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ADC cut points for chronic kidney disease in pathologically-proven cholangiocarcinoma

Jaturat Kanpittaya [a], Wichuda Apipattarakul [a], Verajit Chotmongkol [b], Kittisak Sawanyawisuth [b,*]

[a] Department of Radiology, Thailand
[b] Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

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ABSTRACT

Purpose: Apparent diffusion coefficient (ADC) has been shown to indicate renal function in various conditions. As cholangiocarcinoma may have renal involvement due to immune complex-mediated glomerulonephritis, this study aimed to determine whether or not there is any association between ADC values and renal function in these patients.

Methods: This was a retrospective, analytical study. The inclusion criteria were age over 18 years, pathologically proven cholangiocarcinoma diagnosis and having undergone either 1.5 T or 3.0 T diffusion-weighted MRI. Chronic kidney disease (CKD) was defined as eGFR less than 60 mL/min/1.73m^2. Patients' ADC levels in the CKD and non-CKD groups were compared, and subgroup analysis was performed by MRI field strength and type of cholangiocarcinoma.

Results: One hundred fifty-eight patients participated in the study. Most were male (66.46 %), and the average age (SD) was 61.59 years (7.91). Average ADC levels in the CDK and non-CDK group differed significantly, regardless of MRI field strength or type of cholangiocarcinoma (2.11 mm/s^2 in the ADC group vs 1.91 mm/s^2 in the non-ADC group; $P < 0.001$). An ADC cut-point of 1.75 mm/s^2 yielded sensitivities ranging from 66.67–90.00 in almost all study populations. The distal cholangiocarcinoma group had a perfect cut-point at 1.78 mm/s^2 with 100 % sensitivity and area under the ROC curve.

Conclusions: Radiologists can use ADC to detect CKD in cholangiocarcinoma patients regardless of MRI field strength or type of cholangiocarcinoma.

1. Introduction

Chronic kidney disease (CKD) is a common health problem, with a reported prevalence of 25.5 % in adults in Canada [1]. Estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m^2 is one diagnostic criterion for CKD and is associated with a 1.18 times higher risk of all-cause mortality (95 % CI 1.05–1.32) [2]. Early detection and management of CKD may slow the progression toward end-stage renal disease in these patients.

Cholangiocarcinoma is a bile duct cancer that may be related to *Opisthrochis viverrini* infection [3]. Its prevalence is approximately 2 per 100,000 persons/year but may be high as 60 per 100,000 persons/year in areas endemic for *Opisthorchis viverrini* infection such as those in Southeast Asia [4]. Chronic *Opisthorchis viverrini* infection is asymptomatic but may lead to advanced bile duct fibrosis and cancer. Patients suffering from cholangiocarnioma may present with jaundice and pale stool. The prognosis in non-resectable cases is poor, with a 5-year survival rate of 0%. The use of radiographic imaging, such as ultrasonography or computed tomography, is crucial in the of diagnosis and staging of cholangiocarcinoma [5].

Diffusion-weighted magnetic resonance imaging (MRI) is non-invasive and can be used to calculate an apparent diffusion coefficient (ADC), which is an indicator of renal function [6–9]. Cholangiocarcinoma is a bile duct cancer related to *Opisthorchis viverrini* infection and may require an abdominal MRI as part of the laboratory workup. A previous study showed that *Opisthorchis viverrini* infection may initiate immune complex-mediated glomerulonephritis in cholangiocarcinoma patients, resulting in renal dysfunction [3]. This means

* Corresponding author.
E-mail address: kittisak@kku.ac.th (K. Sawanyawisuth).

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that radiologists may be able to detect early renal dysfunction or CKD in these patients. This study aimed to determine the association between the ADC and renal function in cholangiocarcinoma patients.

2. Methods

This was a retrospective, analytical study conducted at Khon Kaen University's Srinagarind Hospital in Thailand. Inclusion criteria were age over 18 years, pathologically proven cholangiocarcinoma diagnosis and having undergone either 1.5 T or 3.0 T diffusion-weighted MRI. Patients with renal masses, multiple renal cystic lesions, very small renal size, and severe hydronephrosis were excluded due to the ADC measurement limitations caused by these conditions. The study period was between January 2011 and December 2016. The study protocol was approved by the Khon Kaen University Ethics Committee in Human Research.

Baseline characteristics (age, sex, body weight, and co-morbid diseases) and laboratory test results, including eGFR and ADC values of both kidneys, of all eligible patients were reviewed. Patients were categorized into two groups based on eGFR as either CKD (less than 60 mL/min/1.73m^2) or non-CKD (60 mL/min/1.73m^2 or greater). ADC values were evaluated using diffusion-weighted MRI at 1.5 T (MagnetomAera; Siemens Medical Solutions, Erlangen, Germany) or 3.0 T (Phillips Achieva; Philips, Best, Netherlands).

2.1. Image analysis

The MRI was performed using a phased array body coil with the patient in supine position. The whole abdominal MRI protocol included T1w, T2w, in- and opposed-phase gradient echo (GRE) sequences, axial T2-weighted images of variable TE (short or long TE), diffusion-weighted images with 3 b-values (0, 150, 800 s/mm^2), and dynamic contrast-enhanced imaging (DCE) with volumetric 3D GRE T1-weighted sequences. The diffusion-weighted image data were transferred to a workstation (Fujifilm Medical Systems, USA, Inc.), ADC values were calculated, and corresponding ADC maps were generated. Image data analysis was performed by the same radiologist (with 20 years' experience) in all cases. A 1.0 cm^2 of circular region of interest (ROI) was placed at the corticomedullary junction and in the middle portion of the kidney for ADC measurement in order to reduce interference due to perfusion effect. For each kidney, three nonoverlapping ROIs were placed in different locations, and the mean of the six diffusion-weighted image signal intensities was used to calculate ADC. Care was taken during measurement to avoid the kidney border in order to prevent partial volume averaging (Fig. 1).

Cholangiocarcinoma was diagnosed based on the National Comprehensive Cancer Network (NCCN) recommendations and classified into three types according to its anatomic location along the biliary tree: intrahepatic, perihilar, and distal (Fig. 2).

2.2. Statistical analysis

Descriptive statistics were used to calculate the means (SD) and percentages of the studied variables. ADC levels in the CKD and non-CD group were compared, and subgroup analysis was performed by MRI field strength and type of cholangiocarcinoma. Results with a *P* value of 0.05 werenconsidered statistically significant. ADC cut-points for CKD were calculated using logistic regression analysis, and the sensitivity and area under the receiver operating characteristic (ROC) curve of each cut-point (including those derived from the subgroup analysis) are reported below. All statistical analyses were performed using STATA software version 10.1 (College Station, Texas, USA).

3. Results

One hundred fifty-eight patients participated in the study (Table 1), most of whom were male (66.46 %), with an average age (SD) of 61.59 years (7.91). Hypertension was the most common co-morbid disease (21.52 %). More patients underwent 1.5 T MRI than 3.0 T (77.22 % vs 22.78 %). Average eGFR was 75.78 mL/min/1.73m^2, with the highest proportion being between 60−89 ml/min/1.73m^2 (45.57 %). Average ADC was 2.05 mm/s^2 overall (Table 1), and 1.97 mm/s^2 (SD 0.11) in patients eGFR between 30−59 ml/min/1.73m^2.

Average ADC in patients with and without CKD differed significantly, regardless of MRI field strength or type of cholangiocarcinoma (Tables 2,3,4,5). The average ADC in the non-CKD group was higher than in the CKD group (2.11 vs 1.91 mm/s^2; $p < 0.001$). An ADC cut-point of 1.75 mm/s^2 yielded sensitivities ranging from 66.67-90.00 in almost all study populations. The distal cholangiocarcinoma group had a perfect cut-point of 1.78 mm/s^2 with 100 % sensitivity (Table 6) and area under the ROC curve. The overall area under ROC curve was 88.23 (Fig. 3).

4. Discussion

This study showed that ADC levels were significantly lower in cholangiocarcinoma patients with CKD than those without, regardless of MRI field strength or type of cholangiocarcinoma (Tables 2–5).

As previously reported, ADC levels are significantly lower in CKD patients than in normal subjects [10]. Average ADC values may differ

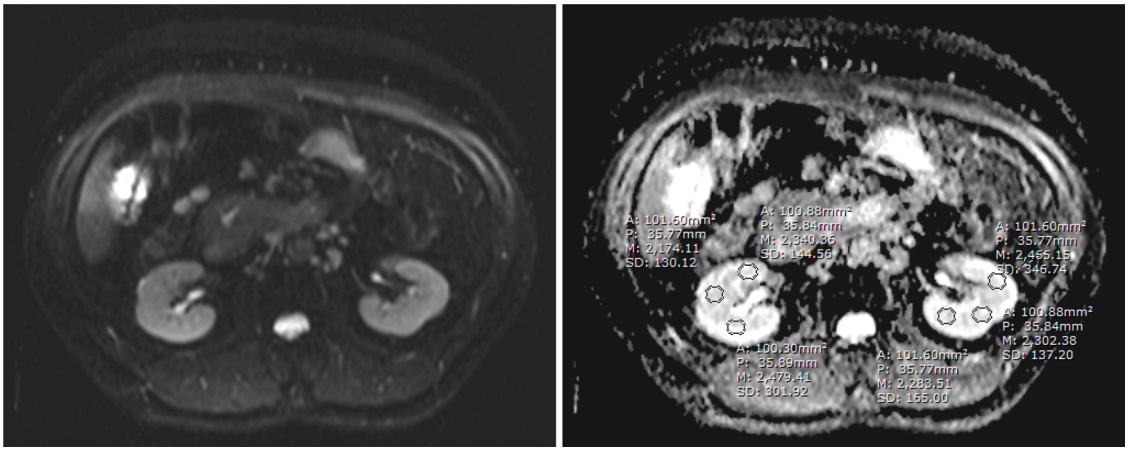

Fig. 1. Diffusion-weighted MRI and apparent diffusion coefficient (ADC) map in a 68-year-old man showing ADC values were 2.1741, 2.3404 and 2.4794 ($\times 10^{-3}$ mm^2/s) of right kidney and 2.4652, 2.3024 and 2.2835 ($\times 10^{-3}$ mm^2/s) of left kidney. Mean ADC value is 2.3408 ($\times 10^{-3}$ mm^2/s). The circles depict examples of region of interest placement.

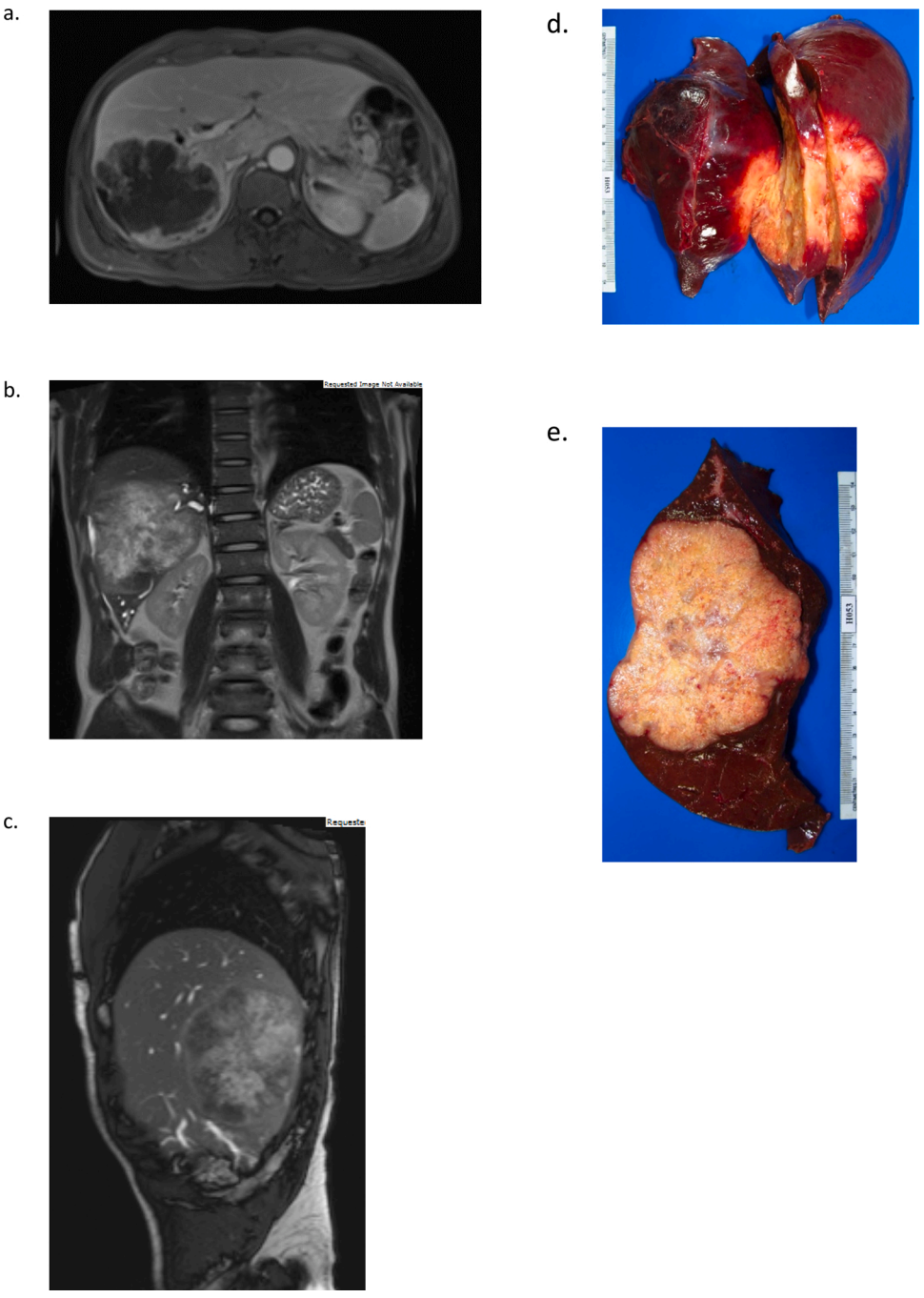

Fig. 2. Intrahepatic cholangiocarcinoma in 45-year-old man, (a-c) Axial T1W after Gd administration in portovenous phase, coronal and sagittal T2W show well-defined mass at hepatic segment 7 and 8 which exhibit heterogeneous high signal intensity on T2W with irregular peripheral enhancement after Gd administration. There is peripheral IHD dilatation around this mass. Right posterior portal vein is involved. (d-e) Gross pathology, pathologic diagnosis reveals well-differentiated adenocarcinoma, consistent with intrahepatic cholangiocarcinoma, mass forming type. The tumor grows nearby liver capsule but did not invades into hilar soft tissue.

depending on the cause of CKD. In this study, cholangiocarcinoma patients with eGFR between 30−59 ml/min/1.73m^2 had an average ADC of 1.97 mm/s^2, while those with diabetic nephropathy or chronic glomerulonephritis with the same eGFR range had average ADCs of 2.04 and 2.16 mm/s^2, respectively [11–13]. The cut-point for CKD in cholangiocarcinoma in our study was 1.75 mm/s^2 indicating that radiologists may be able to accurately detect CKD in cholangiocarcinoma patients if average ADC is lower than 1.75 mm/s^2 in almost 80 % of patients.

A previous study using 3.0 T MRI have found eGFR and ADC to be significantly correlated [13], with coefficients of 0.310 ($P = .017$) and 0.356($P = .010$) in the renal cortex and medulla, respectively. In this study, we used both 1.5T and 3.0T MRI for ADC measurement and determined the optimal ADC cut-point for CKD in cholangiocarcinoma patients to be 1.75 mm/s^2 in both cases, with only slight differences in sensitivity. The 1.5 T MRI had somewhat higher sensitivity than the 3.0 T MRI (86.67 % vs 71.43 %), as shown in Table 5. In generally, the optimal cut-point did not differ by type of cholangiocarcinoma. However, a slightly higher cut-point of 1.78 mm/s^2 yielded the greatest sensitivity in patients with distal cholangiocarcinoma (Table 5; note that only 14 patients had distal cholangiocarcinoma).

Previous studies have shown ADC measurement to have various applications in renal diseases such as diabetes or renal tumors [14,15]. This study found that ADC can also be used to detect CKD in cholangiocarcinoma patients. One previous study found that ADC varied by type of renal tumor, with significantly higher values in clear and papillary renal cell carcinoma than in other types (1.75 vs 1.44×10^{-3} mm^2/s) [15]. However, we found no difference in ADC by type of cholangiocarcinoma (Table 4). We also found slightly lower levels of ADC in cholangiocarcinoma patients than did a previous study

Table 1
Showed baseline characteristics of cholangiocarcinoma patients participated in the study (n = 158).

Factors	Numbers (percentage) or mean (SD)
Age, years	61.59 (7.91)
Male sex	105 (66.46)
Co-morbid diseases	61 (38.61)
Hypertension	34 (21.52)
Diabetes mellitus	21 (13.29)
MRI field strength	
1.5 T	122 (77.22)
3.0 T	36 (22.78)
Body weight, kg	56.98 (9.84)
Blood urea nitrogen, mg/dL	15.11 (12.17)
Serum creatinine, mg/dL	1.03 (0.62)
eGFR, ml/min/ m^2	75.78 (29.99)
> 90, n	42 (26.58)
60-89, n	72 (45.57)
30-59, n	31 (19.62)
15-29, n	12 (7.59)
< 15, n	1 (0.63)
Total bilirubin, mg/dL	3.33 (6.30)
Direct bilirubin, mg/dL	2.39 (4.93)
ADC right kidney	2.05 (0.14)
ADC left kidney	2.06 (0.15)
ADC average	2.05 (0.13)

Note. eGFR: estimated glomerular filtration rate; ADC: apparent diffusion coefficient.

Table 2
Apparent diffusion coefficient (ADC) of cholangiocarcinoma patients categorized by presence of chronic kidney disease (CKD).

Factors	No CKD n = 114	CKD n = 44	p value
Right kidney	2.10 (0.10)	1.92 (0.15)	< 0.001
Left kidney	2.12 (0.10)	1.90 (0.15)	< 0.001
Average	2.11 (0.08)	1.91 (0.14)	< 0.001

Table 3
Apparent diffusion coefficient (ADC) of cholangiocarcinoma patients categorized by presence of chronic kidney disease (CKD): a subgroup analysis by MRI field strength.

Factors	No CKD n = 114	CKD n = 44	p value
1.5 T, n = 122	n = 92	n = 30	
Right kidney	2.11 (0.10)	1.92 (0.14)	< 0.001
Left kidney	2.12 (0.10)	1.90 (0.15)	< 0.001
Average	2.11 (0.08)	1.91 (0.14)	< 0.001
3.0 T, n = 36	n = 22	n = 14	
Right kidney	2.08 (0.07)	1.89 (0.17)	< 0.001
Left kidney	2.11 (0.11)	1.87 (0.15)	< 0.001
Average	2.10 (0.07)	1.88 (0.15)	< 0.001

in CKD patients with comparable eGFR (1.99 vs 1.91 $\times 10^{-3}$ mm^2/s), as shown in Table 2 [16]. These results support the hypothesis that cholangiocarcinoma patients may experience renal damage.

This study used both 1.5 T and 3.0 T MRI to evaluate ADC levels, which may have slightly different cut-points and sensitivity/specificity (Table 6). The sensitivity of 1.5 T MRI was slightly higher than that of 3.0 T MRI at the selected cut-point of 1.75 $\times 10^{-3}$ mm^2/s but may be comparable at different cut-points.

There are some limitations to this study. Although we believe that cholangiocarcinoma patients may experience renal damage, as shown by the lower ADC values discussed above, data with regard to renal pathology and *Opisthorchis viverinin* infection were limited, as such data are not routinely gathered in our clinical practice. Further studies are thus required to prove this hypothesis. In addition, ADC levels differ depending on the MR scanner and field strength used. However, our results show that radiologists can use ADC to detect CKD in cholangiocarcinoma patients regardless of MRI field strength or type of cholangiocarcinoma.

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Table 4
Apparent diffusion coefficient (ADC) of cholangiocarcinoma patients categorized by presence of chronic kidney disease (CKD): a subgroup analysis by cholangiocarcinoma type.

Factors	No CKD n = 114	CKD n = 44	p value
Intrahepatic, n = 62	n = 42	n = 20	
Right kidney	2.11 (0.11)	1.89 (0.15)	< 0.001
Left kidney	2.12 (0.11)	1.88 (0.19)	< 0.001
Average	2.11 (0.08)	1.89 (0.16)	< 0.001
Perihilar, n = 82	n = 64	n = 18	
Right kidney	2.08 (0.07)	1.89 (0.17)	< 0.001
Left kidney	2.11 (0.11)	1.87 (0.15)	< 0.001
Average	2.10 (0.07)	1.88 (0.15)	< 0.001
Distal, n = 14	n = 8	n = 6	
Right kidney	2.11 (0.14)	1.89 (0.11)	0.001
Left kidney	2.08 (0.10)	1.90 (0.12)	0.020
Average	2.10 (0.09)	1.90 (0.11)	0.009

Table 5
Apparent diffusion coefficient (ADC) of cholangiocarcinoma patients categorized by presence of chronic kidney disease (CKD): a subgroup analysis by MRI field strength and cholangiocarcinoma type.

Factors	No CKD n = 114	CKD n = 44	p value
1.5 T, n = 122			
Intrahepatic, n = 45	n = 32	n = 13	
Right kidney	2.10 (0.08)	1.98 (0.15)	0.012
Left kidney	2.13 (0.08)	1.93 (0.13)	< 0.001
Average	2.11 (0.06)	1.95 (0.14)	< 0.001
Perihilar, n = 64	n = 52	n = 12	
Right kidney	2.11 (0.11)	1.87 (0.15)	< 0.001
Left kidney	2.11 (0.11)	1.89 (0.20)	< 0.001
Average	2.11 (0.09)	1.88 (0.16)	< 0.001
Distal, n = 13	n = 8	n = 5	
Right kidney	2.11 (0.14)	1.92 (0.09)	0.040
Left kidney	2.08 (0.10)	1.94 (0.09)	0.019
Average	2.10 (0.09)	1.93 (0.09)	0.003
3.0 T, n = 36			
Intrahepatic, n = 17	n = 10	n = 7	
Right kidney	2.08 (0.09)	1.87 (0.20)	0.011
Left kidney	2.06 (0.11)	1.88 (0.11)	0.005
Average	2.07 (0.06)	1.88 (0.14)	0.008
Perihilar, n = 18	n = 12	n = 6	
Right kidney	2.08 (0.06)	1.94 (0.14)	0.012
Left kidney	2.16 (0.11)	1.88 (0.20)	0.006
Average	2.12 (0.07)	1.91 (0.17)	0.011
Distal, n =1	n = 0	n = 1	
Right kidney		1.74	NA
Left kidney		1.72	NA
Average		1.73	NA

Note. There was no statistical significance of ADC values of intrachepatic and perihilar cell types between 1.5 T and 3.0 T MRI field strength.

Table 6
Apparent diffusion coefficient (ADC) cut point of cholangiocarcinoma patients for chronic kidney disease (CKD) by various study populations.

Group	Cut point ADC, mm/s^2	Sensitivity	Area under ROC
All patients	1.75	79.55	88.23
1.5 T field strength	1.75	86.67	88.39
3.0 T field strength	1.75	71.43	87.34
Intrahepatic	1.75	90.00	85.83
Perihilar	1.75	66.67	87.85
Distal	1.78	100	100

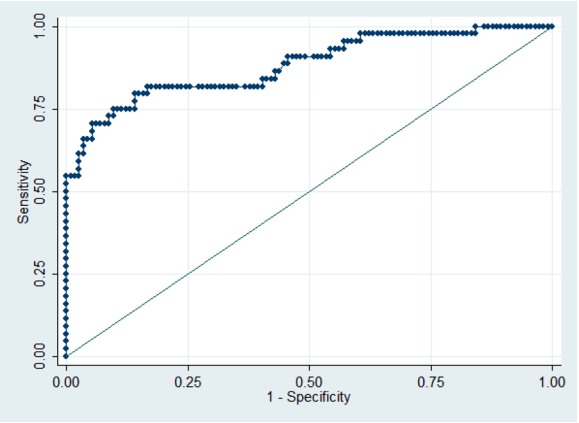

Fig. 3. A receiver operating characteristic (ROC) curve for chronic kidney disease by an apparent diffusion coefficient (ADC) in cholangiocarcinoma patients.

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CRediT authorship contribution statement

Jaturat Kanpittaya: Conceptualization, Methodology, Writing - original draft. **Wichuda Apipattarakul:** Data curation, Investigation. **Verajit Chotmongkol:** Supervision, Writing - review & editing. **Kittisak Sawanyawisuth:** Conceptualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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