Reviewer 1

Thanks for your revision of our work. We have provided an extensive English editing by a native English speaker. We hope that now you could consider “language quality” of our manuscript as “Grade A”.
Concerning your comments/suggestions:

1) A brief description of histologic features of NRH has been added in the manuscript (Lines 93-95).
2) We totally agree with you that the clinical scoring index proposed by Singh et al. is not validated and not widely recognized. We reported this scoring system as a potential tool for physicians who daily deal with HHT patients. However, we add a sentence highlighting the fact that this score is not yet validated (Lines 113-115).

1) Ref. 38 (Ref. 42 after revision) is a recent and complete systematic review about LT in 83 HHT patients (*Riera-Mestre A et al. Perioperative Complications and Long-Term Follow-Up of Liver Transplantation in Hemorrhagic Hereditary Telangiectasia: Report of Three Cases and Systematic Review. J.Clin.Med.2022,11,5624. doi: 10.3390/jcm11195624*). Data of survival and complication rate reported in the “Liver transplantation” paragraph of our manuscript mainly result from the abovementioned paper. However, we added some sentences in order to enhance this point and to give more information on LT (Lines 189-192).
2) Typos have been corrected.
3) Thanks for remarking this mistake. We referred to Figure 1 (Fig. 1A, 1B, 1C). We modified it in the main text.
4) Thanks for this remark. We also consider this as a central topic in the management of HHT patients with hepatic involvement. Regarding the follow-up of liver vascular malformation in HHT patients there are no specific indications about the frequency of imaging re-evaluation. The timing of repetition of US is usually decided case by case (1 or 2 years of interval, based on the grade of liver involvement) but there are no standardized protocols for the re-evaluation of hepatica VMs. We add a sentence about it (Lines 125-127). If you have any reference of a more detailed and standardized procedure, we would be pleased to read it and provide a specific indication for follow-up.
5) The main biliary complication of hepatic AV shunts is bile duct ischemia. In Lines 83-90 we described the pathophysiology of this phenomenon and the possible evolutions (secondary sclerosing cholangitis, infectious cholangitis, bilomas, Caroli’s disease). The paper is addressed to hepatologists so we considered that a more precise description of these clinical manifestations would not be necessary to the readers and may go beyond the aim of this manuscript. Nonetheless, in the “liver transplantation” paragraph (Lines 186-188, 193-194) we state about transplantation indication in biliary ischemia and in the “medical treatments” paragraph (Lines 290-294) we give some indication about the management of biliary complication in HHT patient.
6) We have already described intrahepatic V-V shunts (named as portovenous shunts) as one of the three possible hepatic VMs (Lines 62-65, 71-72). We agree with you that their clinical impact, as well as their frequency, is minor compared to arteriovenous of arterioportal shunts.
7) We added more information about different phenotypic features of HHT1 and HHT2 (Lines 44-46).

Reviewer 2

Thanks for your revision of our work. We have provided an extensive English editing by a native English speaker. We hope that now you could consider “language quality” of our manuscript as “Grade A”.
Concerning your comments/suggestions:

1) In the “introduction” paragraph (Lines 28-30) we already mentioned the link between the mutational status of HHT1 (ENG) and HHT2 (ACVRL1). We added more information about different phenotypic features of HHT1 and HHT2 (Lines 44-46).
2) Thanks for this remark. We were not aware about the possible correlation between HHT and Budd-Chiari syndrome. We added few sentences about it and the reference you proposed (Lines 107-110).
Concerning the possible occurrence of liver cirrhosis in HHT patients, we specified with more details the condition of “pseudocirrhosis” related to the regenerative hepatic modification and we added more references about it (Lines 104-106).

Abstract

Hereditary hemorrhagic teleangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is the most common cause of hepatic vascular malformations in adults. Different vascular shunts (arteriovenous, arterioportal or portovenous) lead to different clinical manifestations. Even though no hepatic-related symptoms are reported in the majority of cases, the severity of liver disease could lead to refractory medical conditions, in some cases ~~even~~ requiring liver transplantation.

The aim of this manuscript is to provide an updated overview of the current evidence regarding the ~~highlight the current evidences about~~ diagnosis and treatment of HHT liver involvement and liver-related complications.

Core Tip

Hereditary hemorrhagic teleangiectasia (HHT) is the most common cause of hepatic vascular malformation in adults. Although liver involvement ~~in HHT~~ is common in HHT, most patients do not present any hepatic-related symptoms ~~but there are no hepatic-related symptoms in the majority of cases~~. Unfortunately, some patients have severe forms of disease with refractory medical conditions related to the hepatic vascular malformations. For those patients the only definitive treatment available at present ~~and, to date, the only curative approach~~ is liver transplantation.

Introduction

Hereditary hemorrhagic teleangiectasia (HHT) or Rendu-Osler-Weber syndrome is a rare autosomal dominant disorder characterized by mucocutaneous teleangiectases and systemic vascular malformations (VMs). HHT can be ruled in by using the Curaçao criteria (recurrent epistaxis, multiple mucosal/cutaneous teleangiectases, visceral VMs and first-degree relative with HHT); if at least 3 of these criteria are met, the diagnosis of HHT is considered to be definite (Table 1).(1,2)

Molecular genetic test is useful in order to detect gene mutations. Endoglin (ENG, on chromosome 9) and activin A receptor type II-like 1 (ACVRL1, on chromosome 12) genes are involved in approximately 90% of cases and ~~they~~ are responsible of HHT1 and HHT2, respectively. In addition to these two genes, mutation of SMAD4 has been identified in patients with the association of juvenile polyposis and HHT (PJ-HHT syndrome, approximately 2% of cases) in which anemia is the predominant symptom due to gastrointestinal bleeding. Mutations of GDF2 and RASA-1 genes have also been described but they are extremely rare (Table 2).(3,4)

Loss of function mutations in ENG and ACVRL1 cause anomalous angiogenesis leading to VMs development.(2) One of the primary mechanisms underlying aberrant vascular endothelial growth factor (VEGF)-related angiogenesis in HHT patients appears to be the overactivation of phosphatidylinositol 3-kinase (PI3K) signaling in endothelial cells. ~~seems to be one of the most involved mechanism for aberrant vascular endothelial growth factor (VEFR) related angiogenesis in HHT patients.~~ (5) High VEGF levels drive VMs development in mouse models and its normalization suppresses progression of these anomalous vascular structures. (6,7)

HHT1 is more frequent in Mediterranean countries and it is characterized by a higher incidence of pulmonary and brain VMs, while HHT2 is more frequent in Northern Europe and North America with a higher incidence of hepatic VMs.(8) No significant difference was found in age at debut of symptoms and the severity of epistaxis between patients with HHT1 and HHT2. On the other hand gastrointestinal bleeding was reported to be more common in patients with HHT1. (9) ~~ACVLR1 mutation~~ HHT2 is associated to a higher risk of symptomatic liver disease. (10)

~~Liver involvement is common and~~ HHT represents the most common cause of congenital hepatic vascular malformations in adults, and liver involvement is a commonly observed feature in the disease (Table 2);(11–13) the mean age at diagnosis is 48 years.(14)

~~Even though~~ Whilst more than 90% of cases do not present any hepatic-related symptoms, patients affected by HHT are susceptible to developing a range of clinical condition with varying presentations depending on ~~could develop variable clinical conditions, mainly related to~~ the type of hepatic VM.(15) In some cases, the severity of clinical conditions requires liver transplantation. Women seems to have a more frequent (female prevalence 4.5 fold higher than males) and more severe liver involvement in both HHT1 and HHT2.(16)

In the following paragraphs we will discuss the diagnostic and therapeutic approach for liver involvement in HHT patients.

Hepatic VMs classification and clinical manifestations

~~Based on liver vascular anatomy,~~ Three types of hepatic VMs have been described based on liver vascular anatomy: arteriovenous (the most frequent, between hepatic artery and hepatic vein), arterioportal (between hepatic artery and portal vein) and portovenous (between portal vein and hepatic vein).(15) These different subtypes of hepatic vascular shunting usually coexist and affect ~~involve~~ the liver diffusely.(17) HHT liver involvement is a continuous process from small teleangiectases to very large VMs; size change during follow up has been observed in 21% of patients. (10)

Arteriovenous shunts could cause high output cardiac failure (HOCF), ischemic cholangitis and mesenteric ischemia. Arterioportal shunts could cause portal hypertension, but also biliary ischemia. Portovenous shunts could cause HOCF, but also portosystemic encephalopathy.(15) Generally, one of them predominates functionally, but fluctuation from a clinical condition to another is common.

HOCF is the most common complication of ~~due to~~ HHT liver involvement and it generally starts being clinically significant when intrahepatic shunt output is >20% of cardiac output. (18) ~~This condition is related to a higher~~ HOCF is associated to an increased risk of atrial fibrillation ~~development and it can subsequently evolve in~~ and the associated increased pulmonary blood flow secondary to liver VMs may lead to the development of post-capillary pulmonary arterial hypertension ~~from a high pulmonary blood flow related to liver VMs~~. Less frequently, HHT patients may develop a pre-capillary pulmonary arterial hypertension that seems to be related to the remodeling of small pulmonary arteries caused by ENG and ACVRL1 gene mutations with histologic features broadly similar to those observed in idiopathic pulmonary arterial hypertension. Right heart catheterization is essential to differentiate between ~~both~~ the two forms.(19)

Arteriovenous shunting can cause a blood steal with secondary bile ducts ischemia; this phenomenon is facilitated by the vascular anatomy of the biliary system, which derives its ~~single~~ blood supply solely from the hepatic artery via the peribiliary plexus. Biliary ischemia can subsequently evolve in biliary strictures and dilations (secondary sclerosing cholangitis) ~~and, occasionally~~, secondary infection of the biliary system (infectious cholangitis), bilomas or biliary cysts (mimicking Caroli's disease), and elevation of serum alkaline phosphatase and gamma glutamyl transpeptidase. In the more severe forms, ischemia also ~~involves~~ affects hepatocytes ~~with~~ causing hepatocellular necrosis leading to hepatic hemorrhage and bile leak. (18,20)

Modification of normal liver perfusion ~~can also entail~~ may increase hepatocytes regenerative activity leading to development of focal nodular hyperplasia (FNH), ~~which is 100-fold~~ 100 times more frequent in HHT patients than in general population, or nodular regenerative hyperplasia (NRH). In NRH the liver parenchyma undergoes a diffuse transformation into multiple regenerative nodules with hepatocytes arranged in plates, without fibrosis separating nodules.

Therefore, portal hypertension in HHT patients may be pre-hepatic, due to the increased blood flow from arterioportal VMs, or pre-sinusoidal, due to NRH (a well-known cause of non-cirrhotic intrahepatic portal hypertension).

Hepatocellular regeneration nodules may be associated with minimal perisinusoidal and portal fibrosis which can mimic cirrhosis on imaging and lead to being diagnosed incorrectly~~, leading to misdiagnosis. , but liver function tests are generally normal~~. (18,21) ~~For these reasons, portal hypertension in HHT patients could have a pre-hepatic etiology, due to increased blood flow, and an~~

~~a pre-sinusoidal etiology, due to NRH that is a well-known causa of non-cirrhotic intrahepatic portal hypertension.~~

This appearance is commonly defined "pseudocirrhosis" since there is no significant liver fibrosis, liver function tests are generally normal and the risk of hepatocellular carcinoma (HCC) is not as increased as for liver cirrhosis. (22)

Xu et al. reported that hepatic involvement in HHT and Budd-Chiari syndrome (BCS) may be linked, suggesting a shared pathogenetic mechanism characterized by vascular dysplasia and a trombophilic condition induced by HHT that would eventually lead to BCS. (23,24) Nonetheless further studies are needed to evaluate the possible relationship between these two diseases.

Several disease progression predictors have been identified. *Singh S et al.* proposed a ~~simple~~ clinical scoring system for the estimation of the probability of clinically significant liver disease in HHT patients. This score ~~is made up of~~ uses readily available information such as patient gender, ~~and~~ age, hemoglobin and alkaline phosphatase at presentation, but is currently not widely recognized and still need to be validated. (Table 3) (25)

Imaging screening and stadiation

Screening for liver VMs should be offered to adults with a definite or suspected diagnosis of HHT (26) and the imaging test of choice for screening is Doppler ultrasound (27) for its accuracy in detecting hepatic VMs, (28) its availability, repeatability, low cost and interobserver agreement. (29–31) In addition, Doppler ultrasound ~~also~~ allows to ~~determine a~~ establish the grade of severity of liver involvement and therefore correlates with patient outcomes and ~~give~~ predictors of clinical outcomes. (27)

Regarding the follow-up of hepatic VMs there are no standardized protocols nor consensus; ultrasound is usually repeated every 1 or 2 years according to the severity of liver involvement and is generally determined case by case.

Caselitz et al. defined major and minor criteria required for the diagnosis of liver VMs in HHT by Doppler ultrasound: a dilated common hepatic artery (>7 mm) and intrahepatic arterial hypervascularization are the two major criteria; minor criteria are either Vmax in hepatic artery >110 cm/s, low resistivity index (RI) of the proper hepatic artery (i.e. <0.60), Vmax of portal vein >25 cm/s and/or a tortuous course of extrahepatic hepatic artery. Presence of liver VMs in HHT is defined by two major criteria or one major ~~criteria~~ criterion and two minor criteria.(28) According to *Buscarini et al*. severity grading ranges from 0.5 to 4 (Table 4). (27,32)

Hepatic artery dilation >4 mm is a very sensitive parameter ~~in differentiating~~ to differentiate HHT patients with or without liver involvement from the very early stages (Figure ~~2A~~ 1A); (32) despite cirrhosis and ~~cirrhotic patients or~~ hypervascular liver tumors may cause a dilation of hepatic artery, ~~hepatic artery dilation usually far~~ this rarely exceeds the upper normal limit as in HHT patients.

Common hepatic artery dilation is also a predictor of HOCF development in patients with liver VMs. (33) A high velocity flow with low RI in intrahepatic branches of hepatic artery is highly suggestive of intrahepatic arterioportal shunt; furthermore, hepatic artery to portal vein shunts commonly ~~usually~~ cause pulsatility of portal flow with phasic or continuous reversal (Figure ~~2C~~ 1C). Arteriovenous shunts, on the other hand, usually result in a change in the Doppler waveform of hepatic veins (from triphasic to biphasic or even continuous patterns in severe involvements). (27,32)

Peripheral subcapsular spots (identified by color Doppler) with high-velocity arterial blood flow and low RI are suggestive of small peripheral VMs, which are usually found from early stage in HHT patients with liver involvement (Figure ~~2B~~ 1B). (27)

FNH is common ~~also usually spotted~~ in HHT patients with liver involvement, ~~as already mentioned,~~ and it generally appears as an isoechoic nodular lesion in liver parenchyma.

~~In more advanced liver involvement, a~~ In those cases where the liver involvement is more severe, common findings are nodular and irregular liver surface with a coarse echo-pattern ~~can be found~~, previously known as pseudocirrhosis, (34) as well as portal vein and hepatic vein dilation ~~are also features usually associated with a more severe liver involvement~~. (27,32)

Multiphase contrast-enhanced abdominal computed tomography (CT) has an excellent yield and accuracy in defining liver vascular malformations and it is easily reproducible across different centers (Figure 2), ~~but~~ however, it does not correlate ~~however~~ with liver VMs severity and clinical presentations and ~~it~~ is therefore recommended only if the expertise in detecting liver VMs using Doppler US is unavailable. ~~lacking in detecting liver VMs~~. (17,35) Nonetheless, it is widely used in complicated liver vascular malformation which are considered for liver transplantation (14) ~~and it has also~~ as it has the advantage of great accuracy in detecting biliary complications (i.e. necrotizing cholangitis with formation of bilomas); (32) it is able to characterize the complexity of hepatic vascular alterations, the different types of shunts and parenchymal perfusion disorders (36,37) and it has great accuracy in differentiation between FNH from regenerative nodules. (38)

Magnetic resonance imaging (MRI) of the liver shows great accuracy in characterizing focal liver lesions and in detecting liver VMs (they are better depicted on MRI angiograms and dynamic MRI images outlining a map of anomalous vessels). (39) MRI is as accurate as multirow CT scan, with the advantage of the absence of ionizing radiations; nonetheless due its high cost and low availability it

is recommended for diagnosis and follow-up of liver AVMs only when expertise in Doppler US is lacking. (26,36)

The role of contrast-enhanced ultrasound (CEUS) with sulfur hexafluoride-filled microbubbles has been recently investigated in a cohort of 18 patients with HHT regarding macro and micro-circulation showing a higher percentage of hepatic VMs (especially of arterioportal shunts) than what is reported in literature. (40) However, CEUS seems to add no further information to Doppler US evaluation that still has great accuracy and sensitivity. It should also be noted that ~~on the other hand~~ the use of sulfur hexafluoride-filled microbubbles ~~seems even~~ is contraindicated in patients with right-to-left shunts and may result in an unjustified risk considering the high percentage of pulmonary VMs in HHT patients. (32)

Liver biopsy is generally not necessary for diagnosis of hepatic VMs due to the increased bleeding risk related to a percutaneous procedure. Therefore, hepatic nodules in HHT patients should be characterized non-invasively when possible. If a biopsy is needed, always consider the increased risk of bleeding in HHT patients. (14,26)

Liver transplantation

The first case of liver transplantation (LT) for HHT was reported in 1995.(41) Nowadays, LT is the recommended surgical option for severe hepatic involvement in HHT patients.(26) The main indication for LT are refractory HOCF and ischemic cholangitis (67.5% and 39.7% of cases, respectively). (42)

A recent systematic review by Riera-Mestre A et al., reported 83 cases of LT for HHT worldwide. Perioperative complications within 30 days were described in 33.7% of patients (mainly bleeding complications) and a survival rate of ~~after LT~~ ~~is excellent with a~~ 88% ~~of survival~~ at six years has been reported ~~after LT~~. (42)

While ischemic cholangitis ~~in~~ is considered ~~as~~ an urgent indication to LT, the best timing for transplantation in a patient with HOCF has not been defined yet.

MELD score was designed for cirrhotic patients and is widely used in defining the LT waitlist priority; HHT patients are exempt from being scored and should be included and prioritized in LT waitlist regardless of MELD score. (43) Right heart catheterization should always be performed in patients with HHT being evaluated for LT, to exclude severe pulmonary hypertension; LT can be undertaken if pulmonary vascular resistance is <240 dynes·sec·cm^{-5} (<3 Woods units). (14)

LT for HHT patients ~~is~~ constitutes a more complex surgical ~~act~~ procedure compared to other indications for LT ~~with~~ and is characterized by higher blood transfusion requirement and more perioperative complications.

The hepatic artery in HHT patients may be dilated, tortuous and/or aneurysmatic and arterial graft anastomosis could be more challenging ~~very difficult consequentially~~. Moreover, there is a high incidence of hepatic artery thrombosis after LT (about 7% of cases) that could result in need for ~~a~~ re-transplantation ~~need~~. The presence of high-flow extrahepatic arterial teleangiectases may cause an arterial steal, so an attentive stadiation of disease before transplantation and an intraoperatively ultrasound arterial flow measurement through the anastomosis are strongly suggested.(42,44)

The hyperdynamic state following recipient hepatic artery dissection constitutes ~~is~~ a potential risk of bleeding in any extrahepatic site of VMs. Fatal pulmonary bleeding has been described in two patients, so embolization of pulmonary VMs should be considered before LT.(45,46)

Intrahepatic relapse of HHT lesions is a late but common event after LT. The median recurrence time is 127 months and can occur up to 19 years after LT; the estimated cumulative risk of recurrence at 5, 10, 15 and 20 years is 0%, 16.7%, 47.9% and 87%, respectively. (42,47–49) For this reason, these patients require a life-long follow-up.

The pathophysiology of recurrence in the transplanted liver is still unclear. Presence of endothelial cells of recipient origin in the transplanted liver has been recently described.(48) Microchimerism after LT is a well-known phenomenon, but in this case the liver graft repopulation by patient endothelial cells may lead to an aberrant angiogenesis causing the recurrence of the disease.(50)

An mTOR inhibitor-based ~~immunosuppression~~ immunosuppressive regimen after LT may reduce hepatic VMs recurrence by blocking the PI3K signaling pathway.(51)

Endovascular and surgical treatments

Hepatic VMs are generally considered not suitable for endovascular or surgical approach due to the high morbidity and mortality rates.

Transarterial embolization is generally used for treating HOCF and portal hypertension. This procedure is performed in ~~more~~ multiple stages (one to five sessions); among the several protocols proposed, the most used one ~~provides for~~ consists in an initial embolization of vascular bed with a mixture of polyvinyl alcohol (PVA) followed by embolization with microcoils. Arterial branches of right and left lobe have to be embolized in different sessions.(52)

A peri-procedural infusion of analgesics, anti-emetics and steroids is generally advised; some authors also consider a peri- and post-procedural prophylactic antibiotic coverage.(53)

The most common complications are biliary or hepatic necrosis that occur in 20-60% of cases (53); ~~emergent LT~~ need for emergent LT and death is reported in up to 10% of cases. (54)

Regarding the high risk of ischemic hepatic damage, transarterial embolization is generally contraindicated in patients with signs of biliary involvement.(14)

~~Very few experiences have been published about~~ There have been very few published accounts of transjugular intrahepatic portosystemic shunt (TIPS) as portal decompressive intervention. The high risk of worsening the cardiac output and the high bleeding risk related to the puncture lead to consider this treatment largely unsuccessful and so not recommended.(55,56)

Hepatic artery banding and/or ligation are other ~~possible~~ potential approaches ~~to manage~~ for managing HOCF due to hepatic VMs. Banding consists in the diameter reduction by one third to a half of the pre-operative diameter of common hepatic artery and potentially lobar arteries; ligation consists in closure of feeding arteries of the lobe predominantly involved by VMs.

~~Extent of~~ The diameter reduction achieved with arterial banding should be sufficient to reduce liver hyperperfusion, ~~but not cause~~ without causing ischemic hepatobiliary damage. Banding should be guided by colorDoppler ultrasound with a desired hepatic artery flow of 330 ± 80 ml/min; (57) another indirect parameter of sufficient arterial banding is the return of arterialized areas of liver surface to normal red color ~~normal liver parenchyma color of red, arterialized areas on liver surface~~.(58)

~~According to extra-hepatic vascular anatomy, that always have to be investigated by CT-angiography before surgery,~~ CT angiography is always recommended before surgery in order to investigate extra-hepatic vascular anatomy. If appropriate, collateral circulation arising from superior mesenteric or left gastric arteries could also be ligated and enlarged gastroduodenal artery banding may also be considered.(58)

Based on the risk of hepatic necrosis, these procedures are contraindicated in case of significant portovenous shunting. (59)

For a long time, hepatic artery ligation or banding has been used in limited number of cases ~~with~~ due to the high rate of ischemic cholangitis and undefined long-term survival. (57,60,61) *Lui ZC et al*. recently reported a series of 13 patients treated with hepatic artery ligation/banding with a low rate of peri- and post-operative complications (only two patients experienced cholangitis, who were treated conservatively), improvement of symptoms and good survival outcome (only one patient died in a median follow-up of 50 months). Authors advise against dissecting malformed and tortuous vessels around extrahepatic biliary tract in order to reduce the risk of ischemic damage and against dividing perihepatic ligaments in order to preserve arterial flow to the liver. (58)

Conventional hepatic surgery, like segmental resection or hemi-hepatectomy, is anecdotal (62) or reported for hepatic shunting in non-HHT patients (63) and for non VM indications in HHT patients (64,65). This approach could be considered in very selected patients with symptomatic disease and very large VMs localized in a single segment/lobe, but such kind of indication should be given with caution.

Considering the high complication and mortality rates, together with their palliative role, endovascular and surgical treatments are still generally not recommended and should be proposed only in severely symptomatic patients that are not transplant candidates and have failed medical therapy; these approaches should be deliberated by a multidisciplinary team and should be performed only by expert physicians in referral centers.(14)

Medical treatments

First-line medical treatment, such as management of anemia with iron replacement therapy or management of mild bleedings with antifibrinolytics, concerns almost all HHT patients but it is not the aim of this paper, so it will not be discussed further. At the same time, first-line medical treatment for hepatic VM-related HOCF should be evaluated ~~and accordingly~~ managed by physicians with expertise in that field (such as cardiologists) and it goes beyond the purpose of this paper.

Management of portal hypertension follows the same principles as in patients without HHT, (66,67) but non-selective beta-blockers should be used with ~~a more~~ caution in patients with HOCF, although they still are the drugs of choice.(26)

Similarly, the management of portosystemic encephalopathy follows the same principles as in cirrhotic patients without HHT (i.e. lactulose and rifaximin).(26,68)

Infectious complications, such as cholangitis and hepatic abscesses, generally require antibiotic therapy ~~administration~~. Large biliary duct obstruction is uncommon in HHT patients, ~~so~~ and endoscopic retrograde cholangiopancreatography (ERCP) with stenting is not indicated, (26) ~~on the contrary~~ because it seems to increase the risk of infection in ischemic ducts and the risk of hemobilia. (69,70)

~~In the last decades, researchers focused their attention on antiangiogenenic drugs in order to directly act on~~ Over the last few decades, research has primarily focused on utilizing antiangiogenetic drugs with the aim of targeting the aberrant angiogenesis causing VM formation and endothelial frailty. Several molecules have been investigated and ~~several~~ multiple clinical trials are ongoing (such as thalidomide, tacrolimus, sorafenib, pazopanib, doxycycline and others) with interesting results on

~~nose~~ nasal and gastrointestinal bleeding control, (71–78) but the only molecule that has been studied for HOCF related to hepatic VMs is bevacizumab.

Bevacizumab is a humanized monoclonal antibody ~~with an~~ which exerts its antiangiogenic activity by inhibiting the vascular endothelial growth factor (VEGF). In 2012, its efficacy has been prospectively investigated in HHT patients with HOCF related to liver VMs resulting in a decrease cardiac output; (79) a reduced or delayed need for transplantation has also been described. (80) ~~At the same times~~ Bevacizumab ~~reduces nose~~ has also demonstrated a reduction in nasal and gastrointestinal bleedings ~~leading to~~ resulting in an improvement of anemia, ~~reduction of the need for transfusion~~ decrease of blood transfusion need and better quality of life.(81,82)

~~Several dose~~ Numerous dosing schedules have been investigated, but the most common dose for initiation was 5 mg/kg every 2 week for a total of 6 injections; infusion duration should be of at least 30 minutes (first administration should be given in at least 60 minutes to assess patient drug tolerance). (79) Despite a high inter-patient bleeding-free interval, almost all patients relapse after a year of discontinuation of bevacizumab ~~withdrawal by one year~~ and they may require maintenance therapy or may repeat a new administration cycle that could become lifelong.(83) To date, there are no prospective studies concerning maintenance therapy; the ~~dose~~ dosing schedule should ~~be~~ therefore be determined based on ~~defined according to~~ patient response and tolerance.(81,83)

Similarly, the safety of ~~for~~ long-term bevacizumab administration has not been prospectively evaluated. ~~yet, but~~ However, it could be inferred indirectly from prolonged administration of the drug for other indication. ~~presumed by evidences derived from long-term administration for indications other than HHT.~~

The most frequent adverse events are generally mild~~-grade~~ and infusion-related, such as headache, nausea and vomiting, asthenia, abdominal pain, muscle pain, diarrhea and rash.(79)

A major concern among drug-related adverse events is addressed to arterial hypertension, venous thrombosis and hemoptysis from pulmonary VMs.(81,84) Therefore, it is crucial to assess ~~For these reasons,~~ patients prothrombotic conditions prior to starting therapy with bevacizumab, ~~should be assessed~~ and pulmonary VMs screening and treatment should be performed according to guidelines as for every HHT patient~~, before starting intravenous bevacizumab~~. Other potentially serious adverse events are gastrointestinal perforation and proteinuria.(84) Since a delay in wound healing has been reported during antiangiogenetic treatment, it is recommended to stop bevacizumab 6-8 weeks before surgery and to restart it only if wounds are totally healed.

Bevacizumab is contraindicated in patients with severe arteriopathy, a ~~with~~ history of ischemic complications, recent deep vein thrombosis (<6 months) or recent severe infection ~~disease~~ (<1 month) and should be used with caution in patients with non-post-capillary pulmonary hypertension.(85) It

is also contraindicated in pregnancy, so effective contraceptive measures should be adopted by women in childbearing age during treatment and for six months after discontinuation. (85)

A recent international expert consensus paper suggests a monitoring protocol for HHT patients treated with bevacizumab ~~that~~ which consists in regular clinical examination (blood pressure measurement, epistaxis monitoring, blood transfusion require recording, adverse events collection) laboratory (blood cell count, liver and kidney function, ferritin, proteinuria) and scheduled echocardiography with cardiac index measurement.(85)

To date, there is not sufficient available evidence ~~are not evidences~~ from randomized control trials and bevacizumab is not market-authorized for HHT, but international expert consensus recommends considering intravenous bevacizumab for severe and refractory nasal ~~nose~~ and/or gastrointestinal bleeding and for HOCF secondary to hepatic VMs not sufficiently responder to first-line medical therapy.(26,85,86) ~~Anyway, considering~~ Based on the rates of ~~non~~ minimal or partial response to bevacizumab and the recurrence after drug discontinuation ~~withdrawal~~, intravenous bevacizumab should be considered as a potential "bridge" therapy to LT.

Conclusions

Liver involvement is very common in HHT patients and hepatologists should be aware of this condition and the available diagnostic and prognostic tools.

Fortunately, clinically significant liver disease is uncommon, but its management could be challenging. Liver transplantation remains the only curative treatment for these patients. Endovascular and surgical approaches should be avoided in patients with liver VMs. Bevacizumab has shown promising results, but it should be used with caution and only in referral centers.

Author contributions: Ielasi L and Tonnini M conceived the manuscript, reviewed the literature and wrote the original draft; Serio I reviewed and edited the manuscript; Piscaglia F supervised. All authors read and agreed to the published version of the manuscript.

Conflict-of-interest statement: All authors declare no conflict of interest.

Funding: This research received no external funding.

References

1. **Shovlin CL**, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Westermann CJ, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet. 2000 Mar 6;91(1):66–7.

2. **McDonald J**, Wooderchak-Donahue W, VanSant Webb C, Whitehead K, Stevenson DA, Bayrak-Toydemir P. Hereditary hemorrhagic telangiectasia: genetics and molecular diagnostics in a new era. Front Genet. 2015;6:1.

3. **Hernandez F**, Huether R, Carter L, Johnston T, Thompson J, Gossage JR, et al. Mutations in RASA1 and GDF2 identified in patients with clinical features of hereditary hemorrhagic telangiectasia. Hum Genome Var. 2015 Dec;2(1):15040.

4. **Viteri-Noël A**, González-García A, Patier JL, Fabregate M, Bara-Ledesma N, López-Rodríguez M, et al. Hereditary Hemorrhagic Telangiectasia: Genetics, Pathophysiology, Diagnosis, and Management. J Clin Med. 2022 Sep 5;11(17):5245.

5. **Iriarte A**, Figueras A, Cerdà P, Mora JM, Jucglà A, Penín R, et al. PI3K (Phosphatidylinositol 3-Kinase) Activation and Endothelial Cell Proliferation in Patients with Hemorrhagic Hereditary Telangiectasia Type 1. Cells. 2019 Aug 24;8(9):971.

6. **Thalgott JH**, Dos-Santos-Luis D, Hosman AE, Martin S, Lamandé N, Bracquart D, et al. Decreased Expression of Vascular Endothelial Growth Factor Receptor 1 Contributes to the Pathogenesis of Hereditary Hemorrhagic Telangiectasia Type 2. Circulation. 2018 Dec 4;138(23):2698–712.

7. **Han C**, Choe S woon, Kim YH, Acharya AP, Keselowsky BG, Sorg BS, et al. VEGF neutralization can prevent and normalize arteriovenous malformations in an animal model for hereditary hemorrhagic telangiectasia 2. Angiogenesis. 2014 Oct;17(4):823–30.

8. **Sánchez-Martínez R**, Iriarte A, Mora-Luján JM, Patier JL, López-Wolf D, Ojeda A, et al. Current HHT genetic overview in Spain and its phenotypic correlation: data from RiHHTa registry. Orphanet J Rare Dis. 2020 Jun 5;15(1):138.

9. **Kjeldsen AD**, Moller TR, Brusgaard K, Vase P, Andersen PE. Clinical symptoms according to genotype amongst patients with hereditary haemorrhagic telangiectasia. J Intern Med. 2005 Oct;258(4):349–55.

10. **Buscarini E**, Leandro G, Conte D, Danesino C, Daina E, Manfredi G, et al. Natural history and outcome of hepatic vascular malformations in a large cohort of patients with hereditary hemorrhagic teleangiectasia. Dig Dis Sci. 2011 Jul;56(7):2166–78.

11. **Letteboer TGW**. Genotype-phenotype relationship in hereditary haemorrhagic telangiectasia. J Med Genet. 2005 Sep 9;43(4):371–7.

12. **Lesca G**, Olivieri C, Burnichon N, Pagella F, Carette MF, Gilbert-Dussardier B, et al.

Genotype-phenotype correlations in hereditary hemorrhagic telangiectasia: Data from the French-Italian HHT network. Genet Med. 2007 Jan;9(1):14–22.

13. **Jelsig AM**, Kjeldsen A, Christensen LL, Bertelsen B, Karstensen JG, Brusgaard K, et al. Hereditary haemorrhagic telangiectasia in Danish patients with pathogenic variants in SMAD4: a nationwide study. J Med Genet. 2022 Aug 29;jmedgenet-2022-108766.

14. **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Vascular diseases of the liver. J Hepatol. 2016 Jan;64(1):179–202.

15. **Khalid SK**, Garcia-Tsao G. Hepatic vascular malformations in hereditary hemorrhagic telangiectasia. Semin Liver Dis. 2008 Aug;28(3):247–58.

16. **Mora-Luján JM**, Iriarte A, Alba E, Sánchez-Corral MA, Cerdà P, Cruellas F, et al. Gender differences in hereditary hemorrhagic telangiectasia severity. Orphanet J Rare Dis. 2020 Dec;15(1):63.

17. **Wu JS**, Saluja S, Garcia-Tsao G, Chong A, Henderson KJ, White RI. Liver Involvement in Hereditary Hemorrhagic Telangiectasia: CT and Clinical Findings Do Not Correlate in Symptomatic Patients. Am J Roentgenol. 2006 Oct;187(4):W399–405.

18. **Buscarini E**, Plauchu H, Garcia Tsao G, White RI, Sabbà C, Miller F, et al. Liver involvement in hereditary hemorrhagic telangiectasia: consensus recommendations. Liver Int Off J Int Assoc Study Liver. 2006 Nov;26(9):1040–6.

19. **Vorselaars VM**. Pulmonary hypertension in hereditary haemorrhagic telangiectasia. World J Cardiol. 2015;7(5):230.

20. **Garcia-Tsao G**. Liver involvement in hereditary hemorrhagic telangiectasia (HHT). J Hepatol. 2007 Mar;46(3):499–507.

21. **Buscarini E**, Danesino C, Plauchu H, de Fazio C, Olivieri C, Brambilla G, et al. High prevalence of hepatic focal nodular hyperplasia in subjects with hereditary hemorrhagic telangiectasia. Ultrasound Med Biol. 2004 Sep;30(9):1089–97.

22. **Cooney T**, Sweeney EC, Coll R, Greally M. 'Pseudocirrhosis' in hereditary haemorrhagic telangiectasia. J Clin Pathol. 1977 Dec 1;30(12):1134–41.

23. **Xu BG**, Liang J, Jia KF, Han T. Liver cirrhosis in a patient with hepatic hereditary hemorrhagic telangiectasia and Budd–Chiari syndrome: a case report. BMC Gastroenterol. 2020 Dec;20(1):169.

24. **Shovlin CL**, Sulaiman NL, Govani FS, Jackson JE, Begbie ME. Elevated factor VIII in hereditary haemorrhagic telangiectasia (HHT): association with venous thromboembolism. Thromb Haemost. 2007 Nov;98(5):1031–9.

25. **Singh S**, Swanson KL, Hathcock MA, Kremers WK, Pallanch JF, Krowka MJ, et al.

Identifying the presence of clinically significant hepatic involvement in hereditary haemorrhagic telangiectasia using a simple clinical scoring index. J Hepatol. 2014 Jul;61(1):124–31.

26. **Faughnan ME**, Mager JJ, Hetts SW, Palda VA, Lang-Robertson K, Buscarini E, et al. Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. Ann Intern Med. 2020 Dec 15;173(12):989–1001.

27. **Buscarini E**, Danesino C, Olivieri C, Lupinacci G, De Grazia F, Reduzzi L, et al. Doppler Ultrasonographic Grading of Hepatic Vascular Malformations in Hereditary Hemorrhagic Telangiectasia - Results of Extensive Screening. Ultraschall Med - Eur J Ultrasound. 2004 Sep 14;25(05):348–55.

28. **Caselitz M**. Sonographic criteria for the diagnosis of hepatic involvement in hereditary hemorrhagic telangiectasia (HHT). Hepatology. 2003 May;37(5):1139–46.

29. **Buscarini E**, Buscarini L, Danesino C, Piantanida M, Civardi G, Quaretti P, et al. Hepatic vascular malformations in hereditary hemorrhagic telangiectasia: Doppler sonographic screening in a large family. J Hepatol. 1997 Jan;26(1):111–8.

30. **Naganuma H**, Ishida H, Niizawa M, Igarashi K, Shioya T, Masamune O. Hepatic involvement in Osler-Weber-Rendu disease: findings on pulsed and color Doppler sonography. Am J Roentgenol. 1995 Dec;165(6):1421–5.

31. **Buscarini E**, Gebel M, Ocran K, Manfredi G, Del Vecchio Blanco G, Stefanov R, et al. Interobserver Agreement in Diagnosing Liver Involvement in Hereditary Hemorrhagic Telangiectasia by Doppler Ultrasound. Ultrasound Med Biol. 2008 May;34(5):718–25.

32. **Buscarini E**, Gandolfi S, Alicante S, Londoni C, Manfredi G. Liver involvement in hereditary hemorrhagic telangiectasia. Abdom Radiol. 2018 Aug;43(8):1920–30.

33. **Cusumano LR**, Tesoriero JA, Wilsen CB, Sayre J, Quirk M, McWilliams JP. Predictors of heart failure symptoms in hereditary hemorrhagic telangiectasia patients with hepatic arteriovenous malformations. Orphanet J Rare Dis. 2021 Dec;16(1):478.

34. **Sharma VK**, Howden CW. Gastrointestinal and Hepatic Manifestations of Hereditary Hemorrhagic Telangiectasia. Dig Dis. 1998;16(3):169–74.

35. **Cavel A**, Bleuzen A, Bertrand P, Patat F, Cottier JP. Comparison between Doppler ultrasonography and multiphase multidetector-row computed tomography in the detection of liver involvement in Rendu-Osler disease: An analysis of 62 patients. Diagn Interv Imaging. 2016 Apr;97(4):451–9.

36. **Scardapane A**, Stabile Ianora A, Sabbà C, Moschetta M, Suppressa P, Castorani L, et al. Dynamic 4D MR angiography versus multislice CT angiography in the evaluation of vascular hepatic involvement in hereditary haemorrhagic telangiectasia. Radiol Med (Torino). 2012

Feb;117(1):29–45.
37. **Memeo M**, Stabile Ianora AA, Scardapane A, Buonamico P, Sabbà C, Angelelli G. Hepatic involvement in hereditary hemorrhagic telangiectasia: Abdom Imaging. 2004 Mar;29(2):211–20.
38. **Dioguardi Burgio M**, Ronot M, Salvaggio G, Vilgrain V, Brancatelli G. Imaging of Hepatic Focal Nodular Hyperplasia: Pictorial Review and Diagnostic Strategy. Semin Ultrasound CT MRI. 2016 Dec;37(6):511–24.
39. **Milot L**, Kamaoui I, Gautier G, Pilleul F. Hereditary-hemorrhagic telangiectasia: One-step magnetic resonance examination in evaluation of liver involvement. Gastroentérologie Clin Biol. 2008 Aug;32(8–9):677–85.
40. **Schelker RC**, Barreiros AP, Hart C, Herr W, Jung EM. Macro- and microcirculation patterns of intrahepatic blood flow changes in patients with hereditary hemorrhagic telangiectasia. World J Gastroenterol. 2017;23(3):486.
41. **Bauer T**, Britton P, Lomas D, Wight DGD, Friend PJ, Alexander GJM. Liver transplantation for hepatic arteriovenous malformation in hereditary haemorrhagic telangiectasia. J Hepatol. 1995 May;22(5):586–90.
42. **Riera-Mestre A**, Cerdà P, Guzmán YC, Iriarte A, Torroella A, Mora-Luján JM, et al. Perioperative Complications and Long-Term Follow-Up of Liver Transplantation in Hemorrhagic Hereditary Telangiectasia: Report of Three Cases and Systematic Review. J Clin Med. 2022 Sep 24;11(19):5624.
43. **Garcia-Tsao G**, Gish RG, Punch J. Model for end-stage liver disease (MELD) exception for hereditary hemorrhagic telangiectasia. Liver Transpl. 2006 Dec;12(S3):S108–9.
44. **Maggi U**, Conte G, Nita G, Gatti S, Paone G, Caccamo L, et al. Arterial Anastomosis in Liver Transplantation for Rendu-Osler-Weber Disease: Two Case Reports. Transplant Proc. 2013 Sep;45(7):2689–91.
45. **Giacomoni A**, De Carlis L, Sammartino C, Lauterio A, Osio C, Slim A, et al. Right hemiliver transplants from living donors: report of 10 cases. Transplant Proc. 2004 Apr;36(3):516–7.
46. **Aseni P**. Massive haemoptysis after living donor liver transplantation. J Clin Pathol. 2003 Nov 1;56(11):876–8.
47. **Dupuis-Girod S**, Chesnais AL, Ginon I, Dumortier J, Saurin JC, Finet G, et al. Long-term outcome of patients with hereditary hemorrhagic telangiectasia and severe hepatic involvement after orthotopic liver transplantation: A single-center study: Hereditary Hemorrhagic Telangiectasia. Liver Transpl. 2010 Mar;16(3):340–7.
48. **Dumortier J**, Dupuis-Girod S, Valette P, Valent A, Guillaud O, Saurin J, et al. Recurrence

505 of Hereditary Hemorrhagic Telangiectasia After Liver Transplantation: Clinical Implications and
506 Physiopathological Insights. Hepatology. 2019 May;69(5):2232–40.
507 49. **Sabbà C**, Gallitelli M, Longo A, Cariati M, Angelelli G. Orthotopic liver transplantation
508 and hereditary hemorrhagic telangiectasia: do hepatic vascular malformations relapse? A long term
509 follow up study on two patients. J Hepatol. 2004 Oct;41(4):687–9.
510 50. **Hove W**. Extensive chimerism in liver transplants: Vascular endothelium, bile duct
511 epithelium, and hepatocytes. Liver Transpl. 2003 Jun;9(6):552–6.
512 51. **Castellote J**, Mora Luján JM, Riera-Mestre A. Letter to the Editor: mTOR-Inhibitor-Based
513 Immunosuppression Following Liver Transplantation for Hereditary Hemorrhagic Telangiectasia.
514 Hepatology. 2020 Feb;71(2):762–3.
515 52. **Chavan A**, Galanski M, Wagner S, Caselitz M, Schlitt HJ, Gratz KF, et al. Hereditary
516 hemorrhagic telangiectasia: effective protocol for embolization of hepatic vascular malformations--
517 experience in five patients. Radiology. 1998 Dec;209(3):735–9.
518 53. **Chavan A**, Luthe L, Gebel M, Barg-Hock H, Seifert H, Raab R, et al. Complications and
519 clinical outcome of hepatic artery embolisation in patients with hereditary haemorrhagic
520 telangiectasia. Eur Radiol. 2013 Apr;23(4):951–7.
521 54. **Whiting JH**, Korzenik JR, Miller FJ, Pollack JS, White RI. Fatal Outcome after
522 Embolotherapy for Hepatic Arteriovenous Malformations of the Liver in Two Patients with
523 Hereditary Hemorrhagic Telangiectasia. J Vasc Interv Radiol. 2000 Jul;11(7):855–8.
524 55. **Lee JY**, Korzenik JR, DeMasi R, Lih-Brody L, White RI. Transjugular Intrahepatic
525 Portosystemic Shunts in Patients with Hereditary Hemorrhagic Telangiectasia: Failure to Palliate
526 Gastrointestinal Bleeding. J Vasc Interv Radiol. 1998 Nov;9(6):994–7.
527 56. **Cura MA**, Postoak D, Speeg KV, Vasan R. Transjugular Intrahepatic Portosystemic Shunt
528 for Variceal Hemorrhage due to Recurrent of Hereditary Hemorrhagic Telangiectasia in a Liver
529 Transplant. J Vasc Interv Radiol. 2010 Jan;21(1):135–9.
530 57. **Koscielny A**, Willinek WA, Hirner A, Wolff M. Treatment of High Output Cardiac Failure
531 by Flow-Adapted Hepatic Artery Banding (FHAB) in Patients with Hereditary Hemorrhagic
532 Telangiectasia. J Gastrointest Surg. 2008 May;12(5):872–6.
533 58. **Liu ZC**, Lu XF, Yang H, Liu HD, Song X, Ning SL, et al. Clinical Outcomes of Patients
534 with Severe Hepatic Hereditary Hemorrhagic Telangiectasia After Banding of the Hepatic Artery
535 and Banding/Ligation of Branches of the Hepatic Artery. Eur J Vasc Endovasc Surg Off J Eur Soc
536 Vasc Surg. 2016 Apr;51(4):594–601.
537 59. **Garcia-Tsao G**, Korzenik JR, Young L, Henderson KJ, Jain D, Byrd B, et al. Liver Disease
538 in Patients with Hereditary Hemorrhagic Telangiectasia. N Engl J Med. 2000 Sep 28;343(13):931–

6.
60. **Song X**, Chen HQ, Chen YX, Cheng Y, Qu CQ, Liu EY, et al. Individualized management of hepatic diseases in hereditary hemorrhagic telangiectasia. Am Surg. 2011 Mar;77(3):281–5.
61. **Zieren J**, Büttemeyer R, Müller JM. [Adjustable 'banding' of the hepatic artery in treatment of shunt-induced heart failure in Osler-Rendu-Weber disease]. Chir Z Alle Geb Oper Medizen. 1998 Jun;69(6):639–41.
62. **Xiang J**, Xie W, Zhang C, Wang H. Right hemihepatectomy combined with ligation of the common hepatic artery and gastroduodenal artery for the treatment of intrahepatic HHT: A case report. Front Surg. 2022 Aug 9;9:900297.
63. **Schmalz MJ**, Radhakrishnan K. Vascular anomalies associated with hepatic shunting. World J Gastroenterol. 2020 Nov 14;26(42):6582–98.
64. **Petrovic I**, Pavlek G, Romic M, Grgic D, Romic I. Rupture of suppurated liver hematoma into the anterior abdominal wall in a patient with Rendu-Osler-Weber syndrome. Cir Cir. 2020 Nov 11;88(92):4495.
65. **Gaujoux S**, Bucau M, Ronot M, Paradis V, Vilgrain V, Belghiti J. Liver Resection in Patients with Hepatic Hereditary Hemorrhagic Telangiectasia. Dig Surg. 2013;30(4–6):410–4.
66. **Angeli P**, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018 Aug;69(2):406–60.
67. **de Franchis R**, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. Baveno VII – Renewing consensus in portal hypertension. J Hepatol. 2022 Apr;76(4):959–74.
68. **Montagnese S**, Rautou PE, Romero-Gómez M, Larsen FS, Shawcross DL, Thabut D, et al. EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. J Hepatol. 2022 Sep;77(3):807–24.
69. **Costa Macedo T**, Maldonado R, Valente A, Palma R, Raimundo M, Liberato M, et al. Hemobilia in hereditary hemorrhagic telangiectasia: an unusual complication of endoscopic retrograde cholangiopancreatography. Endoscopy. 2003 Jun;35(6):531–3.
70. **Hayashi S**, Baba Y, Ueno K, Nakajo M. Small Arteriovenous Malformation of the Common Bile Duct Causing Hemobilia in a Patient with Hereditary Hemorrhagic Telangiectasia. Cardiovasc Intervent Radiol. 2008 Jul;31(S2):131–4.
71. **Invernizzi R**, Quaglia F, Klersy C, Pagella F, Ornati F, Chu F, et al. Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre, phase 2 study. Lancet Haematol. 2015 Nov;2(11):e465–73.

72. **Baysal M**, Ümit E, Kırkızlar HO, Özdöver AC, Demir AM. Thalidomide for the Management of Bleeding Episodes in Patients with Hereditary Hemorrhagic Telangiectasia: Effects on Epistaxis Severity Score and Quality of Life. Turk J Hematol. 2019 Feb 6;36(1):43–7.
73. **Hessels J**, Kroon S, Boerman S, Nelissen RC, Grutters JC, Snijder RJ, et al. Efficacy and Safety of Tacrolimus as Treatment for Bleeding Caused by Hereditary Hemorrhagic Telangiectasia: An Open-Label, Pilot Study. J Clin Med. 2022 Sep 7;11(18):5280.
74. **Kim YH**, Kim MJ, Choe SW, Sprecher D, Lee YJ, P. Oh S. Selective effects of oral antiangiogenic tyrosine kinase inhibitors on an animal model of hereditary hemorrhagic telangiectasia. J Thromb Haemost. 2017 Jun;15(6):1095–102.
75. **Faughnan ME**, Gossage JR, Chakinala MM, Oh SP, Kasthuri R, Hughes CCW, et al. Pazopanib may reduce bleeding in hereditary hemorrhagic telangiectasia. Angiogenesis. 2019 Feb 15;22(1):145–55.
76. **Parambil JG**, Gossage JR, McCrae KR, Woodard TD, Menon KVN, Timmerman KL, et al. Pazopanib for severe bleeding and transfusion-dependent anemia in hereditary hemorrhagic telangiectasia. Angiogenesis. 2022 Feb;25(1):87–97.
77. **McWilliams JP**, Majumdar S, Kim GH, Lee J, Seals K, Tangchaiburana S, et al. North American Study for the Treatment of Recurrent Epistaxis with Doxycycline: The NOSTRIL trial. J Thromb Haemost. 2022 May;20(5):1115–25.
78. **Thompson KP**, Sykes J, Chandakkar P, Marambaud P, Vozoris NT, Marchuk DA, et al. Randomized, double-blind, placebo-controlled, crossover trial of oral doxycycline for epistaxis in hereditary hemorrhagic telangiectasia. Orphanet J Rare Dis. 2022 Nov 7;17(1):405.
79. **Dupuis-Girod S**, Ginon I, Saurin JC, Marion D, Guillot E, Decullier E, et al. Bevacizumab in Patients With Hereditary Hemorrhagic Telangiectasia and Severe Hepatic Vascular Malformations and High Cardiac Output. JAMA. 2012 Mar 7;307(9):948-55.
80. **Mitchell A**, Adams LA, MacQuillan G, Tibballs J, vanden Driesen R, Delriviere L. Bevacizumab reverses need for liver transplantation in hereditary hemorrhagic telangiectasia. Liver Transpl. 2008 Feb;14(2):210–3.
81. **Al-Samkari H**, Kasthuri RS, Parambil JG, Albitar HA, Almodallal YA, Vázquez C, et al. An international, multicenter study of intravenous bevacizumab for bleeding in hereditary hemorrhagic telangiectasia: the InHIBIT-Bleed study. Haematologica. 2020 Jul 16;106(8):2161–9.
82. **Al-Samkari H**. Hereditary hemorrhagic telangiectasia: systemic therapies, guidelines, and an evolving standard of care. Blood. 2021 Feb 18;137(7):888–95.
83. **Albitar HAH**, Almodallal Y, Gallo De Moraes A, O'Brien E, Choby GW, Pruthi RK, et al. Intravenous Bevacizumab in Hereditary Hemorrhagic Telangiectasia–Related Bleeding and High-

Output Cardiac Failure. Mayo Clin Proc. 2020 Aug;95(8):1604–12.
84. **Buscarini E**, Botella LM, Geisthoff U, Kjeldsen AD, Mager HJ, Pagella F, et al. Safety of thalidomide and bevacizumab in patients with hereditary hemorrhagic telangiectasia. Orphanet J Rare Dis. 2019 Dec;14(1):28.
85. **Dupuis-Girod S**, Shovlin CL, Kjeldsen AD, Mager HJ, Sabba C, Droege F, et al. European Reference Network for Rare Vascular Diseases (VASCERN): When and how to use intravenous bevacizumab in Hereditary Haemorrhagic Telangiectasia (HHT)? Eur J Med Genet. 2022 Oct;65(10):104575.
86. **Stillo F**, Mattassi R, Diociaiuti A, Neri I, Baraldini V, Dalmonte P, et al. Guidelines for Vascular Anomalies by the Italian Society for the study of Vascular Anomalies (SISAV). Int Angiol. 2022 Apr;41(2 Suppl 1):1-130.

Tables and Figures

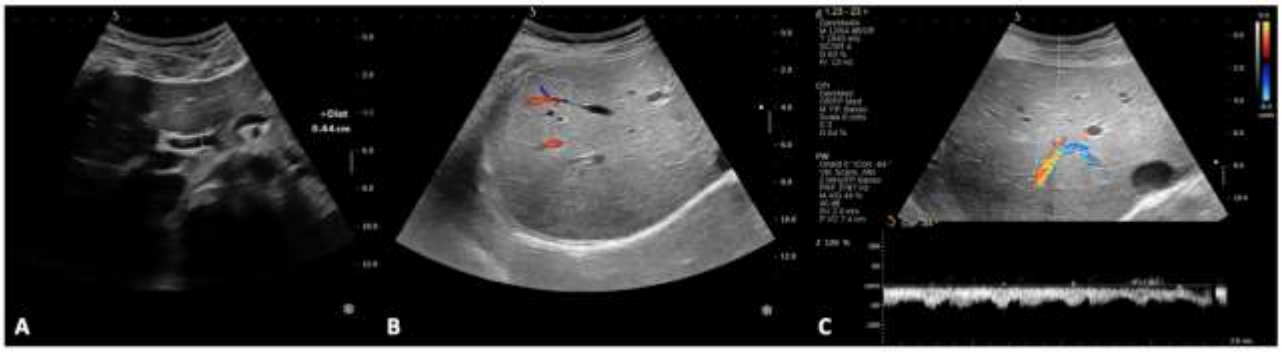

Figure 1: ~~HHT~~ Ultrasound findings in HHT. A: hepatic artery dilation; B: peripheral hepatic hypervascularization; C: pulsatile flow in right portal branch related to arteriovenous malformation.

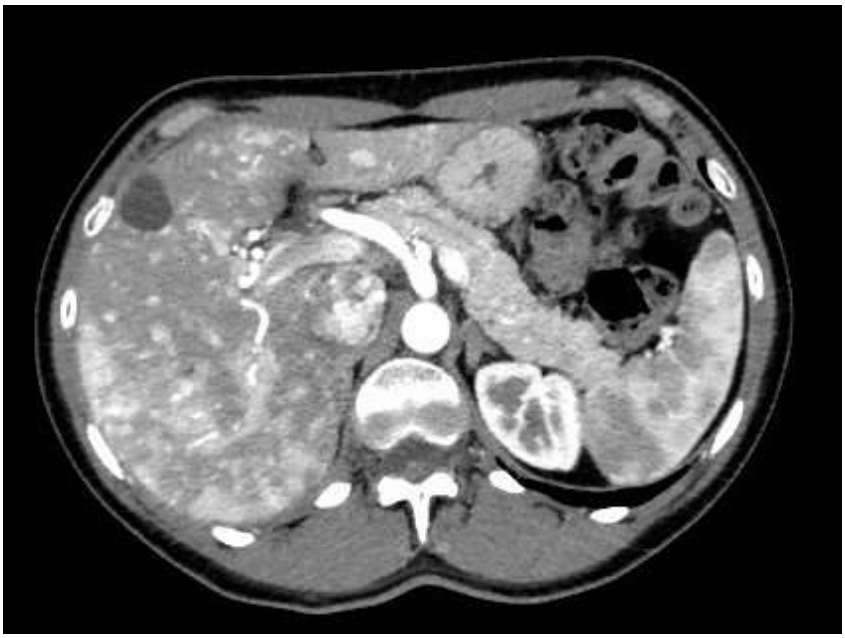

Figure 2: multiple arteriovenous malformations and enlarged hepatic artery in contrast-enhanced CT scan.

675 **Table 1**: Curaçao diagnostic criteria of HHT

Curaçao criteria	**Description**
Epistaxis	Spontaneous and recurrent
Teleangiectases	Multiple, at characteristic sites: lips, oral cavity, fingers, nose
Visceral lesions	GI telangiectasia, pulmonary, hepatic, cerebral or spinal AVMs
Family history	A first degree relative with HHT
Number of criteria	**HHT diagnosis**
3-4	definite
2	possible
0-1	unlikely

676 *AVMs*: arteriovenous malformations; *HHT*: hereditary hemorrhagic teleangiectasia

677

678

679

680

681

682

683

684

685

686

687

688

689

690

691

692

693

Table 2: Genes responsible for HHT, phenotypes and liver involvement prevalence

Gene	Protein	Location	Phenotype	Liver involvement prevalence
ENG	Endoglin	9q34.11	HHT1	7.6 - 43.0%
ACVLR1	ALK1	12q13.13	HHT2	40.6 - 57.6%
MADH4	Smad4	18q21.1	PJ-HHT	33.3%
GDF2	BMP9	10q11.22	HHT-like	Unknown
RASA-1	p120-RasGAP	5q14.3	CM-AVM	Unknown

ACVLR1: activin A receptor type II-like 1; *ALK1*: activin-like receptor kinase 1; *BMP9*: bone morphogenetic protein 9; *CM–AVM*: capillary malformation–arteriovenous malformation syndrome; *GDF2*: growth differentiation factor 2; *ENG*: endoglin; *MADH4*: mothers against decapentaplegic homolog 4; *p120-RasGAP*: p120-Ras GTPase activating protein; *PJ*: juvenile polyposis; *RASA-1*: Ras p21 protein activator 1; *Smad4*: small mother against decapentaplegic

Table 3: Clinical Scoring Index for clinical probability of significant liver disease in HHT patients. *Adapted from Singh S et al, J Hepatol, 2014.*

Criteria		Points
Age at presentation (yers)	>47	1
	≤47	0
Sex	female	1
	male	0
Hb at presentation (g/dl)	<8	3
	8-12	2
	12-16	1
	>16	0
ALP at presentation (IU/L)	>300	4
	225-300	3
	150-224	2
	75-149	1
	>75	0

Clinical Scoring Index	Clinical probability of significant liver disease	
≤2	Low	(0.4-3.2%)
3-6	Intermediate	(8.2-64.1%)
≥7	High	(82.9-93.0%)

ALP: alkaline phosphatase; *Hb*: hemoglobin

730 **Table 4**: Doppler ultrasound grading of hepatic VMs in HHT patients. *Adapted from Buscarini E et*
731 *al, Eur J Ultrasound, 2004.*

VMs Grade	Doppler US findings
0.5	HA diameter 5-6 mm and/or PFV >80 cm/sec and/or HA RI <0.55 and/or Peripheral hepatic hypervascularization
1	HA dilation >6 mm (only extrahepatic) and PFV >80 cm/sec and/or HA RI <0.55 and/or
2	HA dilation intra- and extrahepatic and PFV >80 cm/sec Possible flow abnormality in portal and/or hepatic veins
3	Complex changes in HA end its branches with marked flow abnormalities Flow abnormality in portal and/or hepatic veins
4	Decompensation of arteriovenous shunt with dilatation of portal and/or hepatic vein and marked flow abnormalities in both arteries and vein/s

732

733 *HA*: hepatic artery; *PFV*: peak flow velocity; *RI*: resistivity index; *US*: ultrasound; *VMs*: vascular
734 malformations