Cardiology in the Young

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Additive value of invasive haemodynamic assessment for predicting post-operative outcomes after Fontan

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Original Article

Cite this article: Wood KP, Bonello KE, Plummer ST, Chamberlain RC, Fleming GA, Camitta MGW, and Hill KD (2024) Additive value of invasive haemodynamic assessment for predicting post-operative outcomes after Fontan. *Cardiology in the Young* **34**: 2074–2079. doi: 10.1017/S1047951124025290

Received: 6 October 2023
Revised: 19 April 2024
Accepted: 7 May 2024
First published online: 27 August 2024

Keywords:
Fontan; cardiac catheterization; invasive haemodynamics; non-invasive imaging; post-operative outcomes

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Abstract

Routine pre-Fontan cardiac catheterization remains standard practice at most centres. However, with advances in non-invasive risk assessment, an invasive haemodynamic assessment may not be necessary for all patients.

Using retrospective data from patients undergoing Fontan palliation at our institution, we developed a multivariable model to predict the likelihood of a composite adverse post-operative outcome including prolonged length of stay ≥ 30 days, hospital readmission within 6 months, and death and/or transplant within 6 months. Our baseline model included non-invasive risk factors obtained from clinical history and echocardiogram. We then incrementally incorporated invasive haemodynamic data to determine if these variables improved risk prediction.

Our baseline model correctly predicted favourable versus adverse post-Fontan outcomes in 118/174 (68%) patients. Covariates associated with adverse outcomes included the presence of a systemic right ventricle (adjusted adds ratio [aOR] 2.9; 95% CI 1.4, 5.8; p = 0.004), earlier surgical era (aOR 3.1 for era 1 vs 2; 95% CI 1.5, 6.5; p = 0.002), and performance of concomitant surgical procedures at the time of Fontan surgery (aOR 2.5; 95% CI 1.1, 5.0; p = 0.026). Incremental addition of invasively acquired haemodynamic data did not improve model performance or percentage of outcomes predicted.

Invasively acquired haemodynamic data does not add substantially to non-invasive risk stratification in the majority of patients. Pre-Fontan catheterization may still be beneficial for angiographic evaluation of anatomy, for therapeutic intervention, and in select patients with equivocal risk stratification.

The Fontan procedure was first performed over 50 years ago and remains the final common pathway for patients with single ventricle heart disease.[1] Pre-Fontan risk assessment has traditionally involved invasive cardiac catheterization to ensure good Fontan candidacy and identify patients at higher risk of post-operative complications.

Although cardiac catheterization has been the gold standard for years, it is an invasive test associated with risks of procedural complications and exposure to ionizing radiation that may increase the lifetime risk of cancer.[2–3] With advances in the availability and accuracy of non-invasive imaging and improved non-invasive risk stratification, investigators have questioned whether invasively acquired haemodynamic data is still necessary to predict surgical risk in low-risk Fontan candidates.[4–7]

We sought to determine if invasive cardiac catheterization haemodynamic measurements provide additional benefit in predicting adverse post-operative Fontan outcomes compared to using baseline non-invasive data alone. Using retrospective institutional data, we developed a model to predict adverse post-operative outcomes using known risk factors obtained from clinical history and non-invasive imaging and then incrementally incorporated invasive haemodynamic data obtained from cardiac catheterization to determine if these variables improved risk prediction.

Methods

We performed a retrospective cohort study including all patients who underwent both pre-Fontan catheterization and Fontan surgery at Duke University Hospital between January 2000 and July 2017. During that time period, our institutional approach was to perform invasive

haemodynamic assessment in all patients undergoing Fontan surgery. Subjects were excluded if they did not have pre-Fontan catheterization assessment or if they did not undergo catheterization at our institution (n = 8). Two patients who underwent pre-Fontan catheterization at our institution did not undergo Fontan surgery. One patient with prior total anomalous pulmonary vein repair was excluded due to pulmonary vein atresia. The other patient had multiple risk factors including recurrent arch obstruction, moderate right ventricle dysfunction, and elevated end-diastolic pressure and pulmonary vascular resistance. Neither patient's Fontan candidacy was determined based on abnormal invasive haemodynamics alone. This study was approved by the Duke University Institutional Review Board as a retrospective study without the need for informed consent (IRB #00086324).

Patient data was compiled from the electronic medical record and from existing institutional cardiac catheterization and surgical databases and then entered into a de-identified REDCap database. Clinical data collected for each subject included demographic data; key diagnostic, surgical, and hospitalization variables; catheterization data; and pre-Fontan echocardiographic data. Data was compiled from procedures (catheterization, echocardiography) and clinical records in closest proximity to the Fontan surgery.

Statistical analysis

Standard summary statistics, expressed as median (interquartile range) for continuous variables and count with percent of total for categorical variables, were used to describe patient characteristics and outcomes. A chi-square test was used for univariable statistical comparisons, and a two-tailed p-value < 0.05 was considered significant.

For multivariable analysis, the primary composite outcome was defined *a priori* as post-operative death and/or transplant within 6 months of Fontan, post-Fontan length of stay $\geq$ 30 days, or readmission within 6 months of Fontan surgery for Fontan-related complications (e.g. recurrent pleural effusions, protein-losing enteropathy, plastic bronchitis, desaturation warranting further evaluation). Our baseline multivariable logistic regression model incorporated risk factors known to be associated with adverse post-operative outcomes obtained from non-invasive data only (clinical history and echocardiography). Baseline risk factors incorporated into the model included presence of a systemic right ventricle, heterotaxy syndrome, any systemic ventricular systolic dysfunction, >mild systemic atrioventricular valve regurgitation, surgery date, and performance of any other surgical procedure at the time of Fontan surgery including (but not limited to) pulmonary artery patching, pacemaker implantation, aortic arch revision, and/or atrioventricular valve intervention. To better quantify the effect of surgery date, we reran the model using a binary variable, surgeon era, reflecting Fontan procedures performed from January 2000 to June 2010 (n = 97) versus from July 2010 to July 2017 (n = 77). These two eras reflect eras with different surgical teams in place at our institution.

To evaluate the potential benefit of including invasive haemodynamic data on risk prediction, we then reran the original baseline multivariable model with the addition of individual haemodynamic markers obtained from catheterization including systemic ventricular end-diastolic pressure, transpulmonary gradient, mean pulmonary artery pressure, pulmonary vascular resistance index, and cardiac index. Haemodynamic variables were included individually, and the model was considered improved based on an improvement in the model likelihood ratio. The likelihood ratio is a measure of the model goodness of fit and is used to compare hierarchically nested models such as the ones created in this analysis.[8,9] We also considered the number of positive and adverse outcomes predicted by the model, as well as the overall model accuracy using a critical probability threshold for the model of 0.5 for classifying an observation as a predicted response. Finally, a composite haemodynamic risk marker was created by assigning one point for each haemodynamic variable meeting the following thresholds: end-diastolic pressure > 8 mmHg, transpulmonary gradient > 5 mmHg, mean pulmonary artery pressure > 12 mmHg, pulmonary vascular resistance index > 3.0 Woods units x m2, and cardiac index < 2.5 L/min/m2. These parameters were chosen based on the approximate worst 25th percentile for the cohort with some rounding of variables to a clinically meaningful unit. Once again, the baseline model was rerun with the addition of the composite haemodynamic score as a model covariate and the model likelihood ratio, and prediction accuracy was evaluated as a measure of model improvement.

We performed two sensitivity analyses to assess the potential impact of Fontan fenestration on our model performance. First, we included Fontan fenestration as a model covariate in both the baseline risk model and all models incorporating haemodynamic parameters. Then we repeated the analysis after excluding all patients with Fontan fenestration (n = 89). We performed a third sensitivity analysis including "any trans-catheter intervention" to evaluate the role of pre-Fontan trans-catheter interventions on post-Fontan outcomes. SPSS statistical software (Chicago, Ill) was used for all analyses.

Results

The final study cohort included 174 patients. Patient demographics and risk factors are summarized in Table 1; 52% were male, most underwent extracardiac conduit Fontan (90%), and about half were fenestrated (51%). The median (interquartile range) age at the time of Fontan was 40 months (31, 45) with a median of 52 days (2, 77) between cardiac catheterization and surgery. Overall, 20.7% of patients underwent concomitant cardiac procedures at the time of Fontan operation. Of the baseline non-invasive risk factors, 58% had a systemic right ventricle, 12.6% had heterotaxy, 9.8% had ventricular dysfunction, and 10.9% had greater than mild atrioventricular valve regurgitation.

Post-operative outcomes are summarized in Tables 2 and 3; 65 patients (37%) met the composite primary outcome—12.6% had a prolonged length of stay $\geq$ 30 days, 31.8% had hospital readmission within 6 months, and 2.9% had death and/or transplant within 6 months of Fontan completion. Overall, 50% experienced a post-op complication with the most common being prolonged (>14 days) pleural effusions occurring in 34%. Complications were significantly more common in those with prolonged length of stay (75% vs 42%, $p < 0.01$) with a non-significant trend towards higher prevalence in those with readmission (60% vs 44%, $p = 0.07$).

Table 4 summarizes the risk prediction modelling. The baseline model includes only non-invasively acquired covariates. Significant predictors of adverse post-Fontan outcomes included the presence of a systemic right ventricle (adjusted odds ratio [aOR] 2.9; 95% CI 1.4, 5.8; $p = 0.004$), earlier surgical era (aOR 3.1 for era 1 vs 2; 95% CI 1.5, 6.5; $p = 0.002$), and performance of concomitant surgical procedures at the time of Fontan surgery (aOR 2.5; 95% CI 1.1, 5.0; $p = 0.026$). The baseline multivariable

https://doi.org/10.1017/S1047951124025290 Published online by Cambridge University Press

Table 1. Baseline patient characteristics (N = 174)

Patient demographics and surgery data	
Male gender	91 (52.3%)
Diagnosis	
Hypoplastic left heart syndrome	54 (31%)
Tricuspid atresia	22 (12.6%)
Unbalanced AVCD (hypoplastic RV)	9 (5.2%)
Unbalanced AVCD (hypoplastic LV)	19 (10.9%)
Double inlet left ventricle	14 (8%)
Pulmonary atresia	25 (14.4%)
Double outlet right ventricle	24 (13.8%)
Other	7 (4%)
Time cath to surgery (days)	52 (2, 77)
Age at Fontan (months)	40 (31, 45)
Weight at Fontan (kg)	14.1 (12.3, 15.1)
Fontan type	
Lateral tunnel	18 (10.3%)
Extracardiac conduit	156 (89.7%)
Fenestrated	89 (51.1%)
Concomitant procedure	36 (20.7%)
Bypass time (minutes)	114 (81, 137)
Cross-clamp time (minutes)	10 (0, 0)
Non-invasive risk factors	
Systemic RV	101 (58%)
Heterotaxy syndrome	22 (12.6%)
Ventricular dysfunction	17 (9.8%)
>Mild AV regurgitation	19 (10.9%)
Cath data variables	
Systemic ventricular EDP (mmHg)	6 (5, 8)
Transpulmonary gradient (mmHg)	4 (3, 5)
Mean PA pressure (mmHg)	10.0 (8.5, 11.0)
PVRI (Woods units/m^2)	2.1 (1.4, 3.0)
Cardiac index (L/min/m^2)	3.4 (2.5, 4.3)

Data reported represent n (%) or median (25, 75th percentile). AVCD = atrioventricular canal defect; RV = right ventricle; LV = left ventricle; PVRI = pulmonary vascular resistance index; EDP = end-diastolic pressure.

Table 2. Cohort outcomes

Primary outcomes	
Death and/or transplant ≤ 6 months	5 (2.9%)
Prolonged LOS (≥30 days)	22 (12.6%)
Readmission within 6 months	55 (31.8%)
Composite outcome	65 (37%)

Data reported represent n (%) or median (25, 75th percentile). LOS = length of stay.

model accurately predicted 67.8% of overall outcomes including 84% of patients that did not meet the composite endpoint and 42% of patients that did have an adverse outcome, with a model likelihood ratio of 202.8. Incremental addition of individual haemodynamic variables did not improve the model with a lower model likelihood ratio in all cases and only incremental change in the percentage of predicted adverse outcomes (Table 5). None of the haemodynamic variables reached statistical significance. The inclusion of a composite haemodynamic risk score also did not improve the overall model goodness of fit or performance with the model likelihood ratio reduced to 190.8 and a predictive accuracy of 68%.

Table 3. Cohort outcomes

Other outcomes	
Prolonged pleural effusions (>14 days)	60 (34.4%)
Acute kidney injury	9 (5.2%)
Diaphragm paralysis	8 (4.6%)
Arrhythmia	8 (4.6%)
Sepsis/surgical site infection	8 (4.6%)
Hepatic dysfunction	4 (2.3%)
Arrest/mechanical circulatory support	2 (1.1%)
Neurologic injury	2 (1.1%)

Data reported represent n (%) or median (25, 75th percentile).

In sensitivity analyses, inclusion of Fontan fenestration as a model covariate did not change the baseline model performance (model likelihood ratio = 196.1) or predictive value (69% of outcomes predicted). Fenestration was not significantly associated with the primary outcome measure ($p = 0.07$), and inclusion of fenestration did not affect any of the models incorporating haemodynamic markers. After excluding all patients with Fontan fenestration (n = 89), the overall model performance was significantly reduced due to the lower number of patients; however, the model was once again not improved with addition of any of the individual haemodynamic markers or with the inclusion of the composite haemodynamic risk score. In a third sensitivity analysis, we assessed the potential impact of trans-catheter interventions on the model prediction. Overall, catheter interventions were performed in a third of our cohort (58/174, 33.3%) including collateral occlusion in 51, pulmonary artery or Glenn/SVC angioplasty in 6, and arch angioplasty in 3. In sensitivity analysis, patients receiving a trans-catheter intervention had an increased risk of our composite outcome (OR 2.70, $p = 0.01$), but there was no change to model performance (model likelihood ratio 201.5) or predictive value (70.1% of outcomes predicted).

Discussion

We developed a multivariable model to predict adverse post-operative outcomes following Fontan surgery using exclusively non-invasively acquired risk factors. The model identified expected risk factors, including earlier surgical era, presence of a systemic right ventricle, and need for concomitant surgical procedures at the time of Fontan, and had acceptable performance with respect to risk prediction (68% of outcomes accurately predicted). Addition of invasive haemodynamic variables to the model (either individually or as a composite score) did not improve model performance or prediction (Fig. 1). Our results do not challenge the stand-alone value of haemodynamic data for risk

https://doi.org/10.1017/S1047951124025290 Published online by Cambridge University Press

Table 4. Baseline multivariable model—non-invasive predictors of adverse outcome

Risk factors	OR (95% CI)	P-value	Model LR	Overall % outcomes predicted	% Negative outcomes predicted
Systemic RV	**2.9 (1.4–5.8)**	**0.004**	202.8	67.8%	41.5%
Heterotaxy syndrome	1.3 (0.4–3.7)	0.659			
Any ventricular dysfunction	1.0 (0.3–2.9)	0.954			
>Mild AVV regurgitation	1.4 (0.4–4.1)	0.584			
Surgery date	**1.0 (1.0–1.0)**	**0.001**			
Concomitant surgery	**2.5 (1.1–5.0)**	**0.026**			
Models incorporating haemodynamic variables*					
Systemic ventricle end diastolic pressure	1.0 (0.8–1.2)	0.756	202.4	68.2%	44.6%
Transpulmonary gradient	1.0 (0.8–1.3)	0.972	202.8	67.8%	41.5%
Mean pulmonary artery pressure	1.1 (0.9–1.2)	0.522	197.1	67.8%	42.2%
Pulmonary vascular resistance index	1.1 (0.8–1.5)	0.702	200.9	67.4%	40.6%
Cardiac index	1.0 (0.8–1.3)	0.743	202.6	69.5%	46.2%
Composite haemodynamic risk score	1.2 (0.8–1.9)	0.442	190.8	68.0%	44.3%
Sensitivity analysis including fenestration	0.8 (0.4–1.6)	0.067	196.1	69.4%	47.6%g

RV = right ventricle, AVV = atrioventricular valve. *Haemodynamic variables incorporated individually into the baseline model with no other covariates differing from the baseline model. Bold highlights the risk factors that were statistically significant (P value <.05).

Table 5. Comparison of model performance at baseline, with incremental addition of individual haemodynamic parameters and with inclusion of a composite haemodynamic score

Model	Model LR	Overall % of outcomes predicted	% of negative outcomes predicted
Baseline model	202.8	67.8%	41.5%
Baseline + EDP	202.4	68.2%	44.6%
Baseline + TPG	202.8	67.8%	41.5%
Baseline + mean PA pressure	197.1	67.8%	42.2%
Baseline + PVRI	200.9	67.4%	40.6%
Baseline + cardiac index	202.6	69.5%	46.2%
Baseline + composite haemodynamic score	190.8	68.0%	44.3%
Sensitivity analysis including fenestration	196.1	69.4%	47.6%

LR = likelihood ratio; EDP = systemic ventricle end-diastolic pressure; TPG = transpulmonary gradient; PA = pulmonary artery; PVRI = pulmonary vascular resistance index.

stratification but demonstrate that they do not add to baseline risk prediction above that provided by non-invasively acquired data.

Historically, invasive haemodynamic data have been shown to predict complications with Fontan.[10–13] However, more recent studies have questioned this long-held relationship.[4–7] Similar to our analysis, other investigators have evaluated the utility of non-invasive risk prediction models. Prakash et al. developed an algorithm using history, echocardiogram, and angiography alone for identifying low-risk Fontan candidates that may not require invasive haemodynamic assessment. When they retrospectively applied their algorithm to a cohort of Fontan patients, they successfully identified all inoperable Fontan candidates without needing invasive haemodynamic data. Similar to our analysis, they found no difference in risk prediction with the addition of haemodynamic data; however, sensitivity and risk prediction were modest with a sensitivity of 51% and positive predictive value of 45%.[5] Banka et al. also found that cardiac catheterization prior to Fontan was clinically nonadditive for about half of all patients and found no association between haemodynamic data and post-operative outcomes.[6] However, no prior study has evaluated whether invasive haemodynamic data add incremental value to these non-invasive risk prediction models. Our findings, indicating limited incremental value, are consistent with a retrospective study by Fogel et al. where Fontan candidates underwent pre-operative evaluations with either non-invasive imaging alone (using cardiac MRI and echocardiogram) versus non-invasive imaging plus cardiac catheterization. They found no significant difference in operative or short-term clinical outcomes between the two groups, suggesting that low-risk single ventricle patients can achieve similar short-term outcomes without undergoing routine cardiac catherization.[7] Similarly, Biko et al. used cardiac MRI as part of the pre-Fontan evaluation and found an association between lymphatic malformations and Fontan outcomes.[14] Thus non-invasive assessment continues to evolve and offers increasingly accurate risk prediction. Nonetheless, there may be additive value to haemodynamic evaluation in higher-risk patients where non-invasive evaluation raises concerns.

We recognize that pre-Fontan catheterization offers other benefits beyond haemodynamic evaluation including anatomic definition as well as the potential for intervention when needed. At our institution and most others, angiographic evaluation is performed in all patients undergoing pre-Fontan catheterization. Additionally, catheter interventions were performed in a third of our cohort. However, in sensitivity analysis including catheter interventions in the model, there was again no change to the model prediction. Angiography and interventions are both important components of the pre-Fontan catheterization. Our intent is not to

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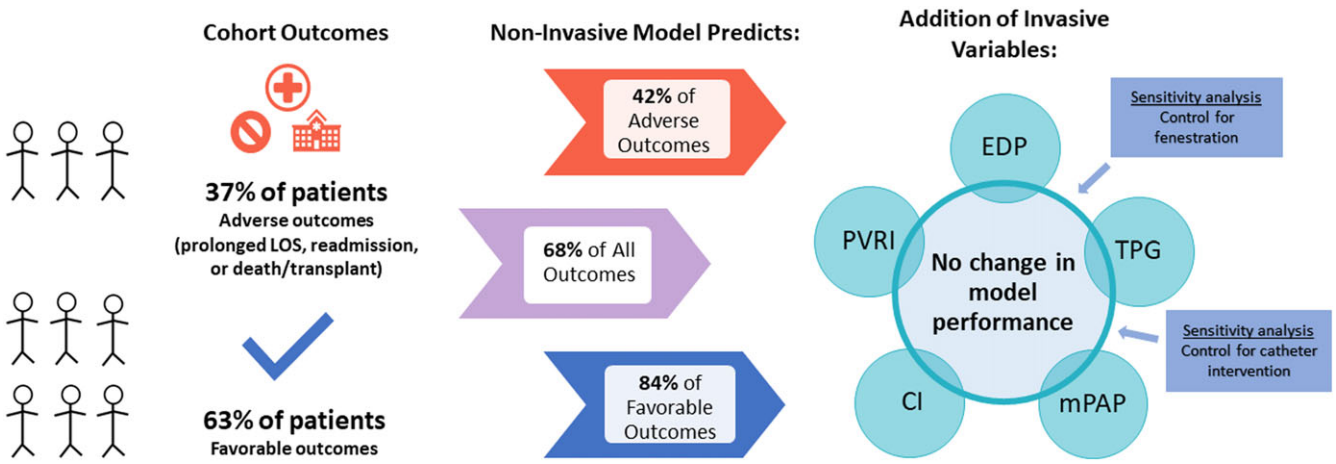

Figure 1. Visual abstract summarizing study outcomes. LOS = length of stay; EDP = end-diastolic pressure; TPG = transpulmonary gradient; mPAP = mean pulmonary artery pressure; CI = confidence interval; PVRI = pulmonary vascular resistance index.

discredit the value of pre-Fontan catheterization but rather to demonstrate that the need for haemodynamic data should not be considered a stand-alone reason for pre-Fontan catheterization in the low-risk Fontan candidate.

In our study, adverse post-operative outcomes were associated with non-invasive factors including a systemic right ventricle, surgical era, and concomitant cardiac surgical procedures at the same time of Fontan. Although studies assessing the impact of ventricular morphology on Fontan outcomes have been conflicting, our results are consistent with recent studies that showed an association between a systemic right ventricle and worse post-Fontan outcomes[15,16], including a recent meta-analysis demonstrating that a systemic right ventricle was associated with longer hospital length of stay after Fontan and increased long-term mortality.[17] Although heterotaxy, atrioventricular valve regurgitation, and ventricular dysfunction are known risk factors associated with adverse post-Fontan outcomes,[13,18,19] these factors were not found to be independently associated with adverse outcomes in our study. Prakash et al. also found that non-invasive risk factors were associated with adverse post-Fontan outcomes, though those risk factors were different and included heterotaxy, genetic syndromes, greater than moderate atrioventricular valve regurgitation, and longer cardiopulmonary bypass times.[5] Patients with a variety of non-invasive risk factors can be identified as higher risk for adverse outcomes following Fontan.

This study is retrospective and subject to limitations inherent in any retrospective design. The study spans over two decades, during which there were multiple cardiac surgeons at our institution with different techniques used for Fontan palliation and with general evolution of surgical practices. Indeed, one of our key findings was an association between earlier surgical dates and a higher presence of post-operative complications. Although we used a sensitivity analysis to assess the potential impact of trans-catheter interventions on outcomes, it remains possible that these interventions might have impacted our outcomes in ways that we could not control for with a multivariable model. It is also possible that haemodynamic findings might have influenced clinical decisions (e.g. placement of a fenestration or use of prophylactic pulmonary vasodilators). It is also possible that our negative findings reflect variability in haemodynamics due to factors such as level of sedation, positive pressure ventilation, and volume status during cardiac catheterization. These variables may distort the risk prediction utility of catheterization-derived haemodynamics. Nonetheless, this would not change our interpretation that invasively acquired haemodynamic data does not add to non-invasive risk prediction. Finally, we investigated short- and intermediate-term outcomes after Fontan completion, but with no long-term follow-up beyond 6 months. It is possible that pre-Fontan catheterization data provides additional long-term clinical utility.

In conclusion, we demonstrated that routine cardiac catheterization for haemodynamic assessment prior to Fontan did not improve the prediction of post-operative outcomes in addition to non-invasive clinical data and imaging alone. Consistent with prior studies, adverse post-operative outcomes were associated with non-invasive risk factors. Overall, our study suggests that avoiding routine pre-Fontan catheterization will not change the prediction of short-term adverse outcomes following Fontan. Centres may consider forgoing pre-Fontan catheterization in low-risk candidates; however, catheterization may still be necessary for angiographic anatomic evaluation in which non-invasive imaging was equivocal or concerning and/or for the purposes of intervention.

Acknowledgements. None.

Financial support. None.

Competing interests. None.

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