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**Research Article**

# Impact of age and tumor size on the development of the Kasabach–Merritt phenomenon in patients with kaposiform hemangioendothelioma: a retrospective cohort study

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## Abstract

**Introduction** The Kasabach–Merritt phenomenon (KMP) is a severe complication of kaposiform hemangioendothelioma (KHE). The risk factors for KMP need further investigation.

**Methods** The medical records of patients with KHE were reviewed. Univariate and multivariate logistic regression models were used for the risk factors for KMP, and the area under the receiver operator characteristic (ROC) curve was used to assess the predictive power of risk factors.

**Results** A total of 338 patients with KHE were enrolled. The incidence of KMP was 45.9%. Age of onset ($P < 0.001$, odds ratio [OR] 0.939; 95% confidence interval [CI] 0.914–0.966), lesion size ($P < 0.001$, OR 1.944; 95% CI 1.646–2.296), mixed type ($P = 0.030$, OR 2.428; 95% CI 1.092–5.397), deep type ($P = 0.010$, OR 4.006; 95% CI 1.389–11.556), and mediastinal or retroperitoneal lesion location ($P = 0.019$, OR 11.864; 95% CI 1.497–94.003) were correlated with KMP occurrence through multivariate logistic regression. ROC curve analysis revealed that the optimal cutoffs were 4.75 months for the age of onset ($P < 0.001$, OR 7.206, 95% CI 4.073–12.749) and a lesion diameter of 5.35 cm ($P < 0.001$, OR 11.817, 95% CI 7.084–19.714). Bounded by a lesion size of 5.35 cm, we found significant differences in tumor morphology, age of onset, treatments, and hematological parameters. Using an onset age of 4.75 months as a cutoff, we found significant differences in tumor morphology, lesion size, hematological parameters, and prognosis.

**Conclusion** For KHE patients with an onset age <4.75 months and/or lesion diameter >5.35 cm, clinicians should be wary of the occurrence of KMP. Active management is recommended to improve the prognosis.

**Keywords:** kaposiform hemangioendothelioma, Kasabach–Merritt phenomenon, age of onset, tumor size, cutoff values

## Introduction

Kaposiform hemangioendothelioma (KHE) is a rare vascular tumor that primarily occurs in early childhood.[1] Although more exploration of the pathogenesis of KHE is still needed, its main pathological features are abnormal angiogenesis and lymphangiogenesis.[2] Generally, KHE presents as a subcutaneous mass that shows purpuric or bruised appearance. For deep KHE, the initial symptoms can be unexplained thrombocytopenia. Previous studies have shown that ~46%–71% of patients with KHE develop the life-threatening Kasabach–Merritt phenomenon (KMP),[3–6] which manifests as profound thrombocytopenia and consumptive coagulopathy. Significantly, Infantile hepatic hemangiomas[7] and rapidly involuting congenital hemangioma[8] can also cause transient thrombocytopenia and coagulopathy, but this is not KMP. Although the cause of KMP is unknown, one possible hypothesis is that the abnormal endothelium and tortuous architecture of the tumor vasculature promote capture, activation, and consumption of platelets. KMP has been associated with increased morbidity and mortality.[9] Patients have an increased risk of severe anemia, bone-joint invasion, decreased range of motion, pericardial/pleural effusions and other complications after the onset of KMP.[4,10] In addition, KMP can affect the health-related quality of life of patients of all ages.[11] Meanwhile, recent research has shown that KMP patients require a longer duration of sirolimus treatment and have a greater rebound rate and more disease sequelae than KHE patients.[12] Given the poor prognosis of the condition and

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sequelae, KHE patients with KMP tend to require more aggressive management in clinical practice than KHE patients without KMP. As a result, it is critical to screen KHE patients with a high risk of developing KMP as early as possible. However, more information is still needed to clarify the risk factors associated with the occurrence of KMP.

Many investigators have studied the risk factors for KMP. Lesions within the retroperitoneum or mediastinum are more likely to be associated with KMP.[13] Additionally, lesion diameters >8 cm appear to be a risk factor for KMP.[14] A study that reviewed many published KHE cases showed that the incidence of KMP decreases with age.[15] We[4] and Croteau *et al*.[5] found that the depth of invasion, lesion size, and age of onset are associated with the development of KMP. Although previous studies have shown that younger ages of onset and larger lesion sizes are more likely to lead to the development of KMP, accurate threshold values would provide additional value to clinicians in managing these cases. Therefore, the aim of the present study was to establish the thresholds or optimal cutoff points of the age of onset and lesion size required for the development of KMP.

# Methods

## Patients and data collection

Institutional review board (IRB) approval for this retrospective study was obtained from the West China Hospital of Sichuan University. All procedures followed the research protocols approved by the West China Hospital of Sichuan University and Sichuan University and were conducted according to the Declaration of Helsinki. We retrospectively analyzed data from patients diagnosed with KHE between January 2014 and January 2022 from the Vascular Anomalies Group of Sichuan Province. Sichuan Province, with a population of 83.72 million people, is in southwestern China. At the diagnosis of KHE, we collected data on sex, age of onset, hematological findings, imaging results, lesion depth, maximum diameter of the lesion, location of the lesion, and prognosis. The inclusion criteria for this study were as follows: (i) the diagnosis of KHE was confirmed by clinical features, magnetic resonance imaging, and histopathologic data; (ii) patients were not receiving any treatment at the time of data collection; and (iii) written informed consent was obtained from the patient or the patient's guardians. For KMP patients, biopsies were performed after hematological parameters had returned to normal. Patients with incomplete data were excluded from this study.

## Definition

According to previous studies, KMP is defined as a platelet count $<100 \times 10^9$/L with hypofibrinogenemia (<1.6 g/L) and consumptive coagulopathy (D-dimer level >0.5 mg/L).[5,12] KHE can be morphologically classified as superficial, deep, or mixed.[4] In the present study, we measured the longest diameter of the lesion to represent the lesion size. Remission of disease was defined as a ≥20% decrease in the volumes of KHE lesions. No change was defined as a <20% increase and a <20% decrease in the volumes of KHE lesions. Further growth was defined as a ≥20% increase in the volume of index KHE compared with the baseline volume measured. In the present study, monotherapy was sirolimus alone, while combination therapy was sirolimus combined with prednisone for treatment.

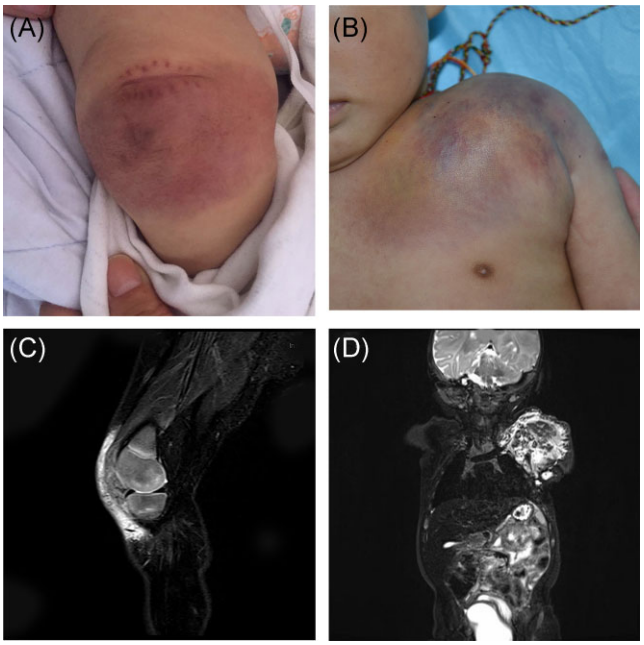


**Figure 1.** KHE involvement of the lower extremities without KMP (**A**, **C**); KHE involvement of the left shoulder with KMP (**B**, **D**).

## Statistical analysis

Categorical data were appropriately expressed as *n* (%), and quantitative data were shown as the median (interquartile range [IQR]) and/or mean (range). Fisher's exact test, chi-square test, or Mann–Whitney U test were used appropriately. Univariate logistic regressions were performed to analyze the factors associated with KMP by calculating the odds ratio (OR; 95% confidence interval [CI]). The variables with $P < 0.10$ from the univariate analysis were selected for inclusion in the multivariate logistic regression model. We used the area under the receiver operator characteristic (ROC) curve to assess the predictive power of risk factors and applied Youden's index to establish the cutoff points. A value of $P < 0.05$ was considered statistically significant. All analyses were performed with SPSS statistical software version 26.0 (IBM Corp).

# Results

## Patient characteristics

The characteristics of KHE patients with or without KMP are summarized in Tables 1 and 2. A total of 338 KHE patients (207 males and 131 females) were enrolled in the study, and 45.9% of the KHE patients developed KMP (Fig. 1). The median age of onset and tumor size were 1.5 months (IQR 0.0–8.0) and 5.1 cm (IQR 3.9–7.1), respectively. The most common lesion location was on the extremities (50.0%), and the most common lesion morphology was the mixed type (63.6%). Compared with KHE patients without KMP, KMP patients had significantly lower hemoglobin, platelet, and fibrinogen levels and significantly higher D-dimer levels. For KMP, the treatment strategies were also significantly different from those for KHE without KMP. Sirolimus monotherapy was more often used in patients with KHE, while patients with KHE combined with KMP tended to take combination therapy.

## Patients' prognosis

We followed up 338 patients, 311 of whom were followed up for 2 years and 27 for 1 year (supplementary Table 1, see online

**Table 1.** Clinical characteristics and univariate analysis of KHE with or without KMP.

| Variable | All patients (*n* = 338) | With KMP (*n* = 155) | Without KMP (*n* = 183) | Odds ratio (95% CI) | *P* value |
|---|---|---|---|---|---|
| Sex, *n* (%) | | | | | |
| Female | 131 (38.8) | 60 (38.7) | 71 (38.8) | [Reference] | |
| Male | 207 (61.2) | 95 (61.3) | 112 (61.2) | 1.004 (0.647–1.557) | 0.987 |
| Age of onset (months) | | | | 0.956 (0.934–0.977) | <0.001 |
| Mean (range) | 16.6 (0.0–600.0) | 3.7 (0.0–120.0) | 27.5 (0.0–600.0) | | |
| Median (IQR) | 1.5 (0.0–8.0) | 0.0 (0.0–2.0) | 4.0 (0.1–23.0) | | |
| Anatomic location, *n* (%) | | | | | |
| Cervicofacial | 80 (23.7) | 33 (21.3) | 47 (25.7) | [Reference] | |
| Extremity | 169 (50.0) | 73 (47.1) | 96 (52.5) | 1.083 (0.632–1.857) | 0.772 |
| Trunk | 89 (26.3) | 49 (31.6) | 40 (21.8) | 1.745 (0.948–3.212) | 0.074 |
| Retroperitoneum or mediastinum | | | | | |
| Yes | 13 (3.8) | 11 (7.1) | 2 (1.1) | 6.913 (1.508–31.686) | 0.013 |
| No | 325 (96.2) | 144 (92.9) | 181 (98.9) | [Reference] | |
| Depth, *n* (%) | | | | | |
| Superficial | 61 (18.1) | 19 (12.3) | 42 (23.0) | [Reference] | |
| Deep | 62 (18.3) | 23 (14.8) | 39 (21.3) | 1.304 (0.617–2.754) | 0.487 |
| Mixed | 215 (63.6) | 113 (72.9) | 102 (55.7) | 2.449 (1.338–4.482) | 0.004 |
| Tumor size (cm) | | | | 1.696 (1.488–1.934) | <0.001 |
| Mean (range) | 6.1 (1.2–25.0) | 8.0 (1.7–25.0) | 4.5 (1.2–16.1) | | |
| Median (IQR) | 5.1 (3.9–7.1) | 7.0 (5.4–9.6) | 4.2 (3.1–5.1) | | |

**Table 2.** Hematological characteristics and management strategies of KHE with or without KMP.

| Variable | All patients (*n* = 338) | With KMP (*n* = 155) | Without KMP (*n* = 183) | *P* value[a] |
|---|---|---|---|---|
| Hemoglobin (g/L) | | | | <0.001 |
| Mean (range) | 117.9 (20.0–234.0) | 102.8 (20.0–171.0) | 130.6 (86.0–234.0) | |
| Median (IQR) | 117.0 (101.3–129.8) | 102.0 (92.0–113.0) | 126.0 (117.0–134.0) | |
| Platelet level ($\times 10^9$/L) | | | | <0.001 |
| Mean (range) | 170.1 (1.0–557.0) | 39.7 (1.0–99.0) | 280.6 (112.0–557.0) | |
| Median (IQR) | 153.5 (38.0–282.8) | 32.0 (16.0–62.0) | 274.0 (214.0–351.0) | |
| Fibrinogen level (g/L) | | | | <0.001 |
| Mean (range) | 1.8 (0.3–5.0) | 1.2 (0.3–2.88) | 2.3 (1.1–5.0) | |
| Median (IQR) | 1.9 (1.1–2.3) | 1.1 (0.8–1.5) | 2.3 (2.1–2.6) | |
| D-dimer level (mg/L) | | | | <0.001 |
| Mean (range) | 5.3 (0.1–62.7) | 10.0 (0.1–62.7) | 1.34 (0.1–23.3) | |
| Median (IQR) | 1.8 (0.7–8.0) | 8.2 (4.1–13.8) | 0.7 (0.4–1.1) | |
| Management, n (%) | | | | <0.001 |
| Monotherapy | 225 (66.6) | 90 (58.1) | 135 (73.8) | 0.002 |
| Combination therapy | 86 (25.4) | 63 (40.6) | 23 (12.6) | <0.001 |
| Surgical excision | 8 (2.4) | 0 (0) | 8 (4.4) | 0.023 |
| Expectant management | 19 (5.6) | 2 (1.3) | 17 (9.3) | 0.001 |

[a]*P* value was calculated using the Mann–Whitney U test.

supplementary material). At the 6-month, 1-year, and 2-year follow-ups, 60.8% (236/388), 85.8% (290/338) and 87.5% (272/311) of patients had remission of the lesions; 26.3% (89/338), 9.8% (33/338) and 7.1% (22/311) had stable disease; and 3.8% (13/338), 4.4% (15/338) and 5.5% (17/311) had progressive disease. Notably, despite disease regression at the previous follow-up, 11 patients experienced disease progression at the 1-year follow-up and 12 patients at the 2-year follow-up. The prognosis of KHE patients with or without KMP was not significantly different at 6 months ($P = 0.113$), 1 year ($P = 0.280$), and 2 years ($P = 0.198$) of follow-up. At the 6-month follow-up, the rate of regression was significantly higher in KHE patients with KMP than in those without KMP ($P = 0.037$). At 2 years of follow-up, although there was no significant difference between KHE with KMP and without KMP, the prognosis was poorer than in patients without KMP.

## Risk factors for KMP

There was no significant relationship between sex and KMP occurrence. Consistent with previous studies, KHE morphology, lesions of the retroperitoneum or mediastinum, age of onset, and lesion size correlated with KMP occurrence based on univariate logistic regression (Table 1). From multivariate logistic regression, we found that the risk of KMP decreased with age ($P < 0.001$, OR 0.939; 95% CI 0.914–0.966) and that a larger lesion diameter was correlated with a higher incidence of KMP ($P < 0.001$, OR 1.944; 95% CI 1.646–2.296) (Table 3). Compared to superficial lesions, mixed ($P = 0.030$, OR 2.428; 95% CI 1.092–5.397) and deep ($P = 0.010$, OR 4.006; 95% CI 1.389–11.556) KHE were more likely to develop KMP. Additionally, four patients with lesions of the mediastinum all had KMP, and 77.8% (7/9) of patients with lesions in the

**Table 3.** Multivariate analysis of risk factors for KMP.

| Variable | Odds ratio (95% CI) | *P* value |
|---|---|---|
| Age of onset (months) | 0.939 (0.914–0.966) | <0.001 |
| Retroperitoneum or mediastinum | 11.864 (1.497–94.003) | 0.019 |
| Tumor size (cm) | 1.944 (1.646–2.296) | <0.001 |
| Anatomic location, *n* (%) | | |
| Cervicofacial | [Reference] | |
| Extremity | 0.625 (0.305–1.281) | 0.200 |
| Trunk | 1.220 (0.533–2.794) | 0.638 |
| Morphology | | |
| Superficial | [Reference] | |
| Deep | 4.006 (1.389–11.556) | 0.010 |
| Mixed | 2.428 (1.092–5.397) | 0.030 |

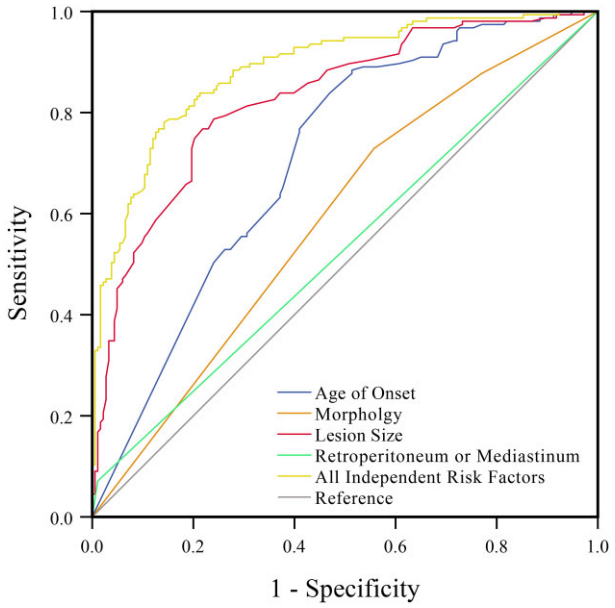


**Figure 2.** ROC curves assessing the link between risk factors and the occurrence of KMP in KHE patients. The blue curve represents age of onset (AUC 0.709, 95% CI 0.654–0.764); the red curve represents lesion size (AUC 0.828, 95% CI 0.784–0.872); the green curve represents retroperitoneum/mediastinum (AUC 0.530, 95% CI 0.468–0.592); the orange curve represents morphology (AUC 0.590, 95% CI 0.529–0.650); and the yellow curve represents all independent risk factors (AUC 0.887, 95% CI 0.852–0.922). AUC, area under the receiver operating characteristic curve.

retroperitoneum had KMP. Overall, patients with mediastinal or retroperitoneal lesions were more prone to developing KMP ($P = 0.019$, OR 11.864; 95% CI 1.497–94.003).

## Predictors of KMP in KHE patients

To further inspect the relationships between the independent risk factors and KMP occurrence, we conducted an ROC curve analysis (Fig. 2). For lesion size, the area under the ROC curve was 0.828 (95% CI 0.784–0.872), suggesting that the model accurately distinguishes between patients who develop KMP and those who do not. For the age of onset, the area under the ROC curve was 0.709 (95% CI 0.654–0.764); this result showed a moderate discriminative ability for KMP. For all the independent risk factors, the area under the ROC curve was 0.887 (95% CI 0.852–0.922). The Youden index indicated that the optimal cutoff values for predicting KMP in KHE patients were 5.35 cm for the maximum lesion diameter (index = 0.549, sensitivity = 76.8%, specificity = 78.1%) and 4.75 months for the onset age (index = 0.370, sensitivity = 88.4%, specificity = 48.6%).

Further analysis showed that a lesion size above the cutoff of 5.35 cm was significant for predicting KMP ($P < 0.001$, OR 11.817, 95% CI 7.084–19.714). Additionally, the risk of developing KMP significantly increased at an age of onset below the cutoff of 4.75 months ($P < 0.001$, OR 7.206, 95% CI 4.073–12.749). For KHE patients with an onset age <4.75 months and a lesion diameter >5.35 cm, the risk of KMP was significantly increased ($P < 0.001$, OR 21.099, 95% CI 11.718–37.992).

## Characteristics of different lesion sizes and onset ages

Using the cutoff points as a boundary, we analyzed the clinical features for different lesion sizes (Table 4) and age of onset (Table 5). We found that the mixed type was more concentrated in the group above the threshold of lesion size ($P < 0.001$), while the deep type was mostly seen below the threshold ($P < 0.001$). For the age of onset, small lesions were more commonly seen at an older onset age ($P < 0.001$). In terms of management strategies, lesions <5.35 cm were more commonly treated with monotherapy ($P = 0.006$), while lesions ≥5.35 cm were more often treated with combination therapy ($P < 0.001$). For patients of onset age <4.75 months, the mixed-type ($P = 0.001$) and superficial-type ($P = 0.012$) were more common, whereas the deep ($P < 0.001$) type was more often seen in patients with onset age >4.75 months. In terms of hematological parameters, there were significant differences in hemoglobin, platelet level, fibrinogen level, and D-dimer level, whether grouped by age at onset or lesion size thresholds. Compared to the age at onset ≥4.75 months group, patients with an onset age <4.75 months had higher disease regression rates at 6 months, 1 year, and 2 years.

## Discussion

KHE, a rare borderline tumor, has attracted the attention of researchers due to its series of complications.[16] Among the complications of KHE, KMP has always been the focus of clinicians because it represents aggressive tumor progression with poor prognosis.[17,18] After the onset of KMP, residual fibrosis tends to affect joint motion, and blood product infusion is needed to correct coagulopathy.[6] We also found a higher incidence of chronic lymphedema in patients with KMP in our previous study.[19] The prognosis of KHE patients can be improved if timely and effective treatment strategies are carried out for KMP patients or timely treatments are taken to prevent the occurrence of KMP.[17] In addition, KHE with KMP has a higher rebound rate and more disease sequelae than KHE without KMP.[12] Consistent with previous studies, more patients with KMP received combination treatment to control the disease, while monotherapy, surgical resection, or expectant therapy were used more often to treat patients with KHE without KMP.[20]

We previously believed that ~70% of KHE would be accompanied by KMP,[4,5] but a recent large retrospective analysis revealed that the incidence of KMP is lower than our previous conclusion.[3] As evidence accumulates from more studies with larger sample sizes, the reported frequency of KMP has decreased. This study showed that 45.9% of patients developed KMP. This decrease in incidence may be attributable to the fact that timely and effective management strategies are provided to most KHE patients. However, it is also possible that a growing number of mild KHE

**Table 4.** Characteristics of KHE for different lesion sizes.

| Variable | Lesion size (cm) | | P value |
|---|---|---|---|
| | <5.35 (*n* = 179) | ≥5.35 (*n* = 159) | |
| Sex, *n* (%) | | | 0.418[a] |
| Female | 73 (40.8) | 58 (36.5) | |
| Male | 106 (59.2) | 101 (63.5) | |
| Anatomic location, *n* (%) | | | 0.299[a] |
| Cervicofacial | 48 (26.8) | 32 (20.1) | 0.149[a] |
| Extremity | 88 (49.2) | 81 (50.9) | 0.744[a] |
| Trunk | 43 (24.0) | 46 (28.9) | 0.306[a] |
| Retroperitoneum or mediastinum, *n* (%) | | | 0.948[a] |
| Yes | 172 (96.1) | 153 (96.2) | |
| No | 7 (3.9) | 6 (3.8) | |
| Depth, *n* (%) | | | <0.001[a] |
| Superficial | 36 (20.1) | 25 (15.7) | 0.295[a] |
| Deep | 47 (26.3) | 15 (9.4) | <0.001[a] |
| Mixed | 96 (53.6) | 119 (74.8) | <0.001[a] |
| Age of onset (months) | | | <0.001[b] |
| Mean (range) | 17.9 (0.0–432.0) | 15.2 (0.0–600.0) | |
| Median (IQR) | 3.0 (0.0–13.0) | 0.5 (0.0–4.0) | |
| Management, *n* (%) | | | <0.001[a] |
| Monotherapy | 131 (73.2) | 94 (59.1) | 0.006[a] |
| Combination therapy | 28 (15.6) | 58 (36.5) | <0.001[a] |
| Surgical excision | 14 (7.8) | 5 (3.1) | 0.062[a] |
| Expectant management | 6 (3.4) | 2 (1.3) | 0.365[a] |
| Hemoglobin (g/L) | | | <0.001[b] |
| Mean (range) | 127.8 (76.0–234.0) | 106.7 (20.0–167.0) | |
| Median (IQR) | 125.0 (111.0–133.0) | 106.0 (95.0–121.0) | |
| Platelet level ($\times 10^9$/L) | | | <0.001[b] |
| Mean (range) | 233.9 (5.0–557.0) | 98.4 (1.0–516.0) | |
| Median (IQR) | 239.0 (156.0–324.0) | 48.0 (19.0–112.0) | |
| Fibrinogen level (g/L) | | | <0.001[b] |
| Mean (range) | 2.1 (0.5–5.0) | 1.4 (0.3–3.6) | |
| Median (IQR) | 2.1 (1.8–2.5) | 1.3 (0.8–1.8) | |
| D-dimer level (mg/L) | | | <0.001[b] |
| Mean (range) | 2.4 (0.1–23.3) | 8.5 (0.1–62.7) | |
| Median (IQR) | 0.9 (0.4–1.9) | 6.9 (1.9–11.3) | |
| 6-month follow up, *n* (%) | | | 0.707[a] |
| Remission | 122 (68.2%) | 114 (71.7%) | 0.479[a] |
| No change | 49 (27.4%) | 40 (25.2%) | 0.644[a] |
| Further growth | 8 (4.5%) | 5 (3.1%) | 0.527[a] |
| 1-year follow up, *n* (%) | | | 0.853[a] |
| Remission | 152 (84.9%) | 138 (86.8%) | 0.622[a] |
| No change | 19 (10.6%) | 14 (8.8%) | 0.576[a] |
| Further growth | 8 (4.5%) | 7 (4.4%) | 0.976[a] |
| 2-year follow up, *n* (%)[c] | | | 0.124[a] |
| Remission | 144 (87.3%) | 128 (87.7%) | 0.916[a] |
| No change | 15 (9.1%) | 7 (4.8%) | 0.140[a] |
| Further growth | 6 (3.6%) | 11 (7.5%) | 0.131[a] |

[a]*P* value was calculated using the chi-square test.
[b]*P* value was calculated using the Mann–Whitney U test.
[c]A total of 311 patients were followed up for 2 years, of whom 165 had lesions <5.35 cm in diameter and 146 had lesions >5.35 cm in diameter.

patients have been diagnosed due to the increased awareness of KHE.

Nevertheless, the understanding of KHE and KMP remains limited at present. Many researchers have proposed the hypothesis that KHE intralesional platelet trapping leads to KMP. Another hypothesis proposes that endothelial damage caused by KHE may lead to platelet activation.[21] However, it has also been hypothesised that highly expressed podoplanin in KHE lesions is associated with platelet aggregation.[22] High shear stress may also be involved in the occurrence and development of KMP.[2] However, regrettably, there is no hypothesis that can clearly explain the occurrence of KMP.

In addition to studies on the pathogenesis of KMP, clinical investigators are also actively searching for risk factors related to the occurrence and development of KMP. Current studies indicate that retroperitoneal/mediastinal lesion location, large lesion size, and young age of onset are risk factors for developing KMP.[4,5] We analyzed the relationship between sex, age of onset, anatomic location, depth of invasion, and tumor size and the occurrence of KMP. Univariate analysis showed that age of onset, lesion size, morphology, and anatomic site of KHE were associated with KMP. Multivariate analysis showed that compared with superficial lesions, the risk of KMP in mixed lesions and deep lesions increased by 2.428- and 4.006-fold, respectively. Finally, this study

**Table 5.** Characteristics of KHE at different ages of onset.

| Variable | Age of onset (months) | | P value |
|---|---|---|---|
| | <4.75 (*n* = 231) | ≥4.75 (*n* = 107) | |
| Sex, *n* (%) | | | 0.544[a] |
| Female | 87 (37.7) | 44 (41.1) | |
| Male | 144 (62.3) | 63 (58.9) | |
| Anatomic location, *n* (%) | | | 0.240[a] |
| Cervicofacial | 60 (26.0) | 20 (18.7) | 0.143[a] |
| Extremity | 115 (49.8) | 54 (50.5) | 0.907[a] |
| Trunk | 56 (24.2) | 33 (30.8) | 0.200[a] |
| Retroperitoneum or mediastinum, *n* (%) | | | 1.000[a] |
| Yes | 9 (3.9) | 3 (3.7) | |
| No | 222 (96.1) | 104 (96.3) | |
| Depth, *n* (%) | | | <0.001[a] |
| Superficial | 50 (21.6) | 11 (10.3) | 0.012[a] |
| Deep | 21 (9.1) | 41 (38.3) | <0.001[a] |
| Mixed | 160 (69.3) | 55 (51.4) | 0.001[a] |
| Tumor size (cm) | | | <0.001[b] |
| Mean (range) | 6.6 (1.3–25.0) | 5.0 (1.2–20.0) | |
| Median (IQR) | 5.7 (4.1–8.0) | 4.3 (3.3–5.5) | |
| Management, *n* (%) | | | 0.367[a] |
| Monotherapy | 148 (64.1) | 77 (72.0) | 0.152[a] |
| Combination therapy | 65 (28.1) | 21 (19.6) | 0.095[a] |
| Surgical excision | 12 (5.2) | 7 (6.5) | 0.617[a] |
| Expectant management | 6 (2.6) | 2 (1.9) | 0.980[a] |
| Hemoglobin (g/L) | | | <0.001[b] |
| Mean (range) | 114.5 (20.0–234.0) | 125.1 (68.0–171.0) | |
| Median (IQR) | 109.0 (99.0–125.0) | 126.0 (118.0–132.0) | |
| Platelet level ($\times 10^9$/L) | | | <0.001[b] |
| Mean (range) | 137.2 (1.0–557.0) | 241.3 (5.0–441.0) | |
| Median (IQR) | 75.0 (24.0–231.0) | 251.0 (189.0–337.0) | |
| Fibrinogen level (g/L) | | | <0.001[b] |
| Mean (range) | 1.6 (0.3–3.6) | 2.2 (0.6–5.0) | |
| Median (IQR) | 1.6 (0.9–2.1) | 2.3 (1.9–2.6) | |
| D-dimer level (mg/L) | | | <0.001[b] |
| Mean (range) | 6.5 (0.1–62.7) | 2.7 (0.1–23.3) | |
| Median (IQR) | 3.9 (0.9–9.4) | 0.8 (0.4–1.9) | |
| 6-month follow up, *n* (%) | | | 0.003[a] |
| Remission | 175 (75.8%) | 61 (57.0%) | <0.001[a] |
| No change | 49 (21.2%) | 40 (37.4%) | 0.002[a] |
| Further growth | 7 (3.0%) | 6 (5.6%) | 0.400[a] |
| 1-year follow up, *n* (%) | | | 0.066[a] |
| Remission | 205 (88.7%) | 85 (79.4%) | 0.023[a] |
| No change | 19 (8.2%) | 14 (13.1%) | 0.162[a] |
| Further growth | 7 (3.0%) | 8 (7.5%) | 0.118[a] |
| 2-year follow up, *n* (%)[c] | 211 | 100 | 0.059[a] |
| Remission | 191 (90.5%) | 81 (81.0%) | 0.018[a] |
| No change | 11 (5.2%) | 11 (11.0%) | 0.063[a] |
| Further growth | 9 (4.3%) | 8 (8.0%) | 0.176[a] |

[a]*P* value was calculated using the chi-square test.
[b]*P* value was calculated using the Mann–Whitney U test.
[c]A total of 311 patients were followed up for 2 years, of whom 211 had an onset age <4.75 months and 100 had an onset age >4.75 months.

demonstrated that age of onset and lesion size were strongly correlated with the incidence of KMP. As platelet trapping can be seen in KHE lesions with or without KMP, we speculated that larger lesions have a stronger ability to capture platelets. Additionally, a younger age of onset is associated with a larger relative area of the lesion in children. Our results also indicated that the risk of KMP in retroperitoneal/mediastinal lesions was 11.864 times higher than that in other sites.

However, knowledge that age and lesion size are related to the occurrence of KMP is insufficient for clinicians. Gruman *et al.* retrospectively reviewed a series of cases and found that a lesion diameter <8 cm may not be enough to directly cause KMP.[14] Our previous study showed that patients with lesion diameters >5 cm were more prone to KMP.[4] However, these thresholds were not calculated by standard statistical methods. The ROC curve was obtained for analysis in this work, and the optimal cutoff point was calculated using Youden's index. In the present study, we reviewed data for many KHE patients, and the best discriminant thresholds of lesion size and age of onset were 5.35 cm and 4.75 months, respectively. Our results suggest that for KHE patients with lesions >5.35 cm in diameter, clinicians should be alert to the occurrence of KMP and undertake active management strategies as

soon as possible. At the same time, patients with KHE whose onset age was ≤4.75 months had a 7.206-fold greater risk of KMP. For KHE patients with an onset age <4.75 months and a lesion diameter >5.35 cm, there was a 21.099-fold increased risk of KMP. For patients with KMP or a high risk of KMP, effective treatment can reduce residual lesions; to this end, sirolimus or vincristine with/without prednisolone might be a good choice.[20,23–26]

However, for lesions in the retroperitoneum/mediastinum, KMP should be considered regardless of the age of onset or size of the lesion. Despite the small number of retroperitoneal/mediastinal lesions, we found that the lesion location corresponded with higher OR values and stronger predictive abilities. In the future, further analysis should be conducted after sufficient patients are available.

We believe that further study and increased awareness of KMP will increase the availability of information to help clinicians manage these patients.

In the present study, there were several limitations. First, this was a retrospective study conducted in the Vascular Anomalies Group of Sichuan Province; fortunately, single-center bias was avoided. Second, our findings need to be confirmed by larger prospective studies in the future. Third, in this study, we did not analyze the long-term prognosis and treatment strategies of KHE with/without KMP; however, we will conduct further studies on this topic.

## Conclusions

In our cohort, 45.9% of KHE patients experienced KMP. Age of onset and lesion size were risk factors for KMP according to the multivariate analysis results. Youden's index was used to calculate the optimal cutoff values, which were found to be 4.75 months for the onset age and 5.35 cm for the lesion size. The risk of KMP in KHE patients with onset ages <4.75 months increased 7.206-fold, and the risk of KMP in KHE patients with lesions >5.35 cm increased 11.817-fold. KHE patients with two simultaneous risk factors had ∼21.099 times the risk of developing KMP than KHE patients without any risk factors. For KHE patients with risk factors, active intervention is recommended to improve their prognoses.

## Supplementary data

Supplementary data is available at PCMEDI online.

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## Author contributions

Conceptualization: Y.J. and S.C. Data curation: J.Z., and TQ. Formal analysis: J.Z., Y.L., X.G., and Z.Z. Funding acquisition: Y.J. and S.C. Investigation: J.Z., Y.L., T.Q., X.G., Z.Z., C.H., and X.Z. Methodology: J.Z., Y.L., C.H., and Q.P. Project administration: Y.J., F.H., G.L., L.Q., and C.H. Software: X.Z. and F.K. Supervision: Y.J., S.C., and C.H., Validation: J.Z., Y.L., and Y.Z. Writing, original draft preparation: J.Z. and Y.L. Writing, review and editing: Y.J.

## Conflict of interest

None declared.

## Compliance with ethics guidelines

The Institutional Review Board of the West China Hospital of Sichuan University approved this retrospective study. All procedures followed the study protocol and were conducted according to the Declaration of Helsinki. All subjects provided informed consent as well as permission for use of their data in scientific publications prior to study participation.

## Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

## References

1. Lyons LL, North PE, Lai FMM, *et al.* Kaposiform hemangioendothelioma: A study of 33 cases emphasizing its pathologic, immunophenotypic, and biologic uniqueness from juvenile hemangioma. *Am J Surg Pathol* 2004; **28**: 559–68. doi:10.1097/00000478-200405000-00001.
2. Ji Y, Chen S, Yang K, *et al.* Kaposiform hemangioendothelioma: Current knowledge and future perspectives. *Orphanet J Rare Dis* 2020; **15**: 1–16. doi:10.1186/s13023-019-1279-y.
3. Zhou J, Yang K, Dai S, *et al.* Clinical features and management of kaposiform hemangioendothelioma and tufted angioma: Similarities and differences. *J Am Acad Dermatol* 2021; **87**: 172–4. doi:10.1016/j.jaad.2021.07.012.
4. Ji Y, Yang K, Peng S, *et al.* Kaposiform haemangioendothelioma: Clinical features, complications and risk factors for Kasabach-Merritt phenomenon. *Br J Dermatol* 2018; **179**: 457–63.
5. Croteau SE, Liang MG, Kozakewich HP, *et al.* Kaposiform hemangioendothelioma: Atypical features and risks of Kasabach-Merritt phenomenon in 107 referrals. *J Pediatr* 2013; **162**: 142–7. doi:10.1016/j.jpeds.2012.06.044.
6. Yao W, Li KL, Qin ZP, *et al.* Standards of care for Kasabach-Merritt phenomenon in China. *World J Pediatr* 2021; **17**: 123–30. doi:10.1007/s12519-020-00379-9.
7. Gong X, Li Y, Yang K, *et al.* Infantile hepatic hemangiomas: Looking backwards and forwards. *Precis Clin Med* 2022; **5**: pbac006. doi:10.1093/pcmedi/pbac006.
8. Baselga E, Cordisco MR, Garzon M, *et al.* Rapidly involuting congenital haemangioma associated with transient thrombocytopenia and coagulopathy: A case series. *Br J Dermatol* 2008; **158**: 1363–70. doi:10.1111/j.1365-2133.2008.08546.x.
9. Ryan C, Price V, John P, *et al.* Kasabach-Merritt phenomenon: A single centre experience. *Eur J Haematol* 2010; **84**: 97–104. doi:10.1111/j.1600-0609.2009.01370.x.

10. San Miguel FL, Spurbeck W, Budding C, *et al.* Kaposiform hemangioendothelioma: A rare cause of spontaneous hemothorax in infancy. Review of the literature. *J Pediatr Surg* 2008; **43**: e37–41. doi:10.1016/j.jpedsurg.2007.08.068.
11. Dai S, Yang K, Qiu T, *et al.* Health-related quality of life in children with kaposiform hemangioendothelioma. *Front Pediatr* 2022; **10**: 1–8.
12. Zhou J, Li Y, Qiu T, *et al.* Long-term outcomes of sirolimus treatment for kaposiform hemangioendothelioma: Continuing successes and ongoing challenges. *Int J Cancer* 2023.
13. Ji Y, Chen S, Peng S, *et al.* Kaposiform lymphangiomatosis and kaposiform hemangioendothelioma: Similarities and differences. *Orphanet J Rare Dis* 2019; **14**: 1–8. doi:10.1186/s13023-019-1147-9.
14. Gruman A, Liang MG, Mulliken JB, *et al.* Kaposiform hemangioendothelioma without Kasabach-Merritt phenomenon. *J Am Acad Dermatol* 2005; **52**: 616–22. doi:10.1016/j.jaad.2004.10.880.
15. Schmid I, Klenk AK, Sparber-Sauer M, *et al.* Kaposiform hemangioendothelioma in children: A benign vascular tumor with multiple treatment options. *World J Pediatr* 2018; **14**: 322–9. doi:10.1007/s12519-018-0171-5
16. Wassef M, Blei F, Adams D, *et al.* Vascular Anomalies classification: Recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics* 2015; **136**: e203–214. doi:10.1542/peds.2014-3673.
17. Enjolras O, Mulliken JB, Wassef M, *et al.* Residual lesions after Kasabach-Merritt phenomenon in 41 patients. *J Am Acad Dermatol* 2000; **42**: 225–35. doi:10.1016/S0190-9622(00)90130-0.
18. Sarkar M, Mulliken JB, Kozakewich HP, *et al.* Thrombocytopenic coagulopathy (Kasabach-Merritt phenomenon) is associated with kaposiform hemangioendothelioma and not with common infantile hemangioma. *Plast Reconstr Surg* 1997; **100**: 1377–86. doi:10.1097/00006534-199711000-00001.
19. Ji Y, Chen S, Xia C, *et al.* Chronic lymphedema in patients with kaposiform hemangioendothelioma: Incidence, clinical features, risk factors and management. *Orphanet J Rare Dis* 2020; **15**: 1–9. doi:10.1186/s13023-019-1279-y.
20. Drolet BA, Trenor CC , 3rd, Brandão LR, *et al.* Consensus-derived practice standards plan for complicated kaposiform hemangioendothelioma. *J Pediatr* 2013; **163**: 285–91. doi:10.1016/j.jpeds.2013.03.080.
21. O'Rafferty C, O'Regan GM, Irvine AD, *et al.* Recent advances in the pathobiology and management of Kasabach-Merritt phenomenon. *Br J Haematol* 2015; **171**: 38–51. doi:10.1111/bjh.13557.
22. Debelenko LV, Perez-Atayde AR, Mulliken JB, *et al.* D2-40 immunohistochemical analysis of pediatric vascular tumors reveals positivity in kaposiform hemangioendothelioma. *Mod Pathol* 2005; **18**: 1454–60. doi:10.1038/modpathol.3800444.
23. Yao W, Li K, Wang Z, *et al.* Comparison of efficacy and safety of corticosteroid and vincristine in treating kaposiform hemangioendothelioma and tufted angioma: A multicenter prospective randomized controlled clinical trial. *J Dermatol* 2021; **48**: 576–84. doi:10.1111/1346-8138.15767.
24. Ji Y, Chen S, Zhou J, *et al.* Sirolimus plus prednisolone vs sirolimus monotherapy for kaposiform hemangioendothelioma: A randomized clinical trial. *Blood* 2022; **139**: 1619–30. doi:10.1182/blood.2021014027.
25. Wang Z, Li K, Yao W, *et al.* Steroid-resistant kaposiform hemangioendothelioma: A retrospective study of 37 patients treated with vincristine and long-term follow-up. *Pediatr Blood Cancer* 2015; **62**: 577–80. doi:10.1002/pbc.25296.
26. Ji Y, Chen S, Xiang B, *et al.* Sirolimus for the treatment of progressive kaposiform hemangioendothelioma: A multicenter retrospective study. *Int J Cancer* 2017; **141**: 848–55. doi:10.1002/ijc.30775.


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