease (ESRD) corresponding to the 5th stage of irreversible CKD, a state in which eGFR is <15 mL/min or permanent renal replacement therapy (RRT) is necessary. [11] Medically-induced kidney disease progresses to CKD and ESRD, typically accompanied by an annual loss of eGFR of 2–5 mL/min/1.73m^2, depending on the underlying etiology. [12,13] To avoid potentially fatal uremia, patients with ESRD must have lifelong dialysis or RRT, such as kidney transplantation. [14] Consequently, as CKD progresses to ESRD, the financial and medical burden on society grows, as the cost of care for patients with dialysis is more than 10 times greater than that of healthy individuals without renal disease. A huge part of the country's medical costs ranging from 3.2% to 4.1%, is consumed by patients with ESRD. [15] Unfortunately, the number of patients undergoing RRT, such as hemodialysis and kidney transplantation, which are indicators of ESRD prevalence, has steadily increased, and the number of patients undergoing dialysis has more than tripled over the past 10 years and long-term dialysis patients over 5 years account for half of the total. [16-17]

Even when other variables are considered, patients with renal cell carcinoma (RCC) have a disproportionately high chance of developing and worsening CKD following nephrectomy. [18] Clinical research has shown that post-kidney surgery is constant regarding prognosis

and complications in patients with RCC or suspected RCC, although up to 50% of patients have surgically-induced CKD (CKD-S). [19] Contrastingly, abrupt or gradual endogenous renal function impairment is referred to as medically-induced CKD (CKD-M). Notably, not all etiologies of CKD have the same long-term follow-up outcomes when these two groups were compared in previous research. [20,21] In contrast to patients with CKD-M, the prognosis for Korean patients concerning the renal function decline following surgery is still not well established.

Thus, the author investigated the risk of ESRD and mortality between individuals with acquired CKD after partial nephrectomy (PN) or radical nephrectomy (RN) for localized RCC without a history of preoperative CKD and those with CKD without a history of renal surgery.

Subjects and Methods

The author conducted two different cohort studies. The general approach was described first, and each analysis's notable aspects were then described separately.

The primary outcome of the present study was progression to ESRD, defined as receiving maintenance dialysis or kidney transplantation. Concerning dialysis, the cases of AKI that recovered after continuous RRT were excluded; only cases with maintenance hemodialysis or peritoneal dialysis for >3 months were included. The secondary outcome of the present study was all-cause mortality.

The chi-squared test was used for categorical variables. A one-way analysis of variance and a T-test were used for continuous variables. Statistical significance was determined as two-sided $p<0.05$. The Kaplan-Meier curves with log-rank tests were used for survival analysis.

Study#1 – Multicenter hospital–based cohort study

The local Institutional Review Board approved this study. The 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine equation ($GFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female]; Scr is serum creatinine (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 of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1) was used.

Study population and definitions

The surgical group (CKD-S) included patients aged 20–85 years who underwent PN or RN for RCC and were followed up for at least 1 year. Patients with preoperative eGFR <60mL/min/1.73m² or eGFR >60 mL/min/1.73m² but with proteinuria were excluded. Patients treated with systemic therapy for RCC pre- and postoperatively were excluded.

Similarly, patients who underwent surgery for RCC more than once were excluded. Patients on dialysis for ESRD or who had undergone a kidney transplant preoperatively and were diagnosed with Von-Hippel-Lindau syndrome were excluded. Only patients with pathologic stage T1N0M0 were included to minimize the effects of RCC on outcomes, and patients with confirmed cancer-specific mortality were also excluded.

The medical group (CKD-M) included patients enrolled in the Korean cohort study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD) from 2011 to 2015. KNOW-CKD is a prospective cohort of nine nephrology centers in major university hospitals throughout Korea. [22] Patients with CKD of various etiologies were included, among whom pediatric patients with renal disease, renal transplant cohort patients, and participants who discontinued the study due to personal wishes other than death were excluded.

Since most renal function is restored 3 months after renal surgery [23], the postoperative eGFR at 3 months was set as the new baseline GFR for CKD-S. Patients with postoperative eGFR >60mL/min/1.73m² without proteinuria at 3 months were excluded. In the CKD-M group, eGFR at enrollment was set as the baseline GFR.

Patients with baseline CKD grade 5 in both groups were excluded because they were already at the level of clinical ESRD and were highly likely to need RRT even if they had not undergone dialysis or renal transplantation at the time of analysis.

Statistical analysis

The implementation of 1:1 propensity-score matching was performed for age, sex, DM, HTN, body mass index (BMI), and baseline eGFR, and the grade of baseline CKD was matched dichotomously by grouping clinically significant CKD (grade 3 or 4) or not (grade 1 or 2). An absolute standardized mean difference of <0.2 was considered balanced. The Statistical Package for the Social Sciences software (version 25.0; SPSS Inc., Chicago, IL, USA) and R software version 4.2.2 were used for all statistical analyses.

Study#2 – **Population-based cohort study**

This study referenced a previous study [24] and was approved by the local Institutional Review Board. The Modification of Diet in Renal Disease (MDRD) formula (GFR=186 × [serum creatinine (mg/dL)] $^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female)) was used.

Data sources

The Korean National Health Insurance Service (NHIS), which stores almost all medical data, was adopted in this population-based cohort study. This service's data set includes demographics, various health checkup surveys, diagnostic codes, insurance-covered treatments, and prescription records. The National Health Insurance covers more than 50 million, almost all Koreans, and offers comprehensive health coverage due to distinctive national policy, which is uncommon in the rest of the world. [25] This study was approved by the local Institutional Review Board, and informed consent was waived by the committee for anonymized data analysis. All data analysis was only available in the closed data room provided by NHIS, and data was anonymized by the privacy guidelines of the Health Insurance Portability and Accountability Act. Exporting raw data was impossible, and only the analyzed results could be exported

Study population and definitions

Patients who underwent radical or PN for RCC from 2007 to 2009 were included in the surgical group. Patients whose 'rare and incurable disease' registration had not been extended after 5 years from diagnosed RCC were included to lessen the disease's burden. Patients who had a repeated history of nephrectomy or who were treated with systemic therapy for RCC pre- and postoperatively were excluded. The baseline grade of the surgical group was categorized according to the eGFR measurements at the health checkups conducted within 2 years of surgery. The medical group consisted of patients without a history of nephrectomy, and the baseline grade was assigned according to eGFR checked at

the 2009–2010 health checkup. Data were extracted until 2020; all participants had a > 5-year follow-up period.

Statistical analysis

The implementation of 1:5 propensity-score matching was performed for age, sex, DM, HTN, BMI, Charlson comorbidity index, smoking status, alcohol consumption status, and baseline eGFR. The incidence rate was calculated and described per 1000 person-years. Hazard ratios (HRs) were analyzed by multivariate Cox proportional hazard regression. All statistical analyses were performed using SAS Enterprise guide version 7.1 (SAS Institute, Carrie, NC, USA) and R project.

Results

Study#1 – Multicenter cohort study

The total number of patients before matching was 2,676 (CKD-S 952, CKD-M 1,724). After 1:1 propensity score matching, 958 (CKD-S 479, CKD-M 479) patients were analyzed (Figure 1). After matching, there was no significant difference in age, sex, BMI, HTN, DM, baseline eGFR, and baseline CKD grade between the two groups (Table 2). Changes in eGFR in each baseline CKD grade were analyzed through trajectory analysis (Figure 2). The gradual decrease in eGFR was greater in the CKD-M group than in the CKD-S group. In the case of baseline CKD grades 3 and 4, recovery of eGFR was observed in the CKD-S group.

In matched cohort without baseline grade 5, patients with CKD-M were at significantly higher risk of progression to ESRD (HR: 9.89, 95% confidence interval [CI]: 4.67–20.92, $p<0.001$). The CKD-M group was at higher risk of overall death, without significance (HR: 1.32, 95% CI: 0.79–2.19, $p=0.288$) (Table 3). The group of matched patients of baseline CKD grade 3 or 4 showed a similar trend (Table 4).

In the Kaplan-Meier analysis between CKD-S and CKD-M, the incidence of ESRD (Figure 3A) was significantly higher in the CKD-M group. All-cause mortality (Figure 3B) was slightly higher in the CKD-M group without significance.

A subgroup analysis was performed on 727 patients who were followed up for over 5 years. After adjusting for age, sex, BMI, HTN, and DM, the probability of a 50% decrease in eGFR or need for RRT within 5 years was relatively higher in the CKD-M group. (Figure 4)

In the multivariable Cox regression analysis in the CKD-S group, HTN (HR: 3.95, 95% CI: 1.01–15.38, $p=0.048$) and DM (HR: 3.44, 95% CI: 1.09–10.79, $p=0.034$) were significantly associated with ESRD (Figure 5A). Further, DM (HR: 2.00, 95% CI: 1.17–3.40, $p=0.011$) and age over 65 years (HR: 5.55, 95% CI: 3.25–9.45, $p<0.001$) were

significantly associated with overall survival (Figure 5(B)).

Study#2 - Population-based cohort study

This study referenced a previous study. [24]

Before matching, there were 213,097 (CKD-S 1,589 and CKD-M 211,508) patients in the database. (Table 5) A total of 8,698 patients without a history of CVD (CKD-S 1,521, CKD-M 7,177) were assessed after propensity score matching (Table 6). There was no significant distinction between the two groups after matching. In the CKD-S group, statistically, significantly more patients had initial CKD grade 3 or above.

In whole matched cohort without CVD history, patients with CKD-M were at higher risk of progression to ESRD (HR: 1.895, 95% CI: 1.044–3.442, p=0.0357), CVD (HR: 1.167, 95% CI: 1.057–1.289, p=0.0023) than CKD-S. Patients with CKD-M were at lower risk of overall death, but it was not statistically significant (HR: 0.922, 95% CI: 0.718–1.185, p=0.5268) (Table 7).

In the group of patients with CKD grade ≥3 without CVD history, those with CKD-M were at significantly higher risk of progression to ESRD (HR: 2.691, 95% CI: 1.361–5.32, p=0.0044) and CVD (HR: 1.308, 95% CI: 1.135–1.508, p=0.0002). Patients with CKD-M were at higher risk of overall death without statistical significance (HR: 1.278, 95% CI: 0.923–1.769, p=0.1395) (Table 8).

In group of patients with CKD grade ≥3 in whole cohort, including CVD history, patients with CKD-M were at significantly higher risk of progression to ESRD (HR: 2.208, 95% CI: 1.474–3.306, p=0.0001), CVD (HR: 1.318, 95% CI: 1.198–1.451, p<0.0001) and overall mortality (HR: 1.497, 95% CI: 1.208–1.856, p=0.0002) (Table 9).

In the Kaplan-Meier analysis, the incidence of ESRD (Figure 6(a)), CVD (Figure 6b), and all-cause mortality (Figure 6c) were significantly higher in the CKD-M group.

In the hazard ratio smoothing plot for ESRD, the lower the eGFR, the higher the HR revealed in the CKD-M group (Figure 7a), and no graphs were obtained for the CKD-S group. In the case of mortality, the lower eGFR was related to higher HR in CKD-S and CKD-M groups (Figure 7b).

Discussion

This study aimed to compare the progression of CKD-S and CKD-M to ESRD and analyzed them using 'multicenter' and 'population-based' cohort studies. Prior research on CKD-S is very rare, and this is notable as a first attempt in Korea. Thus, HR for ESRD was significantly higher in the CKD-M group in both studies. In the case of mortality, the results derived from the two studies were inconsistent, but the risk seems higher in the CKD-M group. The mortality was not statistically significant in the first study, possibly due to the nature of the control group. It has been reported that Asians have a lower mortality rate for CKD than Westerners [26]. This was similar in the KNOW-CKD cohort [27], which was used as a control group in the first study, and it is estimated that there was an effect due to the present study analyzing only Asians of a single ethnicity. A large-scale study involving various races and ethnicities will likely demonstrate significant survival rate differences.

Regarding mortality and progression to ESRD, it might not be accurate to conceive CKD-S and CKD-M as being on the same CKD spectrum. In particular, HRs for ESRD and mortality in CKD-S were significantly higher in patients with DM. This analysis of two different patient groups was to take advantage of the clear advantages and limitations of the two cohorts; it was determined that combining both analyses could have complementary roles.

The hospital-based multicenter cohort of the present study demonstrated clear advantages. In the case of CKD-S, since the database was extracted from the two largest high-volume centers in Korea for RCC, there were plenty of cases, and the reliability of the data was high because it is well-refined and continuously quality-controlled. In the case of KNOW-CKD, which was used for CKD-M, the reliability of the data was also very high because it is a well-planned prospective cohort study involving nine large centers. Indeed, numerous studies have been conducted in this cohort and are currently in progress. However, this study required long-term follow-up results longer than the 5 years normally performed in

patients with RCC without recurrence postoperatively but had a disadvantage in that it was difficult to follow up if the patient was lost to follow-up for various reasons. Patients could progress to ESRD in the group lost to follow-up without being confirmed unless they were followed up at the same hospital where the surgery was performed. Even if the patient was being followed up at the hospital where the surgery was performed, ESRD might not be detected if there was no medical record for dialysis performed at other hospitals. In the case of KNOW-CKD patients, this problem was less in the surgical group because it was a prospective cohort study based on a 10-year follow-up from the beginning.

Big data research using data from the NHIS can compensate for these shortcomings. The laboratory tests included in the health checkup categories can be used as long as the patient has undergone the checkup, regardless of where the checkup was performed, and since creatinine and GFR are included in the health checkup category. In addition, if a patient has undergone medical treatment supported by the NHIS, all of them are recorded on the computer and can be traced. Thus, patients who underwent nephrectomy for RCC or dialysis/kidney transplant for ESRD could be extracted. Conversely, the author could not assess perioperative or postoperative information in the surgical group, which can affect renal function, such as tumor size, ischemic time, or postoperative complications. Since there was no information on specific renal tumors, stages, or operations, it was impossible to control the data of RCC or the degree of nephrectomy, which was an explicit limitation.

The author tried implementing a recently enabled new research method to compensate for the strengths and weaknesses of the two research methods mentioned above. It combined hospital data with data from the NHIS, which can track dialysis treatment at any other hospital using a fee code while including renal mass and clinical information related to surgery to supplement the limitations that the NHIS could not secure. However, this is a very recently opened analysis method, and data provision is not yet smooth, and the procedure is very complicated, so data construction is still in progress. If the data is obtained in the future, it is expected that the shortcomings of this study can be

supplemented and more comprehensive conclusions can be presented.

There are only a few studies on CKD-S; several studies have shown a different course from CKD-M. Lane et al. compared the effects of CKD-S and CKD-M on annual renal function change and overall survival [19], and the annual eGFR decline was 4.7% for CKD-M and 0.7% for CKD-S. In addition, in patients without CKD preoperatively, CKD-S was not a significant predictor of overall survival, and survival of patients with CKD-S was similar to that of patients without CKD postoperatively (postoperative 5-year non-cancer mortality, no CKD 6%, CKD-S 9%, and CKD-M/S 20%). Bhindi et al. reported patients with ESRD postoperatively. [28] They demonstrated a slightly better 5-year overall survival rate in the surgical group than in the nonsurgical group (22% vs. 17%; $p<0.001$). These results support the European Organization for Research and Treatment of Cancer (EORTC)-30904 randomized trial comparing the survival outcomes of RN and PN. [29] Although renal function was preserved more after PN, there was no significant survival benefit. The fact that CKD-S has a smaller-than-expected effect on long-term renal function and survival outcomes may explain the disparities in survival outcomes reported in several studies, including EORTC-30904. Furthermore, these results supported the theory that functional nephron loss alone does not affect GFR reduction in the same way in all patients and that there are covariates to consider.

Only approximately 10% of the non-cancerous kidney tissue near the RCC had a totally normal pathology. There were also major histological abnormalities, such as glomerular hypertrophy, mesangial proliferation, and widespread glomerulosclerosis in more than 60% of the cases. [30-33] This can testify to the newly identified CKD following nephrectomy. Likewise, individuals with normal preoperative GFR had considerably greater recovery of renal function following surgery and fewer GFR drops than patients with low preoperative GFR or CKD-M [34]. When integrated with the findings of other studies on CKD-S, it demonstrates that CKD-S is different from CKD-M and should be identified as a distinct spectrum.

Concerning CKD-S compared to CKD-M at the same GFR, better renal outcomes implied that prevalent pathologic alterations of CKD, such as interstitial fibrosis, tubular atrophy, and microvascular rarefaction, were milder. Tubular epithelial cells in CKD are further harmed by a hypoxic environment induced by accumulating matrix proteins in the interstitium [35]. Senescent and inflammatory reactions may be triggered by the damaged tubular epithelial cells [34]. A vicious cycle of CKD advancement is caused by inflammatory cells like macrophage activation, which promotes myofibroblast growth and tissue fibrosis [36]. When CKD reaches the point of no return, GFR declines due to these subsequent pathogenic processes occurring in the tissue environment. At a similar overall GFR level, patients with CKD-S should have a greater average single nephron GFR than those with CKD-M due to reduced nephron numbers. Therefore, unlike CKD-S, CKD-M can be in a more advanced stage of the pathologic cascade, let alone have permanent harm from the underlying cause.

In CKD-S, decreased nephron mass results in hyperfiltration in the remaining nephrons [37]. Maladaptive alterations, such as secondary focal segmental glomerulosclerosis, are brought on by hyperfiltration, which harms the glomerular filtration barriers. In treating RCC, vascular endothelial growth factor inhibitors have become a standard. Proteinuria can frequently develop or worsen postoperatively because these substances also cause HTN and proteinuria through glomerular damage [38]. Consequently, despite patients with CKD-S having superior renal survival, monitoring renal function and proteinuria may still be necessary, especially in patients who are obese, are expected to have long-term cancer survival, or are potential vascular endothelial growth factor inhibitor candidates. The author examined renal outcomes only between groups in this study based on changes in GFR. Additional consideration should be given to how CKD-S' severity is determined by the proteinuria levels at baseline and throughout time.

Recently, Xiong et al. [39] reported interesting findings on post-nephrectomy CKD. They compared histological changes in the renal parenchyma far from the tumor in 65

patients who underwent RN for tumor recurrence during follow-up after PN. Patients with HTN, DM, and pre-existing CKD demonstrated increased rates and extent of CKD score increase and were predictors of significant CKD score increase in univariate analysis (odds ratio: 3.53 [1.12–11.1]). From these results, they concluded that the histological changes in renal tissue remaining after PN appeared to be due to pre-existing medical comorbidity rather than 'ischemia,' a factor associated with surgery. This may demonstrate that postoperative renal function decline is more affected by medical diseases such as DM or HTN than surgery. The limitations were that the median interval between PN and RN was only 2.4 years, which seems insufficient, and the number of cases was too small. This result can be the basis for the present study. In the present study, CKD-S and CKD-M had similar eGFR at baseline; however, the degree of decline over time was less in CKD-S. Moreover, HTN and DM were significant factors in CKD-S progression to ESRD. Further long-term, large-scale studies are needed.

In interpreting the present study's results, a few limitations need consideration. First, the present study did not consider specific information about HTN and DM for analysis. It is widely known that HTN and DM are closely related to CKD, which should be considered in CKD research, and more specific results could have been drawn if the disease duration and degree of control were considered beyond the presence or absence of the disease. However, patients in the surgery group completely lacked data because most were for only preoperative evaluation, whether they had a disease or not, and whether they were taking medications. In the case of the NHIS study, a better-designed plan for data extraction is required from the beginning. Second, the method used for eGFR in the second study was the MDRD formula. The MDRD formula is one of the most widely used equations for eGFR from serum creatinine levels. However, it has some limitations compared to other GFR formulas. One limitation of the MDRD formula is that it may underestimate GFR in patients with normal- to near-normal renal function. A study by Coresh et al. [40] found that the MDRD formula underestimated GFR by 29% in participants with GFR >60

mL/min/1.73m^2. Another limitation of the MDRD formula is that it may be inaccurate in certain populations, such as individuals with extremes of age or body weight or those with certain medical conditions. A study by Stevens et al. [41] found that the MDRD formula was less accurate in elderly individuals, particularly those >70 years and individuals with higher BMI. Other GFR formulas, such as the CKD-EPI equation, have been developed to overcome some of these limitations of the MDRD formula. The CKD-EPI equation has been shown to be more accurate than the MDRD formula in certain populations, including elderly individuals and those with higher BMI. However, the author inevitably used MDRD-GFR because obtaining an eGFR formula other than MDRD-GFR was difficult due to the health checkup database format.

Due to these limitations, the present study's findings should be cautiously interpreted. Nevertheless, it is notable that the results demonstrate similar tendencies in analyzing the two patient groups with different strengths and weaknesses. The relevance of the present study is that it can be a reference to demonstrate the findings that can give patients who are worried about long-term renal function decline due to renal surgery more precise information. The scope of future research should be increased to more precisely assess the correlation between RCC and CKD and the long-term consequences of nephrectomy on CKD.

Conclusion

Patients with CKD-S appeared to have a lower risk of progressing to ESRD than those with CKD-M in this study. In the case of mortality, the results of the two studies were inconsistent, but the risk seems lower in the CKD-S group. Regarding mortality and progression to ESRD, it might not be accurate to conceive CKD-S and CKD-M as being on the same CKD spectrum. Since postoperative renal function decline appears to have a different course from CKD-M, clinicians should provide more accurate information to patients about to undergo renal surgery. In particular, in the multivariable analysis of the CKD-S, HRs of ESRD and mortality were significantly higher in patients with DM, so caution should be paid to renal function management after renal surgery.

Figure Legends

Figure 1. Flow chart of patient selection of the first study. The left side demonstrated surgically-induced chronic kidney disease, and the right demonstrated medically-induced chronic kidney disease.

Figure 2. The estimated glomerular filtration rate change in each baseline chronic kidney disease (CKD) grade. (a) Baseline CKD grade 1. (b) Baseline CKD grade 2. (c) Baseline CKD grade 3. (d) Baseline CKD grade 4.

Compared to surgically-induced chronic kidney disease, the estimated glomerular filtration rate of medically-induced chronic kidney disease decreases more over time.

Figure 3. Kaplan-Meier analysis between surgically-induced chronic kidney disease and medically-induced chronic kidney disease. Each figure demonstrates the analysis of (A) ESRD (end-stage renal disease), (B) Survival. The incidence of ESRD was significantly higher in surgically-induced chronic kidney disease.

Figure 4. Probability of a 50% decrease in estimated glomerular filtration or need for renal replacement therapy in 5 years. The figure demonstrates multivariable analysis after adjusting for age, sex, body mass index, hypertension, and diabetes. The probability of a 50% decrease in estimated glomerular filtration or need for renal replacement therapy within 5 years was relatively higher in medically-induced chronic kidney disease.

Figure 5. Forest plots showing hazard ratios obtained by multivariable Cox regression analysis of surgically-induced chronic kidney disease. Hypertension and diabetes had a significant influence on end-stage renal disease. Age over 65 and diabetes had a significant influence on overall survival.

Figure 6. Kaplan-Meier analysis between surgically- and medically-induced chronic kidney disease. Each figure demonstrates the analysis of (a) end-stage renal disease, (b) cardiovascular disease, and (c) all-cause mortality. The incidences were significantly higher in medically-induced chronic kidney disease.

Figure 7. Hazard ratio smoothing plot of (a) end-stage renal disease in medically-induced chronic kidney disease and (b) all-cause mortality. In the hazard ratio smoothing plot for end-stage renal disease, the lower the estimated glomerular filtration rate, the higher the hazard ratio revealed in medically-induced chronic kidney disease. The lower estimated glomerular filtration rate was related to a higher hazard ratio for mortality in surgically- and medically-induced chronic kidney disease.

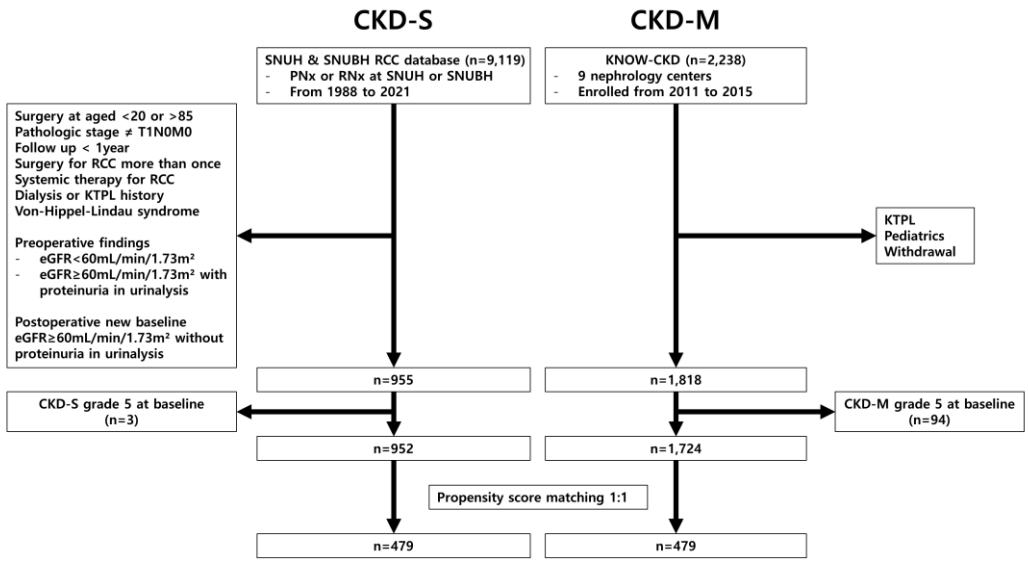


Figure 1. Figure 1. Flow chart of patient selection of the first study. The left side demonstrated surgically-induced chronic kidney disease, and the right demonstrated medically-induced chronic kidney disease.

CKD-S, surgically induced chronic kidney disease; CKD-M, medical chronic kidney disease; RCC, renal cell carcinoma; KTPL, kidney transplantation; eGFR, estimated glomerular filtration rate

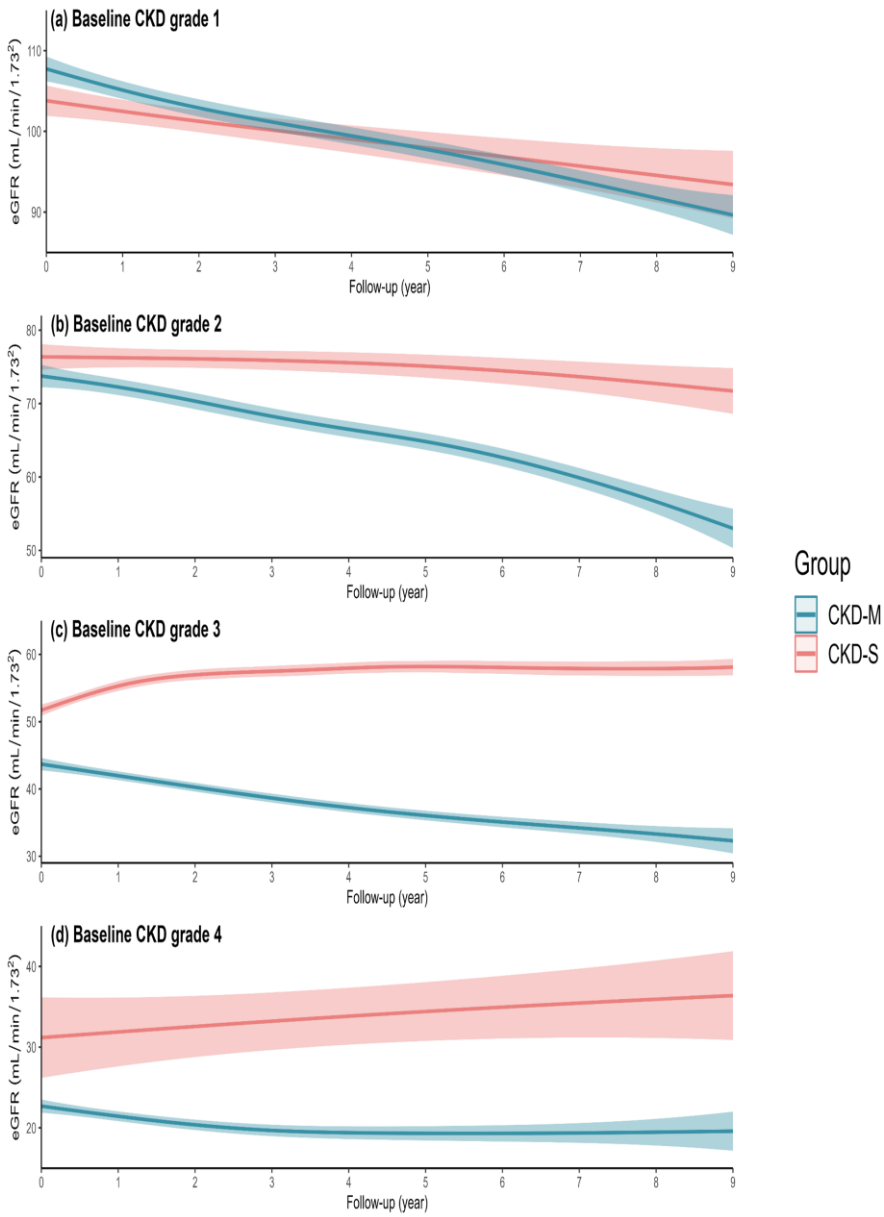


Figure 2. The estimated glomerular filtration rate change in each baseline chronic kidney disease (CKD) grade. (a) Baseline CKD grade 1. (b) Baseline CKD grade 2. (c) Baseline CKD grade 3. (d) Baseline CKD grade 4.

Compared to surgically-induced chronic kidney disease, the estimated glomerular filtration rate of medically-induced chronic kidney disease decreases more over time.

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease

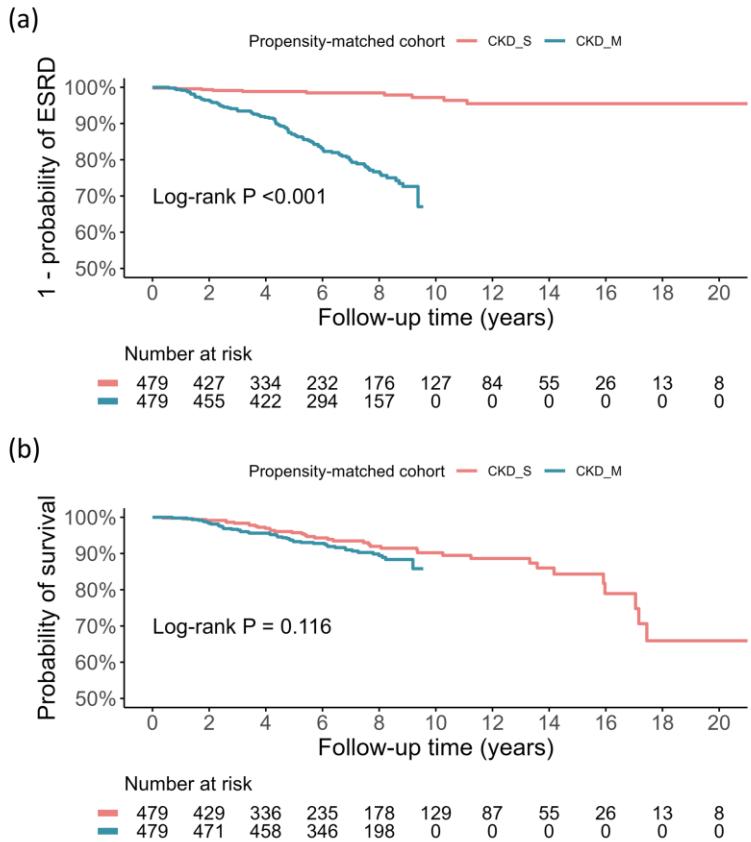


Figure 3. Kaplan-Meier analysis between surgically-induced chronic kidney disease and medically-induced chronic kidney disease. Each figure demonstrates the analysis of (a) ESRD (end-stage renal disease), (b) Survival. The incidence of ESRD was significantly higher in surgically-induced chronic kidney disease.

CKD-S, surgically induced chronic kidney disease; CKD-M, medical chronic kidney disease; ESRD, end stage renal disease

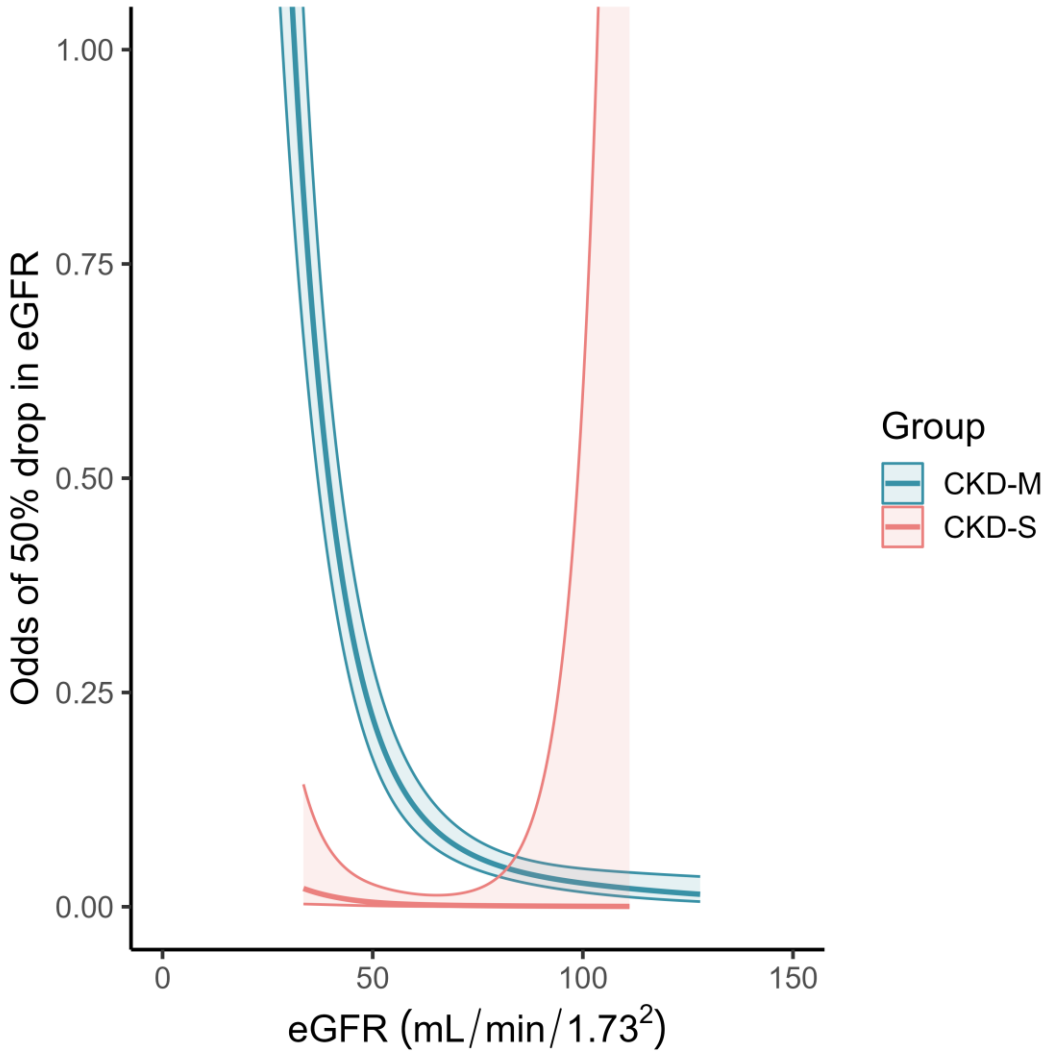
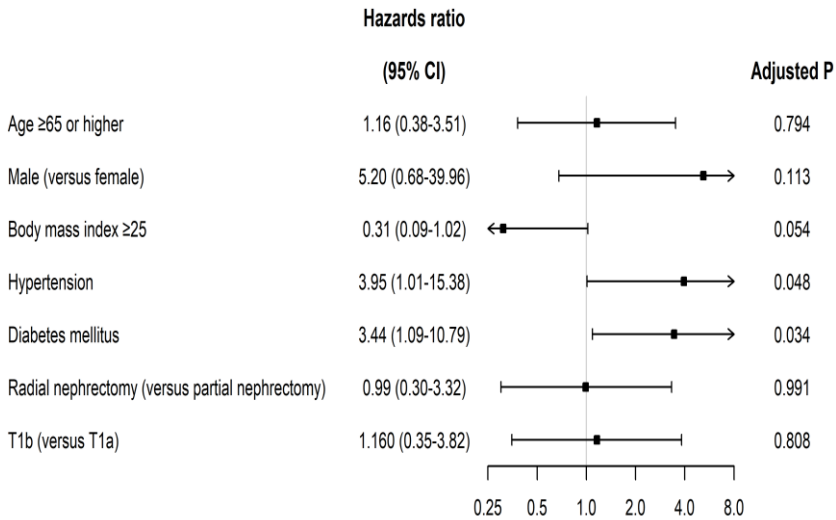


Figure 4. Probability of a 50% decrease in estimated glomerular filtration or need for renal replacement therapy in 5 years. The figure demonstrates multivariable analysis after adjusting for age, sex, body mass index, hypertension, and diabetes. The probability of a 50% decrease in estimated glomerular filtration or need for renal replacement therapy within 5 years was relatively higher in medically-induced chronic kidney disease.

CKD-S, surgically induced chronic kidney disease; CKD-M, medical chronic kidney disease; eGFR, estimated glomerular filtration rate

(a)



(b)

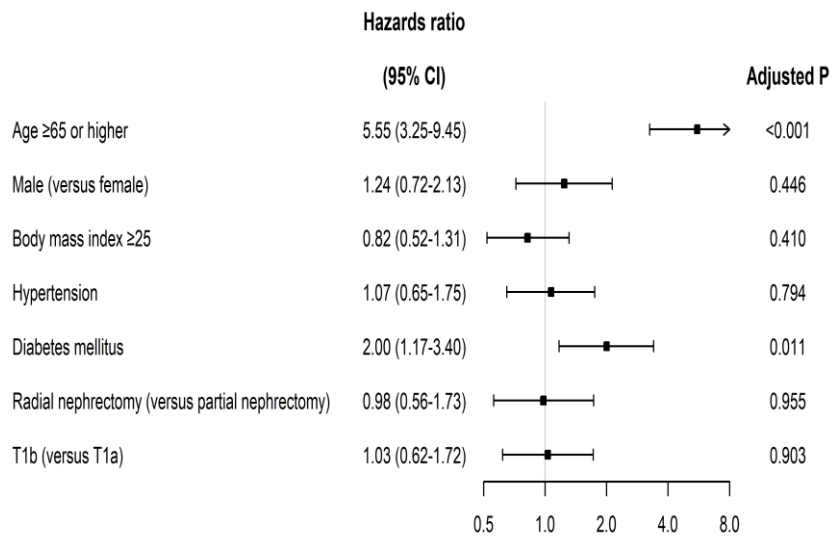


Figure 5. Forest plots showing hazard ratios obtained by multivariable Cox regression analysis of surgically-induced chronic kidney disease. Hypertension and diabetes had a significant influence on end-stage renal disease. Age over 65 and diabetes had a significant influence on overall survival.

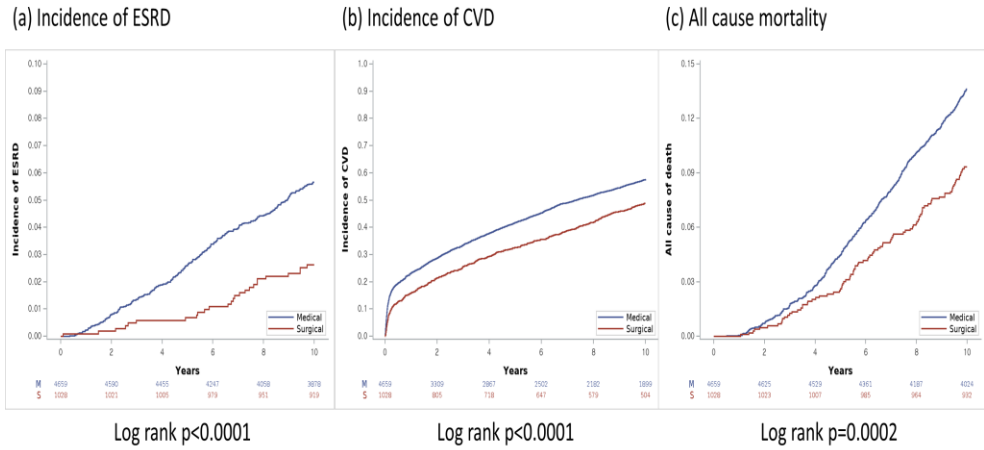


Figure 6. Kaplan-Meier analysis between surgically- and medically-induced chronic kidney disease. Each figure demonstrates the analysis of (a) end-stage renal disease, (b) cardiovascular disease, and (c) all-cause mortality. The incidences were significantly higher in medically-induced chronic kidney disease.

CKD-S, surgically induced chronic kidney disease; CKD-M, medical chronic kidney disease; ESRD, end stage renal disease; CVD, cardiovascular disease

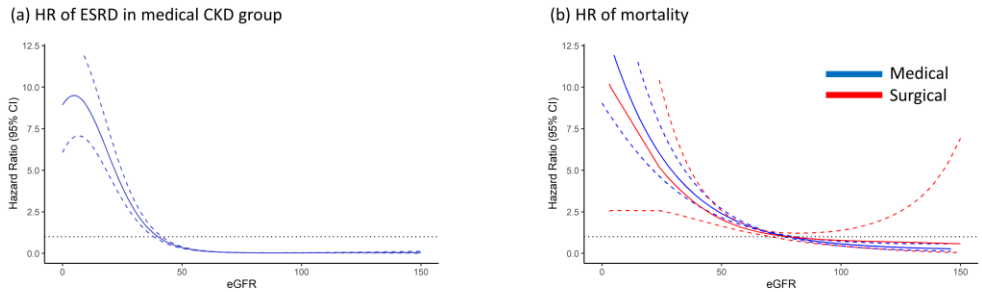


Figure 7. Hazard ratio smoothing plot of (a) end-stage renal disease in medically-induced chronic kidney disease and (b) all-cause mortality. In the hazard ratio smoothing plot for end-stage renal disease, the lower the estimated glomerular filtration rate, the higher the hazard ratio revealed in medically-induced chronic kidney disease. The lower estimated glomerular filtration rate was related to a higher hazard ratio for mortality in surgically- and medically-induced chronic kidney disease.

CKD-M, medical chronic kidney disease; ESRD, end stage renal disease; HR, hazard ratio

Table Legends

Table 1. Stages of chronic kidney disease by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guideline

Table 2. Baseline characteristics after 1:1 propensity score matching

Table 3. Outcomes in the matched cohort, whole baseline chronic kidney disease grade

Table 4. Outcomes in the matched cohort, baseline chronic kidney disease grade ≥3

Table 5. Baseline characteristics before propensity score matching

Table 6. Baseline characteristics after 1:5 propensity score matching

Table 7. Outcomes in the matched cohort without cardiovascular disease history

Table 8. Outcomes in the group of patients with baseline chronic kidney disease grade ≥3 in the matched cohort without cardiovascular disease history

Table 9. Outcomes in the group of patients with baseline chronic kidney disease grade ≥3 in the whole cohort, including a cardiovascular disease history

Table 1. Stages of chronic kidney disease by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guideline

Stages	GFR (mL/min/1.73m^2)	Description
1	≥90	Kidney damage with normal or ↑GFR
2	60-89	Kidney damage with mild ↓GFR
3	30-59	Moderate ↓GFR
4	15-29	Severe ↓GFR
5	<15 (or dialysis)	Kidney failure

GFR, glomerular filtration rate

Table 2. Baseline characteristics after 1:1 propensity score matching

Variables	Surgical (n=479)	Medical (n=479)	p	SMD
Age, median (IQR)	61 (51.2-68)	61 (49-68)	0.168	0.159
Follow-up years, median (IQR)	5.8 (3.2-10.3)	7.2 (5.9-8.7)	0.004	0.049
Male, n (%)	336 (70.1%)	327 (68.3%)	0.529	0.041
DM, n (%)	124 (25.9%)	137 (28.6%)	0.345	0.061
HTN, n (%)	399 (83.3%)	404 (84.3%)	0.661	0.028
BMI (kg/m^2), median (IQR)	25 (23.1-27.6)	24.9 (22.6-27.7)	0.321	0.052
Baseline eGFR, median (IQR)	55.2 (48.5-70.1)	51.7 (38-83.8)	0.002	0.019
CKD grade ≥ 3, n (%)	328 (68.5%)	309 (64.5%)	0.193	0.084
CKD grade, n (%)				
stage1	52 (10.9%)	107 (22.3%)		
stage2	99 (20.7%)	63 (13.2%)		
stage3a	248 (51.8%)	134 (28%)		
stage3b	72 (15%)	109 (22.8%)		
stage4	8 (1.7%)	66 (13.8%)		

Values are presented as mean ± standard deviation or number (%).

DM, diabetes mellitus; HTN, hypertension; CCI, Charlson comorbidity index; BMI, body mass index; CKD, Chronic kidney disease; SD, standard deviation; SMD, standardized mean difference

Table 3. Outcomes in the matched cohort, whole baseline chronic kidney disease grade

Subjects	n	Events	IR (1,000 person-years)	HR	95% CI		p-value
ESRD							
Surgical	479	10	2.906 (1.394-5.345)	ref			
Medical	479	100	32.146 (26.155-39.098)	9.89	4.67	20.92	<0.001
Overall death							
Surgical	479	38	10.945 (7.745-15.023)	ref			
Medical	479	47	13.878 (10.197-18.455)	1.32	0.79	2.19	0.288

***Adjusted for baseline chronic kidney disease grade**

PSM, propensity score matching; ESRD, end stage renal disease; IR, incidence rate; HR, hazard ratio; CI, confidence interval

Table 4. Outcomes in the matched cohort, baseline chronic kidney disease grade ≥ 3

Subjects	n	Events	IR (1,000 person-years)	HR	95% CI		p-value
ESRD							
Surgical	284	9	3.790 (1.733-7.195)	ref			
Medical	284	64	34.820 (26.815-44.464)	10.53	4.67	23.72	<0.001
Overall death							
Surgical	284	32	13.330 (9.118-18.818)	ref			
Medical	284	24	12.009 (7.694-17.868)	1.11	0.61	2.03	0.726

***Adjusted for baseline chronic kidney disease grade**

PSM, propensity score matching; ESRD, end stage renal disease; IR, incidence rate; HR, hazard ratio; CI, confidence interval

Table 5. Baseline characteristics before propensity score matching

Variables	Surgical (n=1,589)	Medical (n=211,508)	p
Age (yr, mean ± SD)	52.69±11.90	53.51±11.48	0.006
Male, n (%)	981(61.74)	120358(56.90)	0.0001
DM, n (%)	452(28.45)	43494(20.56)	<.0001
HTN, n (%)	636(40.03)	62156(29.39)	<.0001
CCI (mean ± SD)	3.94±1.92	1.83±1.69	<.0001
CCI Group			<.0001
≤1	116(7.30)	106705(50.45)	
2	240(15.10)	44535(21.06)	
≥3	1233(77.60)	60268(28.49)	
Smoking ever, n (%)	672(42.29)	83363(39.41)	0.0194
Alcohol ever, n (%)	526(33.10)	98211(46.43)	<.0001
baseline eGFR (mean ± SD)	66.25±41.02	77.54±17.10	<.0001
BMI (kg/m^2) (mean ± SD)	24.32±3.09	23.66±2.55	<.0001
CKD grade			<.0001
stage1	142(8.94)	36995(17.49)	
stage2	734(46.19)	150378(71.10)	
stage3a	572(36)	22124(10.46)	
stage3b	120(7.55)	1718(0.81)	
stage4	5(0.31)	164(0.08)	
stage5	16(1.01)	129(0.06)	

Values are presented as mean±standard deviation or number (%).

DM, diabetes mellitus; HTN, hypertension; CCI, Charlson comorbidity index; CKD, Chronic kidney disease; NA, not applicable

Table 6. Baseline characteristics after 1:5 propensity score matching

Variables	Surgical (n=1,521)	Medical (n=7,177)	p	SMD
Age (yr, mean ± SD)	53.11±11.83	52.92±11.29	0.574	0.02
Male, n (%)	918(60.36)	4321(60.21)	0.914	0.00
DM, n (%)	435(28.60)	1925(26.82)	0.157	-0.04
HTN, n (%)	608(39.97)	2805(39.08)	0.518	-0.02
CCI (mean ± SD)	3.90±1.91	3.80±2.19	0.083	0.05
CCI Group				
≤1	116(7.63)	688(9.59)		
2	239(15.71)	1082(15.08)		
≥3	1166(76.66)	5407(75.34)		
Smoking ever, n (%)	626(41.16)	2901(40.42)	0.595	-0.01
Alcohol ever, n (%)	509(33.46)	2454(34.19)	0.587	0.02
baseline eGFR (mean ± SD)	67.30±41.39	68.00±17.76	0.522	-0.02
BMI (kg/m^2) (mean ± SD)	24.26±3.05	24.22±2.77	0.689	0.01
CKD grade				
stage1	142(9.34)	400(5.57)		
stage2	725(47.67)	4791(66.75)		
stage3a	540(35.5)	1621(22.59)		
stage3b	108(7.1)	265(3.69)		
stage4	3(0.2)	58(0.81)		
stage5	3(0.2)	42(0.59)		

Values are presented as mean±standard deviation or number (%).

DM, diabetes mellitus; HTN, hypertension; CCI, Charlson comorbidity index; BMI, body mass index; CKD, Chronic kidney disease; SD, standard deviation; SMD, standardized mean difference

Table 7. Outcomes in the matched cohort without cardiovascular disease history

Subjects	n	Events	IR (1,000 person-years)	HR	95% CI		p-value
ESRD							
Surgical	1521	12	0.81	ref			
Medical	7177	107	1.53	1.895	1.044	3.442	0.0357
CVD							
Surgical	1521	461	36.32	ref			
Medical	7177	2471	42.33	1.167	1.057	1.289	0.0023
Overall death							
Surgical	1521	75	5.03	ref			
Medical	7177	327	4.64	0.922	0.718	1.185	0.5268

ESRD, end stage renal disease; CVD, cardiovascular disease; IR, incidence rate; HR, hazard ratio; PSM, propensity score matching; CI, confidence interval

Table 8. Outcomes in the group of patients with baseline chronic kidney disease grade ≥ 3 in the matched cohort without cardiovascular disease history

Subjects	n	Events	IR (1,000 person-years)	HR	95% CI		p-value
ESRD							
Surgical	646	9	1.43	ref			
Medical	2778	102	3.84	2.691	1.361	5.32	0.0044
CVD							
Surgical	646	225	43.66	ref			
Medical	2778	1201	56.98	1.308	1.135	1.508	0.0002
Overall death							
Surgical	646	43	6.83	ref			
Medical	2778	234	8.70	1.278	0.923	1.769	0.1395

ESRD, end stage renal disease; CVD, cardiovascular disease; IR, incidence rate; HR, hazard ratio; PSM, propensity score matching; CI, confidence interval

Table 9. Outcomes in the group of patients with baseline chronic kidney disease grade ≥ 3 in the whole cohort, including a cardiovascular disease history

Subjects	n	Events	IR (1,000 person-years)	HR	95% CI		p-value
ESRD							
Surgical	1028	26	2.64	ref			
Medical	4659	251	5.80	2.208	1.474	3.306	0.0001
CVD							
Surgical	1028	496	71.55	ref			
Medical	4659	2662	96.77	1.318	1.198	1.451	<.0001
Overall death							
Surgical	1028	96	9.67	ref			
Medical	4659	635	14.39	1.497	1.208	1.856	0.0002

ESRD, end stage renal disease; CVD, cardiovascular disease; IR, incidence rate; HR, hazard ratio; PSM, propensity score matching; CI, confidence interval

Bibliography

1. Wein AJ, Kolon TF, Partin AW, Dmochowski RR, Kavoussi LR, Peters CA. Campbell-walsh-wein urology. Twelfth edition review. ed. Philadelphia: Elsevier, Inc.; 2020.

2. Wallace MA. Anatomy and physiology of the kidney. AORN J. 1998;68(5):800, 3-16, 19-20; quiz 21-4.

3. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet. 2012;380(9843):756-66.

4. Kim NH. Current Clinical Practice: Treatment of chronic kidney disease. The Korean Journal of Medicine. 2006;70, 5

5. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA. 2015;313(8):837-46.

6. National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1-266.

7. Collaboration GBDCKD. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709-33.

8. Korea National Health and Nutrition Examination Survey. 2021 National health statistics. Available from: https://kosis.kr [accessed on April 13, 2023].

9. Park JI, Baek H, Jung HH. Prevalence of Chronic Kidney Disease in Korea: the Korean National Health and Nutritional Examination Survey 2011-2013. J Korean Med Sci. 2016;31(6):915-23.

10. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889):339-52.

11. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med.

2004;351(13):1296-305.

12. Levey AS, Coresh J. Chronic kidney disease. Lancet. 2012;379(9811):165-80.

13. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med. 1994;330(13):877-84.

14. Evans M, Bain SC, Hogan S, Bilous RW, Collaborative Study Group p. Irbesartan delays progression of nephropathy as measured by estimated glomerular filtration rate: post hoc analysis of the Irbesartan Diabetic Nephropathy Trial. Nephrol Dial Transplant. 2012;27(6):2255-63.

15. Cha J. The Impact of Physical, Psychological, Social Factors on Illness Burden of Long-term Hemodialysis Patients in South Korea. Journal of Health Informatics and Statistics. 2018 Aug 31;43(3):159–66.

16. Yang CW. Current status and future in patients with end stage renal disease in Korea. Journal of the Korean Medical Association. 2013;56(7):560.

17. The Korean Society of Nephrology. Current renal replacement therapy in Korea. Current status of Korean renal replacement therapy in 2022. Available from: https://m.ksn.or.kr/bbs/index.php?code=report [accessed on March 10, 2023].

18. Choi SK, Song C. Risk of chronic kidney disease after nephrectomy for renal cell carcinoma. Korean J Urol. 2014;55(10):636-42.

19. Lane BR, Campbell SC, Demirjian S, Fergany AF. Surgically induced chronic kidney disease may be associated with a lower risk of progression and mortality than medical chronic kidney disease. J Urol. 2013;189(5):1649-55.

20. Lane BR, Demirjian S, Derweesh IH, Takagi T, Zhang Z, Velet L, et al. Survival and Functional Stability in Chronic Kidney Disease Due to Surgical Removal of Nephrons: Importance of the New Baseline Glomerular Filtration Rate. Eur Urol. 2015;68(6):996-1003.

21. Demirjian S, Lane BR, Derweesh IH, Takagi T, Fergany A, Campbell SC. Chronic kidney disease due to surgical removal of nephrons: relative rates of progression and survival. J Urol. 2014;192(4):1057-62.

22. Oh KH, Park SK, Park HC, Chin HJ, Chae DW, Choi KH, et al. KNOW-CKD (KoreaN cohort study for Outcome in patients With Chronic Kidney Disease): design and methods. BMC Nephrol. 2014;15:80.

23. Kawase K, Enomoto T, Kawase M, Takai M, Kato D, Fujimoto S, et al. The Impact of Postoperative Renal Function Recovery after Laparoscopic and Robot-Assisted Partial Nephrectomy in Patients with Renal Cell Carcinoma. Medicina (Kaunas). 2022;58(4).

24. Jung G, Park S, Kim H, Lee J, Jeong CW. Comparative analysis of mortality and progression to end-stage renal disease between surgically induced and medical chronic kidney disease: A study using the National Health Insurance customized database. Investig Clin Urol. 2023;64(4):338-45.

25. Ahn EK. A brief introduction to research based on real-world evidence: Considering the Korean National Health Insurance Service database. Integr Med Res. 2022;11(2):100797.

26. Jolly SE, Burrows NR, Chen SC, Li S, Jurkovitz CT, Norris KC, et al. Racial and ethnic differences in mortality among individuals with chronic kidney disease: results from the Kidney Early Evaluation Program (KEEP). Clin J Am Soc Nephrol. 2011;6(8):1858-65.

27. Ryu H, Kim J, Kang E, Hong Y, Chae DW, Choi KH, et al. Incidence of cardiovascular events and mortality in Korean patients with chronic kidney disease. Sci Rep. 2021;11(1):1131.

28. Bhindi B, Asante D, Branda ME, Hickson LJ, Mason RJ, Jeffery MM, et al. Survival outcomes for patients with surgically induced end-stage renal disease. Can Urol Assoc J. 2020;14(3):E65-E73.

29. Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal

cell carcinoma. Eur Urol. 2011;59(4):543-52.

30. Bijol V, Mendez GP, Hurwitz S, Rennke HG, Nose V. Evaluation of the nonneoplastic pathology in tumor nephrectomy specimens: predicting the risk of progressive renal failure. Am J Surg Pathol. 2006;30(5):575-84.

31. Henriksen KJ, Meehan SM, Chang A. Non-neoplastic renal diseases are often unrecognized in adult tumor nephrectomy specimens: a review of 246 cases. Am J Surg Pathol. 2007;31(11):1703-8. 32. Salvatore SP, Cha EK, Rosoff JS, Seshan SV. Nonneoplastic renal cortical scarring at tumor nephrectomy predicts decline in kidney function. Arch Pathol Lab Med. 2013;137(4):531-40.

33. Garcia-Roig M, Gorin MA, Parra-Herran C, Garcia-Buitrago M, Kava BR, Jorda M, et al. Pathologic evaluation of non-neoplastic renal parenchyma in partial nephrectomy specimens. World J Urol. 2013;31(4):835-9.

34. Takagi T, Kondo T, Iizuka J, Omae K, Kobayashi H, Hashimoto Y, et al. Better recovery of kidney function in patients with de novo chronic kidney disease after partial nephrectomy compared with those with pre-existing chronic kidney disease. Int J Urol. 2014;21(6):613-6.

35. Humphreys BD. Mechanisms of Renal Fibrosis. Annu Rev Physiol. 2018;80:309-26.

36. Wang X, Chen J, Xu J, Xie J, Harris DCH, Zheng G. The Role of Macrophages in Kidney Fibrosis. Front Physiol. 2021;12:705838.

37. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nat Rev Nephrol. 2012;8(5):293-300.

38. Izzedine H, Massard C, Spano JP, Goldwasser F, Khayat D, Soria JC. VEGF signalling inhibition-induced proteinuria: Mechanisms, significance and management. Eur J Cancer. 2010;46(2):439-48.

39. Xiong L, Nguyen JK, Peng Y, Zhou Z, Ning K, Jia N, et al. What Happens to the Preserved Renal Parenchyma After Clamped Partial Nephrectomy? Eur Urol. 2022;81(5):492-500.

40. Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. Am J Kidney Dis. 2002;39(5):920-9.

41. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. N Engl J Med. 2006;354(23):2473-83.

초 록

서론: 만성신장병이 수술로 유발된 경우(CKD-S)와 내과적으로 유발된 경우(CKD-M), 말기신부전으로의 진행과 생존률의 차이가 있는지 두 가지 방법의 연구를 통해 비교 분석하고자 하였다.

방법: 두 가지 다른 코호트 연구를 수행하였다. 첫 번째 연구는 다기관연구였으며, 수술군(CKD-S)은 서울대병원 및 분당서울대병원에서 신장암으로 부분 또는 근치적 신절제술을 시행 받았다. 수술 전 신기능 저하가 없었으나 수술 후 3개월째 검사에서 신기능저하가 확인된 환자를 대상으로 하였다. 내과군(CKD-M)은 만성신장병 국내다기관 코호트(KNOW-CKD)에 등록된 환자였다. 두 번째 연구는 국민건강보험공단의 데이터베이스를 이용한 인구기반 코호트 연구였으며, 건강검진에서 측정된 사구체여과율을 이용했다. 두 연구에서 공통적으로 일차평가변수는 말기신부전으로의 진행이었으며 이는 투석 또는 신장이식을 수행한 환자로 정의되었다. 투석과 관련하여 지속적인 신대체요법 후 회복된 급성신손상은 제외하였으며, 간헐적 혈액투석 또는 복막투석만 확인하였다. 이차평가변수는 모든 원인으로 인한 사망이었다.

결과: 첫 번째 연구에서 수술군은 내과군에 비해 말기신부전으로의 진행 위험도가 통계적으로 유의하게 낮았으며 (HR 9.89, 95% CI 4.67-20.92, p<0.001), 사망의 위험도는 수술군에서 낮았지만 통계적으로 유의하지 않았다 (HR 1.32, 95% CI 0.79-2.19, p=0.288). 두 번째 연구에서 심혈관계 과거력이 없는 환자만을 대상으로 분석하였을 때 수술군은 내과군에 비해 말기신부전으로의 진행 (HR 1.895, 95% CI 1.044-3.442, p=0.0357), 심혈관계질환 발생의 위험도 (HR 1.167, 95% CI 1.057-1.289, p=0.0023)가 유의하게 낮았으며, 사망의 위험도는 낮았지만 통계적으로 유의하지 않았다 (HR 0.922, 95% CI 0.718-1.185, p=0.5268). 심혈관계 과거력과 상관없이 만성신장병 3등급 이상인 환자를 대상으로 하였을 때에는 수술군에서 말기신부전으로의 진행 (HR 2.208, 95% CI 1.474-3.306, p=0.0001), 심혈관계질환 발생 (HR 1.318, 95% CI 1.198-1.451, p<0.0001) 및 사망의 위험도 (HR 1.497, 95% CI 1.208-1.856, p=0.0002)가 모두 유의하게 낮았다.

결론: 수술군은 내과군보다 만성신장병으로 진행할 위험도가 두 연구 모두에서 유의하게 낮았다. 또한 수술군은 내과군보다 사망 위험도가 두 연구의 결과를 종합하였을 때 낮은 경향을 보였다. 만성신장병이 수술로 인해 생긴 경우와 내과적으로 생긴 경우는 서로 동일하지 않은 질환 스펙트럼에 있는 것으로 보인다. 특히 당뇨가 있는 환자는 수술 후 신기능 저하가 발생하면 만성신부전 및 사망의 위험도가 유의하게 높으므로 신기능 관리에 각별한 주의가 요구된다.

주요어: 외과적만성신장병, 내과적만성신장병, 말기신부전, 생존률
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