Received: 5 November 2024 | Accepted: 11 June 2025

DOI: 10.1002/jpn3.70136

JPGN

ORIGINAL ARTICLE

Endoscopy and Procedures

Natural progression and prediction markers in non-clinically significant oesophageal varices in children

Cody Chan[1] | **Akshat Goel**[1] | **Robert Hegarty**[1] | **Bethany Tucker**[1] | **Vandana Jain**[1] | **Eirini Kyrana**[1,2] | **Tassos Grammatikopoulos**[1,3]

[1]Paediatric Liver, GI & Nutrition Centre and MowatLabs, King's College Hospital, London, UK

[2]Roger Williams Institute of Liver Studies, King's College London, London, UK

[3]Institute of Liver Studies, School of Immunology & Microbial Sciences, King's College London, London, UK

Correspondence

Tassos Grammatikopoulos, Paediatric Liver, GI & Nutrition Centre, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK.
Email: t.grammatikopoulos@nhs.net

Funding information
None

Abstract

Objectives: Limited literature exists on non-clinically significant varices (nCSV) and progression in children with portal hypertension (PHT). This study investigates trends and associations in this cohort.

Methods: This retrospective cohort study analysed 70 children with nCSV undergoing surveillance endoscopy between January 2012 and 2024. Laboratory parameters, prediction scores and fibroscan results were collected. Statistical analysis include Mann–Whitney *U* test, chi-squared test and receiver operating characteristic.

Results: Ten children (14.3%) presented with portal vein thrombosis (PVT), 26 (37.1%) with non-biliary atresia chronic liver disease (CLD) and 34 (48.6%) with biliary atresia (BA). Twenty-five children (35.7%) had variceal progression, with median years until progression of 3 years recorded in PVT and CLD (PVT: 1–6 years, CLD: 2–8 years), and 2 years (1–10 years) in BA. Haemoglobin count (Hb) (area under the curve [AUC] = 0.943), risk score (AUC = 0.748), and spleen stiffness by fibroscan (SSM) (AUC = 1.00) revealed optimal accuracy in predicting progression in PVT, with similar findings in CLD (von Willebrand Factor score [vWFAg score]: AUC = 1.00, risk score: AUC = 0.767, SSM: AUC = 0.882). Suboptimal accuracy was seen in BA biomarkers.

Conclusions: Risk score is a reliable marker to monitor variceal progression in CLD and PVT. Interim noninvasive scores could be trialled along with surveillance OGD to validate results. Caution is advised extending endoscopy period for children with BA. Due to small subgroup sizes, larger cohort studies are needed to validate SSM and vWFAg score in children with nCSV.

KEYWORDS

biomarkers, non-clinically significant varices, portal hypertension, risk score, spleen stiffness measurement, variceal progression, Von Willebrand factor antigen

1 | INTRODUCTION

Oesophageal varices are abnormal vessels formation due to increase portal venous pressure (>10 mmHg), known as portal hypertension (PHT). PHT in children can result in prehepatic portal vein thrombosis (PVT) (40%), intrahepatic (presinusoidal and sinusoidal) disease, or posthepatic vessel pathologies.[1,2] Varices are prone to rupture, causing gastrointestinal (GI) bleeding, a major cause of mortality and morbidity in children with liver disease. Grade 3 varices had shown a 10-year survival rate of 73%–85%.[3] Ackermann et al. reported a 45% recurrence rate of varices post-eradication, with a 25% bleeding risk for children with grade 2+ varices.[4]

Based on Baveno VI consensus, children would be considered for surveillance oesophagogastroduodenoscopy (OGD) based on splenomegaly and thrombocytopenia, and commence treatment depending on the grade of varices.[5] Grades are defined as: 0 (no varices found), 1 (small/nontortuous varices), 2 (tortuous varices occupying <1/3 of the distal oesophageal radius), and 3 (tortuous and occupying >1/3 of the distal oesophageal radius).[2] Clinically significant varices (CSV) are defined as grade 2+ oesophageal varices with stigmata of GI bleeding (red colour signs) and/or gastric varices, whereas non-clinically significant varices (nCSV) are oesophageal varices graded 1 or 2 with no stigmata of GI bleeding.[6] Current guidelines suggest a 2-yearly routine OGD for grade 1 varices, and prophylactical treatments (banding, sclerotherapy, or non-selective beta-blockers [NSBB]) for grade 2+ varices in children.[7]

Literature on frequency of routine OGDs in nCSV paediatric cohort and its follow-up period is limited. An international survey showed only 70% of units perform regular surveillance OGD.[8] Few studies also investigated variceal progression and morbidities in this cohort. Prognostic biomarkers (Von Willebrand factor antigen [vWFAg], glycoprotein 1b) and non-invasive techniques like liver/spleen transient elastography, have shown promise in predicting progression in children.[9] This retrospective cohort study aims to investigate variceal grade progression and evaluate biomarkers and risk scores in children who had nCSV.

What is Known

- There is a knowledge gap on the frequency of surveillance endoscopies and follow-up in children with non-clinically significant varices (nCSV).
- Prognostic biomarkers and noninvasive techniques like Von Willebrand factor antigen and transient elastography show promise in predicting variceal progression.

What is New

- 34.7% of children with nCSV progressed to clinically significant varices over 12 years.
- Endoscopy surveillance for portal vein thrombosis and non-biliary atresia chronic liver disease can be extended from 2 to 3 years, based on median progression time of 3.5 and 4 years, respectively.
- Differences in variceal progression patterns and biomarker effectiveness highlight the need for aetiology-specific approaches to portal hypertension.

2 | METHODS

This retrospective cohort study analysed OGD data from Paediatric Liver, GI and Nutrition Centre, King's College Hospital, London, between January 2012 and January 2024. All children underwent surveillance endoscopies for PHT, defined by clinically and/or radiologically confirmed splenomegaly and persistent thrombocytopenia recorded more than one occasion (platelet count below 150×10^9/L). Some children ($n = 11$) had OGD despite not meeting the criteria above due to bleeding of unknown origin ($n = 6$) or pre-liver transplant assessment ($n = 5$). Selection criteria for the study cohort included grade I or II varices upon first OGD with no stigmata of bleeding, classified as nCSV. Varices were graded as per BAVENO VI consensus, and CSV was defined as grade II+ varices with red stigmata, wale signs and/or gastric varices. All patients were treated based on variceal grade and not based on underlying diagnosis. Treatment plan was aimed at variceal eradication and minimising risk of variceal bleeding. A list of abbreviations used in the study is provided for reference in supplementary data (Table S1).

From initial cohort of 144 patients, 74 children were excluded due to gastric varices, grade III varices, red colour signs, absence of thrombocytopenia, or NSBB use. The remaining 70 children were assessed for general demographics, diagnosis, endoscopy frequency, and laboratory parameters associated with variceal progression. Laboratory markers were measured before each OGD on the day of scope, as per departmental protocol. Diagnosis was subcategorised into PVT, biliary atresia (BA) and non-BA chronic liver disease (CLD), in which the most common diagnosis include cystic fibrosis liver disease (CFLD), polycystic liver/kidney disease (PLKD), alpha-1 antitrypsin deficiency and Caroli's disease. Breakthrough bleeds were recorded in three BA, two CLD, and three PVT cases.

Scoring systems used include:

1. Risk score: $[14.2 - 7.1 \times \log_{10}(\text{platelet } (10^9/\text{L}))] + 4.2 \times \log_{10}[\text{bilirubin (mg/dL)}]$.[10]
2. Clinical prediction rule (CPR): [(0.75 × platelet [10^9/L]/(spleen z-score +5)) + 2.5 × albumin [mg/dL]].[11]
3. King's variceal prediction score (KVaPS): [3 × albumin [mg/dL] − 2 × EASS (estimated adult spleen size)].[12]
4. Aspartate-platelet ratio index (APRI): [AST/upper limit of normal/platelet [10^9/L] × 100].[13,14]
5. Variceal prediction rule (VPR): [albumin [mg/dL] x platelet [10^9/L]/1000].[15]
6. vWFAg score[9]:

CLD/BA: CSV = 1/(1 + (−283 + 1.3 × vWF − 0.5 × GPIbR − 0.5 × platelet −0.4 × LSM + 5.6 × spleen stiffness measurement [SSM]).

PVT: CSV = 1/(1 + (−4371 + 11 × vWF + 12 × GPIbR + 5 × platelet + 16 × SSM).

Haematological, coagulation and biochemistry profiles, risk scores and fibroscan (performed by hepatologists) results were analysed with Mann–Whitney *U* and chi-squared tests. Data are reported as median and range, with a *p*-value of <0.05 considered statistically significant. Receiver-operating characteristic (ROC) curves were applied to significant variables. Data analysis were conducted via Microsoft Excel 2019 and IBM SPSS Statistics 2023.

The primary endpoint was identifying trends for earlier variceal progression in the low-risk nCSV cohort. The secondary endpoint was to stratify endoscopic follow-up frequency. All patient records were anonymized before analysis.

2.1 | Ethics statement

This study was approved by the Institutional Review Board (IRAS ID 238002, King's College Hospital NHS Trust).

3 | RESULTS

3.1 | General characteristics

Seventy children, aged 4 months to 18 years, were included in this study, with 24 (34.7%) progressing to CSV (PC). In the non-progressed cohort (NPC), 23 (50.0%) were male in comparison to 14 (58.3%) in the progressed cohort (PC). Diagnoses for PHT included BA ($n = 34$), CLD ($n = 26$) and PVT ($n = 10$).

In NPC, BA was the most common diagnosis (56.5%), followed by CLD (37.0%) and PVT (6.52%). In PC, PVT, CLD and BA had similar prevalence (29.5%, 37.5% and 33%). The most common stigmata in PC were gastric varices (83.3%), followed by grade 3 varices (20.8%), red spots (20.8%) and red wales (8.33%). Liver transplant was performed in 50.0% of NPC and 62.5% of PC in children with BA. All transplants were done post-CSV progression (Table 1).

For OGD characteristics, a total of 270 endoscopies were performed. Median OGDs per child was 3 (range: 3–9) in PC, compared to 2 (range: 1–7) in NPC, with median interval between OGDs 2 years in NPC and 1 year in PC. Majority of PC requiring intervention were given banding therapy (95.8%) (Table 1).

TABLE 1 Patient cohort characteristics.

General characteristics		
	Nonprogressed cohort	Progressed cohort
Total number	46 (65.3%)	24 (34.7%)
Gender (male)	23 (50.0%)	14 (58.3%)
Gender (female)	23 (50.0%)	10 (41.7%)
PVT	3 (6.52%)	7 (29.2%)
CLD	17 (37.0%)	9 (37.5%)
BA	26 (56.5%)	8 (33.3%)
Gastric varices	0	20
Red spots	0	5
Red wales	0	2
Grade 3 varices	0	5
Liver transplant in BA cohort	13 (50.0%[a])	5 (62.5%[a])
Endoscopy characteristics		
Total number of endoscopies	153	117
Median number of follow-up endoscopies per patient	2	3
Median interval between endoscopies (years)	2	1
Sclerotherapy (patients)	0	11
Banding (patients)	0	23

Note: All other percentages are calculated from total number unless otherwise specified.

Abbreviations: BA, biliary atresia; CLD, chronic liver disease; PVT, portal vein thrombosis.

[a]Percentage of the BA cohort.

3.2 | Age distribution at first endoscopy

Age at first surveillance OGD was recorded. In NPC, 26 children (56.5%) had their first endoscopy when they were 1–5 years old, eight children (17.4%) in 6–10 years groups and 12 children (26.1%) in 11–16 years, respectively. In PC, most children were first screened in 6–10 year group (12 children, 50.0%) and only three children (12.5%) first screened in the 11–16 years age group. No significant differences were inferred between age of first OGD and disease type in NPC ($p = 0.295$) and PC ($p = 0.213$). Median variceal progression years was longest in CLD (4 years, interquartile range [IQR]: 3.5 years), followed by PVT (3.5 years, IQR: 6 years) and BA (2 years, IQR: 5 years) (Table 2).

3.3 | Biomarker analysis by disease group

3.3.1 | PVT analysis

Significant intercohort differences were noted in haemoglobin count (Hb) ($p < 0.001$), risk score ($p < 0.01$), and SSM ($p < 0.05$) (Table S2). Hb had shown strongest

TABLE 2 First endoscopy age, initial variceal grade of nonprogression and progression cohort in terms of disease subgroup.

First endoscopy age (nonprogression cohort)	PVT ($n = 3$)	CLD ($n = 17$)	BA ($n = 26$)	Total
1–5 years old	2	7	17	26 (56.5%)
6–10 years old	0	3	5	8 (17.4%)
11–16 years old	1	7	4	12 (26.1%)
Grade of oesophageal varices (NPC) upon first endoscopy				
Nil	1	8	11	20 (43.5%)
Grade 1	1	5	10	16 (34.8%)
Grade 2	1	4	5	10 (21.7%)
First endoscopy age (progression cohort)	PVT ($n = 7$)	CLD ($n = 9$)	BA ($n = 8$)	Total
1–5 years old	3	2	4	9 (37.5%)
6–10 years old	2	7	3	12 (50.0%)
11–16 years old	2	0	1	3 (12.5%)
Median years until variceal progression	3.5[a]	4[a]	2[a]	
IQR years until variceal progression	6[a]	3.5[a]	5[a]	
Grade of oesophageal varices (PC) upon first endoscopy				
Nil	3	3	1	7 (29.2%)
Grade 1	1	2	2	5 (20.8%)
Grade 2	3	4	5	12 (50.0%)

Note: *first endoscopy age* refers to the age of each child at initial endoscopy.

Abbreviations: BA, biliary atresia; CLD, chronic liver disease; IQR, interquartile range; NPC, nonprogression cohort; PC, progression cohort; PVT, portal vein thrombosis.

[a]Value as years. All other *n* values represent number of children.

predictive value, with an AUROC of 0.943 (95% confidence interval [CI]: 0.878–1.000, SE = 0.033). SSM also demonstrated a high AUROC (AUROC = 1.000), though analysis is limited by smaller sample size ($n = 12$). Risk score demonstrated a high AUROC of 0.748 (95% CI: 0.565–0.955, SE = 0.100) (Figure 1).

For specific cutoffs, the optimal cutoff for Hb was 128.5, corresponding to a Youden's Index of 0.784, with sensitivity of 100% and specificity of 78.4%. In SSM, the optimal cutoff was 16.7 kPa, with 100% sensitivity and specificity, and a Youden's index of 1.00. The risk score had an optimal cutoff at 3.176, with a Youden's index of 0.593, sensitivity of 66.7%, and specificity of 92.7%.

3.4 | Non-BA CLD analysis

Strong statistically significant differences were found in platelet count (PLT), vWFAg score, VPR, risk score ($p < 0.001$) and SSM ($p < 0.01$). (Table S2). Among these biomarkers, vWFAg score showed the highest AUROC (1.00), followed by SSM (0.882; 95% CI: 0.731–1.000; SE = 0.077) and risk score (0.767; 95% CI: 0.670–0.864; SE = 0.050). PLT (0.751; 95% CI: 0.651–0.851; SE = 0.051) and VPR (0.723; 95% CI: 0.618–0.828; SE = 0.054) also showed strong AUROC (Figure 2).

vWFAg score had a 100% sensitivity and specificity at a threshold of 0.001625. SSM has a sensitivity of 100% and specificity of 70% at a cut-off of 38.75 kPa. A Youden's index of 0.415 was seen with risk score at the cutoff of 4.1558, with a sensitivity of 72.2% and specificity of 69.2%. PLT, with a Youden's index of 0.389, had a cut-off of 60.5, which shows 92.7% specificity and 46.2% sensitivity (46.2%). VPR showed a moderate performance, with a Youden's index of 0.361 at 3.16 (sensitivity 53.8%, specificity 79.6%). AST was also notable (Youden's index = 0.361) with a threshold of 35.5 (sensitivity 52.8%, specificity 83.3%).

3.5 | BA analysis

In BA, significant difference was inferred in spleen *Z* score within PC and NPC (Table S2), but with modest AUROC (AUC = 0.627) (Figure S1). Analysis was unavailable for vWFAg score and SSM due to small sample size ($n = 2$), and early endoscopies predating routine vWFAg score/SSM testing.

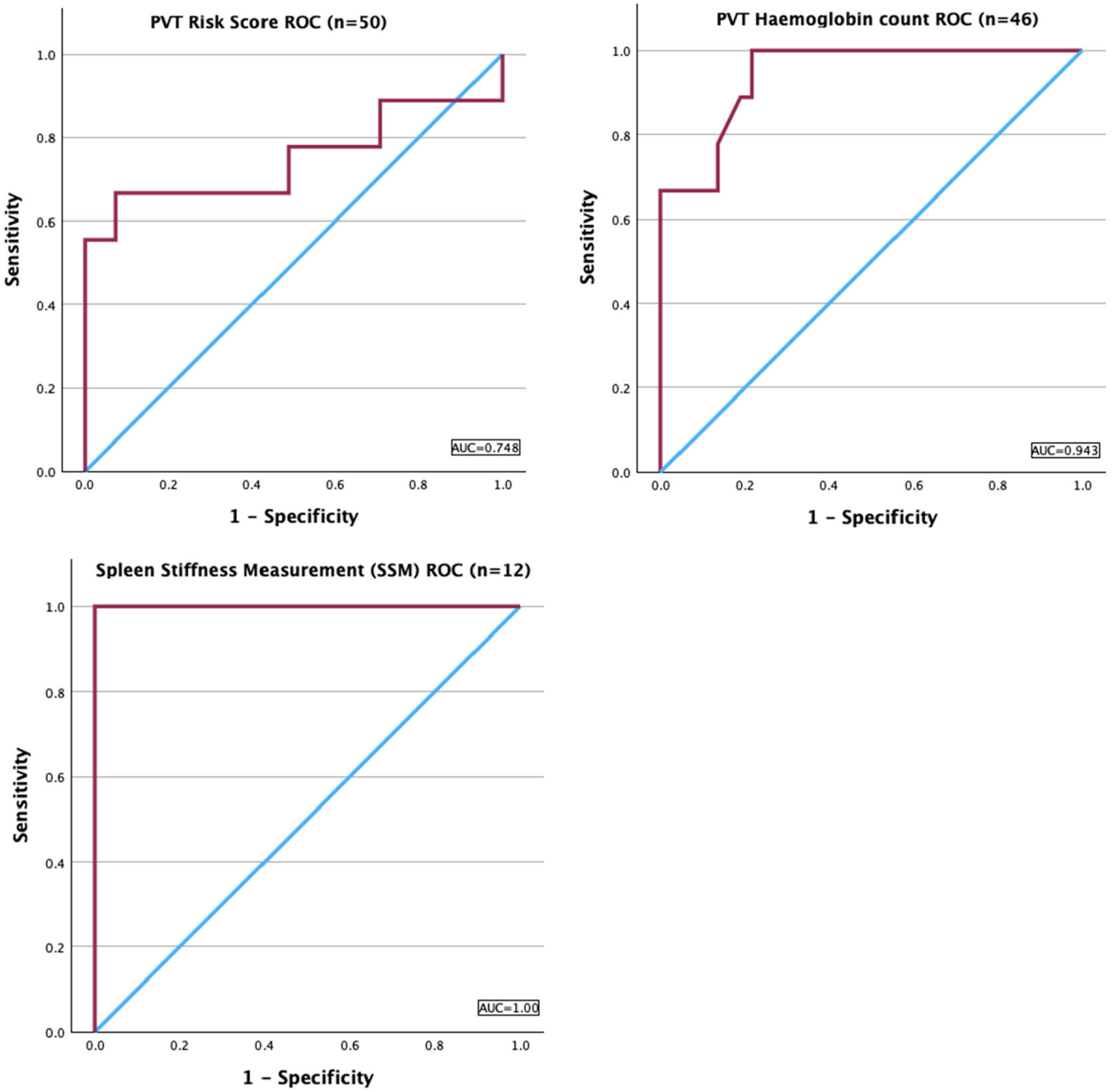

FIGURE 1 ROC curve (with 1-specificity in *x*-axis and sensitivity in *y*-axis) for significant markers between PVT cohorts (NPC vs. PC). NPC, nonprogressed cohort; PC, progressed cohort; PVC, portal vein thrombosis; PVT, platelet; ROC, receiver operating characteristic; SSM, spleen stiffness measurement.

3.6 | Intracohort comparison (NPC and PC)

3.6.1 | BA and PVT

For the progression cohort (PC), statistical significance was seen in KVaPS, INR and albumin ($p < 0.05$). APRI and AST yielded strongest significance in between the diseases ($p < 0.001$) (Table S4). In non-PC, strongest significance was seen in Hb level ($p < 0.001$). SSM and APRI also yielded strong significance ($p < 0.01$), and some significance was inferred in AST ($p < 0.05$) (Table S3).

3.6.2 | PVT and CLD

In PC group, significant differences were observed in SSM ($p < 0.05$), INR ($p < 0.01$) and vWFAg score ($p < 0.001$) (Table S4). In NPC, significance in vWFAg

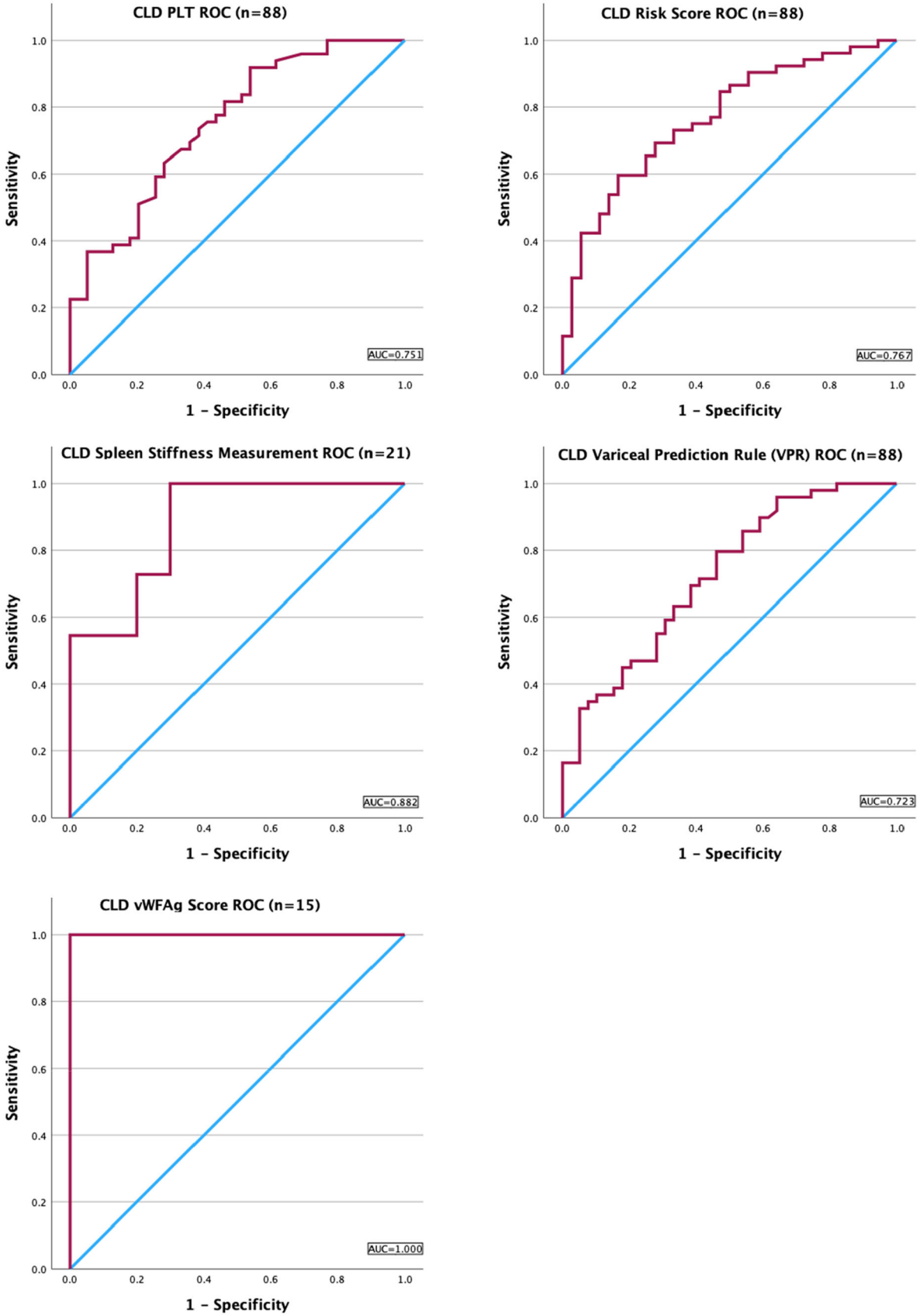

FIGURE 2 ROC curve (with 1-specificity in *x*-axis and sensitivity in *y*-axis) for significant markers in CLD cohorts (NPC vs. PC). CLD, chronic liver disease; NPC, nonprogressed cohort; PC, progressed cohort; PVT, platelet; ROC, receiver operating characteristic; VPR, variceal prediction rule; vWFAg, von Willebrand factor score.

score ($p < 0.05$), Hb and AST ($p < 0.001$) were noted (Table S3).

3.6.3 | CLD and BA

A significant difference ($p < 0.05$) was inferred in the APRI score in PC, with a higher median seen in BA (2.04 vs. 1.06) (Table S4). In NPC, significant difference was inferred in PLT, risk score and APRI ($p < 0.001$), VPR ($p < 0.01$), and INR and SSM ($p < 0.05$) (Table S3).

4 | DISCUSSION

Limited literature exists on children with nCSV and natural progression to CSV. Within our cohort, one in three children with nCSV progressed to CSV within 12 years follow-up. Identifying effective, non-invasive biomarkers and scores for stratification of risk could minimise invasive OGDs, improve waiting times and delays. We attempted to answer these questions and looked into 16 noninvasive markers associated with variceal progression in children with BA, CLD and PVT.

In non-BA CLD and PVT, several promising markers were identified. In both disease groups, risk score and SSM showcased significant difference between NPC and PC.

In biomarkers significant only to particular disease groups, Hb demonstrated highest AUROC in PVT group (0.943), while vWFAg has the highest AUROC in CLD group (1.00). Other biomarkers, such as platelet count (AUROC = 0.751) and VPR (AUROC = 0.723) were also promising in predicting progression of varices, findings which aligned with previous studies.[6,9,16] Given the subjective nature of variceal grading classification,[2] identifying a quantifiable biomarker capable of differentiating disease cohorts could standardise monitoring and triaging varices for endoscopic surveillance.

While intercohort markers, such as risk score and SSM, show promise in identifying children with higher risk of progression, intracohort analysis (comparison of disease groups within same progression status) provides further evidence to suggest surveillance need. Notably, markers which were significant in multiple groups in intercohort analysis (between NPC and PC) were not consistently significant across different disease groups in intracohort analysis. However, AST and APRI, markers which are not significant in intercohort analysis, are significantly higher in BA group compared to CLD or PVT, regardless of progression status, suggesting a more advanced baseline severity in children with BA.

According to BAVENO VI, in compensated patients with no varices, surveillance endoscopy should be repeated at 2-year intervals.[17] However, endoscopy itself is an invasive procedure, with complication rates of up to 2.3% in children.[18] Given the increasing number of non-invasive scoring systems, the question is raised in extending this 2-yearly endoscopy, especially in a low-risk cohort, and increase triaging via biomarkers. PVT showed highest CSV progression (61.5%) but with a median time to progression of 3.5 years. In CLD, 34.6% of children had CSV progression with a median progression of 4 years. This indicates that in low risk NPC children with PVT or CLD, an extension of the endoscopy period to 3 years could be safe to monitor changes to CSV, though further large validation studies are required for confirmation.

A greater proportion of children in PC present with grade 2 varices at baseline compared with non-progression group (50.0% vs. 21.8%), suggesting a possible early sign of variceal progression. However, this trend was not statistical significance ($p = 0.0615$), nor was the difference in follow-up interval between cohorts ($p = 0.429$), which suggest clinicians did not perceive worrying findings upon initial endoscopy. No significance was inferred between age and initial variceal grade across disease groups (BA: $p = 0.372$, PVT: $p = 0.083$, CLD: $p = 0.695$). However, risk score was significantly different between progression and non-progression groups (PVT: $p = 0.033$, CLD: $p = 0.025$), along with Hb in PVT ($p = 0.017$). This supports their potential utility in early risk triaging.

The small patient number in the PVT cohorts was limiting in our study. While vWFAg and SSM yielded highest AUROC, and vWFAg score having lower significance in intracohort analysis between PVT and CLD, scarce data in PC BA ($n = 2$), and in general, due to later introduction of SSM in our centre (2018), lead to difficulty in analysis. 66.8% (187/280) of OGDs were conducted before 2018 and before routine SSM and vWF antigen/G protein 1b activity testing. These tests may not be routinely done at smaller centres, potentially limiting their applicability. In contrast, other scoring systems, such as VPR and risk score, utilise routine biochemical parameters (platelet, bilirubin and albumin), making them more practical for clinical use.

Identifying significant biomarkers remains challenging for BA cohort. Scoring systems, such as risk score, yielded lower predictive values (AUC = 0.545). Spleen Z score showed suboptimal AUC (AUC = 0.627). Several biomarkers (vWFAg, LSM and SSM) are also limited by small sample size. All children in BA cohort underwent liver transplantation post-variceal deterioration; transplanted liver therefore does not influence results. Although the majority of BA children (77.1%) did not progress to CSV, for those who progressed, BA group showed the most rapid progression among all, with 62.5% of cases progressing within 2 years. This lack of significant biomarker, along with the rapid nature of progression and worse ARPI/AST

baseline compared with PVT/CLD, supports routine 2-yearly surveillance endoscopy. Extending endoscopy intervals should be avoided. New biomarkers, such as MMP-7, may play a role in differentiating between BA and non-BA cohorts,[19–21] which warrants further research.

A trend with age was identified between NPC and PC groups. The majority of children in the NPC group had their first endoscopy in the 1–5 years old range ($n = 26$, 56.5% of NPC), with BA being the most common diagnosis within this group of 26 children ($n = 13$). Whereas in PC, the largest centile group ($n = 12$, 50.0% of PC) had their first endoscopy in the 6–10 years old range, with CLD being the most common diagnosis ($n = 7$). This may reflect that BA is diagnosed within the first few weeks of life as is more closely monitored, while CLD manifests later during childhood. This is an interesting observation which shows that age and underlying disease could have an impact on PHT and subsequent development of CSV.

One of the strengths of this study is the breadth of biomarkers analysed, as well as being one of the first studies focusing specifically on NPC. However, there are some limitations. Overall sample size, and more specifically, for PVT in NPC, was small which could skew results. Moreover, this being a single-centre study may not be representative of worldwide practice. Our CLD population included multiple aetiologies, making reproducibility challenging across other centres.

To validate these findings and address limitations in this study, future studies should focus on multicentre collaborative studies, with larger and more representative cohort. Standardisation of emerging biomarkers may provide more insight on PHT progression. Development of disease-specific cutoffs, for example, different risk score thresholds for CLD versus PVT, could also improve its predictive accuracy in progression. Finally, studies comparing biomarker-driven and fixed-interval surveillance could show insight for clinical application.

5 | CONCLUSION

In children with nCSV, risk score was the most practical and consistent predictor of variceal progression in CLD and PVT. Disease-specific biomarkers, such as Hb in PVT, or platelet count and VPR in CLD, also showed utility within their respective clinical context. Although vWFAg score and SSM showcased favourable AUROC, analysis was limited due to their small sample size. Interim non-invasive risk score assessment could support triaging in low-risk cohort and help extend OGD surveillance to 3-yearly interval in CLD and PVT children, provided that large-scale cohort studies across tertiary centres confirm the efficacy of scoring systems. As for BA, the absence of reliable biomarkers and rapid progression warrants caution in extending the endoscopy period from regular 2-yearly interval surveillance.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

REFERENCES

1. Abd El-hamid N, Taylor RM, Marinello D, et al. Aetiology and management of extrahepatic portal vein obstruction in children: King's College Hospital experience. *J Pediatr Gastroenterol Nutr*. 2008;47(5):630-634.
2. D'Antiga L, Betalli P, De Angelis P, et al. Interobserver agreement on endoscopic classification of oesophageal varices in children. *J Pediatr Gastroenterol Nutr*. 2015;61(2):176-181.
3. Lee WS, Song ZL, Em JM, Chew KS, Ng RT. Role of primary prophylaxis in preventing variceal bleeding in children with gastroesophageal varices. *Pediatr Neonatol*. 2021;62(3):249-257.
4. Ackermann O, Darmellah-Remil A, Bernard O, et al. Efficacy and safety of endoscopic primary prophylaxis of bleeding in children with high-risk gastroesophageal varices. *J Pediatr Gastroenterol Nutr*. 2022;75(4):491-496.
5. Shneider BL, de Ville de Goyet J, Leung DH, et al. Primary prophylaxis of variceal bleeding in children and the role of MesoRex bypass: summary of the Baveno VI Pediatric Satellite Symposium. *Hepatology*. 2016;63(4):1368-1380.
6. Sutton H, Fitzpatrick E, Davenport M, et al. Transient elastography measurements of spleen stiffness as a predictor of clinically significant varices in children. *J Pediatr Gastroenterol Nutr*. 2018;67(4):446-451.
7. Grammatikopoulos T, McKiernan PJ, Dhawan A. Portal hypertension and its management in children. *Arch Dis Child*. 2018;103(2):186-191.
8. D'Antiga L. Medical management of esophageal varices and portal hypertension in children. *Semin Pediatr Surg*. 2012;21(3):211-218.
9. Goel A, Hegarty R, Dixit S, et al. Transient elastography and von Willebrand factor as predictors of portal hypertension and decompensation in children. *JHEP Rep*. 2023;5(12):100935.
10. Park SH, Park TE, Kim YM, et al. Non-invasive model predicting clinically-significant portal hypertension in patients with advanced fibrosis. *J Gastroenterol Hepatol*. 2009;24(7):1289-1293.
11. Gana JC, Turner D, Mieli–Vergani G, et al. A clinical prediction rule and platelet count predict esophageal varices in children. *Gastroenterology*. 2011;141(6):2009-2016.
12. Witters P, Hughes D, Karthikeyan P, et al. King's variceal prediction score: a novel noninvasive marker of portal hypertension in pediatric chronic liver disease. *J Pediatr Gastroenterol Nutr*. 2017;64(4):518-523.
13. Grieve A, Makin E, Davenport M. Aspartate aminotransferase-to-platelet ratio index (APRi) in infants with biliary atresia: prognostic value at presentation. *J Pediatr Surg*. 2013;48(4):789-795.
14. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38(2):518-526.
15. Isted A, Grammatikopoulos T, Davenport M. Prediction of esophageal varices in biliary atresia: derivation of the "varices prediction rule", a novel noninvasive predictor. *J Pediatr Surg*. 2015;50(10):1734-1738.
16. Upadhyay P, Khanna R, Sood V, Lal BB, Patidar Y, Alam S. Splenic stiffness is the best predictor of clinically significant varices in children with portal hypertension. *J Pediatr Gastroenterol Nutr*. 2023;76(3):364-370.

17. de Franchis R. Expanding consensus in portal hypertension. *J Hepatol*. 2015;63(3):743-752.
18. Lightdale JR, Liu QY, Sahn B, Troendle DM, Thomson M, Fishman DS. Pediatric endoscopy and high-risk patients: a clinical report from the NASPGHAN Endoscopy Committee. *J Pediatr Gastroenterol Nutr*. 2019;68(4):595-606.
19. Jiang J, Dong R, Du M, et al. Serum matrix metalloproteinase-7 for discriminating biliary atresia: a diagnostic accuracy and validation study. *J Transl Med*. 2024;22(1):636.
20. Wu JF, Jeng YM, Chen HL, Ni YH, Hsu HY, Chang MH. Quantification of serum matrix metallopeptide 7 levels may assist in the diagnosis and predict the outcome for patients with biliary atresia. *J Pediatr*. 2019;208:30-37.e1.
21. Chen X, Dong R, Shen Z, Yan W, Zheng S. Value of gamma-glutamyl transpeptidase for diagnosis of biliary atresia by correlation with age. *J Pediatr Gastroenterol Nutr*. 2016;63(3):370-373.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Chan C, Goel A, Hegarty R, et al. Natural progression and prediction markers in non-clinically significant oesophageal varices in children. *J Pediatr Gastroenterol Nutr*. 2025;1-9. doi:10.1002/jpn3.70136