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Cystic echinococcosis of the liver in the Autonomous Province of Vojvodina, Serbia – challenges in clinical practice

Cistična ehinokokoza jetre u Autonomnoj pokrajini Vojvodini, Srbija – izazovi u kliničkoj praksi

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Abstract

Background/Aim. Cystic echinococcosis (CE) of the liver represents a significant health and economic burden in endemic regions, with a rising incidence in the Autonomous Province of Vojvodina, Serbia. The aim of the study was to investigate the therapeutic modalities applied in patients with hepatic CE treated at the University Clinical Center of Vojvodina over an 11-year period, compare their outcomes, and analyze indirect indicators of economic burden. **Methods.** A retrospective analysis was conducted, including 90 patients with hepatic CE diagnosed and/or treated at the University Clinical Center of Vojvodina between 2013 and 2024. Diagnosis was based on epidemiological data, serological testing, and imaging methods, with liver cysts classified according to World Health Organization criteria. Patients were stratified into five groups according to the therapeutic approach, and treatment modalities were analyzed in relation to the number and length of hospitalizations, cyst stage, antibody titer, and the number of albendazole courses. **Results**. Women comprised the majority of patients (n = 53; 59%; $p < 0.001$), with a mean age of 55 years (range: 16–86 years). The mean length of hospital stay was 32.82 days and did not differ significantly according to the treatment modality ($p = 0.071$). The number of hospitalizations was significantly higher in patients treated with invasive methods (surgery/ puncture, aspiration, injection, and re-aspiration – PAIR; $p < 0.001$). The majority of patients was treated with combination therapy: surgery with albendazole (22/90) or albendazole combined with PAIR (19/90). The highest percentage of patients (25.6%) received a single course of albendazole, whereas the number of albendazole courses differed significantly according to therapeutic approach ($p < 0.01$). Cyst stage and antibody titer showed no significant association with treatment choice ($p = 0.087$; $p = 0.891$). **Conclusion.** A national protocol incorporating established international criteria, with routine serological screening and a structured two-year follow-up, could be useful in the future care of patients with hepatic CE.

Keywords:
albendazole; echinococcosis, hepatic; serbia; surgical procedures, operative; treatment outcome.

Apstrakt

Uvod/Cilj. Cistična ehinokokoza (CE) jetre predstavlja značajan zdravstveni i ekonomski problem u endemskim sredinama, sa porastom incidencije u Autonomnoj pokrajini Vojvodini, Srbija. Cilj rada bio je da se ispitaju modaliteti lečenja primenjeni kod obolelih od CE jetre, lečenih u Univerzitetskom kliničkom centru Vojvodine tokom 11-godišnjeg perioda, uporede njihovi ishodi i analiziraju indirektni pokazatelji ekonomskog opterećenja. **Metode.** Sprovedena je retrospektivna analiza 90 bolesnika koji su imali CE jetre, dijagnostikovanih i/ili lečenih u Univerzitetskom kliničkom centru Vojvodine od 2013. do 2024. godine. Dijagnoza je bila zasnovana na epidemiološkim podacima, serološkom testiranju i radiološkim metodama, uz klasifikovanje cista jetre prema kriterijumima Svetske zdravstene organizacije. Bolesnici su prema terapijskom pristupu bili podeljeni u pet grupa, a potom su analizirani modaliteti lečenja u odnosu na broj i dužinu hospitalizacije, stadijum ciste, titar antitela i broj sprovedenih ciklusa terapije albendazolom. **Rezultati.** Žene su činile većinu obolelih (n = 53; 59%; $p < 0,001$), prosečnog životnog doba od 55 godina (raspon: 16–86 godina). Prosečna dužina hospitalizacije iznosila je 32,82

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dana i nije se značajno razlikovala prema modalitetu lečenja (p = 0,071). Broj hospitalizacija bio je značajno veći kod invazivnih metoda lečenja (hirurgija/ *puncture, aspiration, injection, and re-aspiration* – PAIR; p < 0,001). Većina bolesnika lečena je kombinovanom terapijom: hirurški zahvat uz albendazol (22/90) ili albendazol u kombinaciji sa PAIR (19/90). Najviši procenat bolesnika (25,6%) primio je jedan ciklus terapije albendazolom, dok se broj primenjenih ciklusa albendazola značajno razlikovao u odnosu na terapijski pristup (p < 0,01). Nije utvrđena značajna povezanost stadijuma ciste i titra antitela sa izborom terapijskog pristupa (p = 0,087; p = 0,891). **Zaključak.** Nacionalni protokol koji bi uključivao ustanovljene međunarodne kriterijume, sa rutinskim serološkim skriningom i strukturiranim dvogodišnjim praćenjem, mogao bi biti koristan u budućem lečenju obolelih od CE jetre.

Ključne reči:
albendazol; ehinokokoza jetre; srbija; hirurgija, operativne procedure; lečenje, ishod.

Introduction

Human echinococcosis (HE) is a zoonosis caused by metacestodes of tapeworms belonging to the genus *Echinococcus* (Figure 1). To date, four species of HE causative agents have been described: *Echinococcus (E.) granulosus* – the causative agent of cystic echinococcosis (CE), also known as hydatidosis, and the most common cause of human infection; *E. multilocularis* – the causative agent of alveolar echinococcosis; and *E. vogeli* and *E. oligarthus* – the causative agents of several reported cases of polycystic echinococcosis in Central and South America [1]. The scientific literature also describes two relatively new species, *E. shiquicus* and *E. felidis*, but their significance in human morbidity remains uncertain [2, 3]. Humans serve as intermediate hosts, with transmission occurring accidentally through ingestion of parasite eggs *via* direct contact with definitive hosts (e.g., dogs, foxes, other members of the Canidae family), or indirectly through contaminated food or water. HE is a widely distributed disease, predominating in Europe, Asia, South and Central America, Australia, the European and African parts of the Mediterranean region, the Middle East, sub-Saharan countries, Russia, and China [4]. High endemicity is typically observed in pastoral and livestock-raising communities, particularly in resource-limited rural settings where close contact between dogs and intermediate hosts sustains the parasite life cycle [5, 6]. Increased transmission is consistently associated with home slaughter of livestock, inadequate disposal of infected viscera, and the practice of feeding raw offal to dogs [7–9]. In addition, poor sanitation, limited veterinary supervision, and uncontrolled dog populations further facilitate environmental contamination with *Echinococcus* eggs and endemic transmission [10–12].

The western Balkans region (former Socialist Federal Republic of Yugoslavia – SFRY) is classified as an endemic area for hydatidosis, with an incidence of 4.8 cases *per* 100,000 inhabitants [13]. Hyperendemic areas with a disease incidence of over 12 *per* 100,000 inhabitants are defined as: Dalmatia, Herzegovina, northern Montenegro, eastern Serbia, the Raška region, Autonomous Province of Kosovo and Metohija, and North Macedonia [14, 15]. The cumulative incidence of officially reported cases in the Republic of Serbia over ten years (2001–2010) ranges from 0.46/100,000 in the central part to 39.0/100,000 in the southern part of the country. Traditionally, in the territory of the northern Autonomous Province (AP) of Vojvodina, Serbia, 118 cases of CE of the liver have been recorded over the last 42 years [16]. Over the past three years, a major concern has been the emergence of alveolar echinococcosis caused by *E. multilocularis*, with four cases reported between 2021 and 2024 [17]. The southward shift of the endemic zone has made the Mediterranean one of the main areas for researching the impact of climate change on zoonoses today. The question remains open as to why this disease is moving from the traditionally cold and humid areas of northern Europe to the warm and dry climatic

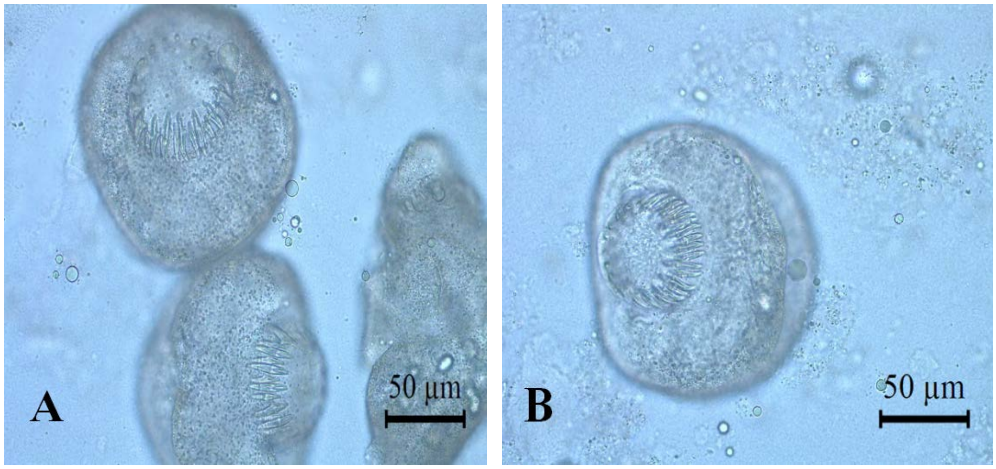

Fig. 1 – Morphologically preserved protoscoleces obtained from a hepatic echinococcal cyst (A, B).
Image courtesy of Professor Lalošević.

zones of the Mediterranean. It has been proven that the expansion of *E. granulosus* in the fox population is a consequence of successful rabies eradication campaigns and colonization of urban environments, representing a paradigm for the rise in prevalence within the human population [18]. Despite activities within the World Health Organization (WHO) "One Health" campaign, awareness regarding the significance of HE has not reached clinicians [19].

The aim of the study was to investigate the therapeutic approaches to liver CE provided in the University Clinical Center of Vojvodina (UCCV), Serbia, encompassing the last decade, as well as to compare treatment modalities and examine indirect indicators of healthcare burden, represented by hospitalization length and hospitalization frequency, in the absence of direct cost data.

Methods

This retrospective study analyzed medical records of patients with hepatic CE who were examined and/or treated at the UCCV. The study encompassed the time period from 2013 to 2024 and included a total of 90 patients who originated from regions of Bačka, Banat, Srem, or the Mačva district. This study was approved by the Ethics Committee of UCCV (No. 00-62, from February 29, 2024). This study was conducted in accordance with the ethical principles for research involving humans and/or human material.

The diagnosis of hepatic CE was established by abdominal ultrasonography (Figure 2) according to the cyst characteristics classified by the WHO Informal Working Group on Echinococcosis (WHO-IWGE) [20]. All of the observed liver cysts were solitary; cysts in other organs were not observed. Serological confirmation was obtained *via* an indirect hemagglutination test. *E. granulosus* antibody titers were classified as non-significant (1/80 or lower), mildly positive (up to 1/320 but above 1/80), or positive (greater than 1/320).

Based on treatment modalities applied, patients were divided into five groups: untreated patients, patients treated with albendazole alone, patients treated with surgery alone, patients treated with surgery combined with albendazole, and patients treated with puncture, aspiration, injection, and re-aspiration (PAIR) combined with albendazole (Figures 3–5). Surgical treatment was performed at the Clinic for Abdominal and Endocrine Surgery of UCCV, while the PAIR procedure was carried out at the Center for Radiology of UCCV. Patients received antihelminthic therapy with albendazole administered at a dose of 400 mg twice daily in the outpatient setting. Treatment was given in 28-day courses in accordance with the protocols available at the time [21]. None of the patients received continuous albendazole therapy. Follow-up examinations were performed at the end of each course by an infectious disease specialist at the Clinic for Infectious Diseases of UCCV. We analyzed the gender and age structure of the patients, length of hospitalization expressed in hospital days, number of hospitalizations, and number of hospitalizations before and after the selected treatment method. The length and number of hospitalizations were compared across treatment modalities. Additionally, cyst stage according to WHO-IWGE was compared across therapeutic modalities, and antibody titer values were also analyzed in relation to the treatment options and WHO cyst development stages.



Fig. 2 – Ultrasonographic appearance of a hepatic echinococcal cyst showing the water lily sign (CE3a stage). The arrow shows the detached, collapsed endocystic membrane floating within the cyst fluid, producing the characteristic water lily appearance. Image courtesy of Assist. Dr. Torbica.



Fig. 3 – Fluoroscopic appearance of a hepatic hydatid cyst during the initial phase of the PAIR procedure. The contrast-opacified cyst shows irregular intraluminal filling defects corresponding to collapsed parasitic membranes. The image depicts the puncture and aspiration phase, which precedes the injection of a scolicidal solution and subsequent re-aspiration.
Image courtesy of Assist. Dr. Torbica.
PAIR – puncture, aspiration, injection, and re-aspiration.



Fig. 4 – Gross specimen obtained after aspiration of a hepatic echinococcal cyst, showing abundant folded membranous material within the aspirated fluid, suggestive of detached hydatid membranes and cyst contents.
Image courtesy of Assist. Dr. Torbica.

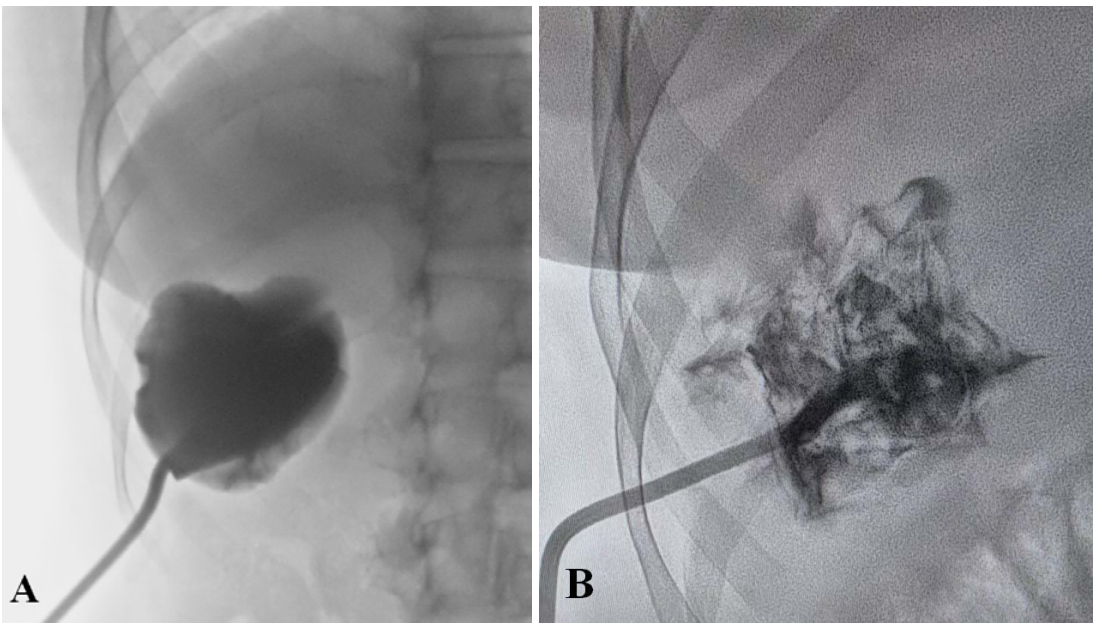

Fig. 5 – PAIR procedure: fluoroscopic images showing (A) instillation of a scolicidal agent and (B) re-aspiration of the scolicidal agent from a previously drained hepatic echinococcal cyst. Image courtesy of Assist. Dr. Torbica.
PAIR – puncture, aspiration, injection, and re-aspiration.

Table 1

Relationship between treatment modality and length of hospitalization

Variable	Albendazole	Surgery	Untreated	Albendazole + surgery	Albendazole + PAIR	*p*-value
Length of stay, days						
mean	26.68	10.25	10.8	42.71	37.88	0.071
range	1.0–79.0	6.0–20.0	1.0–27.0	12.0–143.0	4.0–102.0	

PAIR – puncture, aspiration, injection, and re-aspiration.
***Note*: Differences in length of hospital stay between treatment modalities were assessed using the analysis of variance – ANOVA test.**

Cure was defined as the absence of disease recurrence during the two-year follow-up period after the selected treatment modality. Recurrence was defined as radiologically confirmed cyst reactivation, significant antibody titer changes, or both.

Statistical analysis

Data were processed using the JASP software (JASP 0.19). Categorical variables are presented as numbers (percentages), and differences between groups were compared using the chi-square (χ^2) test, or the *t*-test, as appropriate. Continuous variables are expressed in percentiles, and differences between groups were compared using the analysis of variance – ANOVA test, considering that the distribution for most variables significantly deviated from normal. Data are presented in tabular form. Values of $p < 0.05$ were considered statistically significant.

Results

Of the 90 patients, 53 (59%) were female, and 37 (41%) were male, with a significant female predominance ($p < 0.001$). The mean age of the cohort was 55 years (range: 16–86 years), which was comparable between men (mean: 58 years, range: 25–81 years) and women (mean: 53 years, range: 16–86 years); age did not differ significantly by gender ($p = 0.141$). Notably, the youngest (16 years) and the oldest (86 years) patients in the cohort were both women.

Hospitalization burden

Mean length of hospital stay across the cohort was 32.82 days (range: 1–143 days). This burden varied by treatment modality, with combined albendazole therapy – administered alongside either surgery or PAIR – associated with the longest average hospital stays, although this difference did not reach statistical significance ($p = 0.071$) (Table 1).

While the total duration of hospitalization did not vary significantly by treatment, the number of hospitalizations *per* patient did, ranging from 0 to 7 and skewing higher among patients treated with invasive methods ($p < 0.001$) (Table 2). The single highest number of hospitalizations was seven, in a patient who was treated surgically and with albendazole.

Splitting this hospitalization count into periods before and after the selected treatment clarifies where the burden

falls. Patients who went on to receive combination therapy, required significantly more hospitalizations before the beginning of the treatment than those managed exclusively with pharmacological therapy or surgery alone ($p < 0.001$), consistent with the additional diagnostic workup needed to individualize their therapy. No such association was observed for hospitalizations after treatment ($p = 0.335$) (Table 3). The majority of patients (49/66) required no further hospitalization once their therapeutic protocol had concluded, and only one patient was treated with combined albendazole and surgery and was hospitalized as many as four times afterwards.

Of the 90 patients, 26 (28.9%) remained untreated, 19 (21.1%) received albendazole alone, 4 (4.4%) underwent surgery alone, 22 (24.4%) received combined albendazole and surgical treatment, and 19 (21.2%) were treated with albendazole and PAIR (Table 4). PAIR was never performed without concomitant pharmacological therapy. Among the 60 patients who received albendazole, the largest group, 23 (25.6%), completed a single 28-day course, while one patient (1.1%) completed six courses. The number of courses differed significantly by treatment modality ($p < 0.01$): patients managed with combination therapy were more likely to receive multiple courses, reflecting the standard practice of prolonged adjuvant albendazole alongside surgical or PAIR intervention (Tables 4 and 5).

Treatment modality showed no significant association with cyst development stage ($p = 0.087$), although invasive and combined chemotherapeutic protocols were preferentially applied to advanced CE4 and CE5 cysts, most likely reflecting symptomatic mass effect rather than a formal stage-based algorithm (Table 6).

No data were collected regarding antibody titers for 21 patients, and two patients with positive antibody titers did not undergo radiological evaluation. Neither antibody titer by treatment modality ($p = 0.891$) nor antibody titer by WHO

Table 2

Relationship between treatment modality and hospitalization count

Variable	Albendazole	Surgery	Untreated	Albendazole + surgery	Albendazole + PAIR	Total	*p*-value
Hospitalization count							
0	3	0	21	0	0	24	
1	8	4	4	8	7	31	
2	5	0	0	4	4	13	
3	2	0	0	5	2	9	< 0.001
4	1	0	0	3	5	9	
5	0	0	1	1	1	3	
6	0	0	0	0	0	0	
7	0	0	0	1	0	1	
total	19	4	26	22	19	90	

PAIR – puncture, aspiration, injection, and re-aspiration.
All values are given as numbers.
***Note*: The association was assessed using the Chi-square test (χ^2).**

Table 3

Relationship between treatment modality and hospitalization count before and after treatment

Variable	Albendazole	Surgery	Untreated	Albendazole + surgery	Albendazole + PAIR	Total	*p*-value
Hospitalization count before treatment							
0	0	4	0	8	4	16	
1	10	0	4	10	10	34	
2	3	0	0	3	5	11	
3	3	0	0	1	0	4	< 0.001
4	0	0	0	0	0	0	
5	0	0	1	0	0	1	
total	16	4	5	22	19	66	
Hospitalization count after treatment							
0	16	4	5	12	12	49	
1	0	0	0	7	5	12	
2	0	0	0	1	0	1	0.335
3	0	0	0	1	2	3	
4	0	0	0	1	0	1	
total	16	4	5	22	19	66	

PAIR – puncture, aspiration, injection, and re-aspiration.
All values are given as numbers.
***Note*: The association was assessed using the Chi-square test (χ^2).**

Table 4

The association between the number of patients and the number of albendazole courses

Variable	Values
Treatment modality	
untreated	26 (28.9)
albendazole	19 (21.1)
surgery	4 (4.4)
albendazole + surgery	22 (24.4)
albendazole +PAIR	19 (21.2)
total	90 (100)
Albendazole courses, count	
0	30 (33.3)
1	23 (25.6)
2	4 (4.4)
3	12 (13.3)
4	15 (16.7)
5	5 (5.6)
6	1 (1.1)
total	90 (100)

PAIR – puncture, aspiration, injection, and re-aspiration.
All values are given as numbers (percentages).

Table 5

The association between the treatment modality and number of albendazole courses

Variable	Albendazole	Albendazole + surgery	Albendazole + PAIR	Total	*p*-value
Albendazole courses					
1	6	9	8	23	< 0.01
2	2	1	1	4	
3	6	2	4	12	
4	5	8	2	15	
5	0	1	4	5	
6	0	1	0	1	
total	19	22	19	60	

PAIR – puncture, aspiration, injection, and re-aspiration.
All values are given as numbers.
***Note*: The association between treatment modality and the number of albendazole courses was determined using the Chi-square test (χ^2).**

Table 6

Cyst development stage and treatment modalities

Variable	WHO classification of CE							*p*-value
	CL	CE1	CE2	CE3a	CE3b	CE4	CE5	
Treatment modalities								0.087
pharmacological	1	0	3	5	4	2	4	
surgical	0	0	1	0	0	0	1	
untreated	1	3	1	3	1	3	13	
pharmacological + surgical	0	4	6	2	1	3	5	
pharmacological + PAIR	0	0	5	8	2	2	2	
total	2	7	16	18	8	10	25	

WHO – World Health Organization; CL – cystic lesion; CE – cystic echinococcosis; PAIR – puncture, aspiration, injection, and re-aspiration.
All values are given as numbers.
***Note*: The association between treatment modalities and the WHO classification of CE was assessed using the Chi-square test (χ^2).**

cyst stage ($p = 0.649$) reached statistical significance, indicating that seropositivity did not track cleanly with either the therapeutic decision or the radiological stage of the cyst (Table 7).

Overall, 55 of 90 patients (61.1%) achieved cure and 35 (38.9%) were lost to follow-up, with no confirmed recurrences. Surgery alone had the highest cure rate (4/4, 100%), followed closely by albendazole alone and albendazole with PAIR (each 15/19, 78.9%). Untreated patients had the lowest cure rate (8/26, 30.8%) and the highest rate of loss to follow-up (18/26, 69.2%) (Table 8).

Table 7

Serological and radiological analyses

Variable	Antibody titer				*p*-value
	non-significant	mildly positive	positive	total	
Treatment modality					
albendazole	6	2	9	17	0.891
surgical	0	0	1	1	
untreated	4	3	5	12	
albendazole + surgical	5	3	12	20	
albendazole + PAIR	4	5	10	19	
total	19	13	37	69	
WHO classification of CE					
CL	0	1	1	2	0.649
CE1	4	1	1	6	
CE2	4	3	7	14	
CE3a	3	3	8	14	
CE3b	3	0	4	7	
CE4	2	1	5	7	
CE5	3	4	9	16	
total	19	13	35	67	

PAIR – puncture, aspiration, injection, and re-aspiration; WHO – World Health Organization; CE – cystic echinococcosis; CL – cystic lesion.
All values are given as numbers.
***Note*: The association between antibody titer and treatment modalities, and between antibody titer and WHO cyst stage, was assessed using the Chi-square test (χ^2). Antibody titer was categorized as non-significant (1/80 or less), mildly positive (1/320 or less, but greater than 1/80), and positive (over 1/320).**

Table 8

Treatment outcomes by modality

Variable	Cured	Recurrence	Lost to follow-up	Total
Albendazole	15 (78.9)	0 (0)	4 (21.1)	19 (100)
Surgery	4 (100)	0 (0)	0 (0)	4 (100)
Untreated	8 (30.8)	0 (0)	18 (69.2)	26 (100)
Albendazole + surgery	13 (59.1)	0 (0)	9 (40.9)	22 (100)
Albendazole + PAIR	15 (78.9)	0 (0)	4 (21.1)	19 (100)
Total	55 (61.1)	0 (0)	35 (38.9)	90 (100)

PAIR – puncture, aspiration, injection, and re-aspiration.
All values are given as numbers (percentages).

Discussion

In endemic areas, the wide distribution of pastures and forests, as well as the abundance of animal resources, provides a good environment for the growth and successful reproduction of *E. granulosus* [22, 23]. The infection rate of wild and domestic animals is high, and in the context of specific cultural and socioeconomic factors, all prerequisites for transmission to the human population exist [24, 25]. Over the past 42 years, during which echinococcal disease has been monitored in the AP of Vojvodina, 118 cases have been recorded [16]. However, in the last 11 years, a total of 90 cases of CE have been treated at the UCCV. The diagnosis of echinococcosis is often established late due to the slow and asymptomatic development of the disease in the early phases, as cysts can grow for years before causing clinical symptoms. Additionally, symptoms are often non-specific and can mimic other diseases, which hinders timely recognition and requires detailed radiological and serological processing [26]. People in rural areas discover echinococcosis later due to limited access to healthcare institutions, insufficient information about the disease and its symptoms, as well as due to more frequent contact with domestic animals and dogs, which are the main carriers of the parasite [27]. Preventive measures, such as proper hygienic practices and veterinary surveillance, are often insufficiently implemented in these environments.

Our study shows a significant predominance of female patients ($p < 0.001$). Similar findings have been documented in multiple studies, attributing the observed predisposition to sex hormone-mediated modulation of the immune response [28–30]. Early marriage and frequent pregnancies in rural communities may reduce immunity through the effects of repeated childbirths, thereby increasing the risk of echinococcosis in adult women [25, 31, 32]. The larger share of the female population in our cohort could certainly be explained by the cultural characteristics of the climate, where women usually care for dogs and are involved in gardening tasks. However, the higher prevalence observed among females may also reflect improved health surveillance in women, leading to more frequent detection of this asymptomatic infection; thus, the gender disparity cannot be generalized to the entire popu-

lation. Interestingly, gender bias was not recorded in children who participated in screening programs in some provinces in China [31].

In the observed group of patients, the average age of patients was 55 years, with the youngest being 16 and the oldest 86 years old. These results are expected because echinococcus cysts grow slowly and remain asymptomatic for months, even years, after infection; although most often acquired in childhood, they are often diagnosed later. According to data from the European Register for CE, the disease was diagnosed at a mean age of 46.20 years, while in China, the average age at diagnosis was 44.5 years – in both examples, a significantly younger age of detected patients than in our cohort [33, 34]. Therefore, the average age of the afflicted is conditioned by the degree of development of mass screening programs and surveillance activity over HE, rather than the natural course of the disease itself [35]. The Centers for Disease Control and Prevention advocated the "One Health" approach for controlling numerous zoonoses, including echinococcosis. This approach recognizes that the health of people, animals, and the environment is interconnected, so it requires multidisciplinary cooperation for the effective management of this zoonotic disease. "One Health" implies veterinary interventions, medical staff efforts to educate communities about disease transmission, and multidisciplinary cooperation among doctors, ecologists, and local authorities in raising awareness of environmental factors that support the parasite cycle. By implementing "One Health principles", it is possible to significantly reduce the frequency of echinococcosis, especially in endemic areas, through the synergy of health and environmental measures [36].

Treatment of human CE consumes significant health resources. An extensive study conducted in Spain on 1,004 patients showed an average of 25.5 hospital days required *per* patient [37]. The average number of days spent in hospital in our cohort was considerably higher (32.82 days). Understandably, the treatment modality significantly affects the length of hospitalization, so patients in our cohort treated surgically and then with albendazole were hospitalized the longest on average, spending 42.71 days in hospital. Mean hospital stay was shorter for albendazole monotherapy (26.68 days) vs. combined PAIR-albendazole therapy (37.88 days). Data from contemporary literature support our research, consistently indicating a shorter length of hospital stay for patients treated with the PAIR method compared to open laparotomy [38]. Invasive interventions for the treatment of CE are anticipated to entail a higher complication rate, and thus require prolonged hospitalization [39–42]. In our study, this observation was not substantiated, as no increase in the number of hospitalization days was observed among patients treated with PAIR or surgery ($p = 0.071$). Our study showed statistical significance when observing the number of hospitalizations, indicating the need for a higher number of hospitalizations in patients treated with invasive methods ($p < 0.001$). Although patients treated with invasive methods required a greater number of hospitalizations, no statistically significant difference was observed regarding the total length of hospital stay, as previously stated. These findings suggest that no significant complications were encountered that would have prolonged hospital stays. Our study revealed a statistically significant association between the number of prior hospitalizations and the selected treatment modality, whereas no such association was evident for post-treatment hospitalizations. This disparity likely stems from comprehensive laboratory, radiological, and clinical evaluations undertaken to optimize and individualize therapy for each patient. As noted previously, hospitalization duration varies with cyst location, size, complications, and treatment approach, encompassing costs for examinations, laboratory analyses, perioperative care, surgical procedures, and inpatient days [37, 41, 42]. These thorough assessments are thus essential in managing echinococcal disease, enabling accurate diagnosis, tailored interventions, and reduced healthcare resource consumption.

When discussing CE therapy, there are several treatment modalities, ranging from pharmacological treatment to more invasive procedures. Indications for surgery should be carefully evaluated against alternative treatment options. Surgery remains the primary treatment choice for complex cysts, removal of large CE2–CE3 cysts with a greater number of daughter cysts, superficially located cysts that may rupture spontaneously or as a result of trauma, and cases where PAIR is unavailable. It is likewise indicated for infected cysts, cysts communicating with the biliary tree, or those exerting pressure on adjacent vital organs [38, 43, 44]. PAIR is indicated for inoperable patients, those who refuse surgery, or in cases of recurrence after surgery. Certain studies favor the PAIR method, highlighting lower invasiveness, a lower rate of CE recurrence, a shorter recovery and hospitalization period, and consequently lower costs to the healthcare system [38, 45, 46]. The best results arise from a combination of PAIR with anthelmintics for CE1 and CE3a cysts larger than 5 cm, which can be a first-line treatment, as well as in the therapy of pregnant women with symptomatic cysts or children < 3 years of age [45, 47]. Medications should be used to prevent recurrence following surgery or PAIR [15, 48, 49].

The selection of therapeutic modality is determined by the WHO-IWGE cyst classification [50]. In our study, treatment choice for hepatic CE showed no statistically significant association with WHO-IWGE cyst stage ($p = 0.087$). Analysis of results indicated that invasive-chemotherapeutic protocols were applied to select CE4 and CE5 cysts due to symptomatic mass effect.

Selection of the initial anthelmintic agent for CE does not present a substantial clinical challenge, as albendazole is the sole pharmacotherapeutic option available. The principal considerations, therefore, pertain to its dosage regimen, treatment duration, and vigilant monitoring for adverse effects [51–54]. Patients with larger cysts, multiple or disseminated echinococcosis, and especially with echinococcosis of the liver, central nervous system, and bones, should receive higher doses of albendazole over a longer period of time [15, 48]. In our research, 60 out of 90 patients received albendazole in courses, i.e., cycles of 28 days. Of the 60 albendazole-treated patients, 23 (25.6%) received one course, the most frequent regimen, while a single patient (1.1%) un-

derwent six courses, the highest number observed. The choice of therapeutic modality showed a statistically significant association with the number of albendazole cycles administered ($p < 0.01$), with the highest number of courses (5 to 6) being received by patients undergoing invasive procedures. This association reflects the standard clinical practice of administering prolonged albendazole regimens as adjuvant therapy in conjunction with surgical and PAIR interventions, thereby minimizing the risk of secondary dissemination consequent to cyst rupture or leakage, as well as mitigating the likelihood of disease recurrence.

Various studies show that immune tolerance to *Echinococcus* antigens leaves approximately 30% of patients immunologically silent [55, 56]. The cause of seronegativity may also be the formation of immune complexes. Craig [57] proved back in 1986 that circulating parasitic antigens can "trap" antibodies, which in that case cannot be detected by serological testing, and subsequently, Rogan and Craig [58] proved that seroreactivity is influenced by the ultrasonic morphological type of the cyst. Some authors believe these morphological types represent advanced developmental stages of the hydatid cyst, progressing from highly viable cysts (types CE1 and CE2) to septated and heteroge-neous forms (types CE3 and CE4), and ultimately calcified cysts (type CE5). It has been established that seropositivity increases as the cyst develops and drops sharply with type CE5 [15]. A variety of serological tests are currently used to support the diagnosis of CEs, most commonly the indirect hemagglutination assay, indirect immunofluorescence assay, and enzyme-linked immunosorbent assay (ELISA). Given the varying specificity and sensitivity of these methods, some papers from contemporary literature advise the application of two different serological tests for each tested serum as a way of increasing diagnostic sensitivity [59]. In our center, all sera were tested using the indirect hemagglutination method, and a percentage of tested sera showed mildly positive, i.e., borderline antibody titer values. It is assumed that borderline values occur at the beginning of infection, when the amount of antibodies is small, or because the level of specific antibodies is variable depending on the localization and developmental stage of the cyst. In patients with a borderline antibody titer, repeat analysis of a newly obtained serum sample after 2–4 weeks is recommended, as specific antibody levels may increase during this period to a level detectable by ELISA if the disease is present [4]. In our study, the highest percentage of patients with a positive antibody titer was among patients who were treated with combined surgery and pharmacological therapy, but the results indicate that the choice of treatment method did not show a statistically significant association with the finding of antibodies in the patients' serum ($p = 0.891$). The degree of seropositivity is not the best indicator of cyst avidity, which, in our research, also did not show a statistically significant association with the choice of therapy, as antibody detectability may depend on the location, integrity, or stage of the CE.

Surgery and albendazole-based interventional treatment were associated with the most favorable outcomes in our cohort, while untreated patients had the lowest cure rate and the highest loss to follow-up. This pattern is in agreement with the literature, which identifies surgery as an effective curative modality in selected cases and supports PAIR combined with albendazole as a well-established treatment option for appropriately selected patients with CE [60, 61]. Nevertheless, the lack of observed recurrence should be interpreted cautiously because the relatively high loss to follow-up may have affected outcome assessment.

Echinococcosis has been documented in the AP of Vojvodina since 1982, and numerous studies have established its medical and public health importance as the most common parasitic disease in the region [62]. Established international criteria for cyst classification and treatment selection already exist and are well described in the literature, including the treatment-algorithm studies cited above [20, 38, 43–45, 47, 50, 60, 61]. Despite established diagnostic criteria and ongoing initiatives under the "One Health" framework, diagnosis of infiltrative cystic focal liver lesions locally does not routinely incorporate serological testing for echinococcal disease – reflecting, as previously noted, that awareness of HE has not consistently reached clinicians [19]. Early screening is critical given the asymptomatic progression of infection: undetected cysts can attain considerable size, resulting in compression of adjacent structures and severe, potentially lethal sequelae, whereas timely diagnosis enables a precise therapeutic approach and reduces the need for invasive and costly interventions. Nearly 39% of patients in our cohort were lost to follow-up, which further limits firm conclusions about long-term recurrence. We therefore recommend a national protocol that operationalizes these existing international criteria within local clinical practice, rather than a new set of guidelines. Two steps would close the implementation gap identified in this study. First, serological testing for echinococcosis (indirect haemagglutination assay, repeated after 2–4 weeks if borderline) should become a routine, protocolized step in the diagnostic work-up of any solitary cystic focal liver lesion in patients originating from, or with epidemiological exposure to, the endemic AP of Vojvodina districts of Bačka, Banat, Srem, and Mačva – rather than an *ad hoc* addition left to individual clinician judgement. Second, given the high loss to follow-up observed here, structured two-year serological and radiological follow-up should be built into post-treatment protocols, particularly for patients managed with PAIR or surgery, to allow reliable detection of recurrence. Standardizing these two steps within the existing WHO-IWGE and WHO frameworks would improve care across centers and raise clinical awareness locally, without duplicating criteria that are already well established.

Conclusion

This study demonstrates that the implementation of established international criteria for cyst classification and treatment selection remains limited in routine clinical practice, as serological testing is not routinely performed in patients with focal liver lesions. A national protocol incorporating these criteria, together with routine serological screening and structured two-year follow-up, could help address this implementation gap.

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