Peer Review File

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Review Comments:

Reviewer A:

Great case series covering a very important and under-recognized entity. Only minor revisions suggested.

1. The CT images were somewhat redundant. I would suggest potentially eliminating one from report.

Reply: We have modified our text as advised. Figure 1 has been removed.

2. Some Ultrasound or echocardiographic images would be helpful, since Ultrasound or echocardiography would be the first line modalities used in practice and would educate the readers on how to recognize sonographic signs of PDV.

Reply: Two ultrasound images have been added to Figure 2.

3. Unclear why PDV <3 mm, or patients <2 weeks were excluded rather than followed to see if PDV truly closed or not, rather than assuming so.

Reply: The ductus venosus is an embryonic vascular structure, with failure of spontaneous closure after birth leading to PDV. After birth, the ductus venosus normally closes spontaneously within 2 weeks [reference 2,3]. It is common for ductus venosus to be present in infants less than 2 weeks of age, but based on our experience, the ductus venosus observed after birth is usually less than 3mm. Therefore, follow-up observations are necessary for the ductus venosus larger than 3mm.

4. The follow-up information was vague. It would be helpful to know any available information on the 4 patients who died, (3 of them within 2 weeks of discharge!), to learn if there are any warning signs in this patient population that would warrant keeping as inpatient as opposed to discharging. Also, the telephone follow-up was not informative at all: "parents indicated that the general condition of them are getting worse".

Reply: This section has been revised as follows (see Page 5, line119-128): Because PDV was associated

with complex CHD and other malformations in 3 patients (patients 1, 2, and 5), their parents abandoned treatment, and these 3 patients died within 1 to 2 weeks after discharge. Another patient (patient 4), in whom PDV was associated with ASD, PDA, and Abernethy II malformation, was transferred to another hospital; this patient did not undergo surgery for PDV (no other details are available) and died 15 months after discharge. The remaining 2 patients (patients 6 and 8) were followed up by telephone for 3 years after discharge from our hospital. The parents of these patients reported that they were hospitalized 2-3 times a year at a local hospital for coughing, wheezing, fever, and other problems, with the frequency increasing each year; however, at the time of writing, these 2 patients have still not undergone surgical treatment for PDV. Patient 8 underwent surgical treatment for cerebrovascular malformation in another hospital 1 year ago.

5. Detailing some of the clinical parameters and lab derangements may be useful, in a table or within the text, such as pulse oximetry to reflect degree of hypoxemia, or which cardiac enzymes are elevated (especially that some cardiac enzymes are very nonspecific in newborns), hepatic function, etc.

Reply: In Table 1, specific values have been provided for NH_4. Data on other laboratory tests (i.e. hypoxemia, hyperbilirubinemia, coagulation function, myocardial enzyme, and liver and kidney function) are unchanged. Initially, we considered presenting specific values for these items but, because each item involved multiple laboratory test parameters (e.g. liver function test includes alanine aminotransferase, aspartate aminotransferase, albumin, total bilirubin, direct bilirubin and indirect bilirubin), comprehensive evaluation of all parameters was required. Therefore, presenting the specific data would not help readers intuitively understand the result for each item. In addition, we consulted with professors of cardiology and the ICU to ensure the accuracy of the items presented.

6. A few grammatical/linguistic errors and typos. Examples: Page 3 line 9: suggest changing to "due to higher likelihood of PDV closing spontaneously". Page 4 line 14: Liver should have capital L. Page 6 line 11: high-output not high-discharge. And line 31: residual atrial septal defect not fistula. Suggest

overall tightening the English translation throughout the manuscript.

I think this is certainly worth publishing given most practitioners including me are not very familiar with this topic.

Reply: The above errors have been revised. In addition, we consulted the AME Editing Service to avoid language errors and improve readability and clarity of our manuscript.

Reviewer B:

1.currently, percutaneous closure of PDV is preferred, here not performed in any patient; reason ?

Reply: Two patients (patients 7 and 9) without coexisting malformations underwent surgical ligation of PDV in our hospital. Because these 2 patients had coagulation disorders and 1 presented with recurrent decreases in the platelet count associated with hypersplenism, we chose to ligate the PDV with a surgical procedure instead of percutaneous closure to avoid heparin-induced thrombocytopenia that could aggravate their coagulation disorders. Pulmonary artery and portal vein manometry were performed during the operation. A PDV banding test was performed before ligation, which indicated that the portal venous pressure increased transiently after banding and recovered 15 min later. The pulmonary artery pressure remained stable. The PDV was ligated (double ligation) in 1 step without clinical deterioration in 2 patients. Another patient (patient 3) underwent PDV ligation in another institute (details unclear), and then returned 6 months later to our hospital for examination.

2. hypoxemia: were pulmonary AV fistulae identified ?

Reply: In this study, only patient 8 presented as hemoptysis, and DSA showed a small bronchial artery-pulmonary fistula, but there was no hypoxemia.

3. enlarged liver: specify

Reply: Normal liver size varies with age. Our institution refer to the following literature.

[reference]. Konus OL, Ozdemir A, Akkaya, et al. Normal liver, spleen, and kidney dimensions in neonates, infants, and children: evaluation with sonography. AJR Am J Roentgenol. 1998; 171:1693-1698.

4. screening: very helpfull is colour Doppler of portal vein with centrifugal flow away from hepatic parenchyma: was this used ?

Reply: All the patients underwent the Color Doppler of abdomen. unfortunately, the shunt ratio was not measured. In addition, we know insufficient about PDV, and the PDV was missed in some patients on initial examination in the early stage.

5. explanation for myocardial enzymes: what was volume load of heart ? If not excessive, uxplaantion unlikely

Reply: This section has been revised to "Myocardial damage caused by PDV is rarely reported. In this study, abnormal myocardial enzymes were detected in 4 (44%) patients. All of these 4 patients had a larger PDV diameter, and significant dilated pulmonary artery was observed. we speculated that pulmonary hypertension leads to increased right ventricular afterload and contribute to myocardial damage" (see Page 6, line 150-153).

6. dilated Ri heart: ? PHT ?

Reply: In this study, the dilated right heart (or whole heart), pulmonary artery and LPV were observed in all patients, and the dilated MPV was observed in 8 patients. Two patients (case 7 and 9) underwent surgical ligation of PDV in our hospital. During the operation, right-sided cardiac catheterization was performed. pulmonary arterial hypertension and portal hypertension were detected in both patients.

Reviewer C:

1. ABSTRACT

Material and Method: age/sex and parameters evaluated should be specified.

Abbreviations should be avoided.

Reply: The section of Method has been revised to "Clinical, laboratory, and radiologic data of patients with PDV were analyzed retrospectively. In all, 9 patients with PDV were included in the study (7 male, 2 female; median age 1.6 years, age range 16 days -16.5 years)". (see Page 1, line 9-11).

2. INTRODUCTION

L54 – Please, clarify that only 3/9 patients underwent surgical treatment. Were clinical and radiological findings analysed before or after treatment?

Reply: Two patients underwent surgical ligation of PDV in our hospital and one patient underwent PDV ligation in another institution, then returned to our hospital for examination six months later. The clinical

and radiological findings were analyzed before treatment. The clinical findings after treatment were described simply in our manuscript. Because PDV was associated with complex CHD and other malformations in 3 patients (patients 1, 2, and 5), their parents abandoned treatment, and these 3 patients died within 1 to 2 weeks after discharge. Another patient (patient 4), in whom PDV was associated with ASD, PDA, and Abernethy II malformation, was transferred to another hospital; this patient did not undergo surgery for PDV (no other details are available) and died 15 months after discharge. The remaining 2 patients (patients 6 and 8) were followed up by telephone for 3 years after discharge from our hospital. The parents of these patients reported that they were hospitalized 2-3 times a year at a local hospital for coughing, wheezing, fever, and other problems, with the frequency increasing each year; however, at the time of writing, these 2 patients have still not undergone surgical treatment for PDV. Patient 8 underwent surgical treatment for cerebrovascular malformation in another hospital 1 year ago.

3. M&M

Patients

Inclusion and exclusion criteria are clear. Also Ethics.

Examinations

Why all patients underwent abdominal-CT? What criteria are used in their Institution to perform a CT in patients with PDV? Was abdominal-US performed prior to CT in all patients?

Reply: PDV is an extremely rare disease. As noted in the manuscript, clinicians often failed to perform targeted examinations due to the diversity of clinical symptoms and insufficient knowledge of this disease, resulting in missed diagnoses and misdiagnoses. For example, patient 7 presents in our series presented with recurrent respiratory infections and hemoptysis, and a chest X-ray was performed first, revealing a dilated heart. Then, an echocardiogram of the heart was performed, revealing a dilated right heart and the pulmonary artery. However, the cause of dilation of the right heart and pulmonary artery remained unclear. The patient went to another 3 hospitals, but PDV was not diagnosed. After returning to our hospital again, an abdominal-CT was performed to screen for the cause, at which time PDV was identified. In addition, patients with PDV may have other associated abdominal vascular malformations (e.g. patient 4 had associated Abernethy II malformation). Therefore, we believe that an abdominal CT examination is necessary for patients with PDV. Abdominal-Ultrasound was performed prior to CT in all patients with PDV. However, in some cases, PDV may be missed by the first ultrasound.

4. Why not all patients underwent Brain-MRI?

Reply: We have to admit that we know insufficient about PDV in the early period. If there is no neurological symptoms, brain-MRI was not performed. Therefore, Brain-MRI was not performed in some patients. Later, we get more experienced. In the case of patients with a larger PDV diameter and older age, we suggest brain MRI should be performed, regardless of the presence of neurological symptoms.

5. Please, describe the findings and criteria searched during the retrospective examination of imaging.

Reply: We have a description in the "Materials and methods".

6. Treatment and follow-up

Please, describe the surgical technique and specify if there were any complications and duration of the hospital stay until patients were discharged. Also, if any complication was discovered during follow-up. Was any venous splanchnic congestion test performed during the surgical intervention to determine to perform one or two steps ligation of the shunt?

Reply: This section was revised to "Two patients (patients 7 and 9) without coexisting malformations underwent surgical ligation of PDV in our hospital. Because these 2 patients had coagulation disorders and 1 presented with recurrent decreases in the platelet count associated with hypersplenism, we chose to ligate the PDV with a surgical procedure instead of percutaneous closure to avoid heparin-induced thrombocytopenia that could aggravate their coagulation disorders. Pulmonary artery and portal vein manometry were performed during the operation. A PDV banding test was performed before ligation, which indicated that the portal venous pressure increased transiently after banding and recovered 15 min later. The pulmonary artery pressure remained stable. The PDV was ligated (double ligation) in 1 step without clinical deterioration in 2 patients. Another patient (patient 3) underwent PDV ligation in another institute (details unclear), and then returned 6 months later to our hospital for examination. Patients 7 and 9 were reviewed in our hospital 1 year after their procedures. The remaining 6 patients were discharged from our hospital without surgical intervention for PDV, and were followed up by telephone until February 2022." (see Page 4, line 75-86).

7. RESULTS

Clinical / imaging findings

Authors should specify the analytical and radiological parameters they evaluated and the criteria used to define them as normal or pathologic. How did they measure the liver or the spleen? What scale or criteria were used to establish the liver or the spleen was enlarged or not? The same to measure the diameters of MPV, LFV, RPV, pulmonary artery… The range of age of the patients is wide. This paragraph should be included in Material and Methods before exposing results as requested before.

Reply: Normal liver and spleen size varies with age. Our institution refer to the following literature. [reference]. Konus OL, Ozdemir A, Akkaya, et al. Normal liver, spleen, and kidney dimensions in neonates, infants, and children: evaluation with sonography. AJR Am J Roentgenol. 1998; 171:1693-1698.

The MPV, LFV, RPV and pulmonary artery were not measured. The judgment of image signs was performed by two pediatric radiologists (YHX and KJ, with 20 and 25 years' experience, respectively) and reached a consensus for each patient.

8. Any other shunt (intrahepatic…) was observed?

Reply: Hepatic arteriovenous fistula was observed in patient 3. Abernethy II malformation was observed in patient 4. (described in Table 2).

9. Was thoracic-CT performed to obtain radiological data of the diameters of the pulmonary artery or other criteria of pulmonary hypertension?

Reply: All patients underwent ultrasound and/or CTA of the cardiovascular system. We mainly evaluated imaging signs in this study, and the diameters of the pulmonary artery were not measured.

10. Hypoxemia is referred in 5/9 patients. How do they explain that?

Reply: Although hypoxemia is referred in 5/9 patients, we think that it is not necessarily caused by PDV. Three of them were neonates, associated with congenital heart disease and other malformations, and two of them had pneumonia on admission. Therefore, hypoxemia may be caused by a combination of factors.

11. Did any patient present hepatopulmonary syndrome and/or arteriovenous fistulae?

Reply: Multiple arteriovenous fistulas were observed in patient 1. Hepatic arteriovenous fistula was observed in patient 3. (described in Table 2).

12. Abnormal renal imaging? Please, specify.

Reply: Renal enhancement was reduced and the density was uneven (described in Table 2).

13. I recommend the Authors to explain clinical, analytical and radiological findings separately. Example: Only 2/9 patients presented hyperammonemia but brain-MRI was performed in 7 patients. Why? Any clinical symptoms despite of normal levels of ammonia?

Reply: We have to admit that we know insufficient about PDV in the early period. If there are no neurological symptoms, brain-MRI was not performed. Later, we note that although the blood ammonia and neurological symptoms are normal, hepatic encephalopathy was observed in older PDV children with larger PDV diameter. Two patients in this study had no neurological symptoms, although brain MRI revealed hepatic encephalopathy. Therefore, in the case of patients with a larger PDV diameter and older age, we suggest brain MRI should be performed to detect hepatic encephalopathy, regardless of the presence of neurological symptoms.(we mentioned that in the discussion).

14. L-114 “Genital deformity” Please, specify gender an describe the anomaly.

Reply: It has been revised to “Congenital hypospadias”.

15. Treatment and follow up

Why only three patients underwent treatment? Was endovascular occlusion test performed prior to surgery? Surgical closure was performed in one or two steps? Endovascular closure was considered? L 120 – 123 Authors state “liver function and the general condition of the patients improved”. Please, describe accurately those two. “Wiight gain”? How do the relate it to PDV? L 123 – 124 Two patients died in this series. One of them two weeks after discharge. Do Authors know why? L 126 What Authors do mean when saying “the general conditions” of the non-treated patients got worse?

Reply: This section was revised to “Two patients (patients 7 and 9) successfully underwent surgical ligation of the PDV without clinical deterioration during the procedure. There were no serious

complications after surgery: patient 7 was hospitalized for 24 days (14 days before surgery and 10 days after), while patient 9 was hospitalized for 21 days (9 days before surgery and 12 days after); 1 year after their procedures, patients 7 and 9 showed normal exercise tolerance and weight gain. The laboratory parameters of myocardial enzymes and liver and kidney function were normal. The frequency of recurrent respiratory infections decreased in patient 7, and the jaundice in patient 9 disappeared. In the other patient (patient 3) who underwent PDV ligation in another institution before returning to our hospital for examination 6 months later, serum bilirubin, alanine aminotransferase, and aspartate aminotransferase were decreased.

Because PDV was associated with complex CHD and other malformations in 3 patients (patients 1, 2, and 5), their parents abandoned treatment, and these 3 patients died within 1 to 2 weeks after discharge. Another patient (patient 4), in whom PDV was associated with ASD, PDA, and Abernethy II malformation, was transferred to another hospital; this patient did not undergo surgery for PDV (no other details are available) and died 15 months after discharge. The remaining 2 patients (patients 6 and 8) were followed up by telephone for 3 years after discharge from our hospital. The parents of these patients reported that they were hospitalized 2-3 times a year at a local hospital for coughing, wheezing, fever, and other problems, with the frequency increasing each year; however, at the time of writing, these 2 patients have still not undergone surgical treatment for PDV. Patient 8 underwent surgical treatment for cerebrovascular malformation in another hospital 1 year ago" .(see Page 5, line 110-128).

16. DISCUSSION

The first paragraph of the Discussion should be included in the Introduction. In the next paragraphs, Authors should compare their results with the prior literature and comment the similarities or differences appreciated.

Reply: It has been revised. The first paragraph of the Discussion has been moved to Introduction. (see Page 2, line 34-39).

17. Clinical symptoms and laboratorial tests

L-143 "sings were varied". Please, specify. Authors also state that jaundice and respiratory symptoms were the most common, however these two have not been referred in M&M neither Results. Authors should differentiate between clinical signs and symptoms and laboratory test results.

Reply: The clinical symptoms, signs and laboratory test results were summarized in table 1.

18. L 169 Authors state “renal disfunction remains unclear”. Their statement about decreased renal blood and decreased renal enhancement must be explained. I recommend them to read those papers, among others:

Schaeffer DF, Laiq S, Jang H-J, John R, Adeyi OA. Abernethy malformation type II with nephrotic syndrome and other multisystemic presentation: an illustrative case for understanding pathogenesis of extrahepatic complication of congenital portosystemic shunt. Hum Pathol. 2013;44(3):432–7.

Karashima S, Hattori S, Nakazato H, Awata H, Seguchi S, Ikeda S, et al. Membranoproliferative glomerulonephritis in congenital portosystemic shunt without liver cirrhosis. Clin Nephrol. 2000;53(3):206–11.

Smet AD, Kuypers D, Evenepoel P, Maes B, Messiaen T, Van Damme B, et al. “Full house” positive immunohistochemical membranoproliferative glomerulonephritis in a patient with portosystemic shunt. Nephrol Dial Transplant. 2001;16(11):2258–62.

Reply: Thank you for your valuable recommendation. We read those papers carefully and improved our knowledge of PDV. We have revised this section and cited the literatures.

19. Imaging findings

L 179 How did the Authors measure the density of LPV and hepatic vein?

L 183 And the dilation of right atrium, ventricle or pulmonary artery? Method.

Reply: The density of LPV and hepatic vein is not measured in this study. The dilation of right atrium, ventricle and pulmonary artery were evaluated by two pediatric radiologists (YHX and KJ, with 20 and 25 years’ experience, respectively).

20. Complications and coexistent malformations

First paragraph should be included in the Introduction. Authors should compare their results to prior literature instead of reviewing and explaining physiopathological mechanisms of complications of congenital portosystemic shunts already known.

Reply: The first paragraph of the Discussion has been moved to Introduction. PDV is an extremely rare disease and only a few cases have been reported to date. The clinical symptoms, signs and laboratory

findings were diverse. Our aim is to provide clues for diagnosis and guide treatment by summarizing the clinical, secondary radiological findings and surgical method. Therefore, only some of points were discussed, and this is also the limitation of this paper.

21. L224 Why Brain MRI should be performed to detect hepatic encephalopathy? Clinical symptoms and ammonia levels are usually enough to.

Reply: We note that although the blood ammonia and neurological symptoms are normal, hepatic encephalopathy was observed in patients with larger PDV diameter and older age. 2 patients in the present study had no neurological symptoms, even though brain MRI suggested hepatic encephalopathy. Therefore, in the case of patients with a larger PDV diameter and older age, we suggest brain MRI should be performed to detect hepatic encephalopathy, regardless of the presence of neurological symptoms.

22. L 240 Hemoptysis? How do they explain that? Do they think it was related to the PDV?

Reply: Hemoptysis was observed in patient 8. A small bronchial artery-pulmonary fistula was found by DSA.

23. Treatment

L 250 Authors state catheter procedures require high dose of heparin. Reference, please.

L 256 – 257 This should be included in M&M.

Reply: It has been revised in section of Materials and methods.

24. L 264 – 265 This should be included in Results. Were three or four patients who died?

Reply: It has been revised. Four patients died.

25. CONCLUSION

Authors state patients should be treated but in their small series only 3/9 patients received treatment. Complications of interventions were not explained (if there were).

Reply: PDV is an extremely rare disease and only a few cases have been reported to date. Two patients successfully underwent surgical treatment of PDV in our hospital, without clinical deterioration during the operation. There were no serious complications after surgery, and has a good prognosis. Therefore,

we believed that surgical treatment is benefit to patients with PDV.

26. FIGURES

Fig1. Please, show LPV and IVC. Fig2. Diffuse nodes are not shown, just heterogeneity of liver parenchyma.

Reply: Figure 1 has been removed because there are too many CT images. Two ultrasound images have been added to figure 2. Multiple nodes were shown on a ultrasound image. Previously reported, the multiple liver nodules appear to be related to irregular blood flow and diversion of hepatotrophic substances in the splanchnic venous blood away from the liver, resulting in alterations of development, function, and regenerative capacity of the liver.

27. TABLES

Tables should include the analytical data and radiologic measures instead of “yes/no” or “normal/abnormal”.

Reply: In Table 1, specific values have been provided for NH_4. Data on other laboratory tests (i.e. hypoxemia, hyperbilirubinemia, coagulation function, myocardial enzyme, and liver and kidney function) are unchanged. Initially, we considered presenting specific values for these items but, because each item involved multiple laboratory test parameters (e.g. liver function test includes alanine aminotransferase, aspartate aminotransferase, albumin, total bilirubin, direct bilirubin and indirect bilirubin), comprehensive evaluation of all parameters was required. Therefore, presenting the specific data would not help readers intuitively understand the result for each item. In addition, we consulted with professors of cardiology and the ICU to ensure the accuracy of the items presented.

28. Definitions as “frequent pneumonia” or “external genital deformity” should be avoided.

Reply: “frequent pneumonia” has been revised to “recurrent respiratory infections”. “external genital deformity” has been revised to “congenital hypospadias”.