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EVALUATION OF TREATMENT OUTCOMES AND PROGNOSTIC FACTORS IN PATIENTS AFTER LIVER TRANSPLANTATION DUE TO HEPATIC EPITHELIOID HEMANGIOENDOTHELIOMA

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ABSTRACT

Introduction: Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor of low-to-intermediate malignant potential with an incompletely defined biological behaviour, exhibiting both benign and malignant features. It most commonly affects the liver, but may also involve other organs, such as the lungs and bones. Due to its heterogeneous clinical presentation and similarity to other vascular tumors primarily affecting the liver, misdiagnosis remains a common clinical challenge. Currently, several therapeutic approaches are used depending on various factors, but liver transplantation (LTx) is increasingly considered as the treatment option for patients with metastatic HEHE, particularly in unresectable cases. Several studies indicate a favorable prognosis following transplantation for HEHE.
Aim of the Study: The aim of this study is to review the existing literature on treatment outcomes and to identify prognostic factors in patients undergoing LTx due to HEHE.
Materials and Methods: A comprehensive literature review was performed using the PubMed database.
Results and Conclusions: LTx is a crucial treatment option for patients with unresectable and multifocal HEHE. Current data indicate that post-transplant survival rates are favorable, with the potential to achieve durable, recurrence-free survival - even in the presence of extrahepatic metastases. Several prognostic factors have been identified that may influence post-transplant outcomes, including tumor burden, presence of extrahepatic disease (EHD), vascular invasion and tumor growth dynamics. In light of the limited efficacy of available systemic therapies, LTx should be considered the preferred treatment option in carefully selected patients with advanced HEHE. Nevertheless, long-term follow-up remains crucial to identify potential recurrence or complications.

KEYWORDS

Epithelioid Hemangioendothelioma, Hepatic, Liver Tumor, Liver Transplantation, Prognostic Factors, Survival

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aHR - adjusted Hazard Ratio
CCA - cholangiocarcinoma
DFS - disease-free survival
ELTR - European Liver Transplant Registry
EHD - extrahepatic disease
EHE - epithelioid hemangioendothelioma
Et al. - and others
HAT – hepatic artery thrombosis
HCC - hepatocellular carcinoma
HEHE - hepatoepithelioid hemangioendothelioma
HR - Hazard Ratio
IHC – immunohistochemistry
IQR - interquartile range
LDLT - living donor liver transplantation
LRx - liver resection
LTx - liver transplantation
MaVi - macrovascular invasion
MELD - Model for End-Stage Liver Disease
NET - neuroendocrine tumors
NLRB - National Liver Review Board
OCPs - oral contraceptives pills

OS - overall survival
PHVMs - primary hepatic vascular malignancies
RFA - radiofrequency ablation
TACE - transarterial chemoembolization
UNOS - the United Network for Organ Sharing

1. Introduction:

Epithelioid hemangioendothelioma is a rare, low-grade vascular tumor that may exhibit both benign and malignant features. It most commonly affects middle-aged individuals, with a higher prevalence in women, although it can occur at any age [2]. The exact etiology of EHE remains unclear. However, it has been established that the tumor originates from endothelial cells, which exhibit features of both vascular and epithelial differentiation. EHE, which most frequently affects the liver, belongs to the group of primary hepatic vascular malignancies (PHVMs), accounting for less than 1% of all hepatic tumors [3]. Its clinical course may be slower compared to other primary malignant liver tumors, although disease progression remains unpredictable [1]. Besides the liver, the tumor can also involve other parenchymal organs, such as the lungs or bones. Due to the nonspecific clinical and radiological features of EHE, diagnosis is often challenging and typically requires histopathological confirmation with immunohistochemical analysis. Given the limited number of reported cases of hepatic epithelioid hemangioendothelioma, as well as its overlapping characteristics with other PHVMs, early and accurate diagnosis is essential in the clinical context. Delayed diagnosis at advanced stages adversely affects prognosis and limit the timely initiation of appropriate treatment. Given the absence of universally accepted treatment guidelines, clinical decision-making in HEHE remains highly individualized. Therefore, there is a need to establish optimal therapeutic strategies that provide the best clinical outcomes, including prolonged overall survival (OS) and disease-free survival (DFS) rates. Furthermore, the development of standaridized follow-up protocols is necessary to optimize the management of patients undergoing liver transplantation or other therapeutic approaches. Current evidence suggests that surgical intervention remains the primary therapeutic approach in the management of HEHE. Liver resection (LRx) is preferred for localized, resectable disease, whereas Ltx is reserved for unresectable or multifocal tumors [9]. The choice between these modalities relies on a comprehensive evaluation of patient-related and disease-specific factors, including patient's overall health status, size and distribution of the tumor, and graft availability. Notably, younger age appears to be an important factor associated with improved outcomes, particularly DFS, when transplantation is performed at an early stage of the disease [9]. Several studies indicate a favorable prognosis following transplantation for HEHE. However, there is still a lack of larger, multicenter studies and interdisciplinary collaboration to evaluate specific eligibility criteria and their impact on patient outcomes. This gap in the literature highlights the need for further research to better define optimal patient selection and treatment strategies. The aim of this study is to review the existing literature on treatment outcomes and to identify prognostic factors in patients undergoing liver transplantation for hepatic epithelioid hemangioendothelioma.

2. Materials and Methods:

A literature review was conducted to evaluate treatment outcomes and prognostic factors in patients with HEHE undergoing LTx. During the data collection process PubMed database was searched for studies published between 1999 and 2026. The following keywords were used: epithelioid hemangioendothelioma, hepatic epithelioid hemangioendothelioma, liver, hepatic, liver tumor, liver transplantation, prognostic factors, survival. The analysis included oryginal articles, case series and systematic reviews reporting outcomes in patients undergoing LTx for HEHE. Studies of low methodological quality and publications in language other than English were excluded. The selection of articles was performed in two stages: initially based on titles and abstracts, following the full-text assessment of eligible articles. Extracted data were analyzed systematically, and in cases of overlapping datasets, the most recent and comprehensive data was included to ensure accuracy and consistency. The review was conducted in accordance with PRISMA guidelines.

3. Characteristics of HEHE:

HEHE is a rare vascular tumor with a largely unknown etiology and a nonspecific clinical course. Despite the increasing understanding of its characteristics and molecular variants, the low number of reported cases, the unpredictable disease course, and the absence of well-defined risk and prognostic factors hinder the establishment of precise epidemiological data. It most commonly affects middle-aged individuals, with a higher prevalence in women and estimated incidence of 1-2 cases of every 1 million people [2,10]. No clear geographic distribution has been identified. Several factors including exposure to vinyl chloride, asbestos and thorotrast, as well as a history of major hepatic trauma, viral hepatitis, primary biliary cirrhosis, alcohol and oral contraceptives pills (OCPs) use have been proposed as potential risk factors for HEHE. However these associations remain unclear [3,6-8] as HEHE cases without a medical history of liver injury or systemic disease have also been described in the literature [5]. There are currently no established screening programs for HEHE. Moreover, the disease is difficult to distinguish diagnostically from other PHVMs, which often results in diagnosis at advanced stages [1]. Distant metastases are present at time of diagnosis in approximately 37% of patients, with regional disease in 27,5% [10]. The clinical presentation is often subtle due to the tumor's slow-growing, low-to-intermediate grade nature [10]. Approximately 25% of patients reported in the literature are asymptomatic [4]. The remaining patients typically present with nonspecific symptoms or the tumor is discovered incidentally on imaging [10]. When symptomatic, patients most commonly report right upper quadrant abdominal pain or unintentional weight loss [6]. The differential diagnosis of HEHE remains challenging due to the absence of specific clinical and radiological features. Therefore, definitive diagnosis requires histopathological confirmation, including immunohistochemical staining. Immunohistochemistry (IHC) is positive for vascular markers (factor VIII-related antigen, CD31 and CD34) and negative for cytokeratins. The two main genetic abnormalities are the more common WWTR1-CAMTA1 fusion and the less frequent but more aggressive YAP1-TFE3 fusion [5].

4. Treatment:

A range of therapeutic strategies has been described for the management of HEHE, including liver resection (LRx), liver transplantation (LTx), radiotherapy, chemotherapy, hormone therapy, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and active surveillance [9]. Given the rarity of this tumor, a clearly defined and standardized treatment strategy has not yet been established. Management should therefore be individualized, taking into consideration factors such as tumor location, size, number of lesions, presence of vascular invasion, extrahepatic spread, disease progression rate, severity of clinical symptoms, and response to previous therapies [1,11]. Surgical treatment has been associated with favorable long-term outcomes in selected patients. However, surgical intervention is not feasible in all cases, most commonly due to the multifocal nature of the disease or anatomical limitations preventing complete resection [1]. Among these modalities, liver transplantation has emerged as a particularly important therapeutic option in patients with unresectable or multifocal disease. Current evidence suggests that treatment decisions are primarily guided by tumor burden, extent of disease dissemination, growth dynamics, presence of systemic symptoms, and the likelihood of achieving negative surgical margins. These factors are critical in determining whether LRx, LTx, or alternative management strategies represent the most appropriate therapeutic options.

5. Liver transplantation treatment outcomes [Tab.1]:

Current clinical evidence indicates that LTx in patients with HEHE is associated with excellent long-term outcomes, even in the presence of advanced intrahepatic disease. In a cohort of 59 patients from the European Liver Transplant Registry, most presented with extensive tumor burden, including bilobar involvement in 96% of cases and more than 15 nodules in 86% of explanted livers. Despite this, post-transplant survival rates were favorable, reaching 93%, 83% and 72% at 1, 5 and 10 years, respectively. Disease recurrence occurred in 23.7% of patients after a median of 49 months, indicating that relapse is relatively common but typically delayed. Importantly, a subset of patients with recurrent disease achieved prolonged survival, suggesting that recurrence does not necessarily confer poor prognosis but rather reflects the indolent biology of HEHE. Disease-free survival rates were also high, at 90%, 82% and 64% at 1, 5, and 10 years, respectively. Early post-transplant mortality was low (1.7%), while late mortality reached 22%, reflecting long-term disease-related outcomes rather than perioperative risk. These findings indicate that LTx is a highly effective therapeutic option for HEHE, including in patients with extensive or extrahepatic disease and supports a shift from conventional tumor burden-based selection criteria toward biology-driven models. Furthermore, the potential for prolonged survival after recurrence underscores the importance of active post-

transplant management [14]. These outcome advantages are further supported by a larger analysis of 149 patients with HEHE who underwent LTx between 1984 and 2014 using data from the European Liver Transplant Registry (ELTR-ELITA). This study confirmed the efficacy of LTx, identified key risk factors for recurrence and introduced a prognostic scoring system (HEHE-LT score). Notably, LTx remained effective even in patients with EHD, reinforcing that anatomical extent alone should not preclude transplantation. Three major risk factors for post-transplant recurrence were identified: microvascular invasion, short waiting time for transplantation (≤120 days), and lymph node involvement at the time of LTx. These variables are incorporated into the HEHE-LT score, which stratifies patients into low- and high-risk groups and may guide post-transplant management. Patients with scores of 0-2 had significantly better 5-year DFS than those with a score of 6-10 (93.9% vs 38.5%), demonstrating a clear association between tumor biology and post transplant outcomes. The proposed selection algorithm integrates resectability assessment with biology-based risk stratification, enabling candidate selection based on recurrence risk rather than conventional staging criteria. Accordingly, post-transplant management should include close surveillance and risk-adapted follow-up. Importantly, recurrence does not preclude further treatment and aggressive management may result in prolonged survival, further supporting the concept that outcomes are driven by tumor biology rather than recurrence alone [17]. Consistent with these observations, data from the UNOS database demonstrate favorable outcomes after LTx in HEHE with OS rates of 88.6% at 1 year, 78.9% at 3 years, and 77.2% at 5 years. Survival in HEHE patients was comparable to that of patients with hepatocellular carcinoma (HCC) meeting the Milan criteria and superior to outcomes in cholangiocarcinoma (CCA) or neuroendocrine tumors (NET), further confirming the clinical effectiveness of transplantation in this setting. Notably, HEHE rarely leads to acute liver failure, resulting in low Model for End-Stage Liver Disease (MELD) scores (median of 7), which may limit access to transplantation under standard allocation systems. Consequently, despite favorable outcomes, access to LTx may be restricted without policy adaptation. In the United States, the National Liver Review Board (NLRB) recognizes unresectable HEHE as an indication for MELD exception points. In this context, 91.6% of patients applied for exception points, with nearly universal approval (120/121) and 85% receiving points on the first application. The median number of points requested was 22, resulting in a median MELD score of 25 at transplantation and a median waiting time of 78.5 days [15]. Additional evidence supports the effectiveness of LTx. In the study by Krasnodębski et al., 18 transplant recipients achieved 1-, 5- and 15-year survival rates of 94.0%, 82.6%, and 41.3%, respectively, with no observed disease recurrence during a median follow-up of 65.9 months [18]. Similarly, a large US cohort demonstrated that LTx was associated with superior survival compared with other treatment modalities, with a median survival of 111 months. In multivariable analysis LTx was an independent predictor of improved OS, reducing the risk of death by approximately 39% (HR = 0.61; p = 0.035), even after adjustment for age, sex, comorbidities and tumor size [12]. However, data from the Mayo Clinic highlight the importance of tumor biology in determining outcomes. In this analysis, LTx achieved favorable short-term outcomes (3-year OS 86.7%), comparable to liver resection (80.9%) and superior to nonsurgical management (51.1%). Nonetheless, the type of surgical intervention was not independently associated with survival, indicating that prognosis is primarily driven by tumor biology rather than treatment modality alone. In particular, bone metastasis emerged as the strongest adverse prognostic factor (HR 6.3, $p<0.001$), suggesting that patients with skeletal involvement are unlikely to benefit from aggressive surgical strategies, including LTx. In contrast, lung metastases did not significantly impact survival, indicating that EHD should not be considered an absolute contraindication to transplantation. Notably, the site of metastasis appears to be more relevant than the mere presence of EHD, further supporting a biology-driven approach to patient selection [19]. These conclusions are reinforced by registry-based analyses demonstrating that HEHE does not adversely affect post-transplant outcomes. In a cohort of 111,558 liver transplant recipients, only 121 patients (0.1%) underwent transplantation for HEHE, underscoring the rarity of this indication. Despite differences in baseline characteristics - HEHE patients were younger, more often female, had lower body mass index and had better preserved liver function – post-transplant survival was comparable to that of other indications with median survival of 16.6 years in the HEHE cohort versus 13.8 years in recipients transplanted for other indications, without statistical significance (p = 0.28). Multivariable and propensity score-matched analyses confirmed that HEHE was not associated with increased mortality risk [16]. In contrast, a Chinese cohort of 228 HEHE patients reported strikingly poor outcomes, with LTx identified as an independent adverse prognostic factor (HR 5.5). Among the study population, only 8 patients underwent LTx and this subgroup demonstrated the worst outcomes, with 1- and 3 year OS rates of 62.5% and 25%, respectively. However, these findings likely reflect significant selection bias, as transplantation was reserved for patients with the most advanced and aggressive disease and may also be influenced by differences in

perioperative care or patient selection criteria [20]. Current clinical guidelines support these observations. Both ACG and AASLD/AST guidelines recognize LTx as a key therapeutic option in HEHE, particularly in unresectable disease, where it offers the most favorable long-term outcomes. Importantly, conventional staging systems have limited prognostic value in this setting and extrahepatic spread should not be considered an absolute contraindication to transplantation. Overall, these data support a shift toward individualized, biology-driven decision-making, positioning liver transplantation as a cornerstone treatment for HEHE and a potentially curative strategy in appropriately selected patients [10, 13]. From a clinical perspective, this justifies a more individualized and multidisciplinary approach to patient selection, taking into account tumor behavior, distribution, and overall clinical status [10].

Table 1. Outcomes of liver transplantation in patients with hepatic epithelioid hemangioendothelioma.

Author (year)	Number of transplanted patients	Study design	Overall survival (OS)	Disease-free survival (DFS)	Recurrence (%)	Prognostic factors
Lerut et al. (2007)	59	Retrospective registry study (ELTR)	1-year OS: 93% 5-year OS: 83% 10-year OS: 72%	1-year DFS: 90% 5-year DFS: 82% 10-year DFS: 64%	23,7% (median 49 months)	Vascular invasion (micro- and macrovascular) associated with worse outcomes; no significant impact of EHD, lymph node involvement, pre-LT treatment or tumor burden
Lai et al. (2017)	149	Retrospective registry study (ELTR-ELITA)	1-year OS: 88.6% 5-year OS: 79.5% 10-year OS: 74.4%	5-year DFS: 93,9% (HEHE-LT score ≤ 2) vs. 38,5% (HEHE-LT score ≥ 6)	Not reported	MaVi (HR 4.8), short waiting time ≤120 days (HR 2.6), and hilar lymph node invasion (HR 2.2) associated with higher recurrence risk; no significant impact of EHD
Brahmbhatt et al. (2020)	131 waitlisted, 88 underwent LTx	Retrospective cohort study (UNOS transplant database)	1-year OS: 88,6% 3-year OS: 78,9% 5-year OS: 77,2%	Not reported	Not reported	Effective prioritization system (exception points) (91.6% submitted, 100% approved on review; 85% at first submission); comparable survival to HCC within Milan criteria receiving exception points (P = 0.08); increased early graft failure due to hepatic artery thrombosis (HAT) within 14 days (patients with HEHE: 4.6% vs. others: 0.5%); median MELD at LTx: 7 (IQR 6–11); median waiting time: 78.5 days (IQR 29.5–237.5)
Krasnodębski et al. (2020)	18	Retrospective sigle-center study	1-year OS: 94% 5-year OS: 82.6% 15-year OS: 41.3%	Not reported	0% (median 65.9 months)	Not defined
Kaltenmeier et al. (2022)	334 total; 35 underwent LTx	Retrospective cohort study (NCDB, USA, 2004-2018)	Median OS: 111 months (LTx), 69 months (LRx), 80 months (no surgery), 38 months (ablation); 5-year OS: 62% (LTx), 52% (LRx), 63% (no surgery), 0% (ablation)	Not reported	Not reported	Treatment modality (LTx associated with improved survival), tumor biology (indolent vs aggressive behavior), and patient selection bias; limited impact of traditional clinicopathological factors
Sawma et al. (2024)	80 total; 24 underwent LTx	Retrospective sigle-center study (Mayo Clinic, 1984-2023)	3-year OS: 86.7% (LTx), 80.9% (LRx), 51.1% (medical management)	Not reported	Not reported	Bone metastasis (HR 6.3, p<0.001); lung metastasis - not significant; surgical treatment - not significant

Author (year)	Number of transplanted patients	Study design	Overall survival (OS)	Disease-free survival (DFS)	Recurrence (%)	Prognostic factors
Liu et al. (2024)	228 total; 8 underwent LTx	Retrospective cohort study	1-year OS: 62.5% 3-year OS: 25%	Not reported	High recurrence rate (not quantified)	LTx (HR 5.5), age ≥60 years (HR 4.21), tumor size >10 cm (HR 12.14)
ACG Clinical Guideline (2024)	Not specified (based on pooled registry data)	Evidence-based clinical guideline (systematic review of observational transplant registries)	1-year OS >90% 5-year OS ~70-80% (based on registry data)	Not consistently reported	~20-25% (based on registry data)	Vascular invasion associated with worse outcomes; EHD and lymph node involvement not significant; tumor biology more important than staging
Larson et al. (2025)	121	Retrospective cohort study (UNOS/OPTN database)	Median OS: 16.6 years (HEHE recipients) vs. 13.8 years (non-HEHE recipients); no significant difference (p = 0.28)	Not reported	Not reported	Younger age; female sex; lower MELD score; post-transplant survival comparable to non-HEHE patients (including after propensity score matching).
AASLD/AST Practice Guideline (2025)	Not specified	Evidence-based clinical guidline (literature review and expert consensus)	Not specifically reported (depends on underlying indication; favorbale in selected patients)	Not reported	Not reported	Tumor biology, risk of recurrence, patient selection, disease burden, response to therapy; limited role of strict staging alone

6. Post-transplant prognostic factors:

Based on data from the European Liver Transplant Registry, several traditionally adverse oncologic factors, including pre-transplant treatment, lymph node involvement, and the presence of EHD, did not significantly impact OS. These findings challenge conventional selection criteria applied in other hepatic malignancies. In contrast, vascular invasion emerged as a key prognostic factor. Both microvascular invasion and combined micro- and macrovascular invasion (MaVi) were associated with significantly worse survival, emphasizing the dominant role of tumor biology over tumor burden. Notably, these factors did not significantly influence disease-free survival, further highlighting the unique clinical behavior of HEHE [14]. Tumor biology appears to be the most relevant prognostic determinant, indirectly reflected by treatment allocation and selection bias, whereas classical clinicopathological variables demonstrate limited predictive value [12]. Three major risk factors for post-transplant recurrence have been identified: MaVi (HR 4.8), short waiting time to transplantation ≤120 days (HR 2.6) and hilar lymph node involvement (HR 2.2). These variables form the basis of the HEHE-LT score, which enables risk stratification and guides post-transplant surveillance strategies [17]. This study reported an increased incidence of graft loss due to HAT within 14 days of the procedure in patients with HEHE (4.6%) compared to patients without HEHE (0.5%). The prognostic factors positively impacting the procedure were an effective prioritization system, survival comparable to HCC patients meeting the Milan criteria who received exception points, a median MELD at LTx of 7 (IQR 6–11), and a median waiting time of 78.5 days (IQR 29.5–237.5) [15]. Lung or multiorgan involvement, ascites with serosal metastasis, age >55 years, male sex and angiosarcoma differentiation are all associated with significantly worse outcomes [1,10]. On the other hand, according to the study by Sawma et al., bone metastasis was the strongest predictor of poor survival (HR 6.3), while lung metastasis was not [19]. In the study by Liu et al. (2024), according to multivariable analysis, age ≥ 60 years (HR 4.2), tumor size > 10 cm (HR 12.1) and LTx as a treatment modality (HR 5.5) were identified as independent predictors of poor prognosis [20]. The AASLD/AST guidelines indicate that traditional anatomical staging factors have limited prognostic value in the qualification and outcome assessment of LTx in malignancies, including HEHE. Instead, greater importance is attributed to tumor biology and individual risk of post-transplant recurrence. In HEHE, it is particularly important that the presence of advanced disease features (e.g., multifocality or even EHD), does not necessarily correlate with worse post-transplant outcomes. This implies that conventional staging factors should not be considered absolute determinants of treatment outcomes. According to the guideline-based approach, the most important prognostic factors after transplantation include: tumor biology, risk of recurrence, appropriate patient selection, assessment of disease dynamics and response to treatment [13].

7. Discussion:

Due to extreme rarity of HEHE, knowledge regarding optimal therapeutic pathways remains limited. Multicenter studies involving large patient cohorts are needed, with methodologies focused on evaluating the effectiveness of various treatment modalities, ranging from surgical interventions to conservative approaches, based on clinical characteristics that may predict future prognosis. An important aspect is the comparison of outcomes between patients undergoing LTx and those receiving alternative treatment strategies [20]. LTx in patients with HEHE provides excellent long-term outcomes despite extensive tumor burden, with 1-, 5-, and 10-year OS rates of 93%, 83%, and 72%, respectively. Disease recurrence occurred in 23.7% of patients at a median of 49 months, although some patients achieved prolonged survival despite relapse. Importantly, conventional adverse factors such as EHD, lymph node involvement and prior treatment did not significantly affect survival. In contrast, vascular invasion was associated with worse outcomes, highlighting the dominant role of tumor biology over disease extent. These findings support LTx as an effective treatment option even in advanced HEHE [14]. LTx is associated with favorable long-term survival in patients with HEHE, particularly in those with multifocal disease, although these outcomes may be influenced by selection bias and underlying tumor biology [12]. Despite the rarity and clinically heterogeneous course of HEHE, current evidence supports an active therapeutic strategy based on liver transplantation rather than a watchful waiting approach. Importantly, the presence of EHD should not be regarded as an absolute contraindication to transplantation, as acceptable post-transplant outcomes can still be achieved. These observations are consistent with the ACG Clinical Guideline, which identifies LTx as the treatment of choice for unresectable HEHE and emphasizes favorable survival outcomes despite frequent multifocal or extrahepatic involvement [10]. Similarly, AASLD/AST recommendations highlight the limitations of traditional stage-based selection systems and underscore the importance of tumor biology and individualized risk assessment in transplant decision-making [13]. In this context, conventional staging systems appear to have limited prognostic utility, further reinforcing the central role of tumor biology in outcome prediction and therapeutic planning. The incorporation of the HEHE-LT score into clinical practice may therefore improve patient selection and support more individualized management strategies. Future optimization of treatment algorithms will likely depend on advances in imaging techniques, identification of molecular biomarkers, and development of targeted approaches [17]. Moreover, in the study by Krasnodębski et al., the authors concluded that liver transplantation provides favorable outcomes in selected patients with HEHE. However, the study is limited by its small sample size, retrospective single-center design and lack of a control group, which restricts the generalizability of the findings. Additionally, the absence of multivariable analysis and the relatively short follow-up for a tumor characterized by potentially late recurrence may lead to an underestimation of recurrence risk. Selection bias toward patients with favorable pathological features may further contribute to the excellent outcomes observed [18]. The Mayo Clinic analysis suggests that LTx remains a first-line treatment option in selected patients with HEHE. However, the authors highlight certain limitations of this approach, as outcomes are primarily driven by tumor biology. Bone metastasis emerged as a key negative prognostic factor, whereas EHD did not preclude surgical intervention [19]. Aggressive surgical treatment does not always translate into meaningful clinical benefit for the patient [19,20]. Authors of the Chinese cohort study, based on poor OS outcomes, concluded that the role of LTx should be reevaluated. This stands in contrast to Western registry data and likely reflects significant selection bias, with LTx reserved for the most advanced or aggressive cases, as well as possible differences in perioperative care or patient selection [20]. The AASLD/AST guidelines provide evidence-based recommendations for liver transplantation in patients with HEHE. Based on a comprehensive literature review and expert consensus, transplantation is considered a viable therapeutic option in selected patients with unresectable disease. Candidate evaluation includes assessment of clinical status, imaging findings, laboratory parameters and overall prognosis, allowing for a balance between expected benefit and potential risks. Available data indicate favorable long-term survival following transplantation, although outcomes are strongly influenced by tumor biology and appropriate patient selection. Therefore, LTx should be considered in carefully selected patients, with emphasis on individualized decision-making and the need for further research to optimize selection criteria and treatment outcomes [13].

8. Conclusions:

Guideline-based sources do not provide primary survival data but summarize evidence and define selection criteria [10,13]. In this context, EHD is not considered an absolute contraindication to transplantation, as acceptable outcomes may still be achieved even in patients with pulmonary or other metastases [13]. In HEHE, post-transplant prognosis is primarily determined by tumor biology and risk of recurrence, whereas conventional anatomical staging factors have limited prognostic value [13]. This is supported by registry-based analyses demonstrating that traditionally adverse features, such as multifocality, bilobar involvement or the presence of EHD do not necessarily translate into worse outcomes. Instead, factors reflecting tumor aggressiveness, including vascular invasion and metastatic pattern (particularly bone involvement), play a more critical role in outcome prediction. LTx has been shown to be an effective therapeutic option even in advanced HEHE, providing favorable long-term survival outcomes [14]. Importantly, recurrence after transplantation does not invariably confer poor prognosis, as some patients may achieve prolonged survival despite disease relapse, reflecting the often indolent biological behavior of HEHE. In the MELD-based allocation era, LTx offers acceptable outcomes and the use of exception points facilitates equitable access to transplantation for patients with HEHE. However, a potentially increased incidence of HAT in this population represents a novel observation that warrants further investigation. Additionally, the promotion of living donor liver transplantation (LDLT) may be beneficial in order to minimize the impact on organ availability for other waitlisted patients. Due to the rarity of HEHE, the establishment of dedicated national or international registries and specialized centers of excellence is strongly recommended to optimize clinical decision-making and improve standardization of management strategies. Importantly, exclusion of hepatic angiosarcoma by biopsy remains a prerequisite for eligibility for MELD exception points [15]. Evidence from smaller cohort studies, including the analysis by Krasnodębski et al., further supports the role of LTx in selected patients, demonstrating favorable long-term outcomes with no observed recurrence during follow-up, although these findings are limited by sample size and require validation in larger studies [18]. Overall, current data indicate that LTx should be considered a first-line therapeutic option in carefully selected patients with HEHE, including those with advanced or multifocal disease. Patient selection should be based on tumor biology and recurrence risk rather than conventional staging criteria. In particular, the absence of bone metastases and the presence of limited EHD may identify patients most likely to benefit from transplantation [19]. Finally, given the heterogeneity of HEHE and the limitations of existing evidence, further large-scale, multicenter studies with long-term follow-up are necessary to refine prognostic models, improve patient selection and optimize treatment outcomes.

Author's contribution:

Conceptualization: [AS], [KB], [MP]
Methodology: [AS], [KB], [MP], [KP]
Check: [ASu], [OM], [UJ]
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Data curation: [AS], [KB], [MP], [KP]
Writing - rough preparation: [AS], [KB], [MP], [OM]
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Declaration of the use of AI and AI-assisted technologies in the writing process:

Artificial intelligence (AI) tools such as ChatGPT were employed in this research to assist in refining the academic English language of the manuscript. Their purpose was to ensure clarity, consistency, and adherence to scientific writing standards. AI tools were used strictly for additional linguistic polishing-focused on proper grammar, style, and clarity of the text in presenting the results. Importantly, these tools were used only as support under the direct supervision of the authors. All final interpretations, classification of findings, and conclusions were determined exclusively by human experts with formal training in clinical medicine. The role of AI was limited to enhancing the efficiency of language refinement, pattern recognition, and data processing, and it did not replace human judgment in the analytical process.

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