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Diagnostic value of contrast-enhanced CT-related parameters and ΔCT in evaluating the biological activity and natural course of cystic hepatic echinococcosis

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Diagnostic value of contrast-enhanced CT-related parameters and ΔCT in evaluating the biological activity and natural course of cystic hepatic echinococcosis

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Abstract

Objectives: The aim of this study was to retrospectively analyze the enhanced CT value, ΔCT value, and CT imaging manifestations of 331 cases with cystic hepatic echinococcosis (CE) diagnosed by clinical CT and confirmed by surgical pathology. We also determined the correlation between these quantitative imaging parameters and the biological activity of the hydatid cysts throughout their natural disease course.

Methods and Results: A total of 398 cysts from 331 patients were evaluated based on the WHO-IWGE classification. We observed statistically significant differences in CT values between the different CE stages (CL to CE5) from the delayed phase ($F=253.753$, $P<0.001$), arterial phase ($F=167.235$, $P<0.001$), and portal phase ($F=195.364$, $P<0.001$). Significant differences were also observed in ΔCT values (portal minus delayed phase) ($F=187.753$, $P<0.001$). Spearman correlation analysis showed that biological activity of the cysts had a negative correlation with cyst diameter ($rs<0$, $P<0.01$), while positive correlations were observed with three-phase enhanced CT values and ΔCT values ($rs>0$, $P<0.01$). ROC curve analysis demonstrated that portal CT values, ΔCT values, and their combined predictive values showed statistically significant correlations with cyst inactivation ($P<0.01$). Notably, ΔCT values had superior diagnostic efficacy for predicting cyst inactivation compared to that of portal CT values (AUC: 0.850 vs. 0.731).

Conclusion: Both portal CT values and ΔCT values effectively predict CE biological activity. However, ΔCT values demonstrate better diagnostic efficacy and more accurately reflect the microenvironmental changes that occur during the natural course of CE, and therefore provide a reliable quantitative tool for clinical decision-making.
Keywords: cystic liver biliary hydatid, CT value, ΔCT value, natural course

1. Introduction

Hepatic cystic echinococcosis (CE) is a globally distributed yet widely neglected chronic zoonotic parasitic disease caused by an Echinococcus granulosus infection. CE is therefore a severe public health burden and is very prevalent in the western China regions of Xinjiang, Sichuan, Qinghai and several other regions[1-4]. As humans act as the intermediate hosts, the natural progression of CE in the human body involves a lengthy process of growth, development, degeneration, and eventual inactivation or death, which spans several years to decades[5]. Accurate assessment of the biological activity of the cyst during this natural course is therefore crucial for determining an optimal clinical intervention strategy[6].

Imaging examinations of CE mainly include ultrasound, CT, and MRI. Among these procedures, ultrasound was the first to be applied clinically and formed the basis of the World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) classification[7]. However, ultrasound has significant limitations due to operator dependence, limited imaging data retention, and the inability to fully assess the specific morphology, micro-calcifications, and spatial relationship with biliary structures[8,9]. In contrast, CT imaging provides clinicians with more detailed tomographic data and offers superior spatial resolution and tissue contrast.

Our preliminary clinical observations showed that CT values and imaging manifestations reflected clinical pathological changes, such as the characteristics of the cysts content and calcification trends during different stages of the natural progression of CE. As the cyst degenerates, the intracystic microenvironment undergoes significant alterations, including fluid concentration, accumulation of proteinaceous debris, and eventual fibrosis and calcification of the cyst wall[10,11]. Recent studies have suggested that these pathological changes are possibly mediated by inflammatory responses and autophagy pathways triggered by biliary micro-fistulas or calcification of nanoparticles, thereby fundamentally altering the X-ray absorption characteristics of the cyst[12,13].

Building on these findings, the aim of the current study was to introduce a novel quantitative parameter, the ΔCT value (i.e., the mean of three portal-phase CT values minus the mean of three delayed-phase CT

values). By integrating enhanced CT imaging features with pathological activity, the study measured the correlations between CE biological activity and CT imaging indicators. We hypothesized that the dynamic contrast enhancement pattern (ΔCT) can more sensitively capture the microenvironmental and hemodynamic shifts associated with cyst inactivation than that achieved by static single-phase CT values. Our study may therefore establish a robust, non-invasive diagnostic method for assessing CE activity, thereby assisting clinicians to formulate rational and individualized treatment strategies.

2. Materials and Methods

2.1 Study subjects

The study was a retrospective design that involved collecting 398 cysts from 331 confirmed CE cases treated at the First Affiliated Hospital of Shihezi University. The CT scans were performed between January 2008 and December 2018. The cohort included 179 males and 152 females, with an age range from 5 to 84 years, with a mean age of 42.5 years. The study protocol was approved by the Institutional Review Board of Shihezi University, and informed consent was waived due to the retrospective nature of the study.

Inclusion criteria: (1) Diagnosis of CE prior to surgery using B-ultrasound, CT, MRI, or serological immunological tests; (2) Underwent surgical treatment with confirmed postoperative pathology; (3) Complete clinical and multi-phase CT imaging data available.

Exclusion criteria: (1) Alveolar echinococcosis (AE) or other non-parasitic hepatic cystic diseases; (2) Advanced complicated CE lacking complete imaging; (3) Patients who received conservative medical treatment only.

2.2 CT imaging protocol and classification

The examination was performed using GE Healthcare's Hispeed/Ni dual-slice CT system. The patients were instructed to consume 1000-1500 mL of water whilst sitting in a supine position prior to the scan. The slice thickness and interval were both set to 1 mm. For contrast-enhanced scanning, 100 mL (64.7g) of iohexol was administered via the antecubital vein at a rate of 3 mL/s. Standard three-phase liver scans were performed using the following settings: arterial phase (20-25s), portal venous phase (65-70s), and delayed phase (3-6min). The system was operated at 120 kV and 300 mA.

The cysts were classified according to the WHO-IWGE standardized ultrasound/imaging classification scheme: CL (cystic lesion), CE1 (unilocular, simple cyst), CE2 (multivesicular, multiseptated cyst), CE3 (transitional stage with a detached inner cyst/water-lily sign), CE4 (solid/pseudotumor stage), and CE5 (calcified stage)[7].

2.3 ΔCT calculation and measurement

Using Mimics Medical 21.0 software, the mean CT value of the cyst contents was measured. To ensure accuracy, regions of interest (ROIs) were selected carefully in order to avoid calcified walls or obvious artifacts. (1) The most uniformly representative lesion area in the portal phase was identified, and the CT value (in Hounsfield units, HU) was measured on three adjacent consecutive slices. (2) In the delayed phase, the exact same spatial ROIs were located, with the CT values measured three times. The ΔCT value was defined as the difference between the mean portal-phase CT value and the mean delayed-phase CT value. (i.e., ΔCT=mean CT portal-mean CT delayed). Similarly, ΔCT' was calculated as the difference between the CT values in the arterial-phase and delayed-phase.

2.4 Surgical methods and biological activity assessment

The surgical approach employed was the complete enucleation of the inner and outer capsules. Biological activity was determined based on the intraoperative findings and postoperative pathological microscopic examination of the protoscoleces. Cysts classified as CL, CE1, CE2, or CE3 were generally considered biologically active (or transitional), whereas CE4 or CE5 stages were defined as inactive (dormant/dead)[14].

2.5 Statistical analysis

The statistical analyses were performed using SPSS 25.0. Quantitative data with a normal distribution were expressed as mean±standard deviation. One-way ANOVA was used for the intergroup comparisons between different CE stages. The correlation analyses were carried out using the Spearman rank-order correlation test. Binary logistic regression was used to identify risk factors for cyst inactivation, while diagnostic efficacy was evaluated using receiver operating characteristic (ROC) curves, with the area under the curve (AUC) then calculated. A P value<0.05 was considered statistically significant.

3. Results

3.1 Relationship between CT parameters and CE stages

The CT values within each CE stage were analyzed. Statistical significance was observed across the different stages for delayed-phase CT values (F=253.753, P<0.001), arterial-phase CT values (F=167.235, P<0.001), portal-phase CT values (F=195.364, P<0.001), ΔCT values (F=187.753, P<0.001), ΔCT values (F=134.741, P<0.001), and cyst diameter (F=128.246, P<0.001). These findings indicated that the cysts evolved from CL type to CE5 type, with the mean cyst diameter increasing initially but then decreasing (peaking at CE2: 103.73±34.56 mm and declining at CE5: 37.41±8.84 mm). Concurrently, both the intracystic CT values and ΔCT values showed a gradual but significant increase during the natural progression of the disease.

3.2 Diagnostic efficacy of CT values and ΔCT values

Comparing diagnostic efficacy, ROC curve analysis demonstrated that both portal CT values and ΔCT values had a statistically significant predictive value for CE inactivation (P<0.001). Notably, ΔCT values demonstrated superior diagnostic efficacy (AUC=0.850, sensitivity=87.5%, specificity=86.8% at a cut-off of 2.93 HU) compared to that of portal CT values (AUC=0.731,sensitivity=81.3%, specificity=81.1% at a cut-off of 30.64 HU). This indicated that the dynamic change in density (ΔCT) was a more robust biomarker than static density measurements.

3.3. Pathological changes and CT imaging correlation

In early-stage (CE1/CE2) active disease, CT imaging revealed cystic masses with a uniform, watery, and hypodense appearance. Contrast-enhanced scans demonstrated no significant internal enhancement, while the outer capsule showed marked enhancement. Pathologically, this corresponded to clear cyst fluid and highly active protoscoleces.

In the transitional stages (CE3), the inner capsule collapsed (water-lily sign), while the cyst cavity displayed band-like high-density imaging, accompanied by markedly increased density of intracystic material. The surgical findings often revealed viscous, gelatinous material and necrotic inner capsule tissue, frequently associated with biliary micro-fistulas.

In the inactive stages (CE4/CE5), the hallmark features were solidification and calcification. The CT images showed patchy, annular, or eggshell-like high-density lesions, while the specimens showed a hardened outer capsule with extensive calcium salt deposits which blocked nutrient exchange and confirmed the death of the parasite.

3.4. The relationship between CT values, ΔCT values, and various echinococcosis cyst subtypes was analyzed.

The CT values calculated for each echinococcosis cyst subtype are shown in Tables 1-6. Statistical significance was observed for delayed-phase CT values (F=253.753, P<0.001) **(Table 1)**, arterial-phase CT values (F=167.235, P<0.001) **(Table 2)**, portal-phase CT values (F=195.364, P<0.001) **(Table 3)**, ΔCT values (F=187.753, P<0.001) **(Table 4)**, ΔCT' values (F=134.741, P<0.001) **(Table 5)**, and cyst diameter (F=128.246, P<0.001) **(Table 6)**. As the echinococci evolved from CL type to CE5 type, the liver cyst diameter increased initially but then decreased, with both intracystic CT values and ΔCT values gradually increasing.

Fractal	Cyst counts	Intracapsular CT value（$\bar{x}$ ± s）（HU）	F-value	P-value
CL and CE1	89	11.84±6.23	253.753	<0.001
CE2	81	19.65±8.46		
CE3	106	31.56±10.89		
CE4	83	43.85±11.23		
CE5	39	95.36±43.89		

Table 1. Comparison of CT values between the delayed periods of the various types of hepatic cystic echinococcosis

Fractal	Cyst counts	Intracapsular CT value（$\bar{x}$ ± s）（HU）	F-value	P-value
CL and CE1	89	14.34±4.75	167.235	<0.001
CE2	81	20.13±6.31		
CE3	106	33.93±13.69		
CE4	83	51.16±12.41		
CE5	39	226.30±64.23		

Table 2. Comparison of arterial CT values in the various types of hepatic cystic echinococcosis

Fractal	Cyst counts	Intracapsular CT value（$\bar{x}$ ± s）（HU）	F-value	P-value
CL and CE1	89	15.13±5.23	195.364	<0.001
CE2	81	21.14±4.52		
CE3	106	34.78±10.39		
CE4	83	54.16±13.24		
CE5	39	209.83±59.32		

Table 3. Comparison of the portal CT values in the various types of hepatic cystic echinococcosis

Fractal	Cyst counts	Intracapsular ΔCT2 value ($\bar{x} \pm s$) (HU)	F-value	P-value
CL and CE1	89	0.74±0.14	187.753	<0.001
CE2	81	1.57±0.94		
CE3	106	3.40±2.47		
CE4	83	7.86±4.58		
CE5	39	13.67±7.23		

Table 4. Comparison of intracystic ΔCT values in the various types of hepatic cystic echinococcosis

Fractal	Cyst counts	Intracapsular ΔCT1 value ($\bar{x} \pm s$) (HU)	F-value	P-value
CL and CE1	89	0.56±0.11	134.741	<0.001
CE2	81	1.35±0.53		
CE3	106	2.96±0.98		
CE4	83	6.13±2.56		
CE5	39	11.53±5.63		

Table 5. Comparison of intracystic ΔCT' values in the various types of hepatic cystic echinococcosis

Fractal	Cyst count	Cyst diameter ($\bar{x} \pm s$) (mm)	F value	P value
CL and CE1	89	92.32±25.73	128.246	<0.001
CE2	81	103.73±34.56		
CE3	106	71.15±18.8		
CE4	83	54.68±10.2		
CE5	39	37.41±8.84		

Table 6. Comparison of the cyst diameter in the various types of hepatic cystic echinococcosis

3.5. The relationship between CT values, ΔCT values, and echinococcal activity Based on domestic and international research and clinical experience, we generally consider that as echinococci evolve from the CL type to the CE5 type, their activity decreases gradually. Specifically, the CL, CE1, CE2, and CE3 stages represent active phases, while the CE4 and CE5 stages indicate dormant phases (i.e., loss of activity). Spearman correlation analyses were conducted between the echinococcal activity levels and patient age, gender, cyst diameter, enhanced CT values at three phases, ΔCT values, and ΔCT' values. The results showed no significant correlation between age or gender and echinococcal activity (rs <0.3). However, echinococcal activity showed a negative correlation with cyst diameter (rs <0.01) and positive correlations with enhanced CT values at the three phases, ΔCT values, and ΔCT' values (rs> 0.01) (Table A7). Logistic regression analysis was conducted to examine the association between echinococcosis activity and patient characteristics including age, gender, cyst diameter, enhanced CT values at stage III, ΔCT values, and ΔCT' values. The results indicated that age, gender, cyst diameter, arterial-phase CT values, and ΔCT' values (all P> 0.05) were not risk factors for echinococcosis inactivation. In contrast, the delayed-phase CT values, portal-phase CT values, and ΔCT values (all P <0.05) were identified as significant risk factors for echinococcosis inactivation (Table 8 and Figure 1).

	rs	P
Age	-0.225	0.039
Gender	0.0228	0.799
Cyst diameter	-0.71	＜0.01
Delayed phase CT values	0.716	＜0.01
Arterial CT value	0.751	＜0.01
Portal phase CT value	0.755	＜0.01
CT difference between portal phase and delayed phase (ΔCT value)	0.556	＜0.01
Arterial versus delayed CT difference (ΔCT' value)	0.505	＜0.01

Table 7. Spearman correlation analysis results

	β	P	OR	OR 95%CI lower limit	OR 95%CI upper limit
Age	-0.59	0.100	0.942	0.878	1.011
Gender	-0.981	0.338	0.375	0.050	2.793
Cyst diameter	-0.43	0.057	0.958	0.916	1.001
Delayed phase CT values	0.389	0.007	1.153	1.051	1.265
Arterial CT value	0.118	0.261	1.125	0.916	1.382
Portal phase CT value	0.402	0.008	1.495	1.112	2.009
CT difference between portal phase and delayed phase (ΔCT value)	0.487	0.014	1.628	1.102	2.405
Arterial versus delayed CT difference (ΔCT' value)	0.165	0.210	1.179	0.911	1.526

Table 8. Logistic regression parameter estimation results

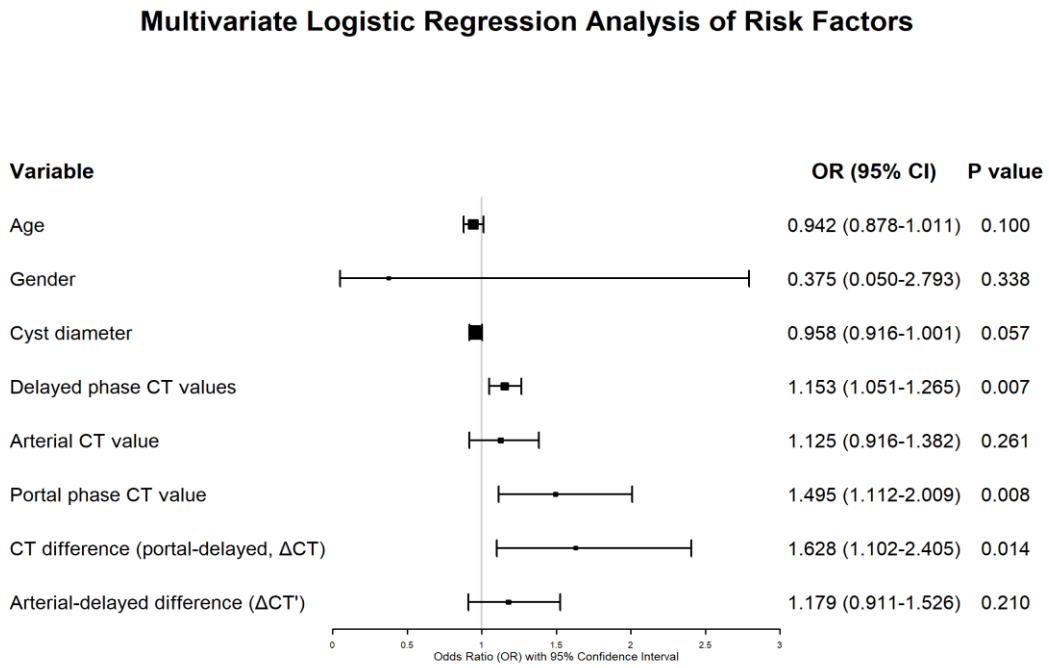


Figure 1. Forest plot

The diagnostic efficacy between CT values and ΔCT values was compared using logistic regression analysis that showed the combined predictors of portal CT values and ΔCT values. ROC curves for portal CT values, ΔCT values, and their combined predictors showed statistically significant correlations (P<0.01). Notably, ΔCT values had superior diagnostic efficacy for predicting echinococcosis inactivation than that of portal CT values, with the combined predictors outperforming single CT value indicators **(Table 9 and Figure 2)**.

	Cut off value	AUC	P	Sensitivity (%)	Specificity (%)
Portal phase CT value	30.64	0.731	＜0.001	81.3	81.1
CT difference between portal phase and delayed phase (ΔCT value)	2.93	0.850	＜0.001	87.5	86.8
Joint Prediction	0.16	0.874	＜0.001	88.9	84.9

Table 9. The diagnostic value of CT and ΔCT in diagnosing echinococcus activity

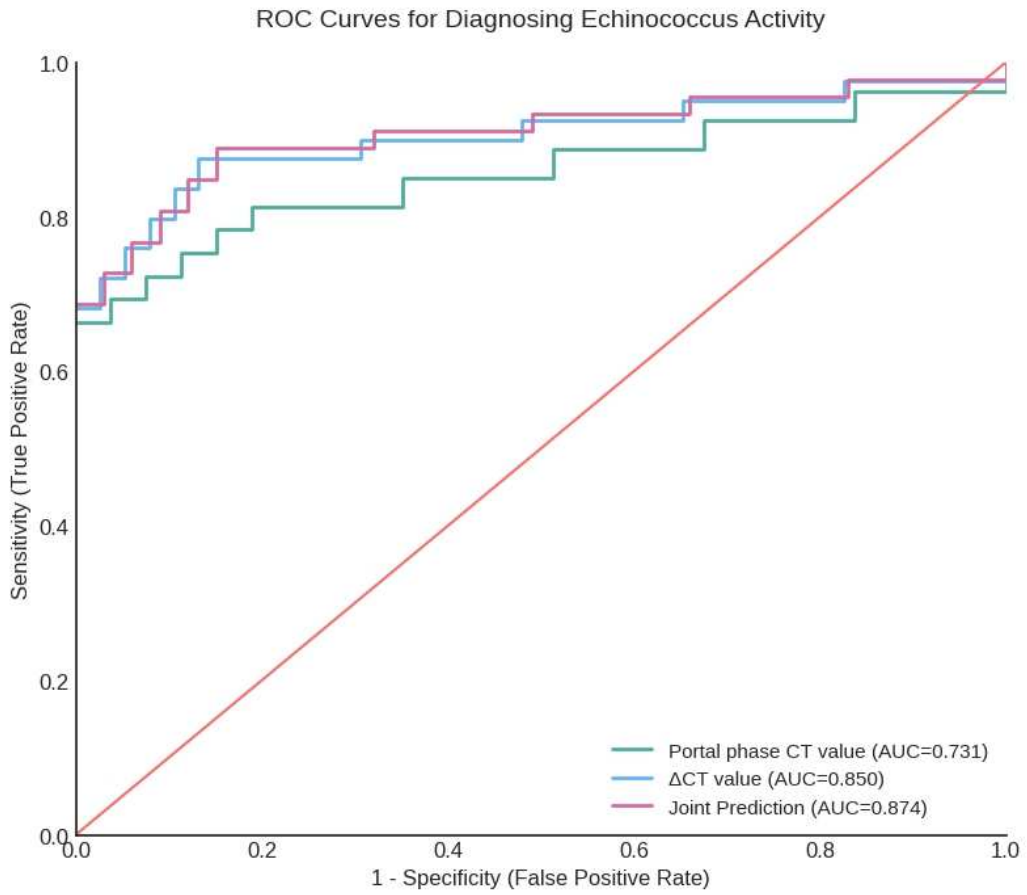


Figure 2. ROC curve of portal CT value and ΔCT value for diagnosis of echinococcus activity

3.6. Pathological changes and CT imaging data of cystic liver hydatid

In the early-stage of solitary cystic hydatid disease, CT imaging showed cystic masses within the hepatic parenchyma. These lesions had a uniform density with a watery hypodense appearance, typically appearing as round-shaped formations with visible outer capsule structures. Contrast-enhanced scans demonstrated no significant internal changes in the core, while the outer capsule showed marked enhancement. The cyst fluid appeared transparent and contained soft and elastic white membranes that formed a thin, tightly adherent layer on the inner surface of the capsule.

As the infection progressed, multiple regular-shaped spherical daughter cysts developed within the parent cyst. These daughter cysts were distributed along the cyst wall in a characteristic "honeycomb" pattern. Compared to the parent cyst fluid, the daughter cyst fluid had greater clarity, whereas the parent cyst fluid had increased turbidity and reduced volume.

In stage III and IV echinococcal cysts, the inner capsule structure had collapsed characteristics. The cyst cavity displayed band-like high-density imaging with significant separation between the inner and outer capsules, accompanied by markedly increased density of the intracystic material. The surgical findings showed that these cystic lesions were often associated with biliary fistula formation. The cyst cavity was filled with viscous gelatinous material, while the inner capsule tissue had undergone necrotic changes, forming a distinct boundary with the outer capsule structure.

As shown in Figure 3, the hallmark of the calcific hydatid disease was the presence of distinct calcified areas, which presented as eggshell-like or arc-shaped high-density lesions. When calcification occurred within the cysts, it manifested as patchy, annular, or petal-shaped dense shadows. Examination of the surgical specimens showed a hardened outer capsule with extensive calcified deposits observed both on the cyst wall and within the cavity.

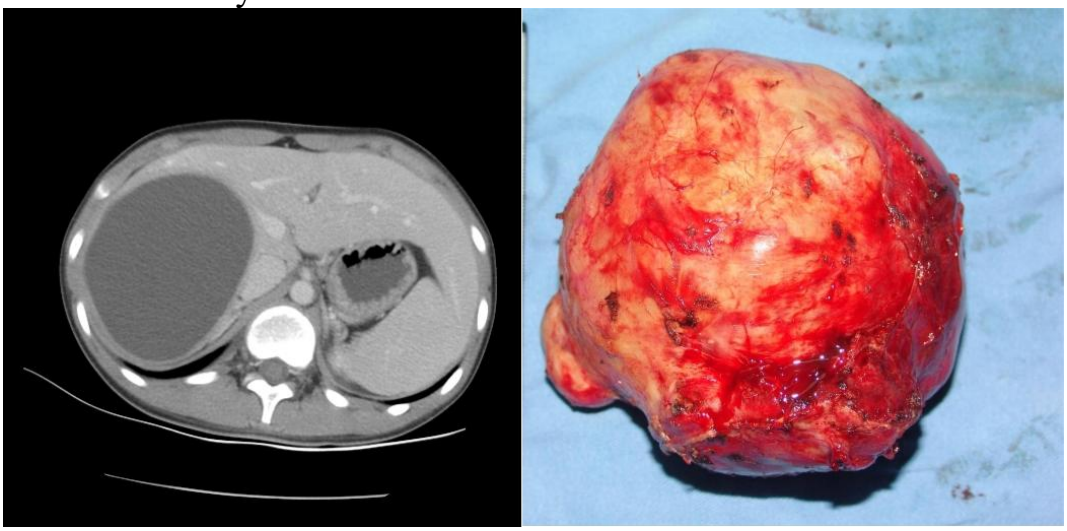


Figure 3. Single sac liver cyst

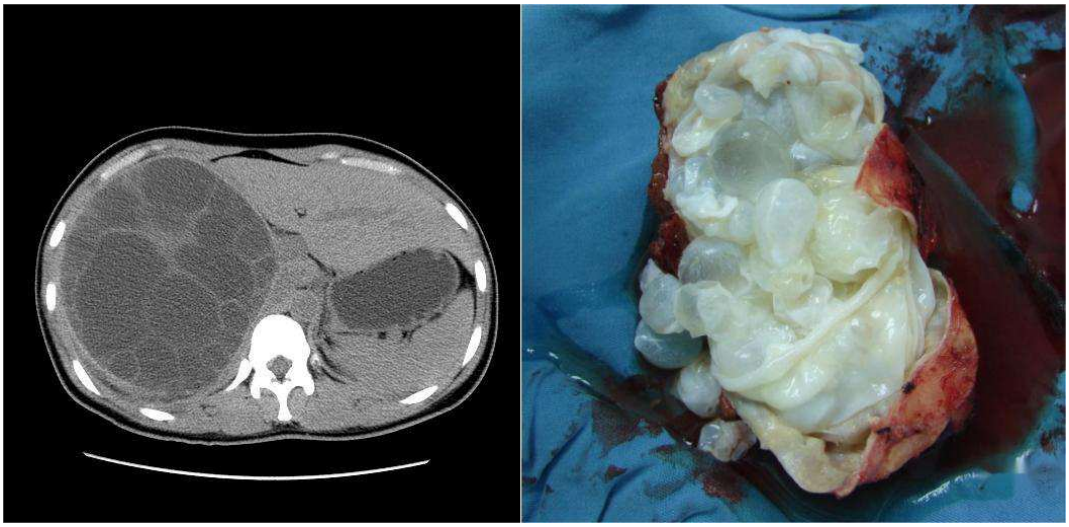


Figure 4. Multicystic echinococcus

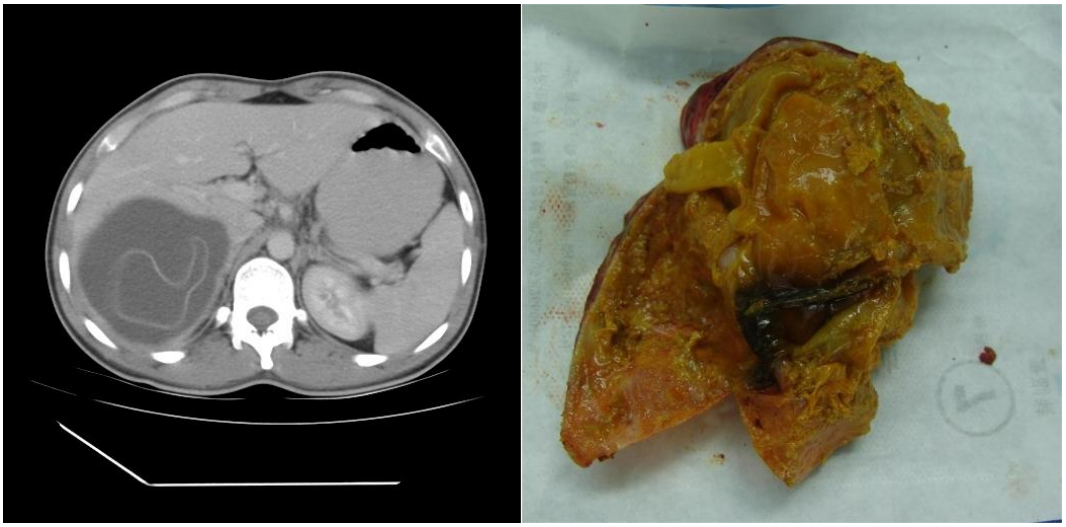


Figure 5. Intra-cystic collapse type hydatid

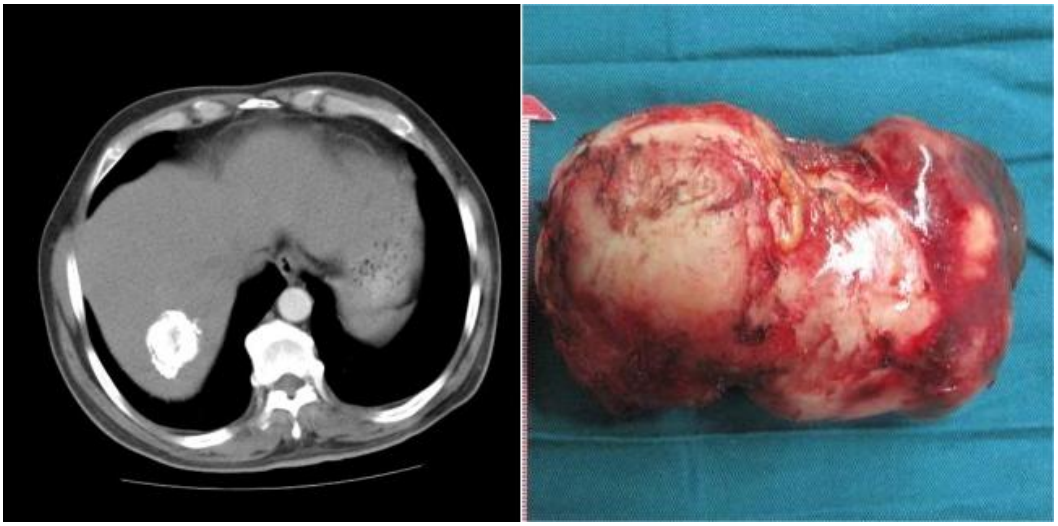


Figure 6. Calcified echinococcus

4. Discussion

Hepatic CE progresses slowly through its stages of growth, degeneration, and eventual inactivation. The WHO-IWGE classification provides a useful framework for staging the cysts, with CE1–CE3 considered active/transitional and CE4–CE5 largely inactive[7]. Accurate assessment of cyst activity is therefore essential for guiding clinical management, such as choosing between radical resection, conservative enucleation, or "watch and wait" strategies[15].

4.1 Advantages of CT in evaluating CE

While ultrasound is the primary screening tool, CT technology has been widely adopted for clinical diagnosis and surgical planning. Compared with ultrasound, CT tomographic imaging has superior spatial resolution and tissue contrast and enables clear visualization of the morphology of the lesion, anatomical positioning, and spatial relationships with adjacent biliary structures[16]. Crucially, CT provides quantitative density measurements (Hounsfield units) that objectively reflect the physical state of the cyst contents, overcoming the dependence of the operator on the use of ultrasound [17].

4.2 Relationship between CT values, CE activity, and the natural course of the disease

CT values, as quantitative parameters used to assess tissue X-ray absorption, show a positive correlation with tissue density. In this study, we observed that as CE progressed from early to advanced stages, intracystic CT values exhibited a significant increasing trend. In the early disease phases (CE1/CE2), low CT values (11-20 HU) were observed, consistent with the presence of clear cyst fluid and highly active parasites [18].

As the disease progressed to the transitional phase (CE3), the CT values increased. Drawing upon recent pathophysiological insights, this stage was often accompanied by the formation of biliary micro-fistulas. The influx of bile altered the intracystic microenvironment, causing the fluid to concentrate and become mucoid or gelatinous [19]. As a consequence, the cyst walls lost elasticity and gradually fibrosed, leading to parasite stress and reduced viability[20].

In advanced stages (CE4/CE5), CT values peaked up to>200 HU. At this stage, the cyst cavity often contained caseous necrotic material that underwent organization. The deposition of calcium salts on the cyst walls also formed a physical barrier that blocked nutrient absorption, ultimately leading to the death of the parasite[21]. Recent studies have suggested that calcifying nanoparticles (CNPs) and autophagy pathways drive this pathological calcification process in the outer capsule[22, 23]. The progressive increase in CT values perfectly mirrors this natural biological trajectory from a fluid-filled active cyst to a solid, calcified, dead lesion.

4.3 The superior diagnostic value of ΔCT

Beyond static CT measurements, our study innovatively introduced the ΔCT value (portal-phase minus delayed-phase CT value) as a dynamic biomarker. Spearman correlation and logistic regression confirmed that ΔCT was a significant independent risk factor for CE inactivation. More importantly, ROC analysis demonstrated that ΔCT (AUC=0.850) outperformed single-phase portal CT values (AUC=0.731) in predicting cyst inactivity.

The physiological basis for this superiority lies in the hemodynamics and tissue permeability of the cyst wall. In active cysts, the intact parasitic membrane prevents rapid contrast exchange, resulting in a minimal ΔCT. However, as the cyst degenerates, the breakdown of the inner capsule, inflammatory neovascularization of the fibrotic outer capsule, and altered permeability due to necrosis result in differential contrast wash-in and wash-out dynamics[24,25]. Therefore, ΔCT captures not only the static density, but also the dynamic physiological state of the cyst-host interface, thereby making it a more sensitive and specific predictor of the natural disease course.

4.4 Clinical implications and limitations

Our findings support ΔCT as a practical, non-invasive imaging biomarker for assessing cyst activity. A ΔCT cut-off of 2.93 HU provides a reliable threshold for identifying inactive cysts. Integration of this biomarker into clinical workflows may improve the early identification of inactive cysts and help clinicians avoid unnecessary surgical interventions for dormant lesions and also provide tailored personalized treatment strategies[26].

However, the study had several limitations as it was a retrospective, single-center design, and in addition, while we hypothesized that the microenvironmental changes and calcification mechanisms (i.e., CNP-mediated autophagy) drove the density changes observed by CT, direct molecular and histological validation was not performed in the study cohort. Future prospective, multicenter studies incorporating molecular pathology are therefore needed to confirm the generalizability and mechanistic basis of ΔCT.

5. Conclusions

The study demonstrated that both static CT values and dynamic ΔCT measurements correlate closely with cystic hepatic echinococcosis activity. While portal-phase CT values are predictive, ΔCT values provide superior diagnostic efficacy and more closely reflect the pathophysiological changes during the natural progression of the disease. By capturing the microenvironmental shifts associated with cyst degeneration and calcification, ΔCT serves as a robust quantitative tool. Its application may therefore assist clinicians to tailor individualized treatment strategies and optimize surgical decision-making.

6. Patents

Author contributions

(I)Conception and design: Jian Yang, Xiangwei Wu; (II) Administrative support: Jian Yang, Xiangwei Wu; (III) Provision of study materials: Meiyan Wang, Aerman Ainiwaer; (IV) Collection and assembly of data: Sanqiang Niu; (V) Data analysis and interpretation: Meiyan Wang, Aerman Ainiwaer; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of The First Affiliated Hospital of Shihezi University (protocol code is KJ2022-221-02 and date of approval is February 11,2023).” for studies involving humans.
Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.Written informed consent has been obtained from the patients to publish this paper.

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Conflicts of Interest: The authors declare no conflicts of interest.

Clinical trial number: not applicable.

Abbreviations
The following abbreviations are used in this manuscript:

AE	Alveolar echinococcosis
AUC	Area Under the Curve
CE	Cystic Hepatic Echinococcosis
CL	Cystic Lesion
WHO-IWGOE	World Health Organization Informal Working Groups on Echinococcosis

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