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ORIGINAL ARTICLE

Outcomes of endoscopic submucosal dissection for gastric epithelial neoplasm in chronic kidney disease patients: propensity score-matched case–control analysis

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Abstract

Background Little is known about the outcomes of gastric endoscopic submucosal dissection (ESD) in patients with chronic kidney disease (CKD). We compared the efficacy and safety of ESD between CKD and non-CKD patients.

Methods From January 2005 to December 2014, 102 CKD patients underwent ESD for gastric neoplasms at a tertiary medical institution were reviewed retrospectively. A propensity score-matched control group (102 patients) was selected from non-CKD patients to compare clinical outcomes between CKD and non-CKD patients.

Results En bloc resection (96.1%) and curative resection (88.2%) rates in the CKD group did not significantly differ from those in the non-CKD group. Median procedure times (25.0 vs. 21.5 min, $p=0.734$) and perforation risk ($p=0.480$) were similar between groups. The CKD group showed a tendency towards more bleeding events ($p=0.052$) and had a significantly longer hospital stay ($p=0.001$). In a subgroup analysis, stage 3 CKD patients exhibited a bleeding risk comparable to that exhibited by non-CKD patients (HR 1.35; 95% CI 0.36–5.06; $p=0.654$), whereas stage 4 (HR 5.79; 95% CI 1.52–22.0; $p=0.010$) and stage 5 (HR 4.80; 95% CI 1.58–14.6; $p=0.006$) patients showed higher bleeding risks than non-CKD patients. In a multivariate analysis, stage 4/5 CKD was a significant predictor for bleeding risk (HR 4.99; 95% CI 1.32–18.8; $p=0.018$).

Conclusions ESD for gastric epithelial neoplasms can be performed in stage 3 CKD patients with comparable efficacy and safety to that performed in non-CKD patients. Stage 4 and 5 CKD patients should be closely monitored for bleeding events after ESD.

Keywords Gastric neoplasms · Endoscopic submucosal dissection · Chronic kidney diseases

Introduction

Although the death rate due to gastric cancer has decreased in Korea over the past decade, it remains a major concern and was ranked as the 3rd leading cause of cancer death in 2014 [1]. As gastrectomy operations have a perioperative mortality rate as high as 1–3% [2, 3], endoscopic treatment is the preferred option for properly selected patients who are not considered to be at risk of lymph node metastasis.

Endoscopic submucosal dissection (ESD) has many advantages over conventional endoscopic mucosal resection (EMR), including higher en bloc resection and complete resection rates [4]. However, there is concern over adverse events, with ESD being shown to have a 7% bleeding and 5% perforation risk in a previous meta-analysis [5]. These concerns are especially true for patients with chronic kidney disease (CKD), who have a tendency towards bleeding and higher cardiovascular comorbidities, and it is crucial to determine whether ESD can be safely performed without high adverse event rates in this patient group. Although several reports suggest that CKD patients on hemodialysis are an independent risk factor for post-ESD bleeding compared with CKD patients without dialysis [6, 7], to our knowledge,

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there have been no reports directly comparing the outcomes of ESD in CKD patients with those in non-CKD patients.

Therefore, in the present study, we retrospectively compared the clinical outcomes of ESD for gastric neoplasms between CKD and non-CKD patients.

Materials and methods

Study subjects

A total of 23,364 patients were diagnosed with chronic kidney disease according to the ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10rd Revision) diagnosis code at Asan Medical Center (Seoul, Korea) between January 2005 and December 2014. Of these, 212 patients (0.91%) underwent endoscopic treatment for gastric neoplasms. Patients were excluded if they met any of the following criteria: an estimated glomerular filtration rate (eGFR) $\geq$ 60 ml/min/1.73 m^2 at the point of the ESD procedure ($n=54$); underwent EMR ($n=39$); underwent kidney transplantation ($n=12$); a pathological examination showed only gastritis ($n=4$), and underwent ESD for a subepithelial tumor ($n=1$). After excluding those patients meeting the above criteria, 102 patients were enrolled as the case group, and their clinical data were retrospectively collected. To compare the therapeutic efficacy and safety of ESD, 102 propensity score-matched non-CKD patients were designated as the control group (Fig. 1). This study was carried out with approval from the institutional review board of Asan Medical Center.

Follow-up schedule

Complete blood cell counts and chest radiographs were taken the day after the ESD procedure. A second-look endoscopy was performed on the second day after the procedure, to evaluate post-procedural ulcers. Oral feeding was started if there was no evidence of bleeding or perforation. An intravenous proton pump inhibitor was administered from the morning of the day of the procedure to the end of the none-per-oral period, followed by oral proton pump inhibitor therapy for 4–8 weeks. Endoscopy follow-up was performed at 3, 6, and 12 months after ESD. Abdominal computed tomography (CT) scans were performed every 6 months for the first year, and annually thereafter, to detect extragastric recurrence in the adenocarcinoma patients.

Definition

CKD was defined as decreased eGFR less than 60 ml/min/1.73 m^2 for 3 or more months before the ESD procedure, with the stage of CKD being determined according to the K/DOQI CKD classification [8], in which the stage of CKD is categorized into the following ranges: stage 3 with an eGFR of 30–59 ml/min/1.73 m^2, stage 4 with 15–29 ml/min/1.73 m^2, and stage 5 with $<$ 15 ml/min/1.73 m^2. The eGFR was estimated using the Modification of Diet in Renal Disease (MDRD) study equation [9].

Macroscopic types were classified according to the Japanese classification of gastric carcinoma: type I (protruded), type IIa (superficial elevated), type IIb (flat), type

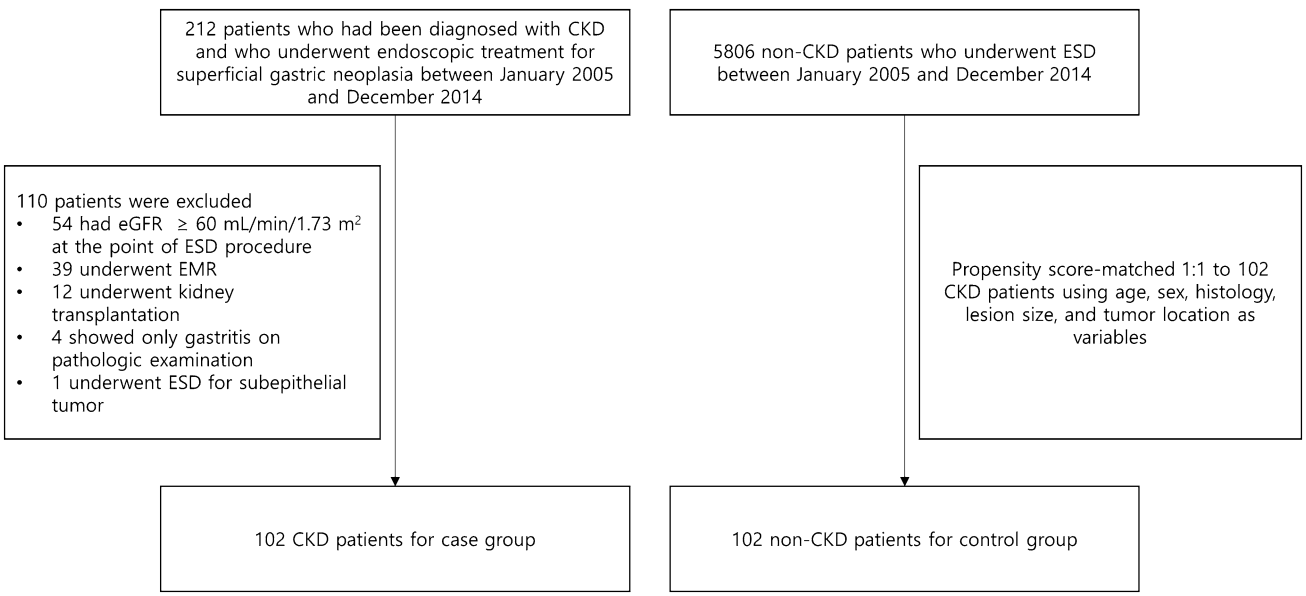

Fig. 1 Flow diagram of patients in this study. CKD: chronic kidney disease; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; eGFR: estimated glomerular filtration rate

IIc (superficial depressed), and type III (excavated). Types I and IIa were classified as the elevated type, and types IIb, IIc, and III were classified as the flat-depressed type [10].

Differentiated EGC with a diameter of ≤ 2 cm without ulcerative findings was designated as an absolute indication. Expanded indications included differentiated type without ulceration but with a diameter of > 2 cm, differentiated type with ulceration and a diameter of ≤ 3 cm, and undifferentiated type without ulceration but with a diameter of ≤ 2 cm [11]. Patients were classified into the absolute and expanded indication groups according to the final pathologic diagnosis. Patients who were not classified into either group were designated as the beyond expanded indications group.

En bloc resection was defined as resection of the neoplastic lesion in one piece without fragmentation. Lesions were considered as completely resected if the lateral and vertical margins were free of tumor. Complete resection of tumors in a piecemeal fashion was defined as complete removal of the entire lesion, including sufficient tumor-free margins after the perfect reconstruction of all pieces. Curative resection was defined as follows: regardless of tumor size, differentiated type, pT1a, ulcer negative; tumor size ≤ 3 cm, differentiated type, pT1a, ulcer positive; tumor size ≤ 2 cm, undifferentiated type, pT1a, ulcer negative; tumor size ≤ 3 cm, differentiated type, pT1b (SM1 < 500 μm from the muscularis mucosae) [11]. The resection was considered non-curative when tumors did not fulfill the abovementioned criteria for curative resection or lymphovascular invasion was identified in the final pathologic diagnosis.

Procedure time was defined as the time from marking to removal of the specimen, including the time for hemostasis. A bleeding event was considered to have occurred if second-look endoscopy showed oozing vessels requiring additional endoscopic hemostasis, or if clinical symptoms such as hematemesis or melena were present. Bleeding was defined as early delayed bleeding when identified during routine second-look endoscopy, or as late delayed bleeding when bleeding occurred > 48 h after the procedure. A diagnosis of perforation was made according to a direct endoscopic observation of mesenteric fat or the presence of free air in an abdominal radiograph or CT scan.

Statistical analysis

The patients in the CKD group ($n = 102$) were propensity score-matched 1:1 with patients without CKD, who underwent ESD because of gastric neoplastic lesions. The propensity score, an estimate of the probability that a patient undergoing ESD had CKD, was calculated using age, sex, histology, location of tumor, and size of tumor as variables. Propensity score matching was performed using the nearest-neighbor method with a caliper width of 0.1 multiplied by the standard deviation for the linearly transformed propensity scores (logit transformation). The distribution of propensity scores for overall enrolled patients is shown in Supplementary Fig. 1.

Differences in the endoscopic resection results between the non-propensity score-matched groups were assessed using Student's t test for continuous variables and the χ^2 test for categorical variables. For the propensity score-matched groups, differences between the groups were assessed using the McNemar's test and paired t test to account for the matched pairing of groups. Differences in bleeding events and survival between the groups were evaluated using Cox-regression models, with robust standard errors to account for the clustering of matched pairs [12]. Survival curves were constructed based on Kaplan–Meier estimates. The index date was defined as the date of the procedure. To assess bleeding risk, the patients were followed up from the index date to the time of bleeding or 30 days after the procedure, and to assess survival probability they were followed up from the index date to the time of death or the latest follow-up evaluation up to May 1, 2017. All reported p values are two-sided, and p values of < 0.05 were considered significant. R 3.4.3 software was used for statistical analysis (R Core Team [2017]; R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/).

Results

The CKD group and overall number of non-CKD patients that underwent ESD exhibited differences in their baseline characteristics, with significant differences in median age (68.0 vs. 64.4) and location of the lesion (58.8, 35.3, and 5.9% vs. 71.5, 20.4, and 8.2% for the upper, middle, and lower thirds, respectively). The proportion of male patients (84.3% vs. 75.8%), proportion of adenocarcinoma (65.7% vs. 59.5%), and median size of the lesion (20.0 vs. 18.0 mm) did not show any significant differences between the groups (Supplementary Table 1).

Baseline characteristics of the CKD and non-CKD groups after propensity score matching

The characteristics of CKD and non-CKD groups within matched cohort are shown in Table 1. Of 19 dialysis patients, 16 were on hemodialysis and 3 were on peritoneal dialysis. The CKD group had more comorbidities than the non-CKD patients, and the proportion of patients taking antiplatelet agents was higher in the CKD group. Other factors influencing bleeding tendency, such as platelet count and coagulation laboratory test, were not significantly different between the groups.

Table 1 Baseline characteristics of gastric neoplasia in CKD and non-CKD groups after propensity score matching

	CKD ($n=102$)	Non-CKD ($n=102$)	P value
Male sex	86 (84.3)	83 (81.4)	0.663
Age, years	68.0 (64.0–74.0)	69.0 (62.0–74.8)	0.927
Differentiation			0.605
Differentiated carcinoma	59 (57.8)	62 (60.8)	
Undifferentiated carcinoma	8 (7.8)	6 (5.9)	
Low grade dysplasia	26 (25.5)	27 (26.5)	
High grade dysplasia	9 (8.8)	7 (6.9)	
Location of tumor			0.279
Lower third	60 (58.8)	62 (60.8)	
Middle third	36 (35.3)	39 (38.2)	
Upper third	6 (5.9)	1 (1.0)	
Size of tumor, mm	20.0 (15.0–25.0)	18.0 (13.0–25.0)	0.746
Elevated/Flat-depressed	48 (47.1)/54 (52.9)	41 (40.2)/61 (59.8)	0.419
Stage of CKD			N/A
3	61 (59.8)	N/A	
4	19 (18.6)	N/A	
5	22 (21.6)	N/A	
Dialysis	19 (18.6)	N/A	
Comorbidities			
Hypertension	85 (83.3)	37 (36.3)	< 0.001
Diabetes mellitus	62 (60.8)	16 (15.7)	< 0.001
Coronary artery disease	11 (10.8)	3 (2.9)	0.061
Cerebrovascular accident	15 (14.7)	3 (2.9)	0.006
Antiplatelet agents	43 (42.2)	16 (15.7)	< 0.001
Platelet counts, × 1000/uL	193 (164–231)	212 (175–256)	0.143
PT, INR	0.98 (0.95–1.04)	0.98 (0.95–1.02)	0.161
APTT, seconds	27.7 (26.5–30.8)	27.8 (26.8–29.4)	0.908

Data represent the number of patients (%) or the median (interquartile range). Differentiated carcinoma: well or moderately differentiated tubular or papillary adenocarcinoma

Undifferentiated carcinoma: poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous carcinoma

CKD chronic kidney disease, *N/A* not available, *PT* prothrombin time, *INR* international normalized ratio, *APTT* activated partial thromboplastin time

Clinical outcomes of ESD

The endoscopic resection rates, including en bloc, complete, and curative resection rates, were similar between the CKD and non-CKD groups (Table 2). The CKD group had a longer duration of hospital stay than the non-CKD group. Twelve patients in the CKD group and seven in the non-CKD group did not obtain curative resection. The reasons for non-curative resection were as follows: undifferentiated carcinoma with a diameter of > 2 cm ($n=6$), tumor invasion of > 500 μm from the muscularis mucosa ($n=5$), positive lymphovascular invasion ($n=4$), a diameter of > 3 cm with submucosal invasion of the tumor ($n=3$), and undifferentiated carcinoma with ulceration ($n=1$). Among the patients with non-curative resection, five patients were sent for surgical treatment and 14 were observed with regular endoscopy follow-up. For the median follow-up period of 55.1 (interquartile range [IQR]: 29.6–73.4) months in the non-curative resection patients, no recurrence was noted in the surgical treatment group, while 1 out of 14 patients in the observation group exhibited a metachronous adenocarcinoma 7 years after the primary ESD. This lesion was successfully removed with an additional ESD procedure.

Adverse events associated with ESD

The CKD groups exhibited more overall bleeding events than the non-CKD group ($p=0.052$; Table 2). All the bleeding events were treated successfully with an endoscopic procedure, and there were no patients who needed additional surgical or angiographic interventions to control bleeding.

Perforation occurred in two patients in the non-CKD group, with endoscopic closure with hemoclip being performed on site for each patient. After conservative

Table 2 Clinical characteristics and outcomes of endoscopic submucosal dissection in CKD and non-CKD groups

	CKD ($n=102$)	Non-CKD ($n=102$)	P value
Criteria			0.703
Absolute	60 (58.8)	63 (61.8)	
Expanded	38 (37.3)	37 (36.3)	
Beyond expanded	4 (3.9)	2 (2.0)	
Procedure time, minutes	25.0 (16.0–33.8)	21.5 (17.0–35.0)	0.734
Size of specimen, mm	45.0 (35.0–51.8)	44.0 (35.3–51.8)	0.879
Results of resection			
En bloc resection	98 (96.1)	100 (98.0)	0.683
Complete resection	100 (98.0)	98 (96.1)	0.683
Curative resection	90 (88.2)	95 (93.1)	0.332
Lymphovascular invasion	3 (97.1)	1 (1.0)	0.617
Submucosal invasion	10 (9.8)	11 (10.8)	1.000
Adverse events			
Overall bleeding	14 (13.7)	5 (4.9)	0.052
Early bleeding	7 (50.0)	4 (80.0)	0.547
Late bleeding	7 (50.0)	1 (20.0)	0.077
Perforation	0 (0)	2 (2.0)	0.480
Hospital duration, days	4 (3–6)	3 (3–4)	0.001
Overall mortality	6 (5.9)	3 (2.9)	0.505
Disease-specific mortality	0 (0)	1 (1.0)	1.000

Data represent the number of patients (%) or the median (interquartile range)

treatment, including fasting and empirical antibiotics use, neither patient needed surgery to repair their perforation.

Subgroup analysis was performed to assess the bleeding risk according to CKD stage. There were four (6.6%) bleeding events in the stage 3 CKD group, five (26.3%) in the stage 4 CKD group, and five (22.7%) in the stage 5 CKD group. When compared with the non-CKD group, the stage 3 CKD group showed a comparable overall bleeding risk (HR 1.35; 95% CI 0.36–5.06; $p=0.654$), whereas the stage 4 (HR 5.79; 95% CI 1.52–22.0; $p=0.010$) and stage 5 CKD (HR 4.80; 95% CI 1.58–14.6; $p=0.006$) groups were associated with a higher bleeding risk (Fig. 2). In the multivariate analysis, the stage 4/5 CKD group exhibited an increased overall bleeding risk compared with the non-CKD group (HR 4.99; 95% CI 1.32–18.8; $p=0.018$; Table 3).

Renal function change in the CKD group was evaluated using serum creatinine level and eGFR measurements before and after the ESD procedure. Before the ESD, the median creatinine level was 1.90 mg/dL (IQR, 1.50–3.18 mg/dL) and the eGFR was 36.5 ml/min/1.73 m^2 (IQR, 18.3–48.0 ml/min/1.73 m^2), while after ESD they were 1.90 mg/dL (IQR, 1.51–3.18 mg/dL) and 36.0 ml/min/1.73 m^2 (IQR, 19.0–45.0 ml/min/1.73 m^2), respectively. There was no statistically significant change in creatinine and eGFR after ESD ($p=0.916$ and $p=0.903$).

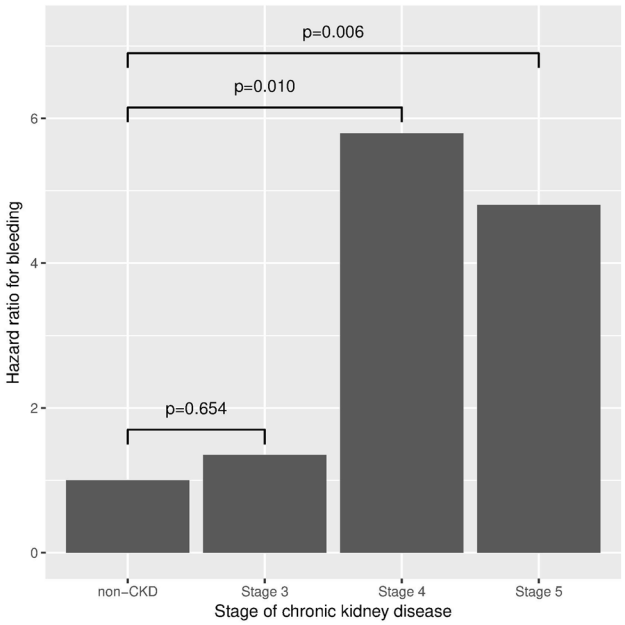

Fig. 2 Subgroup analysis for bleeding risk according to stage of chronic kidney disease

Oncologic outcomes of ESD

The Kaplan–Meier plot showed a survival difference between the groups, and the overall CKD group did not show a significantly poorer overall survival than the non-CKD

Table 3 Results of univariate and multivariate Cox-regression analysis for bleeding after endoscopic submucosal dissection

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Size of specimen	0.998 (0.95–1.04)	0.936		
Piecemeal resection	2.08 (0.24–17.9)	0.507		
Non-curative resection	1.20 (0.26–5.43)	0.817		
Chronic kidney disease				
Non-CKD	1		1	
Stage 3 CKD	1.35 (0.36–5.14)	0.657	1.35 (0.36–5.14)	0.657
Stage 4/5 CKD	5.29 (1.81–15.5)	0.002	4.99 (1.32–18.8)	0.018
Dialysis	3.61 (1.44–9.03)	0.006	1.13 (0.35–3.68)	0.839
Hypertension	2.55 (0.87–7.50)	0.088		
Diabetes mellitus	1.16 (0.49–2.73)	0.735		
Coronary artery disease	0.73 (0.11–4.68)	0.738		
Cerebrovascular accident	1.20 (0.28–5.10)	0.804		
Antiplatelet agents	1.12 (0.47–2.68)	0.805		

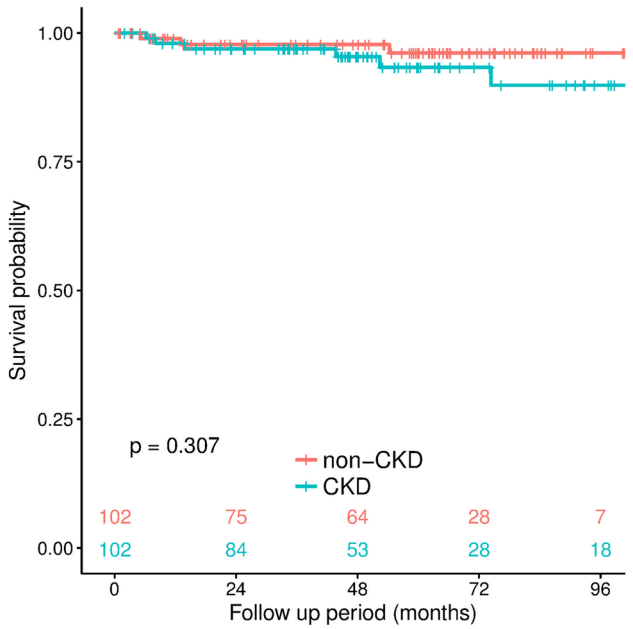

Fig. 3 Comparison of overall survival after ESD between patient groups. There was no significant difference in the overall survival rates between the CKD and non-CKD groups. CKD: chronic kidney disease

group after adjusting for overall follow-up duration (HR 2.09; 95% CI 0.52–8.33; $p=0.307$; Fig. 3). However, the CKD patients on dialysis did show a higher mortality risk than the non-CKD group, as expected (HR 6.32; 95% CI 1.28–31.3; $p=0.024$). No ESD procedure-related death was noted during the duration of follow-up. There was one gastric neoplasm-related death in the non-CKD group, which was a patient who died of postoperative bleeding. The patient underwent laparoscopic total gastrectomy with distal pancreatectomy 3 months after the ESD procedure because of poorly differentiated histology and concurrent intrapapillary mucinous neoplasm in the pancreas tail. The causes of death are depicted in Fig. 4. The median follow-up period was 47.2 (32.8–77.0) months for the CKD group and 59.6 (22.4–74.5) months for the non-CKD group. Disease-specific survival during the follow-up period was 100% for the CKD group and 99% for the non-CKD group.

Discussion

In present study, we compared short-term and oncologic outcomes between CKD and non-CKD patients. We revealed that the en bloc resection (96.1%) and curative resection rates (88.2%) in the CKD group were comparable to those in the non-CKD group. Furthermore, the perforation risk in the CKD group was not significantly different to that in the non-CKD group, although the CKD group did exhibit more bleeding ($p=0.052$), and had a significantly longer hospital stay ($p=0.001$) than the non-CKD group. This observational study showed that stage 4/5 CKD was associated with an increased bleeding risk ($p=0.018$), although stage 3 CKD was not found to be a significant risk factor for bleeding ($p=0.657$). However, given that all the bleeding events were well controlled with endoscopic procedures and that the survival probability of the CKD group was not significantly poorer than that of the non-CKD group ($p=0.307$), ESD could be considered as a treatment option for CKD patients.

A previous report referred to CKD as being a risk factor for a poor survival outcome in patients in need of open abdominal surgery [13], and another recent study exhibited a much higher in-hospital death rate for gastrectomy operations in patients with CKD, as well as increased minor adverse event rates such as anastomotic leakage and intra-abdominal abscess [14]. In addition, it has been suggested

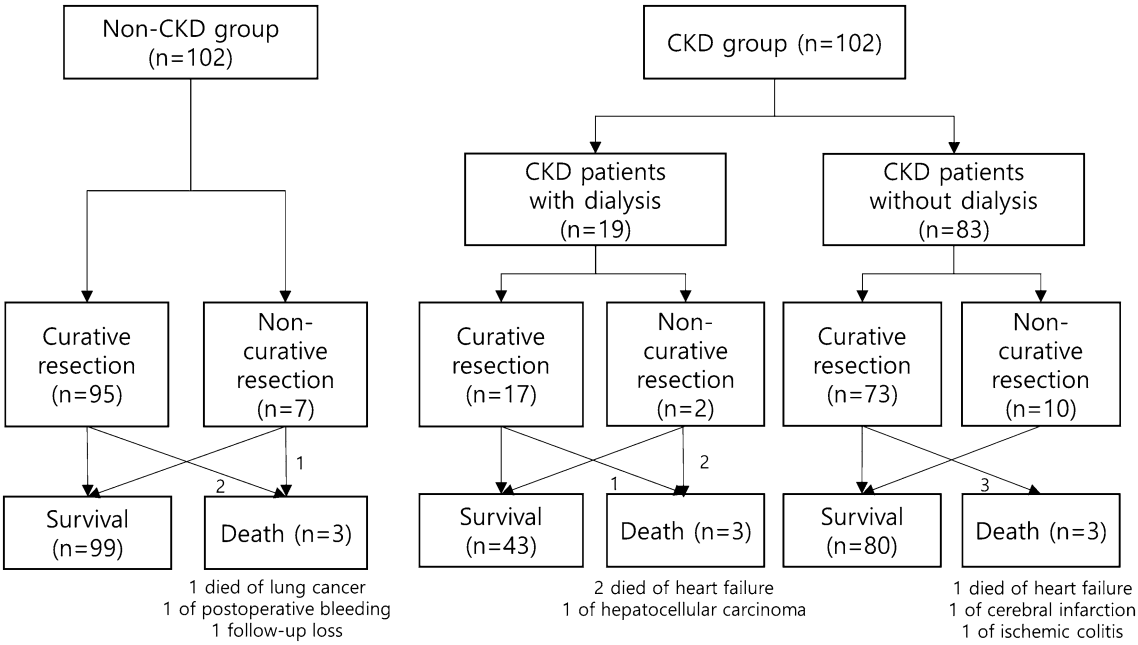

Fig. 4 Flow diagram of clinical outcomes in CKD and non-CKD groups. CKD: chronic kidney disease

that surgery for EGC in elderly patients has worse outcomes than ESD because of a longer hospital stay, and a higher rate of admission to the intensive care unit and occurrence of postoperative renal failure [15]. Therefore, in patients with CKD, ESD could be a more desirable option for treatment of gastric epithelial neoplasms than open gastrectomy. A few studies evaluated the outcomes of ESD in patients with CKD. Reported complete resection rates range from 89.9 to 100% [6, 16], with another study finding a curative resection rate of 86.1% [17]. The complete resection and curative resection rates for CKD patients in the present study were 98.0 and 88.2%, respectively, rates which are concordant with previous study results. Considering that the curative resection rate for ESD in the general population has been reported as 94.7% [18], ESD can be performed on CKD patients with resection results comparable to those in non-CKD patients.

As CKD patients have a tendency for bleeding and more comorbidities such as cardiovascular and cerebrovascular disease, there is concern that adverse event rates from ESD may be much higher than in non-CKD patients. A few previous studies suggest that hemodialysis patients exhibit increased rates of post-ESD bleeding [6, 17, 19], which is in concordance with our univariate analysis result showing that dialysis was associated with an increased bleeding risk ($p = 0.006$).

However, the bleeding risk posed by renal dysfunction itself has been little studied. Although one study suggested that stage 4/5 renal dysfunction may be associated with bleeding risk [17], this study was subject to a limitation, as it compared results within CKD patients, not with those of non-CKD patients. Therefore, it was not possible to evaluate any increased risk associated with performing gastric ESD in CKD patients in comparison with non-CKD patients. To our knowledge, this is the first study to compare the results of ESD in a head-to-head comparison of a CKD and non-CKD group. We suggested here that stage 3 CKD patients had a bleeding risk comparable to that of non-CKD patients, whereas stage 4/5 CKD patients exhibited a significantly higher bleeding risk than non-CKD patients. In addition, a multivariate analysis indicated that severe renal dysfunction itself, and not dialysis, played a major role in the increased bleeding risk. This could be explained by the pathogenesis of bleeding in CKD, which is mainly from abnormalities in platelet–platelet and platelet–vessel wall interactions caused by uremic toxins, not dialysis itself [20]. Therefore, we should bear in mind that not only CKD patients on dialysis, but also those CKD patients with severe renal dysfunction who do not undergo dialysis, are prone to post-ESD bleeding, and should, therefore, be carefully observed after ESD, as a precaution.

This study is subject to several limitations because of the nature of the single center retrospective study design. First, even though we performed propensity score matching to take into account factors influencing the results of ESD, there may still be hidden biases. For example, we did not include factors such as body mass index, comorbidity, and antithrombotic drugs in the matching process that our findings may be confounded by those factors. Second, although we included a relatively large number of patients, adverse

event cases were small that they resulted in this study having only limited power. However, an advantage of this study is that it compared CKD patients head-to-head with non-CKD patients, to confirm the efficacy and safety of ESD. As a prospective study design for the topic of this report is unfeasible due to the rarity of the events, we assumed that a retrospective matched case–control study was the best way to evaluate the subject.

In conclusion, we suggested here that patients with stage 3 CKD can safely undergo ESD with comparable oncologic outcomes to non-CKD patients, and without increased adverse event rates. However, stage 4/5 CKD patients were shown to have an increased risk of bleeding that precautions should be taken. In addition, as end-stage CKD patients exhibited poorer survival prognosis, we need to be cautious about performing ESD in elderly patients with stage 4/5 CKD after considering the remaining life expectancy.

Compliance with ethical standards

Conflict of interest The authors have no potential conflict of interest relevant to the present study.

Ethical statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The exemption from the informed consent requirement permitted by the Asan Medical Center Institutional Review Board.

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