

Letter to
the Editor

Comment on Evaluating Giant Hydatid Cysts: Factors Affecting Mortality and Morbidity

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Keywords: hydatid disease, pulmonary hydatid cyst, postoperative complications, risk factors

Dear Editor

We read the recent article published by Dogru and colleagues with great interest.¹⁾ We would like to commend the authors for this study which is prepared as a detailed literature review. However, we would like to emphasize several points regarding the present study.

The authors have stated that the patients have received 10 mcg/kg/day albendazole during the follow-up. The albendazole dose should be corrected as 10 mg/kg/day. Also, the duration of the adjuvant therapy is reported as 6–9 months. Current literature recommends that adjuvant albendazole treatment following surgery for pulmonary hydatid cyst disease (PHCD) should be given 1–6 months following the operation in a cyclic manner with a dose of 10–15 mg/kg/day. Liver function test should be regularly checked during the treatment period.^{2–6)}

The necessity of postoperative routine albendazole therapy also needs clarification. The authors stated that 24.7% of the patients with PHCD received a radical operation. Studies on PHCD recommend that adjuvant albendazole treatment is not indicated in situations where there is no probability of remnant disease such as

surgery after uncomplicated cysts, solitary cysts, in patients who received radical surgery.²⁾

Neoadjuvant albendazole treatment in PHCD is a matter of debate. There are studies recommending neoadjuvant albendazole treatment in cysts with small diameter, multiple cysts and in cysts with a high risk of intraoperative spread.^{5,7)} On the contrary, various studies state that there is a high risk of rupture following neoadjuvant therapy and it should be avoided in PHCD.⁸⁾ The authors should clarify why they have not given neoadjuvant albendazole treatment.

The authors stated that they have used Student's t-test, Mann–Whitney U test, and Kruskal–Wallis test for comparison of the continuous variables. Since there are no three or more groups for comparison, Kruskal–Wallis test could not have been performed. Furthermore, the mean and standard deviation is very close to each other for the continuous variables which means they are not distributing normally. For this reason, Student's t-test cannot be used and the continuous variables should be expressed as median (min-max) or median (interquartile range [IQR]). In the first sentence of the results section, the authors stated that “a total of 382 patients (145 females and 138 males) were included in the study.” Instead of 382, it should be corrected as “283 patients.”

In the results section, the authors stated that “postoperative recurrence occurred in eight patients (2.8%), all of whom had undergone thoracotomy. Recurrence was attributed to continued exposure to animals.” The main factor that causes a recurrence is remnant germinant membrane due to inadequate surgery. Therefore, this statement is not compatible with current literature. The authors should provide the studies that they have used to support their statement.

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The major point regarding the present study is related with the discordance between the title and the evaluation of the data of the study cohort. The title clearly states that “factors affecting mortality and morbidity” which requires the use of multivariate logistic regression analysis for evaluation of the independent risk factors for any given clinical condition. Since mortality was observed in only one patient, a risk factor analysis is not possible. However, morbidity was observed in 29 patients and a multivariate analysis could have been performed.

The authors have used univariate analysis in the study but have not evaluated these results in the article text. This is a high-volume study and the readers would have benefitted from such an analysis. In Tables 1 and 2, it is seen that the two groups that are formed according to the diameter of the cysts (>10 cm vs <10 cm) had significant difference in terms of age ($p = 0.009$), symptoms ($p < 0.001$), management of the cysts ($p = 0.004$), and the type of operation ($p = 0.008$). We used the MedCalc program to evaluate the correlation between the diameter and the symptoms of the patients from the data presented by the authors in Tables 1 and 2. The frequency of symptomatic patients with a cystic diameter >10 cm was 4.96 times higher than the patients with a cystic diameter <10 cm (OR = 4.96, $p = 0.0011$ 95% CI = 1.9–12.9). This suggests a correlation between the diameter of the cyst and the symptoms of the patients. For this reason, the authors could have performed a receiver operating characteristic (ROC) curve analysis to calculate the cutoff diameter of the cyst in relation to the symptomatic state of the patients. Analysis of Table 1 shows that video-assisted thoracoscopy (VATS) was used in cysts <10 cm. In cysts >10 cm, conservative treatment was used more frequently than radical procedures.

In Table 2, it is seen that in patients with and without morbidity, the diameter of the cyst is the only parameter that showed a significant difference and clinical parameters such as Charlson comorbidity index, the type of operation showed no difference among these groups. A ROC curve analysis could have been performed to determine the optimal cutoff value for the development of postoperative morbidity. Nevertheless, we analyzed the relationship between the cystic diameter and development of postoperative morbidity using the MedCalc program. The risk of postoperative morbidity development in patients with a cyst >10 cm was 2.32 times higher than patients with a cyst diameter <10 cm (OR = 2.32, $p = 0.046$ 95% CI = 1.01–5.31). These results obtained from the univariate analysis could have been analyzed using

multivariate analysis which would have shown the independent risk factors that were related with development of postoperative morbidity.

Humans are accidental hosts in the life cycle of echinococcus, this is an accidental infection by ingestion of the eggs of the parasite. The eggs penetrate the intestinal wall and is carried to the liver by the portal circulation where it settles in the hepatic sinusoids. Larvae that are smaller than 0.3 mm pass through the sinusoidal filter system (the first Lemman’s filter) and reach the lungs. In the lungs, the larvae pass through the second capillary filter system (The second Leman’s filter) and some of the parasites are stuck in the pulmonary capillaries.⁹⁾ These two filter systems explain the mechanism behind the observations that the liver is the most frequent site of echinococcal disease which is followed by the lungs. In the present study, majority of the patients have concomitant hydatid disease in the liver. The main point that needs clarification is the use of neoadjuvant anthelmintic therapy in these patients. This is a clinical dilemma that we also encounter.

The authors have stated that they have performed indirect hemagglutination test in 201 patients; however, they have not stated the positive test rate among these patients. If the authors can share their results, an analysis including the differences in the rate of test positivity in patients with lung-only versus combined lung and liver hydatid disease could have been performed. The later analysis would provide valuable information.

Disclosure Statement

The authors declare no conflicts of interest related to this article.

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Reply to Dr. Akbulut

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The treatment of hydatid cyst is surgical and / or medical depending on various factors. The most important factors are the size, location, viability of the cyst, rupture of the cyst and accompanying bacterial infections. Surgical excision is the main treatment for pulmonary cystic lesions. In cases that are inoperable, treatment options such as benzimidazoles, albendazole, mebendazole are used¹⁾.

Since curative results have been seen with the use of benzimidazole, albendazole and mebendazole have also been used in the treatment of hydatid cysts since the 1980s. In patients with hydatid cyst, andazol treatment is recommended to be used routinely as 10–15 mg/kg/day (max 800 mg/day) for a period of 1 to 6 months as you have mentioned¹⁾. In our text we wrote 10 mcg/kg/day. There has been a typographical error in the text. In our clinic, we use andazol therapy (10 mg/kg/day) in postoperative patients for 6 months (**p165, line43 left column**). However, there are patients in our study who did not receive regular treatment. In these patients the duration of treatment was prolonged up to 9 months.

Consequently, we specified the duration of treatment as approximately 6-9 months in our study

In Shields General Thoracic Surgery, which is one of the fundamental textbooks of thoracic surgery, andazol treatment is recommended as a treatment protocol for postoperative pulmonary hydatid cysts in all patients after surgery¹⁾. Kilicgun et al.²⁾ administered albendazole treatment to all postoperative patients with PHCD (pulmonary hydatid cyst disease), unless contraindicated.

Neoadjuvant treatment protocol however is not recommended for pulmonary hydatid cysts. Topcu et al.³⁾ emphasized that the use of neoadjuvant treatment leads to perforation, expectoration, and anaphylactic shock. Likewise, Keramidas et al. state that preoperative andazol treatment increase secondary infections. In their study, it is stated that the duration of in-patient stay of patients who were operated on following andazol treatment was doubled due to complications⁴⁾. In Kilic et al.'s study, it is stated that treatments given preoperatively inactivate the protoscolices causing the intracystic pressure to decrease. Therefore, the risk of perforation increases following medical treatments in preoperative non-perforated pulmonary hydatid cysts⁵⁾. Usluer et al. compared preoperative and postoperative andazol treatment in their publication in 2014⁶⁾. It was found that preoperative andazol treatment increased the risk of perforation in patients. Therefore, surgical resection is primarily recommended before medical treatment in patients with lung cysts. The treatment of pulmonary hydatid disease is different from that of hydatid liver disease. In our clinical practice, we do not prefer andazol treatment before surgery. Therefore, in accordance with the literature, we did not apply neoadjuvant therapy to the patients included in our study.

There has been a typographical error in the conclusion part stating 382 patients. 283 patients are included in our study. (**p165, line37 right column**). In the study, Kruskal - Wallis analysis was used to determine the relationship between tomographic cyst diameters and the type of surgery performed. However, the results have been removed from the publication since the groups were divided as above and below 10 cm according to the design of the article. The result of the Kruskal-Wallis test analysis performed shows: cystotomy capitonnages mean / median (6.8 ± 3.9 / 6 cm), wedge resection mean / median (4.8 ± 2.0 / 4.5 cm),

lobectomy mean / median ($5.8 \pm 3.3 / 5.3$ cm), segmentectomy mean / median ($5 \pm 3.6 / 5$ cm) and a p value of 0.03. The distribution analysis of age among groups in our study was performed using the Mann – Whitney U test, which is the nonparametric equivalent of the Student-T test. However, the removal of these two tests was forgotten in the statistical analysis method paragraph (**p165, line20 right column**).

In our study, we did not consider open surgery, nor incomplete resection in the foreground due to small lesions. Mottaghian et al.'s study⁷⁾ supports our inference; they stated that patients in endemic areas may develop new primary cysts that cannot be easily distinguished from secondary cysts (recurrence after surgery).

Our study was designed to evaluate the factors affecting mortality and morbidity in Giant pulmonary hydatid cyst surgery. Although the statistical analysis expressed in the letter written to the editor, can be performed if desired, they are not related to the results of our study (correlation between hydatid cyst diameter and being symptomatic). Therefore, such analyses are not mentioned in the article.

When the factors affecting morbidity in our study were examined with univariate analysis, it was determined that the only factor affecting the morbidity was the giant cyst. Other factors cannot be considered to be confounding factors since p values > 0.05 in univariate analysis. For this reason, it is not statistically suitable to perform a multivariate analysis in a single factor and to include other statistically insignificant factors in the analysis. The Charlson comorbidity index (CCI) was used as ordinal categorical data instead of measuring data, as in many other studies⁸⁾. Therefore, ROC curve analysis is not mentioned in our article since it is not used in categorical data.

Radical resections (lobectomy, segmentectomy or pneumonectomy) are performed if the lesion is in close proximity to the pulmonary artery, vein or hiller structures or if the lesion is too large. If the lesion is located peripherally, even if its diameter is 10 cm, lung-sparing surgery is attempted as much as possible. In the letter to the editor, conservative treatment was specified in patients with lesions 10 cm and above. There is no conservative treatment method in our study. We operate on our patients with either VATS of thoracotomy.

As mentioned in the title of the study, morbidity factors in giant cysts were evaluated in the study. In this concept, giant cyst is defined as 10 cm and above⁹⁾. Therefore ROC curve analysis could not be performed with the diameters of the cysts in this study. Cyst diameters were evaluated as categorical values and as above and below 10 cm.

Kurkcuoglu et al.¹⁰⁾ also stated in their study that medical treatment should not be given prior to the removal of the pulmonary hydatid cyst in patients with pulmonary hydatid disease associated with multiple organ involvement. They emphasized that neoadjuvant medical treatment may cause rupture of the pulmonary cyst and lead to respiratory problems, hence medical treatment should be given after surgical treatment in hospitalized patients. In our study and clinical practice, we do not administer neoadjuvant albendazole therapy in PHCD cases.

In our study, the indirect hemagglutination test (IHA) positivity rate was 57.2% (n: 162). Our study is the evaluation of the factors affecting morbidity and mortality in PHCD. As stated in the literature, Indirect hemagglutination test positivity was not included in our study due to, as stated in the literature, its weak correlation with PHCD. Therewithal, our study is not a study investigating multiorgan involvement.

The criticisms in the letter to the editor have been answered by us and do not change the statistical results and conclusion of our study.

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