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Case Report

Inhaled nitric oxide as a salvage therapy for refractory hypoxemia in the post-transplantation period of hepatopulmonary syndrome: An explorative report of three cases

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ABSTRACT

Liver transplantation (LT) is the only effective treatment for hepatopulmonary syndrome (HPS). Moreover, perioperative refractory hypoxemia (pRH) is a prevalent life-threatening condition and has extremely limited treatment options. Here, we report three patients with HPS who experienced pRH after LT and were consecutively treated with different salvage therapies, ephedrine inhalation, intravenous use of methylene blue with nitric oxide (NO) inhalation, and NO inhalation alone. The results showed that unresolved severe hypoxia may induce fatal morbidity such as early biliary leakage and acute kidney injury. Early initiation of NO inhalation, rather than ephedrine, can significantly improve oxygenation in patients with pRH and may help prevent hypoxia-related complications. Therefore, based on the response to these exploratory salvage treatments, we further demonstrate the unique ventilation-perfusion mismatch pathophysiology in specific lung regions during pRH in HPS. We propose that early inhalation of NO is an important treatment option to rescue severe hypoxia in patients with HPS during the perioperative period of LT.

1. Introduction

Hepatopulmonary syndrome (HPS) is a prevalent complication associated with end-stage liver disease, and liver transplantation (LT) is the only definitive treatment for HPS.[1,2] However, approximately 12% of patients with HPS experience perioperative refractory hypoxemia (pRH) during LT. This condition is characterized by the inability to sustain a pulse oxygen saturation (SpO_2) of >88% despite the administration of 100% oxygen.[3] In patients with HPS, pRH is a significant threat to early postoperative survival. Moreover, the pathogenesis of pRH is poorly understood, and effective treatment options are currently lacking.

Pulmonary vascular dilation is the primary pathophysiological mechanism underlying hypoxemia in patients with HPS and can lead to intrapulmonary shunting. However, perioperative factors such as fluid overload, surgical stress, and prolonged bed rest can significantly exacerbate ventilation-perfusion (V/Q) mismatch, resulting in a rapid decline in blood oxygen levels. In addition to restrictive fluid management and pulmonary or physical rehabilitation, different vasoactive drugs are prescribed to prevent hypoxemia in patients with HPS during the perioperative period. However, the mechanisms of action and effectiveness of these drugs remain unexplored.[4]

Thus, this case report aimed to present explorative management strategies in three patients with HPS undergoing LT to elucidate the nature of the outcomes and the therapeutic value of nitric oxide (NO) in pRH.

2. Case report

2.1. Ethical approval

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of The Third Affiliated Hospital

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of Sun Yat-sen University (approval No. CR2024-016-01). All three patients or their parents provided written informed consent for clinical data review, analysis, and publication.

2.2. Case 1

A well-developed 4-year-old girl, weighing 17 kg, was in the waiting list for LT due to decompensated cirrhosis. She has been diagnosed with biliary atresia at birth and underwent the Kasai procedure at 6 months of age. Postoperatively, she gradually developed recurrent decompensation in the next 3 years.

Approximately one year prior to her clinic visit, she had progressed platypnea-orthodeoxia syndrome with digital clubbing. HPS was diagnosed by blood gas analysis (BGA) with an arterial oxygen pressure (PaO_2) of 45 mmHg, and alveolar-arterial oxygen difference (A-aDO_2) of 73 mmHg while breathing room air, and a 56% fraction of intrapulmonary shunt by technetium-99m-labeled macroaggregated albumin (99mTc-MAA) lung perfusion scanning.

The patient had a PELD score of 7, but due to a special exception related to HPS, she received a whole liver transplant from an ABO-compatible donor on October 4, 2019, following brain death of the donor. The cold ischemia time was 9.5 h. Before anesthetic intubation, her SpO_2 was 65%, with a 100% fraction of inspired oxygen (FiO_2), and fluctuated between 82% and 94% in the pre-anhepatic phase. In the next 34 min of the anhepatic phase, SpO_2 dropped significantly after inferior vena cava (IVC) clamping and briefly increased to 97%–99% in the neohepatic phase (Fig. 1A, blue line). Then, SpO_2 gradually declined to 84% within the first hour after surgery, and this level remained until in the intensive care unit (ICU).

Initially, in the transplant ICU, under an FiO_2 of 100% ventilation and conservative fluid management, SpO_2 was only maintained between 90% and 95%. After awakening from anesthesia, the patient exhibited no signs of dyspnea, and graft function improved instantly. However, FiO_2 could not be reduced, and SpO_2 decreased to 83%–85%. After the administration of nebulized ephedrine (15 mg in 5 mL of normal saline, qid), SpO_2 slightly improved to 90% temporally; however, the PaO_2/FiO_2 ratio did not significantly change. Because SpO_2 could be maintained at approximately 90% over the next 2 days, the patient was weaned off the ventilator on postoperative day (POD) 3. Subsequently, she received high-flow nasal cannula (HFNC) oxygen therapy (flow rate, 34 L/min, FiO_2, 70%–80%) combined with nebulized ephedrine after extubation, maintaining an SpO_2 of 90% (Fig. 1B, blue line). In addition to coughing during ephedrine nebulization, episodes of cyanosis, and increased respiratory and heart rates during rehabilitation therapy, the patient showed no signs of dyspnea at rest. The patient was transferred to the ward for further treatment on POD5.

During ward treatment, the patient could not tolerate ephedrine inhalation and showed significant coughing reactions, irritability, and gradually worsening oxygenation. By POD10, SpO_2 could not be maintained >85% even with high FiO_2 (90%), and the patient had high fever and abdominal pain. Emergency computed tomography (CT) revealed bile leakage and secondary abdominal infection. Despite adequate drainage, the patient experienced severe hypoxia, which rapidly progressed to septic shock, and she died on the next day.

2.3. Case 2

A 64-year-old man with decompensated hepatitis B cirrhosis, complicated by progressive platypnea-orthodeoxia and oliguria, was referred to our center for LT after 2 months of unsuccessful oxygen and diuretic therapies. Arterial BGA showed a PaO_2 of 56 mmHg, A-aDO_2 of 72 mmHg and hemoglobin oxygen saturation (SaO_2) of 88% in room air. Transthoracic echocardiography (TTE) indicated no significant pulmonary hypertension. However, an intrapulmonary shunt was confirmed by cardiac contrast-enhanced ultrasonography (CEUS) with agitated saline and 99mTc-MAA lung perfusion scanning (intrapulmonary shunt rate of 55%). In addition, the patient was diagnosed with nephrotic syndrome, with >2 months of persistent oliguria.

After waiting for 1 month for pretransplant rehabilitation, the patient underwent LT on May 23, 2021. The donor risk index was 1.09. The cold ischemia time of the graft was 6 h, the anhepatic time was 48 min, and the intraoperative blood loss was 1000 mL. During the operation, there was a transient increase in SpO_2 to 99% in the early neohepatic phase, followed by a decrease to 90%–92% (Fig. 1A, red line). On POD1, early weaning and extubation were performed in the ICU, maintaining SpO_2 at 95% using HFNC at a flow rate of 50 L/min and FiO_2 of 65%. However, in the following hours, the SpO_2 dropped to 88% (PaO_2: 47 mmHg, A-aDO_2: 378 mmHg), despite increasing HFNC flow and FiO_2 to 60 L/min and 80% (Fig. 1B, red line). No sign of pneumonia, pulmonary edema or pleural effusion by radiologic examinations. Concurrently, oliguria was checked without apparent hypovolemic acute kidney injury (AKI). Because of severe respiratory distress, mechanical ventilation was reinitiated on POD3. Over the next day, despite high ventilator FiO_2

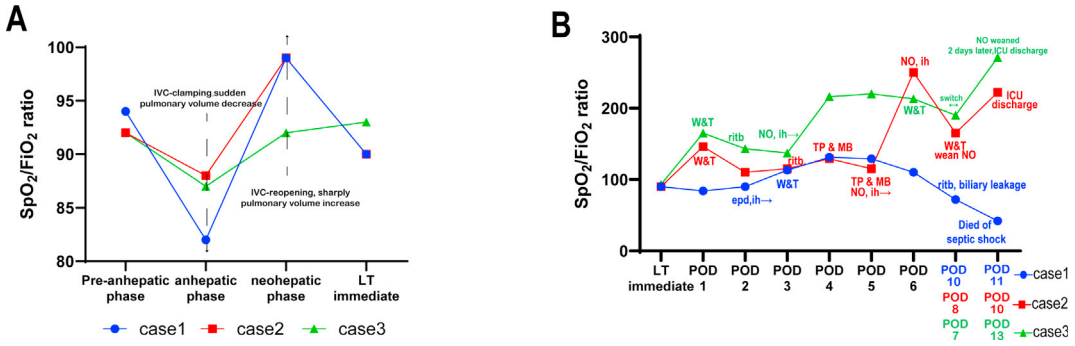

Fig. 1. Perioperative management of three patients with HPS undergoing liver transplantation (LT). (A) SpO_2/FiO_2 changes during LT. IVC clamping in the pre-anhepatic phase suddenly reduced pulmonary perfusion, causing a decrease in SpO_2. However, SpO_2 sharply increased in the early neohepatic phase when the IVC is reopened. **(B)** SpO_2/FiO_2 changes in the early period after LT. Ephedrine inhalation increased oxygenation slightly but induced intolerable adverse effects and resulted in biliary leakage in Case 1 (blue line). In case 2 (red line), TP was transiently effective, and MB (iv.) was ineffective. iNO increased oxygenation rapidly, promoting early extubation. Early initiation of iNO quickly increased SpO_2 and facilitated extubation and ICU discharge in Case 3 (green line). Abbreviations: epd,ih, ephedrine inhalation; FiO_2, fractional inspired oxygen; HPS, hepatopulmonary syndrome; ICU, intensive care unit; iNO, inhaled nitric oxide; IVC, inferior vena cava; MB, methylene blue; NO, nitric oxide; POD, postoperative day; ritb., reintubation; SpO_2, peripheral capillary oxygen saturation; TP, Trendelenburg position; W&T, weaning and extubation.

settings of up to 80%, the patient's oxygenation worsened (PaO_2 dropped to 69 mmHg, A-aDO_2 reached 457 mmHg). Because of persistent anuria, continuous renal replacement therapy (CRRT) was initiated.

In the next 2 days, repeated Trendelenburg positioning (TP) and intravenous methylene blue (MB) 3 mg/kg were administered. TP induced a transient increase in SpO_2. MB was ineffective but worsened oxygenation, which significantly increased the central venous pressure by 3–5 mmHg. Thus, on POD5, inhaled nitric oxide (iNO) was administered at a concentration of 20 parts per million (ppm, 1 ppm = 1.339 mg/m^3) using a NO supply device (BG-95, Foshan Analytical Instrument Co., Ltd.). The injector module was connected directly to the dry side of the humidifier chamber. NO gas flow was set according to the tidal volume, respiratory rate, and inspiration/expiration ratio on a ventilator. The FiO_2 was set at 40%, and the SpO_2 dropped to 93% at the beginning. After 30 min, his SpO_2 improved rapidly to 100% (Fig. 2A, red line in upper panel). In the next several hours, urine output increased nearly tenfold (from 5 to 15 mL/h to 110–160 mL/h). Even when iNO was reduced to 13 ppm, PaO_2/FiO_2 (Fig. 2A, red bar in lower panel) and urine output (Fig. 2A, blue line in lower panel; Fig. 2B, bubble size) were maintained. Over the next 24 h, he could tolerate physical therapies well and showed rapid improvement in transplant liver function and sustained oxygenation (PaO_2: 70–93 mmHg, A-aDO_2: 149–191 mmHg). Thus, CRRT was promptly discontinued. Over the next 2 days, iNO was gradually reduced to 5 ppm and successfully weaned off on POD8, along with extubation. Using HFNC with FiO_2 at 60%, his SpO_2 easily remained >99%. On POD10, when switched to a standard nasal cannula at 6 L/min, his oxygenation remained good (PaO_2: 132 mmHg, A-aDO_2: 173 mmHg), and he was discharged from the ICU. He was discharged on POD42, with progressive recovery of physical function at home and complete cessation of oxygen therapy dependence after 6 months.

2.4. Case 3

A 6-year-old boy with a 2-year history of cirrhosis of unknown origin showed progression to acute-on-chronic liver failure over the past 6 months and was listed for LT at our hospital. During the waiting period, he experienced recurrent respiratory infections, progressive orthodeoxia and clubbing. His PELD score was 21. Arterial BGA in a seated position revealed a PaO_2 of 43 mmHg and an A-aDO_2 of 77 mmHg. Intrapulmonary shunt was confirmed by 99mTc-MAA lung perfusion scanning (56%) and cardiac CEUS with agitated saline. Preoperative chest imaging was clear on CT.

After 6 months, the child received a split left lateral lobe liver graft on November 11, 2022. The LT proceeded smoothly, with 200 mL of blood loss, cold ischemia time of 4 h, and anhepatic phase of 45 min. After reperfusion, under 100% FiO_2, his SpO_2 was maintained at 93%–95% until the end of the operation (Fig. 1A, green line).

Postoperatively, under 60% FiO_2, his SpO_2 was 95%–98%; however, his arterial PaO_2 was only 50–60 mmHg. He has no dyspnea and explicit hemodynamic disorders. On POD1, ventilation was weaned off, and sequential HFNC was initiated with 60% FiO_2 after extubation. Subsequently, he exhibited profound desaturation, with FiO_2 gradually increasing to 100%, while SpO_2 maintaining at only 82% and PaO_2 at 43 mmHg. He manifested with significant dyspnea and cyanosis but without any abnormality on chest imaging. However, the CEUS with agitated saline still revealed a significant increase in intrapulmonary shunt. On POD2, reintubation and mechanical ventilation were initiated with high FiO_2 at 80% and positive end-expiratory pressure at 8 cm H_2O, maintaining SpO_2 at 88% but with a PaO_2 of only 46 mmHg and central venous oxygen saturation ($ScvO_2$) of 58.9%. Concurrently, graft function significantly deteriorated. Inhaled NO therapy was initiated at 20 ppm, leading to a significant improvement in oxygenation within 30 min, allowing a reduction in FiO_2 to 45% while maintaining good SpO_2 at 94%–97%. The next day, with 40% FiO_2, the PaO_2 increased to 65 mmHg and SpO_2 reached 98%–100% (Fig. 1B, green line). Over the next 2 days, the NO concentration gradually reduced (20 to 10 to 5 to 1 ppm), and the patient was weaned off from mechanical ventilation. On POD7, extubation was successful, and HFNC connected with aerosolized treprostinil 0.1 mg by Aerogen® Ultra every 8 h was initiated, maintaining SpO_2 at 88%–95% with 45%–60% FiO_2, without respiratory distress and chest imaging abnormalities. Graft function was also gradually recovered. However, oxygenation improvement could only be maintained during treprostinil nebulization and rapidly dropped after stopping (Fig. 1B, green line). Four days later (POD11), continuous NO inhalation at 1 ppm was

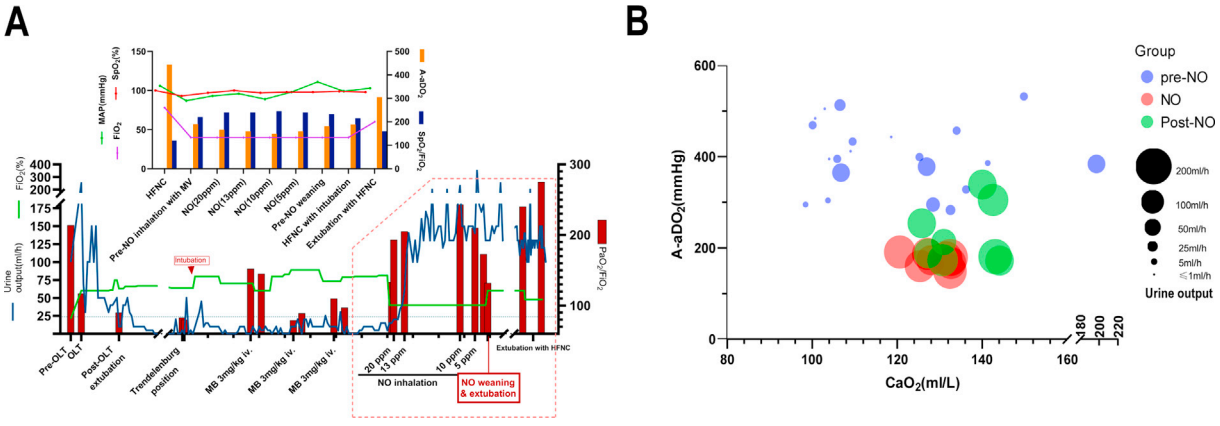

Fig. 2. Explorative findings in Case 2. (A) Oxygenation and kidney function improved by iNO in Case 2. Refractory hypoxemia occurred on POD3 (referring to Fig. 1B red line), followed by invasive MV. TP and MB achieved neither a sustainable oxygenation improvement (PaO_2/FiO_2 ratio, red bar in lower panel), nor the urine output (green line in the lower panel) increase. After the initiation of iNO, both oxygenation and kidney function were quickly improved and maintained to iNO and MV weaning. Stable MAP and reduced FiO2 (lower risk of hyperoxic lung injury) accompanied with SpO_2/FiO_2 increase after iNO therapy, implies the safety of iNO. **(B)** NO improved the V/Q ratio and oxygen delivery accompanied by increased urine output in Case 2. V/Q ratio, A-aDO_2, increased distinctly after iNO, followed by CaO_2 and urine output increase. 1 ppm = 1.339 mg/m^3. Abbreviations: A-aDO_2, alveolar-arterial oxygen difference; CaO_2, arterial oxygen content; FiO_2, fractional inspired oxygen; HFNC, high-flow nasal cannula; iNO, inhaled nitric oxide; MAP, mean arterial pressure; MB, methylene blue; MV, mechanical ventilation; NO, nitric oxide; PaO_2, arterial partial pressure of oxygen; SpO_2, peripheral capillary oxygen saturation; TP, Trendelenburg position.

restarted along with HFNC, rescuing SpO_2 >95% with 35% FiO_2 sustaining. On POD13, NO was successfully discontinued. On POD15, HFNC was withdrawn, and the child was transferred out of the ICU. Two months later, he was weaned off oxygen and discharged. At the 6-month follow-up, CEUS with agitated saline showed a significant reduction in intrapulmonary shunt, and 1 year after LT, he returned to school normally.

3. Discussion

This study presents explorative management strategies and their outcomes in three consecutive patients with HPS who experienced pRH after LT. Based on these cases, we propose the early inhalation of vasodilators (NO) as a salvage therapy to rapidly improve severe perioperative hypoxemia and potentially prevent hypoxia-related complications.

Ephedrine is a sympathomimetic α- and β-adrenergic receptor agonist that can dilate bronchi and constrict blood vessels. It has been used for treating lower respiratory tract diseases, such as asthma and bronchitis by its pulmonary vasoconstriction properties,[5] and studies in China have reported the use of ephedrine inhalation in treating HPS.[6,7] However, in this study, the first case of ephedrine inhalation for vasoconstriction treatment was unsuccessful. These might be explained by several reasons. First, inhaled vasoconstrictors are more likely to enter the upper or well-ventilated anterior lung segments. More dilated vessels are commonly found in the dorsal or lower lobes in patients with HPS,[8] where ventilation is relatively insufficient because of hypostasis or atelectasis during the perioperative period, resulting in poor treatment effects. Second, aerosol inhalation through conventional devices can be mostly intercepted in the upper respiratory tract, making it difficult to reach the deeper alveoli. Furthermore, given the high rate of adverse effects, the Global Initiative for Asthma and the National Asthma Education and Prevention Program have not recommended ephedrine for the treatment of asthma since 2007. Therefore, the administration of inhaled ephedrine for perioperative hypoxia in patients with HPS requires extreme caution.

In recent years, with a better understanding of the pathophysiology of HPS, several strategies have emerged. For example, using TP to increase blood flow to the upper lungs with normal ventilation improves the V/Q ratio. In this report, all three patients achieved a transient improvement in oxygenation. It revealed that acute pulmonary circulation congestion in the early neohepatic phase mimicked the same perfusion effect like TP. However, this effect quickly disappeared with fluid redistribution. Thus, positional and volume congestive interventions cannot provide lasting benefits but may be harmful because of the risk of pulmonary complications.[9]

MB is an inhibitor of guanylate cyclase and nitric oxide synthase, and its intravenous injection can reduce the response of low-resistance vessels to NO within minutes, alleviating the vasodilatory effects of NO in patients with HPS.[4] Therefore, intravenous MB therapy may effectively reduce pulmonary vascular shunting by constricting dilated pulmonary vessels. However, intravenous MB therapy can also affect the monitoring of blood oxygen saturation, making it difficult to observe treatment effects.[10]

For Case 2, positioning and intravenous MB administration did not improve oxygenation significantly but increased cardiac preload, indicating a limited effect of MB in this scenario. Therefore, NO inhalation was introduced, which exerted a rapid and significant effect. For Case 3 with severe hypoxia, NO inhalation therapy was directly implemented, and switching to treprostinil inhalation resulted in similar effects. However, the effect of treprostinil at a draught is short-lived, whereas continuous NO inhalation showed persistent effect.

In the report, imaging and airway secretions did not reveal significant abnormalities when severe hypoxia occurred in the three patients with HPS postoperatively, indicating that these factors may not be the main cause. The persistent intrapulmonary shunt formed by pulmonary vasodilation in gravity-dependent areas remains the basis for postoperative hypoxia.[8] Perioperatively, various stress factors such as surgical trauma, blood loss, and reperfusion injury can induce pulmonary vasoconstriction, further increasing dead space ventilation in non-gravitationally dependent areas.[3,11] Inhaled vasodilators can act effectively in these well-ventilated areas, whereas gravity-dependent areas with remodeled pulmonary vasculature are less responsive to vasodilation.[11] Therefore, NO inhalation therapy might significantly improve the V/Q ratio.

Insufficient oxygen delivery may also be related to various postoperative complications.[12] A large-scale randomized controlled trial demonstrated that perioperative hypoxia significantly increases the risk of surgical site infections.[13] An increase in intrapulmonary shunting is correlated with a higher incidence of biliary leakages, potentially attributable to compromised oxygen delivery to the bile ducts.[14–16] This finding is consistent with the Case 1 in the report, where the patient had an abdominal infection caused by impaired healing at the biliary-enteric anastomosis, a complication exacerbated by persistent hypoxia. Most patients exhibit high systemic oxygen consumption early after graft reperfusion; thus, maintaining appropriate oxygen delivery may help in the recovery of the graft and vital organ functions. Kim *et al.*[17] reported that oxygen delivery levels during LT are closely related to the occurrence of postoperative AKI. Shiba *et al.*[18] reported that early systemic oxygen consumption after LT is related to graft function recovery and recipient outcomes.[19] Thus, the oxygen supply-consumption imbalance is common in the early postoperative period of patients with HPS having low arterial oxygen levels. Furthermore, NO inhalation therapy not only improves pulmonary blood flow but also reduces graft ischemia-reperfusion injury.[20] The treatment processes of Case 2 and Case 3 indicate that improving blood SpO_2 through the inhalation of vasodilators significantly parallels the recovery of kidney or graft function. However, further increasing oxygen delivery may not be beneficial because excessive oxygen therapy early after LT can be harmful.[21] Therefore, the oxygen concentration after inhaling vasodilators was reduced to meet the appropriate oxygen supply for the body. NO inhalation should be initiated before the onset of systemic oxygen delivery failure. This early intervention is crucial because it cannot guarantee survival without the potential need for extracorporeal membrane oxygenation support.[22]

The limitations of this study include the lack of direct evidence of the changes in the V/Q ratio before and after NO inhalation therapy based on clinical pathophysiological parameters. Electrical impedance tomography monitoring can reflect real-time changes in ventilation and blood flow in different lung regions and might help further confirm our hypothesis.[23] In addition, this report is based on a case analysis of three consecutive cases; thus, further controlled studies in a broader population are required. However, in Case 2 and Case 3, inhaled vasodilators (NO or treprostinil) showed strong association with oxygenation improvement, which is in line with the results of a previous study,[24] suggesting that vasodilator inhalation therapy might be at least superior to existing conservative treatments.

In summary, this report indicates that perioperative inhalation of vasodilators, such as NO, may provide beneficial effects for patients with HPS undergoing LT. The findings of this report underscore the need for careful monitoring and individualized treatment plans to address the complex challenges of perioperative hypoxia in this patient population. More studies are required to validate these findings and optimize treatment strategies for patients with HPS.

Data availability statement

The data presented in the case report are available from the corresponding authors upon reasonable request.

Authors' contributions

Haijin Lyu, Xiaomeng Yi and Yunshan Zou contributed equally to this work and should be considered co-first authors. **Haijin Lyu:** Writing – review & editing, Writing – original draft, Validation, Investigation, Conceptualization. **Xiaomeng Yi:** Investigation, Data curation. **Yunshan Zou:** Resources, Investigation. **Pinglan Lu:** Methodology, Investigation. **Lijuan Li:** Methodology, Investigation. **Jianrong Liu:** Methodology, Investigation. **Senbiao Chen:** Methodology, Investigation. **Xuxia Wei:** Writing – review & editing, Writing – original draft, Supervision. **Yang Yang:** Supervision, Resources, Data curation, Conceptualization. **Huimin Yi:** Writing – review & editing, Writing – original draft, Validation, Resources, Conceptualization.

Declaration of competing interest

Yang Yang is an executive associate editor for *Liver Research* and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

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