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Review Article

Analysis of Risk Factors for Lymph Node Metastasis in Hepatic Alveolar Echinococcosis

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Abstract

Background: This study was designed to investigate the high-risk factors causing lymph node metastasis in Hepetic Alveolar Echinococcosis (HAE)

Methods: The collection of clinical data of 621 patients with hepatic AE admitted to the First Affiliated Hospital of Xinjiang Medical University from January 2012 to January 2022, 191 of them were selected based on the baseline data. These were divided into a metastasis group (55 cases) and a non-metastasis group (136 cases) according to the occurrence of lymph node metastasis. A univariate and multivariate analysis of the general characteristics, lesion characteristics, and laboratory test results of the two groups of patients was conducted.

Results: Univariate analysis revealed that gender (P=0.004), age (P=0.027), ethnicity (P=0.001), presence or absence of distant organ metastasis (P=0.000<0.01), location of lesions (P=0.001), portal vein invasion (P=0.016), direct bilirubin (P<0.01), and percentage of neutrophils (P=0.012) in the two groups The difference was statistically significant. The multivariate analysis suggested that female gender (P=0.011, OR=3.019), combined distant organ metastasis (P=0.001, OR=5.325), and lesion location (P=0.009) were independent risk factors for lymph node metastasis in hepatic AE."

Conclusion: Female gender, combined distant organ metastasis, and lesions simultaneously involving the left and right eylobes of the hepatic are high-risk factors for lymph node metastasis in hepatic AE. For patients with the above factors, it is recommended to perform intraoperative prophylactic lymph node clearance in the affected area.

Introduction

"Human Alveolar Echinococcosis (AE) is a severe parasitic disease commonly known as 'worm cancer', usually caused by infection with the multilocular echinococcus tapeworm. The hepatic is the most commonly affected organ (96.8%) [1]. Although it is a benign disease, it exhibits malignant biological characteristics. It can spread to distant sites through infiltration, blood circulation, and lymph nodes. Numerous studies have been conducted on the hematogenous metastasis of hepatic AE both domestically and internationally [2], but there are fewer reports on lymph node metastasis, with only a few case reports available [3,4]. The mechanism of lymph node metastasis remains unclear, but it is speculated that AE spreads to regional lymph nodes through intrahepatic lymphatic vessels [5]. Lymph node metastasis in hepatic AE usually occurs in the advanced stages of the disease and can lead to severe complications such as cholangitis, obstructive jaundice, and portal vein cavernous transformation depending on the site of metastasis [6]. Lymph node metastasis in hepatic AE should be given high attention, and currently, there are no research reports analyzing the risk factors associated with lymph node metastasis in hepatic AE. This study retrospectively analyzed the clinical data of 621 hepatic AE patients admitted to the First Affiliated Hospital of Xinjiang Medical University from January 2012 to January 2022. Among them, the lymph node metastasis rate was 8.8% (55 cases). A total of 191 cases were selected (55 cases in *the metastasis group and 136 cases in the non-metastasis group) for statistical analysis to explore the high-risk factors that may cause lymph node metastasis in hepatic AE.*

Materials and Methods

Patients

From January 2012 to January 2022, 191 patients with hepatic Alveolar Echinococcosis (AE) who underwent curative surgery at the First Affiliated Hospital of Xinjiang Medical University were selected as the study subjects. Inclusion criteria: (1)

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Patients with hepatic AE who underwent curative surgery; (2) Patients without immunological disorders or malignant tumors; (3) Patients with complete clinical data and available follow-up. Exclusion criteria: (1) Patients with hepatic cystic echinococcosis; (2) Patients who did not undergo curative surgery or received palliative treatment; (3) Patients with incomplete clinical data; (4) Patients with Child-Pugh C stage or severe cardiopulmonary diseases, or patients with concomitant malignant tumors. The patients were divided into two groups based on the presence of lymph node metastasis. The metastasis group consisted of 55 patients, including 17 males and 38 females, with an average age of (35.56±1.58) years. The non-metastasis group consisted of 136 patients, including 73 males and 63 females, with an average age of (40.04±1.17) years. There was a statistically significant difference in gender distribution between the two groups (P=0.004<0.05), with a predominance of females in the metastasis group.

Research Indicators

In this study, based on literature reports and clinical practice, patient data including history of echinococcosis, preoperative imaging findings, and laboratory test results were collected. A total of 26 factors that may affect the occurrence of lymph node metastasis were observed, including gender, age, ethnicity, whether from an endemic area, presence of distant organ metastasis, size of the lesion (long diameter and short diameter), location of the lesion, solitary or multiple lesions, invasion of the portal vein, invasion of the hepatic vein, invasion of the hepatic artery, invasion of the inferior vena cava, invasion of the bile duct, duration of the disease, preoperative total bilirubin levels, direct bilirubin levels, indirect bilirubin levels, albumin levels, AST levels, ALT levels, alkaline phosphatase levels, percentage of neutrophils, percentage of lymphocytes, platelet count, and hemoglobin levels.

Methods

This study used SPSS 26.0 for statistical analysis. Group differences in categorical data were tested using the chi-square test, while differences in ordinal data were assessed using non-parametric tests such as the Mann-Whitney U test. Normally distributed continuous data were described using Mean ± SD, and group comparisons were analyzed using independent sample t-tests. Non-normally distributed continuous data were described using the median (interquartile range), and comparisons between groups were made using non-parametric tests such as the Mann-Whitney U test. Factors that showed statistical significance in the univariate analysis were further analyzed through logistic multivariate regression analysis to identify independent risk factors. The results were presented as adjusted Odds Ratios (OR) with corresponding 95% Confidence Intervals (CI). A p-value of less than 0.05 was considered statistically significant.

Results

General Characteristics

Analysis of general data showed in the metastasis group, there were 17 males (30.9%) and 38 females (69.1%). In the non-metastasis group, there were 73 males (54.1%) and 63 females (45.9%). The proportion of females in the metastasis group was significantly higher than that in the non-metastasis group, with a statistically significant difference (P=0.004). There were ethnic differences between the two groups, with a higher proportion of Tibetan ethnicity in the metastasis group (58.1%) compared to the non-metastasis group (23.3%), with a statistically significant difference (P=0.001). There was a statistically significant difference in the comparison of age groups between the metastasis and non-metastasis groups (P=0.027). However, there was no statistically significant difference in the comparison of geographical origin and disease course time between the two groups (P>0.05), as detailed in Table 1.

Table 1: General characterization of patients with hepatic vesicular echinococcosis.

Patient Profile	Metastasis group (n=55)	Non-metastasis group (n=136)		
Patient Profile	35.53±1.55	40.13±1.16	2.226	0.027
Year			8.403	0.004
Sex	17 (30.9%)	74 (54.1%)		
Male	38 (69.1%)	63 (45.9%)		
Female			25.419	0.001
Ethnic group	5 (9.1%)	40 (29.4%)		
Han Ethnic group	35.53±1.55	40.13±1.16	2.226	0.027
Tibetan ethnic group	32 (58.2%)	32 (23.5%)		
Kazakh ethnic group	10 (18.2%)	38 (27.9%)		
Hui islamic ethnic group	2 (3.6%)	4 (2.9%)		
Kyrghiz ethnic group	3 (5.5%)	5 (3.7%)		
Mongol ethnic group	2 (3.6%)	12 (8.8%)		
Uyghur ethnic group	1 (1.8%)	2 (1.5%)		
Salar efrmic group	0	3 (2.2%)		
Endemic area			1.035	0.33
YES	50 (90.9%)	129 (94.9%)		
NO	5 (9.1%)	7 (5.1%)		
Length of illness (nrnths)	12 (1-48)	4 (1-24)	-1.53	0.126

Characteristics of Lesions

The study showed that there were statistically significant differences (P<0.05) between the metastasis group and the non-metastasis group in terms of distant organ metastasis, lesion location, and portal vein invasion. The proportion of distant organ metastasis in the metastasis group (34.5%) was higher than that in the non-metastasis group (10.3%), and the proportion of lesions located in the left and right lobes of the hepatic in the metastasis group (40%) was significantly higher than that in the non-metastasis group (14.7%). The non-metastasis group had a significantly higher rate of portal vein invasion than the metastasis group, hence it could not be included in the multivariate analysis. There were no statistically significant differences (P>0.05) in other indicators between the groups, as detailed in Table 2.

Laboratory Test Results

The comparison of hepatic function and blood routine test results upon admission between the two groups of patients showed that there were statistically significant differences (P<0.05) in direct bilirubin and the percentage of neutrophils (P=0.012), with a significance level of P=0.048. However, there were no statistically significant differences (P>0.05) in total bilirubin, indirect bilirubin, AST, ALT, alkaline phosphatase, presence of hypoalbuminemia, percentage of lymphocytes, platelet count, and hemoglobin between the groups, as detailed in Table 3.

Multivariable Logistic Regression Analysis

In order to further examine the correlation between the

Table 2: Analysis of lesions in patients with hepatic vesicular echinococcosis.

Variables	Metastasis group (n=55)	Non-metastasis group (n=136)	X2 value	P value
Remote metastasis, no vs yes			16.115	<0.01
YES	19 (34.5%)	14 (10.3%)		
NO	36 (65.5%)	122 (89.7%)		
Lesion site			14.613	0.001
Left Lobe	8 (14.5%)	29 (21.3%)		
Right lobe	25 (45.5%)	87 (64%)		
Left lobe AND Right lobe	22 (40%)	21 (14.7%)		
Number of lesions				
Single	30 (54.5%)	84 (61.8%)	0.848	0.357
Multiple	25 (45.5%)	52 (38.2%)		
Portal vein invasion	36 (65.5%)	111 (81.6%)		
YES	19 (34.5%)	25 (18.4%)		
NO				
Hepatic venous invason				0.794
YES	25 (45.5%)	59 (43.4%)		
NO	30 (54.5%)	77 (56.6%)		
Hepatic artery invason				0.794
YES	25 (45.5%)	59 (43.4%)		
NO	30 (54.5%)	77 (56.6%)		
IVC invasion				0.9
YES	31 (56.4%)	78 (57.4%)		
NO	24 (43.6%)	58 (42.6%)		
Bile duct invasion				0.123
YES	18 (32.7%)	61 (44.9%)		
NO	37 (67.3%)	75 (55.1%)		
Long-diameter	12.93±0.61	11.48±0.42	-1.906	0.058

Table 3: Analysis of laboratory findings in patients with hepatic alveolar echinococcosis.

Patient Profile	Metastasis group (n=55)	Non-metastasis group (n=136)	X2 value	P value
Total bilirubin (TB)	15.41 (9.85-37.97)	17.9 (10.13-41.85)	-0.287	0.781
Direct bilirubin (DBB)	2.17 (0.3-7.16)	5.88 (3.12-20.68)	-4.497	P<0.05
Indirect bilirubin	9.95 (7.27-19.88)	10.6 (6.52-21.98)	0.678	0.498
AST	36.3 (25.69-65.06)	29.7 (20.5-74.6)	-1.019	0.308
ALT	38.1 (22.49-74.9)	31.7 (16.7-81.06)	-0.496	0.62
Alkaline phophatase	167.19 (102.65-402.6)	164.9 (96.13-359.78)	-0.376	0.707
Neutrophils 100 percent NE	58.7 (53-66.9)	63.85 (55.8-72.08)	-2.5	0.012
Lymphoyte percentage	25.1 (18.7-30.8)	23.65 (15.63-27.78)	-1.461	0.144
Preoperative platelets	252 (215-332)	239 (172-313.25)	-1.782	0.075
Preoperative hemoglobin hypoproteinemia)	123 (105-140)	11- (106.25-136.75)	-587	0.557
YES	14	48	1.729	0.188
NO	41	88		

seven observed indicators that showed differences in univariate analysis and the occurrence of lymph node metastasis, and to investigate their relationships, binary logistic regression was employed. The occurrence of metastasis was used as the dependent variable, while gender, age, ethnicity, distant organ metastasis, lesion location, portal vein invasion, direct bilirubin, and percentage of neutrophils were included as independent variables. All the data were standardized before conducting the binary logistic regression.

The logistic regression results showed a significant positive correlation (P<0.05) between gender, distant organ metastasis, lesion location, and the occurrence of lymph node metastasis. Moreover, they were identified as independent risk factors (OR>1) influencing lymph node metastasis. Specifically, the probability of lymph node metastasis was higher in females and in those with concurrent distant organ metastasis. The probability of lymph node metastasis in females was 3.019 times higher than that in males, and the probability of lymph node metastasis in patients with distant organ metastasis was 5.325 times higher than that in patients without distant organ metastasis. Patients with lesions located in the right or left lobes of the hepatic had a significantly lower risk of lymph node metastasis compared to those with lesions involving both lobes. However, age, ethnicity, direct bilirubin, and percentage of neutrophils showed no significant correlation with the occurrence of metastasis. For more details, please refer to Table 4.

Discussion

AE is a zoonotic parasitic disease that poses a serious threat to global public health [7]. After humans ingest eggs of the Echinococcus Multilocularis (EM) tapeworm, they are digested into eggshells and oncospheres (25-30μm) in the small intestine, which then invade the hepatic through the portal vein system [8]. Hepatic AE can spread to distant organs such as the lungs, brain, bones, and kidneys, with lymph node metastasis being relatively rare. Eckert J and Mehlhorn et al [9]. first reported in animal experiments that AE might lead to "lymph node metastasis" by damaging the interlobular lymphatics after detachment from the hepatic and subsequently draining into the local lymph nodes. The lymph nodes adjacent to the hepatoduodenal ligament are the most common site of metastasis, and depending on the location of metastasis, it can cause more serious complications such as jaundice and portal hypertension [10]. Radical hepatic resection is the preferred treatment for hepatic AE, but there is no standardized approach for managing hepatic AE with lymph node metastasis. Intraoperative regional lymph node dissection is considered a key step in reducing the risk of persistent infection and preventing recurrence [11]. The purpose of this study is to explore the risk factors for lymph node metastasis in hepatic AE, providing a scientific reference for clinical diagnosis, assessment, and intervention.

A global epidemiological study has shown that parts of Western, Northern, and Eastern Europe, as well as some pastoral areas in Central Asia, are high-risk regions for hepatic Alveolar Echinococcosis (AE). Rodents and dogs are the main transmission vectors [12]. In regions of China such as Tibet, Qinghai, Gansu, and Xinjiang, where animal husbandry is a major occupation and there is a high number of domestic dogs, the population's exposure to AE eggs is increased. Additionally, in some areas with lower levels of medical and educational resources, the likelihood of contracting alveolar echinococcosis is increased. In this study, univariate analysis of two groups of hepatic AE patients showed significant statistical differences in gender, age,

Table 4: Multifactorial Logistic Regression Analysis of Factors Influencing Liver AE Lymph Node Metastasis.

Sports event	B	SE	Wald	df	P value	OR	95% CI	
							Lower limit	Limit
Sex	1.105	0.435	6.459	1	0.011	3.019	1.288	7.8
Year	-0.017	0.016	1.093	1	0.296	0.983	0.953	1.015
Ehni group			14.682	7	0.04			
Han etnic group	18.346	22796.285	0	1	0.999	92771756.81		
Tibetan ethnic group	20.25	22796.285	0	1	0.999	623187710.6		
Kazakh ethnic group	18.887	22796.285	0	1	0.999	159338481.1		
Hui Islamic ethnic group	19.574	22796.285	0	1	0.999	316826595.7		
Kyrghiz ethnic group	19.367	22796.285	0	1	0.999	257693667.8		
Mongol ethnic group	18.302	22796.285	0	1	0.999	88793703.78		
Uyghur etnic group	9.277	22796.285	0	1	0.999	235545782.5		
lesion location			9.418	2	0.999			
right lobe of the liver	-1.416	0.469	9.112	1	0.003	0.243	0.097	0.609
left lobe of the liver	-1.218	0.601	4.115	1	0.043	0.296	0.091	0.96
Whether distant metastasis		0.491	11.578	1	0.001	5.325	2.032	13.953
Percentage of neutrophils	-0.028	0.015	3.364	1	0.067	0.972	0.943	1.002
direct bilirubin	-0.001	0.004	0.018	1	0.894	0.999	0.991	1.007

and ethnicity (P<0.05), which is consistent with the results of past epidemiological investigations. Wang et al.'s epidemiological meta-analysis suggested that female gender, age ≥30 years, and engagement in animal husbandry are high-risk factors for hepatic AE [13]. In this study, compared to males, females with hepatic AE had a higher probability of lymph node metastasis, with multivariable logistic regression indicating that the probability of metastasis in females was 3.019 times higher than in males. These higher probabilities may be due to the fact that in pastoral areas, women are responsible for feeding dogs, leading to direct and frequent contact with the definitive hosts [14]. Additionally, as the primary participants in household chores, women are more exposed to contamination from animal feces or Echinococcus multilocularis eggs. Studies have also indicated that estrogen can enhance cell proliferation and metastasis [15]. Echinococcus cells may be more prone to cause lymph node metastasis under the influence of estrogen. As a result, specific lifestyle habits and elevated estrogen levels may be the reasons why women are a high-risk population for hepatic AE, leading to a higher incidence of lymph node metastasis in female patients with hepatic AE. The long incubation period of hepatic AE (5-15 years) leads to a delayed onset of clinical symptoms[16], making the disease more easily detectable in individuals aged 30 and over. In this study, 69.1% of patients with hepatic AE and lymph node metastasis were aged 30 and above, with no significant difference in age observed in the multivariable analysis between the two groups. The likelihood of hepatic AE patients in pastoral regions of Northwest China developing lymph node metastasis is relatively high.

In hepatic Alveolar Echinococcosis (AE), the primary lesion is most commonly located in the right lobe of the hepatic (80%), followed by involvement of both the left and right lobes [17]. In this study, there was a statistically significant difference in the location of the primary lesion between the two groups of hepatic AE patients. Multivariable analysis revealed that patients with lesions involving both the left and right lobes had a higher probability of lymph node metastasis compared to patients with lesions confined to one side of the hepatic. The main reasons for this, as supported by the pathological and anatomical characteristics of AE, seem to be more convincing. AE colonizes the hepatic through the portal vein and then damages the intrahepatic blood vessels, bile ducts, and lymphatic vessels through external budding, compression, infiltration, and other means [18]. Dislodged AE can be transported to regional lymph nodes through the deep and superficial lymphatic drainage systems of the hepatic along with the lymphatic fluid, leading to lymph node metastasis. Approximately 80% or more of the lymphatic fluid enters the first hepatic hilum lymph node through the deep lymphatic drainage system distributed around the portal vein [19]. Therefore, in patients with hepatic AE with larger diameters, lesions spanning the left and right lobes, or diffuse growth, the invasion of the hepatic portal vein and microlymphatic vessels is more severe, providing a better opportunity for lymph node metastasis.

Hepatic Alveolar Echinococcosis (AE) is the only parasitic disease with malignant biological characteristics and can cause both intrahepatic and extrahepatic metastasis through infiltration and hematogenous spread. Literature reports suggest that the incidence of hepatic AE with distant organ metastasis is approximately 20%-40% [20]. Currently, there are no articles specifically addressing the correlation between lymph node metastasis and distant organ metastasis in hepatic AE. However, the results of this study, through univariate and multivariable analysis, indicate that the presence of distant organ metastasis is an independent risk factor for lymph node metastasis in hepatic AE (P=0.001, OR=5.37). There are two possible reasons for this. First, distant organ metastasis is a manifestation of advanced stages of hepatic AE. Studies by Long Dan et al. [21] have shown that when distant organ metastasis occurs, the intrahepatic lesions have larger diameters, multiple lesions, and more severe invasion of intrahepatic blood vessels and bile ducts. When the portal vein and hepatic veins are significantly affected, the deep lymphatic drainage system of the hepatic can also be compromised, making it easier for AE to spread to various regional or distant lymph nodes through lymphatic fluid. Second, lesions from distant organ metastases can cause lymph node metastasis through local lymphatic flow. For example, pulmonary AE can spread to the hilar and mediastinal lymph nodes [10], pancreatic AE can cause metastasis to peripancreatic lymph nodes, and when the adrenal glands and kidneys are involved, AE can flow out along the hepatorenal ligament through lymphatic fluid, leading to metastasis in the para-aortic lymph nodes. Therefore, when hepatic AE is accompanied by distant organ metastasis, lymph node metastasis should be given special attention.

Inflammation is a key characteristic of AE infection, and he-

matological inflammatory markers such as neutrophils, lymphocytes, and platelets are involved in the chronic inflammatory response to the parasite, indirectly reflecting the body's immune status [22]. In the present study, univariate analysis revealed a statistical difference in the Neutrophil Percentage (NE) in the blood routine tests of the two groups of hepatic AE patients (P=0.048<0.05). In patients with Echinococcus infection, neutrophils, through the activation of pro-inflammatory cytokines (IL-6, IL-8, α-tumor necrosis factor), promote the inflammatory response and tissue damage [23]. They can also secrete Vascular Endothelial Growth Factor (VEGF) to facilitate angiogenesis, thus promoting the metastasis and invasion of AE [24]. However, multivariable analysis did not show a significant positive correlation between NE and lymph node metastasis in hepatic AE. In advanced stages of hepatic AE, obstruction jaundice can result from lesion invasion or compression of the intrahepatic and extrahepatic bile ducts, leading to direct bilirubin level elevation. Additionally, extensive hepatic cell damage can cause abnormal hepatic function and indirect bilirubin elevation. Furthermore, lymph node metastasis in hepatic AE most commonly occurs adjacent to the hepatoduodenal ligament [10], where these lymph nodes can compress or erode the common bile duct and portal vein, leading to obstructive jaundice, portal vein cavernous transformation, and consequent direct bilirubin level elevation. Univariate analysis in this study showed a statistical difference in the direct bilirubin levels between the groups, while multivariable analysis did not reveal a significant correlation with lymph node metastasis.

In conclusion gender is female, combined with extrahepatic distant organ metastasis, and lesions invading both right and left lobes of the hepatic are independent risk factors that may cause lymph node metastasis of hepatic AE. Clinical physicians should pay attention to and take preventive measures against the identified risk factors. Our center recommends routine prophylactic clearance of regional lymph nodes in patients with hepatic AE who have these risk factors during surgery to improve patient quality of life and reduce recurrence rates. This study is retrospective in nature and not a randomized controlled trial, thus there is a certain degree of selection bias. Additionally, this is a single-center clinical trial with a relatively small sample size, and larger multi-center clinical trials are still needed.

Author Statements

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Author Contributions

Tuerganaili·Aji and Tieminjiang designed the research and approved the submitted manuscript. Ainiwaer·Aikebai and Yierfan·Yilihaer drafted the manuscript. Ainiwaer·Aikebai and Yilizhati·Aimaitijiang collected the data and analyzed the data. All authors read and approved the final manuscript.

Institutional Review Board Statement

This study was approved by the Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University (No. 20211015-53) and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects and/or their legal guardians. All methods used in this study were performed in accordance with the approved guidelines.

Conflict of Interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

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