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REVIEW

A systematic review of diagnostic and interventional techniques in non-occlusive hepatic artery hypoperfusion syndrome

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Abstract

Objective This systematic review aims to elucidate the diagnostic capabilities of imaging techniques in identifying Non-Occlusive Hepatic Artery Hypoperfusion Syndrome (NOHAH) and to evaluate the efficacy and outcomes of splenic artery embolization (SAE), including the choice and placement of embolic agents.

Materials and methods A comprehensive literature search was conducted using PubMed, CINAHL, and Scopus databases, adhering to PRISMA guidelines. Fifteen studies encompassing 240 patients treated with embolization (using coils or Amplatzer Vascular Plugs (AVP)) were analyzed. Key metrics assessed included patient demographics, embolization techniques, embolic agents, technical success, radiologic findings pre- and post-embolization, and complication rates.

Results Among the 240 patients studied, 177 (73.8%) were reported by gender, with a majority being male (127/177, 71.7%). Doppler ultrasonography (DUS) emerged as the primary initial screening tool in 80% of studies. The hepatic arterial resistive index (RI) was a critical parameter, with mean values significantly decreasing from 0.84 pre-embolization to 0.70 post-embolization ($p < 0.001$). All cases confirmed technical success via digital subtraction angiography, revealing delayed hepatic arterial filling without stenosis or thrombosis. Coils were the predominant embolic agent, used in 80.8% of patients, followed by AVP in 16.3%. The overall mortality rate was 4.58%, with 29 major and 3 minor complications noted. Notably, proximal placement of coils in the splenic artery was associated with lower mortality rates compared to distal placement and showed comparable complication rates to AVPs.

Conclusion DUS is a reliable screening modality for NOHAH, with post-SAE assessments showing significant improvements. The choice and location of embolization significantly impact patient outcomes, with proximal placement of coils emerging as a preferable strategy due to lower mortality rates and comparable complication profiles to alternative methods.

Keywords Splenic Artery Embolization · Hepatic hypoperfusion · Endovascular techniques

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Introduction

Non-Occlusive Hepatic Artery Hypoperfusion Syndrome (NOHAH), frequently encountered in orthotopic liver transplantation (OLT), significantly impacts graft survival. Occurring in 0.6–10% of OLT cases [1–3], NOHAH is characterized by impaired graft perfusion despite an open hepatic artery, contrasting with excessive perfusion of the splenic artery [4, 5]. Renamed from its initial concept as a 'steal' syndrome, NOHAH involves a decrease in hepatic arterial flow due to an increase in portal vein flow, eliciting the hepatic arterial buffer response (HABR) [6, 7]. The resulting ischemic damage and sinusoidal injuries underscore the need for prompt and effective intervention [8].

In this context, Doppler ultrasonography (DUS) plays a crucial role in diagnosing NOHAH, complemented by modalities such as contrast-enhanced ultrasonography (CEUS), computed tomographic angiography (CTA), and digital subtraction angiography (DSA) [8]. However, the cornerstone of treatment is Splenic Artery Embolization (SAE), a technique that has significantly improved patient outcomes in NOHAH. SAE demonstrates effectiveness in mitigating graft dysfunction, with fewer complications and improved functional restoration compared to traditional surgical methods [9]. The significance of SAE is further highlighted in post-treatment evaluations. Radiological follow-ups, particularly changes in DUS indices and CT findings, offer crucial insights into the success of SAE interventions [10]. This study explores the impact of SAE on the treatment of NOHAH post-OLT, aiming to underscore its efficacy through a comparative analysis of pre and post-embolization radiological features. The focus is to emphasize SAE role in improving patient outcomes and advancing the management of hepatic artery disorders.

Materials and methods

Search strategy

Adhering to PRISMA guidelines, a comprehensive search of PubMed, CINAHL, and Scopus databases was undertaken to gather relevant studies on Non-Occlusive Hepatic Artery Hypoperfusion Syndrome (NOHAH). This search, encompassing literature published from 2002 to 2021, utilized keywords "Non-Occlusive Hepatic Artery Hypoperfusion", "Splenic Steal Syndrome", "Splenic Artery Embolization" and "SAE." The focus was on English-language publications, offering a broad yet precise collection of data.

Study selection and data extraction

Our initial database exploration yielded 185 potential sources. Inclusion criteria mandated that studies should address NOHAH treatment via embolization using coils or plugs, with a minimum of three case reports and documented pre- and post-radiologic observations. Exclusions applied to duplicates, review articles, pediatric-only studies, non-English reports, and animal studies. This refined the selection to 37 articles, of which 22 were further excluded due to irrelevant outcomes or insufficient follow-up data. Ultimately, 15 articles qualified for systematic review (Fig. 1).

Quality assessment

The National Institutes of Health's Quality Assessment Tool for Case Series was employed to evaluate the selected studies. Two independent authors assessed each article against criteria including objective clarity, population definition, patient comparability, outcome validity, and statistical methodology. All 15 articles were uniformly rated as 'fair' in quality (Supplementary Table).

Data extraction and outcome definition

Data extraction, conducted by two authors, encompassed publication year, study location, design, case numbers, gender ratio, mean age, embolic agent type and quantity, intervention technicalities, and pre- and post-intervention radiologic features. Complications were categorized according to SIR guidelines, and mortality rates post-intervention were noted. Follow-up durations and imaging methods were also recorded (Tables 1 and 2). Effectiveness was gauged through comparisons of embolic agents, resistance index values, arterial and venous velocities, and mortality rates. Technical success was defined as post-SAE angiography confirming cessation of splenic artery trunk flow. Clinical success was measured by improvements in splenomegaly, liver function tests, and sustained arterial diameter improvements on CEUS or CT during follow-up. The study's primary endpoint was the success rate of SAE in preventing liver failure and the need for repeat OLT. Secondary and tertiary endpoints included the necessity for additional treatment via repeat SAE and post-SAE mortality from various complications, respectively.

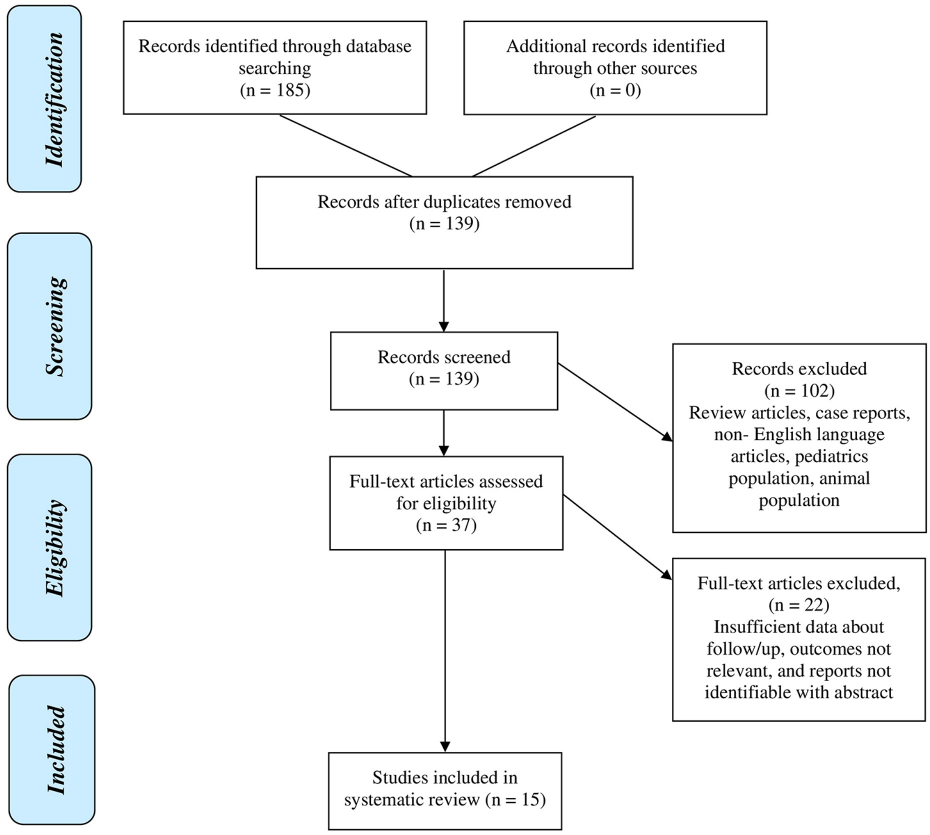

Fig. 1 Flow diagram demonstrating study selection process for meta-analysis

Results

Study overview and demographics

Our review included 15 retrospective studies, encompassing 240 cases of Non-Occlusive Hepatic Artery Hypoperfusion Syndrome (NOHAH) treated through splenic artery embolization. The studies varied in size, with an average of 16 patients per study and a range from 3 to 50 patients. Among the 12 studies reporting gender distribution, a notable majority, 72.3% of NOHAH cases post-transplant, were male.

Etiology of liver transplantation

Nine studies provided detailed etiology for orthotopic liver transplantation (OLT). The causes included postinfectious hepatitis (38 cases, 15.8%), alcoholic liver cirrhosis (21 cases, 8.7%), hepatosteatosis (15 cases, 6.2%), cryptogenic cirrhosis/failure (13 cases, 5.4%), and Wilson disease (9 cases, 3.8%). Other less common causes were primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular carcinoma, and conditions like Laennec's cirrhosis, autoimmune hepatitis, and alpha-1 antitrypsin deficiency, each contributing to a small percentage of cases [6, 11–17].

Diagnostic imaging and follow-up

All studies reported on the imaging modalities used for follow-up. Doppler ultrasound (DUS) was the predominant tool, employed in 12 studies for assessing post-SAE improvement [1, 6, 11–16, 18–21]. Contrast-enhanced ultrasound (CEUS) was used in two studies to track improvements [13, 21]. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) were also used, either alone or in conjunction with other modalities, in 5 and 2 studies respectively [10, 12, 17, 19, 21]. The median time from OLT to NOHAH diagnosis varied among patients, with a range of 0.25-66 months [10, 11, 13, 18, 19]. Notably, one study using DUS identified asymptomatic NOHAH with a median duration from OLT to diagnosis of just 4 days (range, 1–9 days) [18].

Computed tomography angiography (CTA)

CTA is instrumental in diagnosing NOHAH post-liver transplantation. CTA effectively highlights crucial anatomical changes, including splenic artery (SA) dilation and hepatic artery (HA) constriction. Diagnostic criteria for NOHAH encompass an SA diameter > 6 mm, HA-SA diameter differential > 4 mm, and SA-CHA diameter ratio > 1.5 [8]. Some studies using CTA precisely measured arterial dimensions

Table 1 Summary of Included Studies for NOHAH Treatment

Author, Year	Study Location, Multi/ Single Center	Prospective/ Retrospective Study Design	Number of Cases Treated with Embolization / Male	Mean Age, Y	Coil / Embolic Agent
Chao et al., 2007	USA	Retrospective/single center	5/ 3	52.2	Pt 1: PVA, Coils Pt 2: Coils Pt 3: Gelatin sponge slurry Pt 4: PVA Pt 5: PVA, Coils
Kim, J. H. et al., (2011)	South Korea	Retrospective /single center	9/ 6	44	Coils
Li, C., et al., (2016)	USA	Retrospective/ single center	50/ 39	57.5 ± 9.9	Coils
Liu, D. Y., et al.. (2015)	China	Case series/multicenter	3/ 2	53 ± 1	Coils
Mogl, M. T., et al., (2010)	Germany	Retrospective/single center	26/NA	53	Coils
Nüssler, N. C., et al., (2003)	Germany	Retrospective/multicenter	29/NA	NA	Coils
Saad, W. E., et al., (2012)	USA	Retrospective/single center	4/1	53.3	Pt1: coils and AVP Pt2: coils Pt3: coils Pt4: coils and AVP
Teegen, E. M., et al., (2017)	Germany	Retrospective/single center	8/5	56.9 ± 10.8	AVP
Zhu, X., et al., (2011)	China	Retrospective/single center	40/28	42.2	18 AVP 22: Coils
Zhu, X. S., et al., (2012)	China	Retrospective/single center	8/	NA	Coils
Renan Uflacker et al., 2002	USA	Retrospective/single center	11/ 9	52	Coils
S Sevmis et al., 2006	Turkey	Retrospective/single center	10/ 8	24.7 ± 11	9 patients with coils 1 patient with endoluminal narrowing stent
Uslu et al., 2012	Turkey	Retrospective/single center	20/ 15	20	Coils
M. H. Maurer et al., 2010	Germany		13/ 9	56	AVP
Cristiano Quintini et al., 2008	Cleveland	Retrospective/case series	4/3	26.3	Coils

Key Abbreviations and Definitions - Femoral Artery (Femoral A.), Follow Up (F/U), Data Not Available (N/A), Celiac Axis (CA), Common Hepatic Artery (CHA), Splenic Artery (SA), Peak Systolic Velocity (PSV), Portal Venous Velocity (PVV), Doppler Ultrasound (DUS), Contrast-Enhanced Ultrasound (CEUS), Digital Subtraction Angiography (Q-DSA). SIR Complication Guidelines: Minor Complications: A. No therapy, no consequence B. Nominal therapy, no consequence; includes overnight admission for observation only. Major Complications: C. Require therapy, minor hospitalization (<48 h) D. Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 h) E. Permanent adverse sequelae F. Death. * Reported complications were classified according to the SIR classification

for monitoring pre- and post-SAE [10, 19] and planning Amplatzer Vascular Plug (AVP) placement [17]. They also assessed the common hepatic artery (CHA). Notable findings include Celiac axis (CA) diameter reduction from 8.4 ± 1.3 (pre-treatment) to 6.9 ± 1 (one-year post-treatment, $p < 0.01$) and CHA diameter increase from 4.3 ± 0.6 to 4.9 ± 0.6 ($p = 0.016$) [10]. SA diameter decreased from 7.7 ± 1 to 3.9 ± 0.7 ($p < 0.01$), altering SA/CHA relative diameters from 1.8 ± 0.3 to 0.8 ± 0.1 ($p < 0.01$). One study tracked CTA assessments at one week, one month, and one year post-SAE, revealing early diameter fluctuations followed by stabilization [10]. In AVP-assisted SAE for NOHAH post-OLT, pre-SAE CT scans assessed SA diameter at the intended AVP site. Post-SAE CT scans for 9 patients confirmed AVP positioning, except one case with extensive splenic infarction leading to splenectomy [17].

Doppler ultrasound (DUS)

Doppler ultrasonography (DUS) plays a crucial role in diagnosing Non-Occlusive Hepatic Artery Hypoperfusion Syndrome (NOHAH) in 12 out of 15 studies [1, 6, 11–16, 18–21]. It offers non-invasive, radiation-free insights into vascular dynamics. NOHAH, often observed in orthotopic liver transplantation (OLT) recipients, involves factors like high portal flow, graft-to-hepatic artery size discrepancies, and splenomegaly, leading to hepatic artery hypoperfusion. DUS detects this as increased resistive index (RI > 0.8) and decreased peak hepatic artery velocity (<35 cm/s) [8]. Studies analyzed RI changes in 115 patients. Pre-SAE RI was 0.88 (range: 0.49-1.0), post-SAE significantly reduced to 0.67 (range: 0.4-1.0) ($p < 0.001$) [6, 13, 14, 18–20, 1, 11–15, 19, 16]. Uslu et al. reported a significant drop in hepatic arterial peak systolic velocity (PSV) from 65 cm/sec to 47 cm/sec ($p \leq 0.01$) [16]. Mogl et al. found a reduction in hepatic artery RI from 0.79 ± 0.14 to 0.65 ± 0.09

Table 2 Treatment Techniques and Outcomes in Included Studies

Author, Year	Number of Cases with embolization / Number of Male	Type/ number of Coil or Embolic Agent	Where the embolic agents were placed	Pre- Radiologic Feature	Post-Radiologic Feature	Complications based on SIR guideline	Mortality Rate	Mean F/U & Imaging modality
Chao et al., (2007)[10]	5/ 3	Polyvinyl alcohol microspheres (Contour SE, Boston Scientific, Natick, Mass, United States) Gelatin sponge slurry Coils	Embolization was performed in the **proximal** splenic artery to counteract the hyperdynamic flow while preserving the short gastric and pancreatic collaterals to prevent splenic infarction.			C: 3 patients D: 2 patients	0%	20.2 Months with DUS + MRI + CT + endoscopy
Kim, J. H. et al., (2011)[9]	9/ 6	0.018-inch soft platinum microcoils (Cook Inc, Bloomington, IN)	SAE was performed by selective catheterization of the splenic artery (SA) using a superselective coaxial technique with a 2.2-F microcatheter (Progreat, Terumo, Tokyo, Japan), followed by deployment of 0.018-inch soft platinum microcoils (Cook Inc, Bloomington, IN) of various lengths and diameters in the **middle** part of the SA.	CA: 8.4 ± 1.3 (6.6–9.8) CHA: 4.3 ± 0.6 (3.2–5.3) SA: 7.7 ± 1 (6.4–9.4) SA/CHA: 1.8 ± 0.3 (1.4–2)	CA: *Short term(1 W): 8.1 ± 1.6 (5.7–10.3) *Mid-term(1 M): 7.1 ± 1.6 (5.2–10) *Long term(1Yr): 6.9± 1 (5.4–8.7)CHA: *Short term: 5.5 ± 1 (4.4–7.3), *Midterm: 5.3 ± 1 (3.9–7.3) *Long term: 4.9 ± 0.6 (3.9–5.7) SA: *Short-term: 5.6 ± 1.1 (4–7.3) *Midterm: 4.3 ± 1.2 (3.2–6.8) *Long term: 3.9 ± 0.7 (2.9–5.5) SA/CHA: *Short term: 1 ± 0.2 (0.8–1.3)*Mid-term: 0.8± 0.2 (0.5–1) *Long term: 0.8 ± 0.1 (0.6–1.0)	None	0%	12 ± 1 Months with CT
Li, C., et al., (2016)[11]	50/ 39	NA	**Proximal** splenic artery embolization, defined as embolization of the splenic artery distal to the dorsal pancreatic artery (first large branch) and proximal to the most peripheral pancreatica magna branch (second large branch).	RI: 0.95 ± 0.09 PSV: 68.0 ± 37.7 cm/s PVV: 87.9 ± 25.2 cm/s Spleen size: 16.4 ± 4.1 cm	RI: 0.77 ± 0.11 PSV: 72.1 ± 41.6 cm/s PVV: 43.1 ± 17.7 cm/s		5 patients (10%): multiple organ failure, sepsis with multiple organ failure, graft failure due to hepatic artery thrombosis, acute liver failure, and unknown.	Median 7 Months with DUS

Table 2 (continued)

Author, Year	Number of Cases with embolization / Number of Male	Type/ number of Coil or Embolic Agent	Where the embolic agents were placed	Pre- Radiologic Feature	Post-Radiologic Feature	Complications based on SIR guideline	Mortality Rate	Mean F/U & Imaging modality
Liu, D. Y., et al. (2015)[12]	3/ 2	NA	-P1: The closure device was placed in the middle of the splenic artery to achieve a fixed role, and then coils were placed in the **proximal** occluder.	Pt1: RI) POD2: 1 POD3: 1 Pt2:RI) POD3 :0.9 Pt3: RI) POD6: 0.5, POD7: 0.48 Pt2: S/D) POD3 :13 Pt3: S/D) POD6:2, POD7:1.9 Pt1: PV) POD2:53, POD3:61.4 pt2: PV) POD3:65 pt3: PV) POD6:47.6, POD7:46	Pt1: RI) POD4 (1st day after SAE):0.5 Pt2: RI) POD4 (1st day after SAE):1,POD6 (3rd day after SAE):0.7 Pt3:RI) POD13 (1st day after SAE):0.4 Pt1:S/D) POD4 (1st day after SAE):3.2 Pt2:S/D) POD6 (3rd day after SAE):3 Pt3:S/D) POD13 (1st day after SAE):1.67 Pt1: PV) POD4 (1st day after SAE):24 Pt2: PV) POD4 (1st day after SAE):73, POD6 (3rd day after SAE):33 Pt3:PV) POD13 (1st day after SAE):32	A: 3 patients		DUS, CEUS
Mogl, M. T., et al., (2010)[13]	26/NA	NA		RI:0.79 ± 0.14 PVV:37.3 ± 12.8	RI:0.65 ± 0.09 PVV: 29.4 ± 9.3	38.5%		Median 35 months with DUS, MRI, CT
Nüssler, N. C., et al., (2003)[3]	29/NA	NA	15 pt: coils were placed in the **distal** parts of the splenic artery 14 pt: coils were placed in the **central** parts of the artery			D: 15 patients F: 5 patients	5 patients (4 died of graft failure, 1 died of sepsis and multiorgan failure)	NA DUS
Saad, W. E., et al., (2012)[14]	4/1	Amplatzer vascular plugs (AGA Medical Corp, Plymouth, Minnesota) and/ or 0.035 inch coil embolization (Cook Corp., Bloomington, Indiana)	**Proximally** placed Amplatzer vascular plugs and coils placed more distally in the proximal to mid splenic artery.	Case 1: RI: 0.88, PSV: 95 Case 2: RI: 0.70, PSV: 36 Case 3: RI: 0.82, PSV: 38 Case 4: RI 0.88, PSV: 95	Case 1: RI: 0.67 PSV:109 Case 2: RI: 0.63, PSV:53 Case 3: RI: 0.78, PSV:64 Case 4: RI:0.67 PSV:109			9.1 Months with DUS/Q-DSA

Table 2 (continued)

Author, Year	Number of Cases with embolization / Number of Male	Type/ number of Coil or Embolic Agent	Where the embolic agents were placed	Pre- Radiologic Feature	Post-Radiologic Feature	Complications based on SIR guideline	Mortality Rate	Mean F/U & Imaging modality
Teegen, E. M., et al., (2017)[15]	8/5	Vascular plug (Amplatzer Plug II, St. Jude Medical, St. Paul, MI, USA)	NA, likely proximal	RI: 0.70 ± 0.24 Maximum Arterial Velocity: 47.1 ± 11.4 Maximum Portal Velocity: 63.3 ± 23.2 Portal flow: 1.81 ± 0.76	RI: 0.60 ± 0.21 Maximum arterial velocity: 57.7 ± 17.2 Maximum portal velocity: 41.4 ± 11.0 Portal flow: 1.29 ± 0.94	E: 2 patients F: 1 patient	1 death after cerebral bleeding	Median 30 Months with DUS
Zhu, X., et al., (2011)[16]	40/28	Physician choice, manufacturers included Terumo, Boston, and Cook.	**Proximal** splenic artery AVP I was used in 10 patients as the primary embolic agent, but none achieved complete occlusion as a solitary device. Additional AVP devices were required in 7 out of 10 cases and 6 of the 10 procedures also needed additional coils. In the 8 cases in which the AVP II was the primary embolic agent, complete occlusion without additional material was achieved in four procedures. One patient had a single AVP II combined with two additional coils. Two patients needed two AVP II with additional coils. One patient required two AVP II and a single AVP I as well as one coil before complete occlusion			None	0% from SAE	12 Months with CT, DUS
Zhu, X. S., et al., (2012)[17]	8/ NA	NA	NA	Portal vein volume: 76 ± 6 Portal vein velocity: 962 ± 47 Hepatic artery diameter: 2.5 ± 0.3	Portal vein volume: 55 ± 8 Portal vein velocity: 851 ± 78 Hepatic artery diameter: 3.7 ± 0.5	None	0%	CEUS
Renan Uflacker et al., (2002)[2]	11/ 9	Gianturco Coils, Cook Inc., Bloomington, IN	Deployment of 3 to 8 metal Gianturco coils, ranging from 5- to 8 mm in diameter in the **middle** part of the splenic artery.			D: 1 patient	0%	12 Months with DUS

Table 2 (continued)

Author, Year	Number of Cases with embolization / Number of Male	Type/ number of Coil or Embolic Agent	Where the embolic agents were placed	Pre- Radiologic Feature	Post-Radiologic Feature	Complications based on SIR guideline	Mortality Rate	Mean F/U & Imaging modality
S Sevmis et al., (2006)[18]	10/ 8	Gianturco coils, Boston Scientific, Cork Ltd, Cork, Ireland Stent from Wallstent, Boston Scientific, Naticks, Mass, USA	Selective catheterization of the artery, which was followed by the deployment of three to eight fibered platinum coils ranging from 5 to 8 mm in diameter. One patient with splenic arterial steal syndrome was treated with the placement of an endoluminal stent. All patients were treated with the coil embolization of **distal** branches of the splenic artery.			None	1 pt (died from sepsis due to retransplant)	10.2 ± 7.2 Months with DUS
Uslu et al., (2012)[19]	20/ 15	NA	Embolization material was placed in the **proximal** portion of the splenic artery.	Intraoperative: PSV: 53, RI: 0.73, PVV: 9 Preprocedural: PSV: 47, RI: 0.67, PVV: 88	PSV: 65 RI: 0.64 PVV: 72	None	0%	DUS

Table 2 (continued)

Author, Year	Number of Cases with embolization / Number of Male	Type/ number of Coil or Embolic Agent	Where the embolic agents were placed	Pre- Radiologic Feature	Post-Radiologic Feature	Complications based on SIR guideline	Mortality Rate	Mean F/U & Imaging modality
M. H. Maurer et al., (2010)[20]	13/ 9	The plugs ranged in diameter from 6 to 16 mm, and they were introduced through femoral ($n=9$), axillary ($n=3$), or brachial ($n=1$) access using a 5–8 F guiding catheter Three of the 13 patients required two AVPs to achieve complete occlusion 2 AVP4 (1 / patient) and 11 AVP2 (3 of the patients had 2 placed)	Embolization of the **proximal** third of the splenic artery using the AVP.			None	2 pt (1 died from multiorgan failure after a severe pulmonary infection 5 weeks after embolization, and 1 died 5 months after embolization from unstoppable stomach bleeding primarily based on low thrombocytes after liver transplant failure.	8.02 Months with CT
Cristiano Quintini et al., (2008)[1]	4/3	Gianturco coils	Deployed in the **proximal** portion of the SA	RI: Case 1: POD1: 0.8 POD 4: 1.0 Case 2: 1.0 Case 3: 1.0 Case 4: POD 1 :0.7 POD 2: 0.83	RI: -Case 1) 0.6 -Case 2) 0.72 -Case 3) 0.86 -Case 4) 0.68	None		DUS

Femoral A.: Femoral Artery, F/U: Follow Up, N/A: Data Not Available, CA: Celiac Axis, CHA: Common Hepatic Artery, SA: Splenic Artery, PSV: Peak Systolic Velocity, PVV: Portal Venous Velocity, DUS: Doppler Ultrasound, CEUS: Contrast-Enhanced Ultrasound, Q-DSA: Digital Subtraction Angiography. SIR Complication Guidelines: Minor Complications: A. No therapy, no consequence B. Nominal therapy, no consequence; includes overnight admission for observation only. Major Complications: C. Require therapy, minor hospitalization (< 48 h) D. Require major therapy, unplanned increase in level of care, prolonged hospitalization (> 48 h) E. Permanent adverse sequelae

F. Death. * Reported complications were based on SIR classification post-coil embolization ($p=0.02$) [19]. Saad et al. used DUS and angiography, showing increased hepatic arterial flow post-splenic artery occlusion [20]. Li et al.'s study revealed reduced portal venous velocity (87.9 cm/sec ± 25.2 to 43.1 cm/sec ± 17.7; $P<0.001$) post-SAE [18].

Contrast-enhanced ultrasound (CEUS)

Contrast-Enhanced Ultrasound (CEUS) revolutionizes hepatic artery imaging through micro or nanobubble administration [22, 23]. It outperforms Doppler Ultrasound (DUS), excelling in visualizing vascular structures, especially in severely constricted hepatic arteries. This distinction proves crucial in distinguishing occlusive from non-occlusive diseases.

For Non-Occlusive Hepatic Artery Hypoperfusion Syndrome (NOHAH) post-liver transplant, CEUS featured in one study with 8 patients [24]. Zhu et al. employed CEUS when Color Doppler Flow Imaging (CDFI) showed weak or absent hepatic artery signals. CEUS confirmed NOHAH using specific criteria: a distinctive peak in contrast enhancement signal and delayed, low wash-in contrast enhancement, rectifying initial misdiagnoses of hepatic artery thrombosis. Post-SAE, CEUS gauged treatment efficacy by revealing reduced portal vein contrast-enhanced blood flow, signaling the decline in high portal flow seen in NOHAH. CEUS's proficiency in visualizing challenging vascular scenarios makes it invaluable for post-liver transplant hepatic artery assessment [24].

Celiac angiography/digitally subtracted angiography

Celiac angiography, often coupled with digitally subtracted angiography (DSA), is helpful in diagnosing Non-Occlusive Hepatic Artery Hypoperfusion Syndrome (NOHAH) [8, 10, 20]. This method offers direct visualization of hepatic and splenic artery blood flow, with qualitative criteria such as delayed hepatic artery filling and increased splenic artery filling confirming NOHAH [20]. Evaluating splenic artery embolization (SAE), these techniques monitor changes in blood flow patterns. Successful SAE restores balanced hepatic and splenic artery flow [10, 20]. Kim et al. found congruence between angiography and computed tomography post-embolization [10]. While quantitative NOHAH values are lacking, DSA serves as the gold standard for diagnosing hepatic arterial hypoperfusion [10, 20]. Celiac angiography and DSA play important roles in NOHAH diagnosis and post-treatment evaluation [10, 20].

Treatment

In NOHAH treatment, Splenic Artery Embolization (SAE) is the preferred choice to redirect splenic flow to the hypoperfused hepatic artery [1, 6, 7, 11, 15, 19, 25]. When deploying coils in the proximal or central splenic artery, there's minimal risk of splenic infarction, unlike the distal position where collaterals remain intact [1, 6, 11, 20]. Various embolic materials are employed, including coils and Amplatzer Vascular Plugs (AVPs). AVPs offer shorter occlusion times and lower radiation doses but have limitations due to vessel sensitivity. Coils have a broader range of applications but can migrate, require more time, and may necessitate multiple coils for symptom relief. Among 240 treated patients, 80.8% received coils, 16.3% AVPs, and a few other treatments were reported [11, 12, 14, 15, 17, 20].

Comparing AVP and coil procedures, no significant difference in duration was observed (53.8 min in the coil group vs. 43.7 min in the AVP group, $p=0.16$). However, AVP reduced procedure time, leading to lower average radiation doses (1,309 mGy in the coil group vs. 842 mGy in the AVP group, $p=0.04$) [21]. Small diameter and tortuosity in the splenic artery could induce vascular spasm with the 5-Fr sheath for AVP placement [17]. Most patients required only one plug for complete occlusion (76.9%) [17].

SAE complications encompass splenectomy, portal vein thrombosis, re-OLT, and reoperation [18]. Out of 240 cases, there was a 4.58% mortality rate [1, 14, 15, 17, 18]. Among these, 5.8% required re-transplantation, and 0.7% needed splenectomy [1, 17, 18]. Applying SIR-defined categories, 32 complications arose: 9.3% were SIR-category A, 9.3% were SIR-category C, and 56.2% were SIR-category D. A few cases of SIR-category E and F complications were linked to AVPs, while the rest were associated with coils. Notably, a single study accounted for 5 out of 6 category F complications, as coil placement in the distal splenic artery led to complications, prompting a shift to more proximal coil placement, proving it as a safer NOHAH treatment [1].

Discussion

The journey to understand Non-Occlusive Hepatic Artery Hypoperfusion Syndrome (NOHAH), initially termed Splenic Steal Syndrome, has seen significant progress in diagnostics and treatments since its first report by Manner et al. in 1991 and its renaming by Langer et al. in 1992 [4, 5]. The redefinition of NOHAH as a nonocclusive hypoperfusion condition by Quintini et al. in 2008 and Saad in 2012 marked a crucial turning point, highlighting the significance of early detection and intervention [6, 7, 26].

In diagnosing NOHAH post-liver transplantation, Doppler Ultrasound (DUS) serves as a crucial initial screening tool due to its efficiency and non-invasiveness [8]. DUS helps identify key NOHAH mechanisms, including high portal flow, graft-to-artery size discordance, and pre-existing splenomegaly in OLT recipients. The effects of NOHAH on hepatic artery perfusion include increased portal vein velocity, decreased volume, and elevated vascular resistance. This is indicated by a loss of diastolic component, a high resistive index (RI > 0.8), and reduced peak velocity (< 35 cm/s) in the hepatic artery [7, 8]. Contrast-Enhanced Ultrasound (CEUS) complements DUS, especially in cases with narrow hepatic arteries, enabling differentiation between non-occlusive hypoperfusion and occlusive diseases [22, 23]. CEUS effectively visualizes weak and delayed hepatic artery flow concurrent with enhanced portal flow, a hallmark of NOHAH [24]. Multidetector Computed Tomographic Angiography (MDCTA) and Digital Subtraction Angiography (DSA) provide additional diagnostic insights. They reveal splenic artery vasodilation and hepatic artery narrowing, helping rule out occlusive events. MDCTA can predict pre-transplant NOHAH based on specific arterial diameter criteria [8]. However, the invasive nature of DSA and its limitations in real-time hemodynamic assessment reinforce DUS as a practical and patient-friendly choice [8].

Treatments may encompass conventional surgical approaches such as splenectomy or minimally invasive techniques like embolization of the splenic artery. Prophylactic treatment has gained support, with Mogl et al. highlighting its safety and suggesting its consideration for all Orthotopic Liver Transplant (OLT) patients to reduce the risk of graft loss due to NOHAH [19]. The most effective treatment method is embolization of the splenic artery, although it does carry some potential complications, including postembolization syndrome, affecting approximately 30% of patients with symptoms like fever, nausea, vomiting, and abdominal pain. Less common complications involve infections, renal, pulmonary, or liver function damage, and portal vein thrombosis [27]. The rate of complications and the duration of hospitalization post-embolization can be influenced by the extent of spleen involvement during the procedure. Hadduck and McWilliams observed that extensive embolization affecting more than 70% of the splenic volume resulted in higher complication rates, while less extensive embolization (below 50% splenic volume) correlated with lower rates of postembolization syndrome, shorter hospital stays, and no serious complications [28]. Thus, a cautious approach with the possibility of repeated embolization until clinical improvement is achieved is often preferred.

Conventional surgical approaches, including splenic artery banding, ligation, and splenectomy, redirect splenic artery flow to the hepatic artery. Splenic artery banding involves creating artificial stenoses, while ligation severs the vessel. Splenectomy is reserved for cases with additional pathologies, like splenic artery aneurysm, due to its higher risk of complications, including portal vein thrombosis or infections [1]. Splenectomy carries a complication rate of 13.3%, while splenic artery banding has a lower rate of 2.4%, making it safer [1]. Prophylactic splenic artery banding may benefit high-risk NOHAH patients with factors like splenomegaly, enlarged splenic artery relative to the hepatic artery, or hypersplenism [1]. However, predictive factors need further research as current indicators like the MELD score lack statistical significance [29].

Splenic Artery Embolization (SAE) emerges as the premier choice for directing splenic flow to the hypoperfused hepatic artery in NOHAH [1, 6, 7, 11, 15, 19, 25]. Notably, minimal complications arise when coils are strategically placed in the proximal or central splenic artery, preserving collateral circulation [1, 6, 11, 20].

In the realm of SAE, various embolic agents come into play, including coils and Amplatzer plugs (AVPs). Delving into studies under review, we find that 10 exclusively focused on coils, 2 on AVPs, 2 on both, and 1 integrated coil embolization along with an endoluminal stent, encompassing 198 patients treated with coils alone, 43 with plugs alone, 2 with a combination, and 1 with a stent. These differences will be explored in detail, but first, let's consider the overarching benefits and risks of SAE for NOHAH treatment.

SAE stands as a minimally invasive technique to redirect splenic artery flow to the hepatic artery, mitigating the need for associated surgical complications, notably spleen removal during splenectomy. Stenting enters the picture when NOHAH co-occurs with stenosis, offering an alternative avenue for intervention [3]. The overall complications associated with SAE are relatively few, especially when performed with meticulous embolic agent placement. In a pivotal study by Nüssler et al., comparing therapeutic approaches for NOHAH, they explored 18 splenectomy cases, 9 banding procedures, and 29 embolizations. Remarkably, splenectomy exhibited a mortality rate with re-OLT in 2 cases, while banding showed no complications. Conversely, among SAE patients, 7 required re-OLT, with 4 succumbing to graft failure and 1 to multiorgan failure and sepsis. Notably, all SAE complications stemmed from distal coil placement, obstructing splenic collaterals and leading to splenic infarction and abscesses. Subsequent central coil placement in other patients revealed no complications, firmly establishing proximal SAE as a secure and minimally invasive NOHAH treatment option [1]. It's worth noting that this single study contributed to 5 out of 6 category F complications, and excluding them underscores the safety of proximal SAE. However, contrary to Nüssler et al.'s findings, another study measuring liver function test values post-SAE of both proximal and distal splenic arteries showed no statistically significant differences after one month, indicating a self-adjusting equilibrium. Nevertheless, a statistically higher thrombocyte count was observed 3 days after proximal artery intervention, supporting the consensus that embolization at this site reduces infarction risk and improves perfusion. Over the long term, both proximal and distal embolization exhibited similar outcomes due to autoregulation. Comparing these studies remains challenging due to differences in follow-up periods and the lack of post-SAE imaging in the latter, signaling the need for further research in this area [30, 31].

Amplatzer plugs (AVPs), when compared to coils, showcase advantages such as shorter occlusion time and reduced radiation exposure. AVPs even allow for single-plug treatments, although supplemental coil use is often necessary. However, AVPs are more sensitive to kinking and narrow vessels, limiting their applicability compared to the versatile coils. Coils may find a wider range of use, but they carry a higher migration risk, require longer placement times, and often demand multiple coils for symptom relief. Zhu et al.'s observations indicated that AVPs, in conjunction with coils, are better suited for spleen trauma due to their shorter mean occlusion time, while coils are preferred for NOHAH and portal hypertension. However, their values yielded statistically insignificant differences, emphasizing that the choice between coils and plugs hinges on specific clinical scenarios and provider preferences [21].

Conclusion

NOHAH management involves diverse strategies. While DUS and CEUS aid diagnosis, arteriography remains the definitive method. Splenic artery banding prevents complications, while splenectomy addresses specific issues.

Simultaneous SAE during arteriography, using coils or AVPs in the proximal splenic artery, ensures safety and preserves liver function. These techniques collectively advance NOHAH management, holding the potential for improved patient outcomes.

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Declarations

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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