

Clinical characteristics and risk factors for acute abdomen in patients with abdominal lymphatic malformations

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ABSTRACT

Objective: The diagnosis of abdominal lymphatic malformations (ALMs) is often overlooked in clinical practice. However, reports in the literature about ALMs are limited to case reports and series with small sample sizes. This study aimed to review our currently available data to describe the clinical characteristics of ALMs and evaluate the risk factors for acute abdomen caused by ALMs.

Methods: We reviewed the records of patients with ALMs who were diagnosed between December 2008 and January 2023 in our institution. The associations between acute abdomen and ALMs were analyzed based on single-factor and multivariate logistic regression analyses.

Results: This study included 345 patients with pathologically confirmed ALMs, with a slight female predominance of 1:1.4. Approximately 39.1% (135/345) of patients were asymptomatic, and 24.6% (85/345) presented with acute abdomen. Among the ALMs in the cohort, 42.6% (147/345) were retroperitoneal lymphatic malformations (LMs). The maximal lesion dimensions in patients with acute abdomen and nonacute abdomen were 10.0 cm and 7.8 cm, respectively, with no significant difference based on multivariate analyses. Children were more likely to develop acute abdomen than adults were (P = .002; odds ratio, 5.128; 95% confidence interval, 1.835-14.326). ALMs accompanying acute abdomen were more common for lesions involving the small intestinal mesentery (P = .023; odds ratio, 2.926; 95% confidence interval, 1.157-7.400).

Conclusions: ALMs are rare with an insidious onset, and retroperitoneal LMs are the most common ALMs, followed by jejunal mesenteric LMs. Our retrospective analysis suggested that young age and small intestinal mesenteric lymphatic malformation are independent risk factors for acute abdomen with ALMs. (J Vasc Surg Venous Lymphat Disord 2025;13:101969.)

Keywords: Abdominal lymphatic malformations; Clinical characteristics; Mesenteric site; Acute abdomen; Risk factors

Lymphatic malformations (LMs) are slow-flow vascular malformations. The mechanism of LMs has not been elucidated fully. One theory postulated is somatic mutations. According to the latest classification by the International Society for the Study of Vascular Anomalies in 2018, LMs can be divided into common LMs, generalized

lymphatic anomaly (GLA), LM in Gorham-Stout disease, channel type LM, acquired progressive lymphatic anomaly, primary lymphedema, and others. Based on the cystic maximum diameter, with a boundary of 2 cm, common LMs can be classified as macrocystic, microcystic or mixed LMs.^{2,3} Common LMs are most commonly found in the neck, whereas abdominal LMs (ALMs) are very rare, with an incidence of approximately 1/140,000 hospital admissions.^{4,5}

A previous study showed that approximately 50% to 60% present clinically within the first year of life, and 90% of patients with ALMs enter the medical system within the first 2 years of life. Delayed detection of ALMs into adulthood is rare, with macrocystic LMs being the most frequent. The clinical presentations of ALM are highly varied and mainly depend on the size and location of the lesions, as well as the incidence of complications. Many patients with ALMs are asymptomatic and are often detected incidentally during imaging evaluations or surgery for other indications. However, some patients may also experience complications such as intracystic bleeding or infection, intestinal volvulus, or mass effects such as ureteric obstruction or hematuria.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

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https://doi.org/10.1016/j.jvsv.2024.101969

exacerbating abdominal discomfort.⁹⁻¹¹ ALMs can also be detected antenatally via ultrasound or magnetic resonance imaging as early as the first trimester of pregnancy.^{9,12,13} The diagnosis of ALMs can be challenging owing to its insidious onset. However, ALMs can also present with acute onset, which may be difficult to distinguish from other diseases that cause acute abdominal pain.^{6,14-18}

Here, we conducted a retrospective single-center study that included the largest cohort of patients with ALMs to date. The main objective of this study was to explore the clinical characteristics of ALMs and the risk factors for acute abdomen, with the aim of better understanding the clinical features and management of ALMs.

METHODS

Study patients. We reviewed the records of patients with pathologically confirmed ALMs from December 2008 to January 2023 (Fig 1). The clinical data were obtained from West China Hospital of Sichuan University. This study was approved by the ethics committee of the West China Hospital, Sichuan University (approval number 2021-1738) and was conducted in accordance with the Declaration of Helsinki. All patients were initially diagnosed by medical history and radiological examinations, and ultimately confirmed by histopathological data. Once patients experienced systemic signs or symptoms such as pleural effusion, protein-losing enteropathy, other abnormal complaints, or abdominal imaging examinations revealed diffuse lesions of the ALMs, then whole-body magnetic resonance imaging were performed to eliminate the risk of GLA. The inclusion criteria were as follows: patients who were

ARTICLE HIGHLIGHTS

- Type of Research: Single-center retrospective cohort study
- **Key Findings:** Of the 345 patients with abdominal lymphatic malformations, 24.6% suffered from acute abdomen. Risk factors associated with acute abdomen included young age, small intestinal mesentery lesions, infection, intracystic hemorrhage, and intestinal volvulus. The complications of abdominal lymphatic malformations in different locations are different.
- Take Home Message: Timely recognition and diagnosis of abdominal lymphatic malformations are essential to avoid serious complications, especially for children.

diagnosed with ALMs based on clinical features, radiological examinations (ultrasound, computed tomography and/or magnetic resonance imaging), histopathological data, and consensus of the multidisciplinary vascular anomaly group; patients who had no other vascular malformations present throughout the body; patients who had no previous history of abdominal surgery; patients who had not received other treatments (eg, oral medication or sclerotherapy) for ALMs before referral; and patients whose complete diagnosis and treatment processes were recorded. The exclusion criteria for patients were as follows: patients did not have a pathological diagnosis and patients with GLA. 19-22

If LMs are accompanied by osteolytic lesions, nonmalignant chylous effusion, or protein-losing enteropathy without a primary cause, GLA may be highly

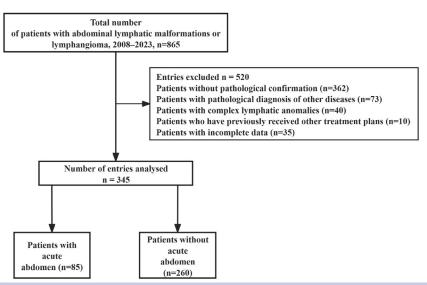


Fig 1. Flow diagram of entries for abdominal lymphatic malformation (ALM), with reasons for exclusion from the study.

Table I. Clinical characteristics of abdominal lymphatic malformations (ALMs) with acute abdomen and without acute abdomen

	Acute	Without acute		
	Abdomen (n = 85)	Abdomen (n = 260)	<i>P</i> value	Odds ratio (95% CI)
Age, years			<.001 ^b	14.438 (6.690-31.156)
Children (<18)	77 (90.6)	104 (40.0)		
Adults (≥18)	8 (9.4)	156 (60.0)		
Sex			.037 ^b	1.692 (1.033-2.773)
Male	43 (50.6)	98 (37.7)		
Female	42 (49.4)	162 (62.3)		
Location				
Small intestinal mesentery	46 (54.1)	34 (13.1)	<.001 ^b	7.840 (4.485-13.706)
Colonic mesentery	13 (15.3)	22 (8.5)	.070 ^b	1.953 (0.937-4.072)
Omentum	14 (16.5)	35 (13.5)	.490 ^b	1.268 (0.646-2.489)
Retroperitoneum	11 (12.9)	136 (52.3)	<.001 ^b	0.136 (0.069-0.267)
Spleen	1 (1.2)	33 (12.7)	.002 ^b	0.082 (0.011-0.608)
Maximal lesion dimension, cm ^a	10.0 (3.0-21.5)	7.8 (1.5-40.0)	.019 ^d	N/A
Infection	6 (7.1)	4 (1.5)	.017 ^c	4.861 (1.338-17.659)
Intracystic hemorrhage	17 (20)	19 (7.3)	<.001 ^b	3.171 (1.563-6.434)
Mass effect	9 (10.6)	30 (11.5)	.810 ^b	0.908 (0.413-1.998)
Obstruction/volvulus	40 (47.1)	4 (1.5)	<.001 ^b	56.889 (19.406-166.773)
Rupture	4 (4.7)	6 (2.3)	.270 ^c	2.091 (0.576-7.592)

CI, Confidence interval; N/A, data not available.

suspected.^{1,23} GLAs can be characterized by abdominal lesions as the initial symptom; therefore, our study strictly excluded patients suspected of having GLA through comprehensive physical examination and radiological examinations.

Definition. The characteristic of acute abdomen is the sudden onset of severe abdominal pain, which requires emergency medical treatment or surgical consultation.²⁴ The acute abdomen referred to in this study mainly refers to a surgical acute abdomen. In this study, based on the practical guidelines on acute abdomen in 2015, we classified all patients who met one of the following three conditions as the acute abdomen group: abdominal symptoms that appeared within 1 week and required emergency intervention measures, such as surgical treatment; abdominal symptoms that appeared after 1 week and were accompanied by acute attacks within 1 week and required emergency intervention measures; or sudden onset of obvious clinical manifestations of intestinal obstruction.²⁴

Chronic abdominal pain was defined as continuous or intermittent abdominal discomfort for \geq 3 months.²⁵ A cyst aspirate containing white blood cells and pathogens was the gold standard of cyst infection in the literature,

and abdominal pain and fever are important indicators of cyst infection.²⁶

Statistical analysis. All statistical analyses were conducted with IBM SPSS software version 27 (IBM, Armonk, NY). The χ^2 test or Fisher's exact test were used for categorical variables, and the nonparametric Mann-Whitney U test was used for continuous variables. Univariate analysis was performed using binary logistic regression to evaluate the associations between age, sex, lesion location, preoperative lesion dimension, infection, bleeding, mass effect, obstruction, rupture, and acute abdomen. With acute abdomen as the dependent variable, variables with a P value of <.05 in the univariate analysis were retained for multivariate logistic regression. When two independent variables were related closely, they were excluded from multivariate analysis. Differences were considered to be statistically significant at a P value of < .05.

RESULTS

Demographic characteristics of patients with ALMs. After applying the strict inclusion and exclusion criteria, 345 patients were enrolled in our study. As shown in Table I, the female-to-male ratio was 1.4:1. Among the

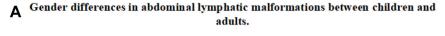
Values are number (%) or median (interquartile range) unless otherwise indicated.

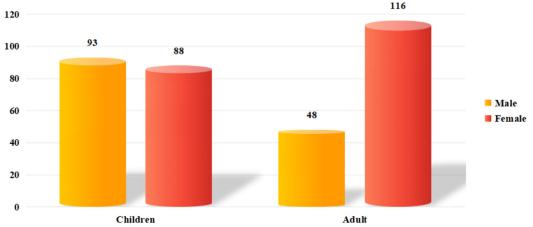
^aThe maximal dimension of the cyst indicated by preoperative computed tomography scan.

 $^{^{\}mathrm{b}}P$ value was calculated using the χ^2 test.

^c P value was calculated with Fisher's exact test.

^dP value was calculated using the Mann-Whitney U test.





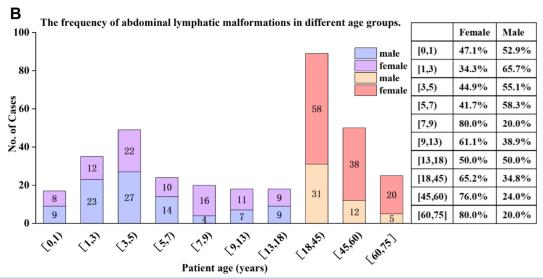


Fig 2. Clinical manifestations of abdominal lymphatic malformations (ALMs). (A) The number and proportion of patients suffering from ALMs in adults and children stratified by sex. (B) The number of ALMs discovered in different age groups among the 345 patients.

enrolled children, the proportions of male and female children were similar. However, there was a female preponderance in adult patients, with a female-to-male ratio of 2.4:1 (Fig 2, A). In addition, ALMs mainly present clinically symptomatic at the age of 3 to 5 years in pediatric patients, whereas in adult patients, more than one-half of patients seek medical attention before the age of 45 years (Fig 2, B). In the entire patient cohort, there was a significant difference in the incidence of acute abdomen between the sexes (P = .037; odds ratio [OR], 1.692; 95% confidence interval [CI], 1.033-2.773). Among pediatric patients with ALMs, 42.5% (77/181) experienced acute abdomen, whereas among adult patients, <4.9% (8/164) experienced acute abdomen, directly indicating that children are more prone to acute abdomen than adults are (P < .001; OR, 14.438; 95% CI, 6.690-31.156).

Clinical features of common ALMs. A total of 39.1% of patients (135/345) were asymptomatic, and their ALMs were discovered incidentally during examination for an unrelated complaint. Prenatal diagnosis of ALMs was documented in 3.2% of patients (11/345). Other common complaints included long-term intermittent abdominal pain (93/345 [27.0%]), acute abdominal pain (85/345 [24.6%]), and abdominal masses (21/345 [6.1%]). Nearly one-quarter of patients experienced acute abdomen throughout the entire course of the disease (Supplementary Table I, online only) before referral.

ALMs can occur in any part of the abdominal cavity. The most frequent site of onset was the retroperitoneum (42.6%), followed by the mesentery (33.3%), omentum (14.2%), and spleen (9.9%). A total of 115 of 345 patients (33.3%) suffered from mesenteric LMs (MLMs) (Fig 3), including 57 case s(49.6%) of jejunal MLMs and 23 cases

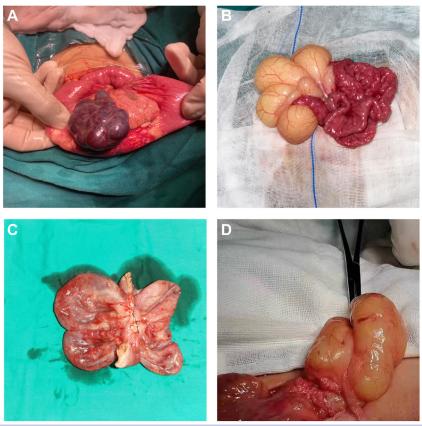


Fig 3. A gross intraoperative photograph of the resected masses. The abdominal lymphatic malformations (ALMs) were located in the jejunal mesentery (A), ileal mesentery (B), small intestinal mesentery (C), and jejunal mesentery (D).

(20.0%) of ileal MLMs. Nearly one-half of the MLMs in the colon were located in the transverse colon (16/35) (Fig 4). There were four main types of cystic fluid in our patients, and the most common type was serous fluid (66.4%), followed by chyle fluid (21.5%).

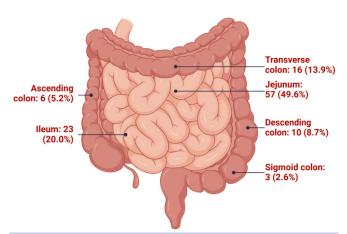


Fig 4. The number and proportion of lymphatic malformations occurring in different parts of the mesentery.

The entire cohort had an average follow-up time of 5.0 years after surgical resection. Two patients (0.60% [2/345]) experienced LMs relapse at the primary site at 6 months and 1 year after surgery with the lesions smaller than before treatment and without abdominal discomfort.

Complications of common ALMs. Although some patients develop complications, they did not complain of any discomfort (Supplementary Table II, online only). Among patients with retroperitoneal LMs, 23.8% (35/147) experienced complications. However, only 11 patients presented symptoms of acute abdomen, including 1 patient with acute back pain caused by cyst rupture, 5 patients with intermittent abdominal pain caused by ureteric obstruction owing to the mass effect, and 5 patients with sudden cyst enlargement.

Twenty-eight patients with small intestinal MLMs underwent emergency surgery for intestinal volvulus leading to acute intestinal obstruction. Six patients had dumbbell-shaped lesions surrounding the intestinal wall, leading to acute abdominal pain. Intestinal volvulus or obstruction are the most common complications of small intestinal mesenteric lesions, accounting for

Table II. Univariate and multivariate regression analysis of risk factors for acute abdomen caused by abdominal lymphatic malformation (ALM)

	Univariate analysis	Multivariate analysis	
	P value ^a	P value ^b	Odds ratio (95% CI)
Age	<.001	.002	5.128 (1.835-14.326)
Sex	.037	.475	0.744 (0.331-1.674)
Location			
Small intestinal mesentery	<.001	.023	2.926 (1.157-7.400)
Colonic mesentery	.074		
Omentum	.491		
Retroperitoneum	<.001	.496	0.691 (0.239-2.001)
Spleen	.014	.481	0.440 (0.045-4.326)
Maximal lesion dimension	.019	.749	1.012 (0.941-1.089)
Infection	.016	.001	11.546 (2.572-51.822)
Intracystic hemorrhage	.001	<.001	8.748 (3.348-22.857)
Mass effect	.810		
Volvulus/obstruction	<.001	<.001	34.358 (10.201-115.720)
Rupture	.262		
CI, Confidence interval. ^a P value was calculated with univariate lo ^b P value was calculated with multivariate			

approximately 35.0%, followed by acute bleeding of cysts (13.8%). Colonic MLMs mainly cause mass effect issues

and then resultant symptoms.

In our patient cohort, a total of 10 patients developed cyst infections. The main clinical complaint was sudden and intolerable acute abdomen, with six patients having MLMs; some patients even experienced significant increases in white blood cell and neutrophil counts (Supplementary Table III, online only).

Subgroup analysis. As shown in Table I, the incidence of acute abdomen was higher in small intestinal MLMs (P < .001; OR, 7.840; 95% CI, 4.485-13.706), and it was lower in retroperitoneal LMs (P < .001; OR, 0.136; 95% CI, 0.069-0.267). To further compare the clinical characteristics between MLMs and retroperitoneal LMs, we performed a subgroup analysis. A total of 84.3% of patients suffering from MLMs were pediatric patients. However, among patients with retroperitoneal LMs, only 24.5% were pediatric patients (P < .001; OR, 16.616; 95% CI, 8.867-31.134). The most common complaint of MLMs was acute abdomen, whereas retroperitoneal LMs were mainly discovered by chance. The median duration of symptoms in patients with MLMs was shorter than that in patients with retroperitoneal LMs (P < .001). Patients with MLMs sought medical assistance earlier than those with retroperitoneal LMs. The reason for this phenomenon might be the greater frequency of clinical signs in patients with MLMs (Supplementary Table IV, online only).

Risk factors for acute abdomen. To understand the risk factors for acute abdominal pain caused by ALMs, a

regression analysis was conducted. As revealed in Table II, we conducted a multivariate analysis of nine clinicopathological factors and identified five independent preoperative predictors of acute abdomen: young age (P = .002; OR, 5.128; 95% CI, 1.835-14.326), small intestinal MLMs (P = .023; OR, 2.926; 95% CI, 1.157-7.400), cyst infection (P = .001; OR, 11.546; 95% CI, 2.572-51.822), intracystic hemorrhage (P < .001; OR, 8.748; 95% CI, 3.348-22.857), and volvulus/obstruction (P < .001; OR, 34.358; 95% CI, 10.201-115.720). However, there were no statistically significant difference in the maximal lesion dimensions between patients with and without acute abdomen (P = .749; OR, 1.012; 95% CI, 0.941-1.089). There was also no statistically significant differences in the incidence of acute abdomen between the sexes (P =.475; OR, 0.744; 95% CI, 0.331-1.674).

DISCUSSION

LMs are uncommon congenital low-flow vascular anomalies that can be found on any anatomical site in the body but are most frequently located in lymphatic-rich areas such as the head, neck region, and armpits. Fewer than 5% of LMs are intra-abdominal. Owing to the lack of information from a large patient population with ALMs, we reviewed the largest cohort of patients with ALMs to date. Our study systematically summarized the clinical characteristics of patients with ALMs and their associations with acute abdomen, providing abundant information for the diagnosis and management of ALMs.

Previous studies have shown that common ALMs are detected mainly in childhood, especially within the first 2 years of life. However, in the present study, pediatric patients with ALMs mainly sought medical attention at 3 to 5 years of age. In adult patients, we found that ALMs were mainly identified at 18 to 45 years of age. One potential reason may be that with increasing age, children aged 3 to 5 years are more active, which is more likely to induce complications and cause corresponding symptoms, such as acute abdomen. In addition, it is possible that the incidence of adult ALMs has been underestimated significantly in the past. In our study, we found that more than one-third of ALMs were detected incidentally on imaging, further suggesting that the true prevalence and incidence of ALMs may be underestimated greatly because of misdiagnosis or missed diagnosis owing to the lack of obvious symptoms and signs.²⁷

Furthermore, we demonstrated that there were no significant sex differences in pediatric patients. However, among the adult patients, a female preponderance was found in our cohort, which was consistent with a previous report. Some investigators presumed that estrogen may stimulate the growth or expansion of LMs lesions in female patients. During periods of relatively vigorous estrogen secretion, ALMs may be discovered based on the presence of obvious symptoms and signs owing to enlargement of the cyst. Nevertheless, the exact correlations between estrogen and cyst growth remain unclear, and further mechanistic studies are needed.

Some investigators have suggested that MLMs are the most common ALMs.³⁰ Our study revealed that the most common ALMs were retroperitoneal, which is consistent with the findings of several studies.^{31,32} In an analysis of the clinical characteristics of 32 patients, Maghrebi et al³¹ reported that 25.0% of their patients had retroperitoneal LMs and 21.9% had MLMs. The mesentery has a certain degree of mobility within the abdominal cavity and has a relatively large space for movement, increasing the likelihood of complications such as cyst pedicle torsion or intestinal volvulus, which are more likely to be detected earlier. In addition, MLMs are more prone to severe complications, resulting in acute abdomen, which has been reported frequently in the literature. 17,33-38 In contrast, because of the small space of the retroperitoneal cavity and the poor mobility of the LMs lesion, we speculate that patients with retroperitoneal LMs are not prone to obvious symptoms and signs. The differences in the incidence of symptoms before referral can also be seen by our subgroup analysis between MLMs and retroperitoneal LMs.

MLMs accompanied by acute abdomen and intestinal volvulus have been reported in small sample series in the field of clinical practice. Yan et al published a large study in 2020, examining the preoperative and postoperative features of 157 patients and proposed an

improved MLM classification based on the location of the lesions. The manifestations of MLMs are diverse and nonspecific. Patients may be asymptomatic, or the lesions may associated with acute abdomen, chronic abdominal pain, palpable masses, abdominal distension, and severe anemia requiring multiple blood transfusions. 16,37,40-42 In addition, MLMs might be misdiagnosed as an internal disease such as gastroenteritis or lymphadenitis.³⁵ As observed in our study, MLMs were more prone to complications such as volvulus than lesions in other parts of the abdominal cavity. Our results indicated that MLMs had a higher risk for intestinal volvulus, especially LMs involving the jejunal mesentery. This observation was similar to the findings of previous studies. 35,36,39,43 Children are more likely to experience acute abdomen, which is probably related to their smaller body habitus and abdominal cavity.²⁸ Walker and Putnam⁸ suggested that lesion size plays a much greater role in determining clinical symptomology than does lesion location. However, our data revealed that lesion location is a more important factor than lesion

Common ALMs need to be differentiated from various cystic abdominal masses,44 and ultimately, the diagnosis relies on pathologists.²⁷ Notably, differentiating mature teratomas from ALMs is important in clinical practice.⁴⁵ On computed tomography scans, ALMs typically appear as unilocular or multilocular septate cystic lesion with fluid attenuation, contrast enhancement of the wall and septum and even calcification in a few cases, similar to teratomas. 46 The typical whirlpool sign was used to indicate the outcome of intestinal volvulus, and patients usually suffer from acute abdominal pain. ALMs present as cystic lesions with low or no echogenicity and clear boundaries on ultrasound examination.9 Because cystic teratomas contain a variety of tissues, imaging often reveals cystic lesions with hyperechoic nodules (Rokitansky's nodules) protruding into the cystic cavity, followed by diffuse or local solid isoechoic masses with or without cyst wall calcification. 47,48 It should be noted that a small number of LMs are challenging to distinguish by special imaging findings alone, and the nature of the cystic fluid can also be used as a means of auxiliary diagnosis. We observed that, when blood or even necrotic substances appear, the risk of acute abdomen increases.

The management options for ALMs are diverse, among which surgical resection historically remains the standard of management. Surgical resection will inevitably involve the necessity of resection of intestinal segments, especially MLMs. We suggest that complete lesion resection and segmental intestinal resection are necessary to avoid recurrence of MLMs with chylous fluid, because the presence of chylous fluid likely implies the involvement of the bowel wall. In addition, Maruani et al suggested that common LMs seem to be the best indication for sirolimus therapy, which can decrease the

volume of lesions, bleeding, and oozing effectively, even increase patient quality of life. Similarly, we found that patients withs common LMs and kaposiform hemangioendothelioma, have an objective response to sirolimus, with a ≥20% decrease in lesion volume before and after treatment in >80% of patients. However, patients may potentially suffer from the side effects of oral sirolimus. For patients with extensive lesions that cannot be removed completely, mammalian target or rapamycin inhibitors, such as sirolimus or everolimus, could be important options on decreasing lesion size and controlling lesion progression. 1.22,34,50

LIMITATIONS

Several limitations of our study deserve comment. First, our study was a single-center retrospective study. This factor may limit the generalizability of our results to other centers. Therefore, the establishment of multiregional and multicenter studies is one of the directions of our future efforts. Second, we strictly selected patients who underwent surgical resection, making it difficult to evaluate differences in various management options. The comparison of the efficacy of various treatment options for ALMs is, therefore, also one of the directions we will explore. Furthermore, we enrolled only patients with common LMs, so the results cannot be generalized to all management practices or research settings for LMs. However, to the best of our knowledge, this study is the largest to date to analyze systematically the clinical characteristics of ALMs and risk factors for developing acute abdomen, providing important evidence in support of the management of ALMs.

CONCLUSIONS

ALMs are rare slow-flow vascular malformations of the abdomen. The results of our study suggest that retroperitoneal LMs are the most common ALMs, followed by jejunal MLMs. ALMs have no special symptoms or signs, and their onset may be insidious. Therefore, ALMs can be missed and misdiagnosed in the clinic. ALMs located in different locations may have different accompanying symptoms. MLMs might present with complete or incomplete intestinal obstruction owing to volvulus, while retroperitoneal LMs are mainly characterized by mass effects. In addition, our data revealed that young age, small intestinal mesentery lesions, chronic infection, intracystic hemorrhage, and intestinal volvulus were independent risk factors for acute abdomen in patients with ALMs.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author (Prof. Ji Yi) upon reasonable request. Research Registration Unique Identifying Number - Our study was registered in "clinicaltrials.gov" (NCT06257719).

AUTHOR CONTRIBUTIONS

Conception and design: CY, TQ, MY, SC, YJ Analysis and interpretation: CY, TQ, MY

Data collection: CY, JZ, XG, KY, ZXZ, YL, XZ, ZLZ, YZ, SX Writing the article: CY, TQ, MY, JZ, XG, KY, ZXZ, YL, XZ, ZLZ, YZ, SX, SC, YJ

Critical revision of the article: CY, TQ, MY, SC, YJ Final approval of the article: CY, TQ, MY, JZ, XG, KY, ZXZ, YL, XZ, ZLZ, YZ, SX, SC, YJ

Statistical analysis: CY, TQ, MY, JZ, XZ

Obtained funding: Not applicable

Overall responsibility: YJ

CY and TQ contributed equally to this article and share co-first authorship.

CY, TQ, and MY contributed equally to this article and share co-first authorship.

FUNDING

This work was supported by the National Natural Science Foundation of China (grant number 82273556), the Key Project in the Science & Technology Program of Sichuan Province (grant numbers 2022YFS0233 2022YFS0225), the '0 to 1' Project of Sichuan University (grant number 2022SCUH0033), the Med-X Center for Informatics Funding Project (YGJC004), the 1·3·5 Project for Disciplines of Excellence-Clinical Research Incubation Project of West China Hospital of Sichuan University (grant numbers 2023HXFH004, 2020HXFH048 and 2019HXFH056), and the 1·3·5 Project for Disciplines of Excellence-Clinical Research Interdisciplinary Innovation Project of West China Hospital of Sichuan University (ZYJC21060).

DISCLOSURES

None.

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Submitted Jun 18, 2024; accepted Sep 10, 2024.

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