Acquired cystic disease-associated renal cell carcinoma is the most common subtype in long-term dialyzed patients: Central pathology results according to the 2016 WHO classification in a multi-institutional study

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New pathological subtypes of renal cell carcinoma (RCC) were designated in the 2016 World Health Organization (WHO) classification corresponding to the features commonly seen in patients with end-stage renal disease (ESRD). To determine the clinicopathological findings of new subtypes, we reanalyzed all sections from 315 kidneys in 291 ESRD patients bearing RCC tumors surgically resected in three Japanese institutes by the central pathologist. Clear cell RCC was diagnosed in 144 kidneys (45.7%), acquired cystic disease (ACD)-associated RCC in 100 (31.7%), papillary RCC in 41 (13.0%), and other minor subtypes in 30 (9.5%). Multivariate analysis showed that longer duration of dialysis, young age, and male sex were independent prognostic clinical factors for the occurrence of ACD-associated RCC. ACD-associated RCC included more WHO/International Society of Urologic Pathology (ISUP) grade 3/4 cases compared to other RCCs. In contrast, other unfavorable findings were less frequent in ACD-associated RCC, including the presence of a sarcomatoid component, lymphovascular invasion, and necrosis. In conclusion, ACD-associated RCC is a common histology in Japanese patients with ESRD. ACD-associated RCC showed more cases with a higher WHO/ISUP grade, but fewer cases with other unfavorable pathological features, suggesting a favorable prognosis of ACD-associated RCC.

Key words: cystic kidney disease, dialysis, end-stage renal disease, pathology, renal cell carcinoma

Patients with end-stage renal disease (ESRD) have been reported to bear a 1.4-times higher risk of developing malignant disease than the general population.1,2 Of these malignant neoplasms, renal cell carcinoma (RCC) shows an even higher risk; the standardized incidence ratio of RCC in patients with ESRD is reported to be four to five times greater than the general population in Western countries1,2 and about 10 times greater in Japan.3 Additionally, the majority of patients with ESRD develop acquired cystic disease of the kidney (ACDK) in the native kidney as dialysis duration increases.4 Moreover, the clinical characteristics of RCC in ESRD patients are likely to be different from those in the general population, since RCC patients with ESRD have a more favorable overall prognosis owing to a higher proportion of stage 1 disease.5,6 Thus, the carcinogenic mechanism of RCC may be different in ESRD patients, which may account for the characteristic histological manifestation in ESRD patients.

Tickoo et al. reported that RCC arising in patients with ESRD shows characteristic morphological features that cannot be classified into any conventional histological subtype.7 These include ACD-associated RCC, in which tumors show a cribriform/sieve-like appearance composed of abundant granular eosinophilic cytoplasm, and clear cell papillary RCC, which exhibits a papillary architecture and clear cytoplasm (Fig. 1). Because of these findings, new pathological subtypes of RCC were designated in the 2016 World Health Organization (WHO) classification corresponding to the features commonly seen in patients with ESRD.8 Since most of their data were based on consultation cases in tertiary centers, the true incidence and clinicopathological characteristics of these subtypes has not been demonstrated in ESRD patients.
In the present study, we conducted a retrospective, multi-institutional study in Japan, in which a central pathologist reanalyzed pathological findings of RCC using consecutive nephrectomized sections from patients with ESRD, based on the new classification. We also examined the clinico-pathological findings of ACD-associated RCC.

MATERIALS AND METHODS

Patients

Three hundred and twelve patients underwent radical nephrectomy and were diagnosed with RCC by local pathologists in three Japanese institutes from January 1987 through December 2015. Twenty-nine patients underwent concurrent or metachronous bilateral nephrectomy. Thus, 341 kidneys were originally diagnosed as bearing RCC tumors. Of these, the pathological findings from 73 kidneys of 69 patients had been already analyzed and published elsewhere. All patients were receiving chronic dialysis therapy at the time of nephrectomy. Patients with a dialysis duration shorter than 6 months were not included in this study because these tumors may have been carried over from the pre-dialysis status of CKD and were not considered to be influenced by ESRD. Patients who had undergone renal transplantation after receiving dialysis therapy for longer than 6 months were included. A central pathologist diagnosed 17 kidneys as no tumor found, 8 as benign lesions, and 1 as urothelial carcinoma. Thus, 315 kidneys in 291 patients diagnosed as bearing RCC tumors were the subjects of this study (Table 1). This retrospective study protocol was approved by the institutional review boards of each institute. All the procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Pathological examination

A central pathologist (T. Tsuzuki) reviewed sections from all patients according to the 2016 WHO classification. Tumor grade was determined according to the WHO and International Society of Urologic Pathology (ISUP) grading system. Pathological stage was determined according to the 2016 TNM classification. When multiple histological subtypes were found in one kidney, the subtype with the highest proportion was considered as the representative histology. When patients had different representative histologies in bilateral kidneys, the tumor with the higher stage or larger size was considered as the representative tumor for these patients. The primary pathological factors as determined by local pathologists and the clinical factors were examined from the medical chart of each patient, and the influence of these clinical factors on the occurrence of ACD-associated RCC was analyzed.

Statistical analysis

Univariable analysis was performed using the Mann-Whitney U test to compare continuous variables between...
groups. The chi-square test or ANOVA was used to compare categorical variables between groups. Predictive factors for the occurrence of ACD-associated RCC were examined using a logistic-regression model in multivariable analyses. A difference was considered significant when \( P \) was <0.05.

**RESULTS**

**Patient characteristics**

Table 1 shows the characteristics of 291 of the patients in this study. Men accounted for 83.5% of the patients, and the mean hemodialysis period was 13.3 years. The primary causes of ESRD were chronic glomerular nephritis (54.0%) and diabetic nephropathy (8.5%); the underlying disease was not identified in 27.5% of patients. Pathological nodal metastasis was found in 17 patients (5.8%), and 7 patients (2.41%) showed metastasis to distant organs at the time of presentation. Of 315 kidneys, 75.9% had ACDK. The pathological T stage was pT1 in 268 kidneys (85.1%), pT2 in 9 (2.86%), and pT3a in 37 (11.7%). The tumors of 3 kidneys (0.95%) extended to the inferior vena cava. More than half of the tumors (61.0%) showed a high WHO/ISUP grade (grade 3 or 4).

Table 1 shows the distribution of histological subtypes from the review by the central pathologist. Clear cell RCC was the most common subtype, accounting for 45.7% of the RCC tumors (Table 1). ACD-associated RCC was found in 31.7% of patients, and papillary RCC in 13.0%. The incidence of clear cell papillary histology was very low and found in only three kidneys (0.95%). In this study, we focused on the major three subtypes, namely clear cell, ACD-associated, and papillary RCCs. The patient backgrounds for patients with clear cell, ACD-associated, and papillary RCCs are shown in Table 1. Patients with ACD-associated RCC were younger than those with clear cell or papillary RCC (mean, 53.8 vs 58.1 vs 55.5 years; \( P = 0.01 \)).

**Distribution of histological subtypes**

Figure 2 shows the distribution of histological subtypes from the review by the central pathologist. Clear cell RCC was the most common subtype, accounting for 45.7% of the RCC tumors (Table 1). ACD-associated RCC was found in 31.7% of patients, and papillary RCC in 13.0%. The incidence of clear cell papillary histology was very low and found in only three kidneys (0.95%). In this study, we focused on the major three subtypes, namely clear cell, ACD-associated, and papillary RCCs. The patient backgrounds for patients with clear cell, ACD-associated, and papillary RCCs are shown in Table 1. Patients with ACD-associated RCC were younger than those with clear cell or papillary RCC (mean, 53.8 vs 58.1 vs 55.5 years; \( P = 0.01 \)).

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Table 1 Patient characteristics

| Histological subtypes | Overall | ACD-associated | Clear cell | Papillary | Others | \( P^* \) |
|-----------------------|---------|----------------|------------|----------|--------|----------|
| No. of patients       | 291     | 85             | 137        | 41       | 28     |          |
| Age (years)           | 56.3 ± 11.6 | 53.8 ± 11.1 | 58.1 ± 11.9 | 55.5 ± 11.7 | 56.4 ± 10.8 | 0.08 |
| Sex (M/F)             | 243 (83.5%)/48 | 78 (91.8%)/7 | 107 (78.1%)/30 | 38 (92.7%)/3 | 20(71.4%)/8 | 0.004 |
| Dialysis duration (years) | 13.3 ± 7.9 | 16.8 ± 6.3 | 10.2 ± 7.5 | 15.7 ± 8.2 | 14.7 ± 8.1 | <0.001 |
| Primary cause of ESRD |         |                |            |          |        |
| Chronic glomerular nephritis | 157 (54.0%) | 53 (62.4%) | 68 (49.6%) | 20 (48.8%) | 16 (57.1%) | 0.08 |
| Diabetic nephropathy | 25 (8.5%) | 3 (3.53%) | 16 (11.7%) | 4 (9.76%) | 2 (7.1%) | 0.08 |
| Nephrosclerosis | 13 (4.47%) | 1 (1.18%) | 11 (8.03%) | 0 | 1 (3.5%) | 0.08 |
| Polycystic kidney | 4 (1.37%) | 0 | 3 (2.19%) | 1 (2.44%) | 0 | 0.08 |
| Others | 12 (4.12%) | 3 (3.53%) | 7 (5.31%) | 2 (2.5%) | 1 (3.5%) | 0.08 |
| Unknown | 80 (27.5%) | 25 (29.4%) | 32 (23.4%) | 15 (36.6%) | 8 (28.5%) | 0.08 |
| pN stage (0/1/x) | 35 (12.0%)/17 | 10 (11.8%)/3 | 19 (13.9%)/6 | 3 (7.32%)/5 | 3 (10.7%)/5 | 0.42 |
| pT stage (1a/1b/2a/2b/3a/3b/4) | (5.84%)/239 | (3.53%)/72 | (4.38%)/112 | (12.2%)/33 | (12.0%)/22 | (78.6%)/22 |
| Distant metastases at surgery | 7 (2.41%) | 3 (3.53%) | 1 (0.73%) | 2 (4.88%) | 1 (3.5%) | 0.30 |
| No. of kidneys | 315 | 100 | 144 | 41 | 30 |
| Presence of ACDK | 239 (75.9%) | 100 (100%) | 88 (61.1%) | 29 (70.7%) | 22 (73.3%) | <0.001 |
| Multiplicity | 117 (37.1%) | 56 (56.0%) | 36 (25.0%) | 16 (39.0%) | 9 (30%) | <0.001 |
| pT stage (1a/1b/2a/2b/3a/3b/4) | 246 (78.1%)/22 | 86 (86.0%)/5 | 115 (79.9%)/14 | 23 (56.1%)/3 | 22 (73.3%)/0/2 | 0.003 |
| WHO/ISUP Grade (1/2/3/4) | (2.86%)/0/34 | (2.00%)/0/7 | (1.39%)/0/12 | (7.32%)/0/10 | (16.7%)/0/1 | <0.001 |
| (10.8%)/31 | (7.69%)/0/0 | (3.83%)/1 | (0.69%)/0 | (4.88%)/0 | (16.7%)/0/1 | <0.001 |
| (0.95%)/1 | (0.32%) | (0.32%) | (0.32%) | (0.32%) | (0.32%) | (0.32%) |
| WHO/ISUP Grade (1/2/3/4) | 26 (8.25%)/97 | 0/10 (10.0%)/88 | 24 (16.7%)/69 | 0/8 (19.5%)/27 | 2 (6.7%)/10 | <0.001 |
| (30.8%)/170 | (88.0%)/2 | (47.9%)/42 | (29.2%)/9 | (14.6%)/1 | (43.3%)/5 | (16.7%)/5 |
| (54.0%)/22 | (2.00%) | (47.9%)/42 | (29.2%)/9 | (14.6%)/1 | (43.3%)/5 | (16.7%)/5 |
| (6.98%) | (0.32%) | (0.32%) | (0.32%) | (0.32%) | (0.32%) | (0.32%) |

* Analyzed among ACD-associated, clear cell, and papillary renal cell carcinomas using ANOVA

Data are presented as n, n (%), or mean ± SD (range).

ACD, acquired cystic disease; ESRD, end-stage renal disease; ACDK, acquired cystic disease of the kidney; WHO/ISUP, World Health Organization and International Society of Urologic Pathology.
The proportion of men was higher in the ACD-associated (91.8%) and papillary RCC groups (92.7%) than in the clear cell RCC group (78.1%) ($P < 0.0001$). The hemodialysis duration was also longer in patients with ACD-associated (mean: 16.8 months) and papillary RCC (15.7 months) than in those with clear cell RCC (10.2 months). There was no significant difference in the primary cause of ESRD, pN stage, or the presence of distance metastases among the three groups. All patients with ACD-associated RCC had ACDK in their native kidney. The incidence of multiplicity was significantly higher in patients with ACD-associated RCC than in those with clear cell or papillary RCC ($P < 0.001$). The papillary RCC group showed a higher incidence of pT3 or higher than the ACD-associated or clear cell RCC groups (29.3% vs 7.00% vs 9.03%, $P = 0.003$). The incidence of grade 3 or 4 disease was higher in the ACD-associated RCC group (90.0%) than in the clear cell RCC (35.4%) or papillary groups (80.5%) ($P < 0.0001$).

**Influence of dialysis duration on the incidence of ACD-associated RCC**

We next examined the influence of dialysis duration on the distribution of subtypes in the reviewed diagnosis (Fig. 3). In patients for whom the dialysis duration was less than 10 years, the major subtype was clear cell RCC, accounting for 76.1%. However, the incidence of ACD-associated RCC increased to 40–50% as the dialysis period increased after 10 years, although it declined to 37.8% after 20 years. The incidence of clear cell RCC decreased as the incidence of ACD-associated RCC increased; however, it increased slightly in patients who received 20 or more years of dialysis. The incidence of papillary RCC increased in patients who received dialysis for longer than 20 years.

**Conventional pathological features in ACD-associated RCC**

In order to investigate the pathological characteristics of ACD-associated RCC, we compared the conventional pathological features between ACD-associated RCC and non ACD-associated RCC (Fig. 4). In this analysis, the pathological findings of 210 kidney tumors in 187 patients were studied. Seventy-one kidneys (33.8%) showed ACD-associated RCC as the primary tumor, whereas 139 kidneys (66.2%) had other histological subtypes. There was a discrepancy in the conventional pathological features among ACD-associated and non-ACD-associated RCCs. High tumor grade (WHO/ISUP grade 3/4) was more frequently seen in ACD-associated tumors than in non-ACD-associated tumors (88.5% versus 47.4%, $P < 0.001$). Sarcomatoid features were found in only one ACD-associated tumor (1.4%) but were found in six non-ACD-associated tumors (4.3%). The incidence of lymphovascular invasion, necrosis, and sarcomatoid features were lower in ACD-associated tumors than in non-ACD-associated tumors.

The tumor grade was grade 4 in one case and grade 3 in 69 ACD-associated RCC cases. Of these, the grade 4 tumor showed hemorrhage, necrosis, and sarcomatoid features, whereas 67.7% of the grade 3 tumors showed hemorrhage, 3.2% showed necrosis, and 0% showed sarcomatoid features.

![Figure 2](image1.png)  Distribution of renal cell carcinoma (RCC) histological subtypes from the review by the central pathologist. Light gray indicates clear cell histology, black indicates acquired cystic disease (ACD)-associated histology, and dark gray indicates papillary histology. Other minor subtypes, chromophobe, clear cell papillary, translocation, and unclassified, are indicated with different dotted or striped patterns.

![Figure 3](image2.png)  Distribution of renal cell carcinoma (RCC) subtypes from the reviewed diagnosis according to dialysis duration. Black indicates acquired cystic disease (ACD)-associated RCC, light gray indicates clear cell RCC, dark gray indicates papillary RCC, and dotted patterns indicate other minor subtypes.
Table 2 shows the findings of multivariate analysis for prognostic clinical factors for ACD-associated RCC. Dialysis duration (odds ratio [OR], 1.01; P < 0.001), young age (OR, 0.97; P = 0.01), and male sex (OR, 2.99; P = 0.01) were independent prognostic factors for ACD-associated RCC.

DISCUSSION

In the present study, we examined the histological distribution of RCC subtypes in patients with ESRD treated in multiple Japanese institutions. ACD-associated RCC accounted for 31.7% of RCCs that occurred in patients undergoing dialysis. ACD-associated RCC was also more frequently found in patients with a longer dialysis period (10 years or more). Unfavorable pathological features were less frequent in ACD-associated RCC than in other subtypes, whereas the majority of tumors with this subtype unexpectedly showed a higher tumor grade.

Acquired cystic disease-associated RCC was first described by Tickoo et al. as tumors with a characteristic pathological appearance occurring only in kidneys with ACDK. In their patient series, this subtype accounted for 36% of dominant tumors in patients with ESRD. This is similar to our finding that 31.7% of primary tumors were ACD-associated. Microscopically, the tumor shows a cribriform/sieve-like appearance in a low-power field. In a high-power field, the tumor cells have an ill-defined cell membrane, abundant granular eosinophilic cytoplasm, large nuclei, and prominent nucleoli. According to the reports from Tickoo et al., ACD-associated RCC shows an immunohistological pattern distinct from the clear cell and papillary subtypes that are commonly seen in sporadic RCCs, including the lack of a-methylacyl-CoA racemase (AMACR), a characteristic marker for the papillary subtype, and strong positivity for cytokeratin 7, unlike the clear cell subtype. In contrast, Kuroda et al. reported completely contrasting results in which tumor cells were diffusely positive for AMACR in all seven cases, but negative for cytokeratin 7. Thus, a characteristic staining pattern based on immunohistochemical studies remains to be determined. According to molecular genetic profiling studies, ACD-associated RCC shows frequent gains on chromosomes 3 and Y, and shows some similarity with papillary RCC. According to these findings, the latest WHO classification designated ACD-associated RCC as the characteristic subtype in RCC patients with ESRD.

The pathogenesis of ACD-associated RCC remains unclear. ACDK is commonly seen in ESRD patients. The incidence of ACDK has been reported to increase as the dialysis duration extends, and can reach 90% in patients with long-term dialysis (10 years or longer). This finding is similar to our results showing an increased incidence of ACD-associated RCC in patients with a dialysis duration...
of 10 years or longer. It is well known that the incidence of RCC is 3 to 10 times higher in patients with ESRD.\textsuperscript{3,17,18} The present multi-institutional study confirmed our original results, in which we showed that the incidence of ACD-associated RCC increased from 8% to 33% with a hemodialysis period longer than 10 years in 73 kidneys from 69 patients in early stages.\textsuperscript{9} The report from Nouh et al. also showed a similar tendency, wherein the incidence of ACD-associated RCC increased from 7% to 58% in patients with a hemodialysis period longer than 10 years.\textsuperscript{19} Thus, uremic status may be associated with the pathogenesis of ACD-associated RCC. In support of this hypothesis, Tickoo et al. reported a high incidence of putative precursor lesions, such as papillary adenoma (39%) or clustered microcystic lesions (91%), in kidneys bearing ACD-associated RCC.\textsuperscript{7} Thus, the intracystic cells in patients with ACDK may function as the tumor cells of origin. It was also reported that mutagenic or oxidative stress-inducing compounds accumulate in the cystic fluid in ACDK.\textsuperscript{20,21} The exposure of the intracystic cells to carcinogens may induce carcinogenesis, which may explain the higher incidence of ACD-associated RCC in ESRD patients who receive long-term dialysis.

The pathological behavior of ACD-associated RCC also remains unclear. According to our results, the majority of ACD-associated tumors (88.5%) were high grade, whereas sarcomatoid features were found in only 1.4%. In addition, other unfavorable pathological features, such as necrosis or lymphovascular invasion, were less frequent in ACD-associated RCC than in non-ACD-associated RCC. These findings suggest that ACD-associated RCC is a less aggressive tumor than other subtypes. This finding is similar to that of our previous report, in which we showed a favorable prognosis of most cases with ACD-associated RCC, regardless of unfavorable pathological features.\textsuperscript{9} The large nuclei and prominent nucleoli observed with ACD-associated RCC may be morphological characteristics, and do not necessarily reflect the malignant behavior of the tumor. This phenomenon is also found in chromophobe RCC tumors, in which the majority of tumors have a high Fuhrman grade that is not associated with clinical aggressiveness.\textsuperscript{22} Therefore, the WHO recommends applying WHO/ISUP grading only for clear cell and papillary RCC. There are currently no data as to whether WHO/ISUP grading is applicable for ACD-associated RCC. Grade 4 is still likely to indicate a highly aggressive tumor in ACD-associated RCC as one tumor with grade 4 showed sarcomatoid features, hemorrhage, and necrosis. However, a novel grading system may be needed for the evaluation of ACD-associated RCC. We are conducting further studies to examine the clinical behavior and prognosis of ACD-associated RCC with more patients.

Another interesting finding from this study was that the incidence of papillary clear cell RCC was very low, accounting for only 0.95% of our patient cohort. This unique subtype is characterized pathologically by bland clear epithelial cells arranged in tubules and papillae, with at least a predominantly linear nuclear alignment away from the basement membrane, and a distinctive immunophenotype.\textsuperscript{8} The study by Tickoo et al. showed that clear cell papillary RCC was found in 12% of noncystic ESRD kidneys and 23% of ACDK kidneys.\textsuperscript{7} We do not have a clear answer for this discrepancy; however, it should be noted that the molecular characteristics of clear cell papillary RCC are still under investigation.\textsuperscript{23,24} One possible explanation for this discrepancy is that the average dialysis period in our study was 13.3 years, which is much longer than that in their cohort. Another possibility is selection bias in Tickoo's study, because most of their data were based on consultation cases, not consecutive data. Recent studies show that clear cell papillary RCC is not a rare disease entity and occurs in non-ESRD patients.\textsuperscript{24,25} Because our data were based on consecutive data of high volume centers in Japan, they are more likely to reflect the true incidence of clear cell papillary RCC in ESRD patients.

Finally, we should emphasize the limitations of the study. First, this is a multi-institutional study, but includes data from only three institutes. An increased number of institutes or patients will be needed to further support our results. Second, this is a retrospective study and the number of patients is too low to draw a definite conclusion. Finally, patient survival is not clearly described in this study. We are currently investigating oncological outcomes with an increased number of patients.

In conclusion, the present study shows that ACD-associated RCC accounts for 31.7% of RCC in patients with ESRD, and a long dialysis duration, young age, and male sex are significantly associated with the occurrence of this histology. Further investigation is required to clarify the biological behavior and clinical implication of this RCC subtype.

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