ORIGINAL ARTICLE

Sisyphus's Dilemma: Measurement of Ventricular-Arterial Coupling by Doppler Echocardiography Predicts the Incidence of Right Ventricular Failure after Heart Transplantation Better than Right Catheterization

El dilema de Sísifo: La medición del acople ventrículo arterial medido por eco-Doppler predice la incidencia de falla del ventrículo derecho postrasplante cardíaco mejor que el cateterismo derecho

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Sisyphus,King of Ephira, was condemned by Zeus to remain in Hades, from which he could leave if he managed to climb up the steep slope of a mountain with a heavy stone. The same, before reaching the top, rolled down again, repeating over and over again the frustrating process.

Does Sisyphus problem lie in his strength or in the weight of the stone?

ABSTRACT

Background: Increased pulmonary vascular resistance, assessed by right catheterization, is usually mentioned as a relative contraindication for inclusion in the list of heart transplantation since it is associated with failure of the implanted right ventricle. There is evidence suggesting that the behavior of the pulmonary circulation depends on its interaction with the right ventricle, so a parameter that evaluates ventricular-arterial coupling could predict right ventricular failure better than isolated hemodynamic parameters.
Objective: The aim of this study was to assess the ability of the tricuspid annular plane systolic excursion/pulmonary systolic pressure ratio (TAPSE/PSP) to predict the incidence of post-transplantation right ventricular failure compared with invasive hemodynamic parameters measured before transplantation.
Methods: This was a retrospective cohort study using variables prospectively collected from the heart transplantation database of a University Hospital of the City of Buenos Aires. A total of 56 consecutive patients with complete echocardiographic and hemodynamic tests, undergoing heart transplantation between January 2012 and April 2017, were included in the study. Patients with more than one parenchymal transplantation, retransplantation, congenital heart disease, those requiring ventricular assistance at the time of pre-transplantation assessment or with incomplete data were excluded.
Results: Three patients (5.3%) died within the first 30 days, 2 from right ventricular failure. No preoperative hemodynamic or echocardiographic parameters were associated with mortality. The incidence of right ventricular failure in the immediate postoperative period was 28.5% (16 patients). All the hemodynamic variables of pulmonary pressure and resistance, and the TAPSE/PSP ratio measured by echocardiography were associated with the development of right ventricular failure after heart transplantation. In a multivariate analysis including hemodynamic and echocardiographic variables, the TAPSE/PSP ratio was the only one independently associated with right ventricular failure (0R>10, 95% CI 2.2->100, p=0.03). A TAPSE/PSP cut-off value of 0.26 showed sensitivity of 81% and specificity of 88% to predict right ventricular failure, with an area under the ROC curve of 0.84 ± 0.06 and X2=0 in the Hosmer-Lemeshow test (p=1) when considering quartiles of TAPSE/PSP. A predictive model of right ventricular failure composed of hemodynamic variables showed a sensitivity of 38% and a specificity of 97.5%, with an area under the ROC curve of 0.78±0.06 and X2=2.37 (p=0.3) in the Hosmer-Lemeshow test.
Conclusions: We can conclude that the TAPSE/PSP ratio showed better discrimination and calibration to predict right ventricular failure, with 0.26 as the best prognostic performance value.

Key words: Heart failure - Right ventricular dysfunction - Heart transplantation - Pulmonary hypertension - Heart ventricles/physiopathology - Tricuspid valve/diagnostic imaging

RESUMEN

Introducción: El aumento de la resistencia vascular pulmonar (RVP), evaluada por cateterismo derecho suele citarse como una contraindicación relativa para la inclusión en lista de trasplante cardíaco debido a que se asocia a la falla del ventrículo derecho (VD) implantado. Existe evidencia que sugiere que el comportamiento de la circulación pulmonar depende de su interacción con el ventrículo derecho por lo que un parámetro que evalúe el acople ventrículo – arterial podría predecir la falla de VD mejor que parámetros hemodinámicos aislados.

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Objetivos: El objetivo de este estudio fue evaluar la capacidad de la relación TAPSE / PSP de predecir la incidencia de falla de VD post-trasplante en relación con parámetros hemodinámicos invasivos medidos antes del trasplante.
Material y Métodos: Estudio de cohorte retrospectiva utilizando variables recolectadas en forma prospectiva de la base de trasplante cardíaco de un Hospital Universitario de la Ciudad de Buenos Aires. Se incluyeron 56 pacientes consecutivos sometidos a trasplante cardíaco entre Enero de 2012 y Abril de 2017, de los cuales se contaba con la totalidad de las variables ecocardiográficas y hemodinámicas. Se excluyeron los pacientes con trasplante de más de un parénquima, los retrasplantes, aquellos con cardiopatías congénitas, los que presentaron requerimiento de asistencia ventricular al momento de la evaluación pretrasplante, y los pacientes con datos incompletos.
Resultados: Tres pacientes (5.3%) fallecieron dentro de los primeros 30 días, en 2 de estos se objetivó falla del VD. Ningún parámetro hemodinámico ni ecocardiográfico preoperatorio se asoció con mortalidad. La incidencia de falla VD en el posoperatorio inmediato fue del 28.5% (16 pacientes). Todas las variables hemodinámicas de presión y resistencia pulmonar, y la relación TAPSE / PSP medida por ecocardiogrfía se asociaron con el desarrollo de falla del VD post trasplante. Luego de realizar un análisis multivariado incluyendo variables hemodinámicas y ecocardiográficas la relación TAPSE/PSP fue la única que se asoció en forma independiente a falla de VD (OR >10; IC95 2.2->100; p=0.03). Un valor de corte de TAPSE / PSP de 0.26 mostró una sensibilidad de 81% y una especificidad de 88% para predecir falla de VD, con un ABC ROC de 0.84±0.06 y el valor de X2 en la prueba de Hosmer-Lemeshow fue 0 (p=1) al considerar cuartiles de TAPSE / PSP. Un modelo predictivo de falla de VD compuesto por variables hemodinámicas mostró una sensibilidad del 38% y una especificidad del 97.5%, con un área bajo la curva ROC de 0.78±0.06 y un valor de X2 en la prueba de Hosmer-Lemeshow de 2.37 (p=0.3).
Conclusiones: Podemos concluir que la relación TAPSE/PSP mostró una mejor discriminación y calibración para predecir la falla de VD, siendo 0.26 el valor con mejor desempeño pronóstico.

Palabras clave: Insuficiencia cardíaca - Disfunción Ventricular Derecha - Trasplante de corazón - Hipertensión pulmonar - Ventrículos Cardíacos/fisiopatología – Válvula tricúspide/diagnóstico por imágenes

Abbreviations

Ees	End-systolic elastance	**PVR**	Pulmonary vascular resistance
EDRVV	End-diastolic right ventricular volume	**SV**	Stroke volume
Ea	Pulmonary arterial elastance	**RV**	Right ventricular
PHT	Pulmonary hypertension	**TAPSE**	Tricuspid annular plane systolic excursion
mPAP	Mean pulmonary artery pressure	**WU**	Wood unit
PSP	Pulmonary systolic pressure		

INTRODUCTION

The presence of pulmonary hypertension (PHT) with increased pulmonary vascular resistance (PVR) greater than 5 Wood units (WU), evaluated by right catheterization, is usually mentioned as a relative contraindication for the inclusion in the list for heart transplantation due to its correlation with higher post-transplantation morbidity and mortality, especially secondary to right ventricular (RV) failure. (1, 2)

In recent years, increasing attention has been paid to RV-arterial coupling as a predictor of events in patients with heart failure. This relationship between RV systolic function and pulmonary vascular compliance is theoretically defined as the ratio between end-systolic ventricular elastance and arterial elastance. The direct measurement of elastance requires precise data of the pressure/volume ratio throughout the cardiac cycle, which cannot always be obtained. For this reason, surrogate variables that can replace them and maintain their prognostic value have been proposed. (1, 2) In this sense, the use of the ratio between the tricuspid annular plane systolic excursion (TAPSE) and pulmonary systolic pressure (PSP) has proved to have a prognostic value in patients with chronic heart failure and PHT. (3)

The aim of this study was to evaluate the ability of the TAPSE/PSP ratio to predict the incidence of post-transplantation RV failure compared with invasive hemodynamic parameters measured before transplantation.

METHODS

A retrospective cohort study was performed using variables prospectively collected from the HEART transplantation database of a University Hospital of the City of Buenos Aires. Among a total of 117 heart transplantations conducted between January 2012 and April 2017, 56 consecutive patients with complete echocardiographic and hemodynamic variables were included in the study. Exclusion criteria were lack of complete echocardiographic evaluation (37 patients), having undergone two or more parenchymal transplantations simultaneously (8 patients), heart retransplantation (2 patients), requiring ventricular assistance at the time of the pre-transplantation cardiac evaluation (9 patients) and patients with congenital heart disease (5 patients).

Hemodynamic and ultrasound determinations

The last right catheterization before heart transplantation was used to obtain complete hemodynamic data. The transpulmonary gradient was calculated as the difference between mean pulmonary artery pressure (mPAP) and wedge pressure (Pw). Pulmonary vascular resistance (expressed in WU) was estimated from the ratio between the transpulmonary gradient and cardiac output (CO). These measurements were made with a Swan Ganz catheter capable of estimating CO by thermodilution (Vigilante II computer, Baxter-Edwards, Santa Ana, CA, USA). The invasive measurement of end-diastolic right ventricular volume (EDRVV) was performed with the same catheter, during the same procedure from which the rest of the data were obtained. The EDRVV is calculated from the difference between the end-diastolic and end-systolic temperatures detected by the catheter thermistor. This difference estimates the RV residual fraction, which in turn allows the calculation of ejection fraction (RVEF=1-residual fraction). Stroke volume (SV) is obtained from CO and heart rate. Then, EDRVV is calculated from the equation EDRVV=SV/EF.

Echocardiographic variables were obtained from the last complete study performed before transplantation, considering as valid the studies carried out within 6 months prior to transplantation. The TAPSE/PSP ratio was estimated using measurements from the same study. The cut-off values published by the American Society of Echocardiography and the European Association of Cardiovascular Imaging were used to define "dilatation" and RV "dysfunction". (6)

The primary end point was the incidence of RV failure, which was defined as the presence of echocardiographic evidence of RV dysfunction, associated with inotropic requirements in order to maintain a cardiac index greater than 2.2 l/m2.

Statistical analysis

Continuous variables are expressed according to their distribution, as mean and standard deviation in case of normal distribution, or as median and interquartile range in case of asymmetric distribution. Categorical variables are reported as percentages. The Mann-Whitney test or t-test was used to compare continuous variables; and the chi-square or Fisher's exact test for categorical variables. A linear regression analysis was performed using the endpoints as dependent variables. The variables that showed significant differences were included in a multivariate analysis. ROC curves were constructed to determine the diagnostic performance of each variable with respect to the development of RV failure. The Hosmer-Lemeshow test was used to compare calibration and the discrimination of the TAPSE/PSP ratio with respect to invasive hemodynamic variables. Statistical analyses were carried out with STATA 12 software package and p values<0.05 were considered statistically significant.

Ethical considerations

The present work was carried out in accordance with the international ethical guidelines in force for studies with human beings established in the Declaration of Helsinki (World Medical Association, 1964, last update 2013). All the study data were treated with maximum confidentiality, with restricted access only to authorized personnel for the purposes of the study, in accordance with the National Law on Protection of Personal Data 25.326 (Habeas Data Law).

The study was approved by the Institutional Research Protocols Ethics Committee.

RESULTS

Fifty-six patients were included in the analysis. Baseline characteristics (Table 1) showed that they had lower left ventricular ejection fraction and greater RV impairment than patients who were not included in the study. There were no differences regarding the rest of the variables. The prevalence of PHT with hyper-resistance, defined as mPAP ≥25 mmHg with PVR ≥3 WU, was 50% (28 patients).

Thirty-day mortality was 5.3% (n=3). Two patients died due to RV failure and one due to sepsis. No clinical, hemodynamic or preoperative echocardiographic variable was significantly associated with mortality.

Post transplantation right ventricular failure

The incidence of RV failure in the immediate postoperative period was 28.5% (n=16) and was significantly associated with a higher inotropic requirement (2.1 vs. 4.5 days, p <0.0001).

Ultrasound variables

A higher PSP (59±14 mmHg vs. 42±10 mmHg, p<0.001) was associated with a higher incidence of post-transplantation RV failure, whereas a lower TAPSE (13.2±2.8 mm vs. 15.6±3.6 mm, p=0.057) showed a non-significant trend.

The combination of both variables in a TAPSE/PSP ratio was associated with the occurrence of RV failure (0.24±0.09 vs. 0.40±0.15 mm/mmHg, p<0.001), 0.26 mm/mmHg being the cutoff value that best predicted its incidence. The diagnostic performance of each of the variables is shown in Table 2.

Regarding the hemodynamic variables assessed invasively, the increase in PVR expressed in WU (3.0±1.3 vs. 4.7 ± 2.5, OR 1.58 (1.12-2.24); p 0.008), PSP (44±15 mmHg vs. 60±17 mmHg; OR 1.06 (1.01-

Table 1. Baseline Characteristics

	Included	Not included	p
Male gender (%)	75	75	0.43
Age (years)	50 ± 11	50 ± 11	0.28
EF (%)	22 (IQ25-75 17-25)	22 (IQ25-75 17-25)	0.025
PSP (mmHg)	49±17	49±17	0.20
mPAP (mmHg)	34±11	34±11	0.13
mPAP >25mmHg + WU >3	50%	50%	0.15
Wedge (mmHg)	20±8	20±8	0.14
PVR (WU)	3.2 (IQ25-75 2.1-4.3)	3.2 (IQ25-75 2.1-4.3)	0.17
EDV (ml)	281 (IQ25-75 234-393)	281 (IQ25-75 234-393)	0.35
PDG > 7 mmHg (%)	25	25	0.53
CO (l/m)	3.8 (IQ25-75 3.3-4.5)	3.8 (IQ25-75 3.3-4.5)	0.90
Dilated RV (%)	60	60	0.31
Moderate. or Sev RV. (%)	69	69	0.019

EF: Ejection fraction. PSP: Pulmonary systolic pressure. mPAP: Mean pulmonary artery pressure. PVR: Pulmonary vascular resistance. EDV: End-diastolic volume. PDG: Pulmonary diastolic gradient. CO: Cardiac output. Sev: Severe: RV: right ventricle.

1.11); p 0.006) and mPAP (31±11 mmHg vs. 41±11 mmHg; OR 1.08 (1.02-1.15); p 0.009) were associated with the development of postoperative RV failure.

Of all the variables that were significantly associated to RV failure, the one with the best diagnostic performance was the TAPSE/PSP ratio by Doppler echocardiography. A TAPSE/PSP value of 0.26 mm/mmHg showed an area under the ROC curve of 0.84 with very good calibration according to the Hosmer-Lemeshow test (X2=4.7, p=0.1). (Table 4) Considering TAPSE/PSP by quartiles, the calibration capacity of this ultrasound parameter becomes perfect, reaching a value of X2=0 in the Hosmer-Lemeshow test (p=1) (Table 3). The performance of TAPSE/PSP to predict RV failure was even better than that of a model that integrates the invasive assessment of PVR, mPAP and CO (model 8 in Table 2, Figure 1)

In a multivariate analysis including hemodynamic and echocardiographic variables, the TAPSE/PSP ratio was the only variable independently associated with RV failure (OR>10, 95% CI 2.2->100, p=0.03). The integration of hemodynamic variables with TAPSE/PSP in a predictive model of RV failure marginally improved the discrimination of the model reaching an area under the ROC curve of 0.87 95% CI 0.76-0.98), at the expense of model calibration. (Table 2)

Correlation between ultrasound and invasive variables

The PSP value measured by Doppler ultrasound that best discriminated the development of RV failure was 57 mmHg, while for PSP measured by catheterization it was 56 mmHg. Both variables had a comparable diagnostic performance and a good correlation was observed between both PSP assessment methods (r=0.60, p<0.0001).

Ventricular-arterial coupling (V-A) can be estimated invasively in two ways: through pulmonary artery compliance (stroke volume/(systolic pressure-diastolic pressure) (7), or through the relationship between end-systolic elastance and pulmonary arterial elastance (Ees/Ea) which can be calculated in a simplified form as SV/end systolic volume (8, 9) Neither compliance (2.8±1.8 vs. 1.8±0.75, OR 0.53 (0.27-1.04), p 0.066) nor the Ees/Ea ratio (0.26±0.22 vs. 0.17±0.1, OR 0.01 (0.0001-10); p 0.2) were significantly associated with the incidence of RV failure. However, the TAPSE/PSP ratio had a good correlation with compliance (r=0.55, p<0.0001) and a moderate correlation with the elastance ratio (r=0.43; p<0.0051).

DISCUSSION

The TAPSE/PSP ratio was first described in 2013 by Guazzi et al. (10) Since then, its clinical value has been demonstrated in patients with PHT and in patients with heart failure with preserved systolic function (11, 12). To our knowledge, this is the first work that evaluates the usefulness of this parameter to predict the risk of RV failure after heart transplantation.

The hypothesis that gave rise to the work is that a variable, in this case TAPSE/PSP, integrating a RV

Table 2. Diagnostic performance of different predictors of right ventricular failurestress.

		Value	Area under the ROC curve	Calibration X2	Calibration P	Sensitivity	Specificity	Youden Index
				Ultrasound variables				
1	PSP by echo	57	0.82	24	0.85	56%	90%	0.46
2	TAPSE/PSP	0.26	0.84	4.7	0.1	81%	88%	0.69
				Invasive hemodynamic variables				
3	PSP (mmHg)	56	0.77	26	0.53	66%	77%	0.43
4	mPAP (mmHg)	37	0.75	8	0.01	81%	72%	0.53
5	PVR (WU)	5.6	0.67	1.04	0.59	44%	97%	0.41
6	Compl. (ml/mmHg)	2.7	0.33	1.3	0.52	18%	70%	-0.12
7	Ees/Ea	0.34	0.36	1.08	0.58	15%	89%	0.04
				Multivariate model				
8	mPAP+PVR+CO	-	0.76	2.31	0.31	38%	92%	0.30
9	2+4+5	-	0.87	6.51	0.03	50%	92%	0.42

9: Model composed of mPAP, PVR and TAPSE/PSP.
Sensit.: Sensitivity. Specif. Specificity. PSP: Pulmonary systolic pressure. TAPSE: Tricuspid annular plane systolic excursion. mPAP: Mean pulmonary artery pressure. PVR: Pulmonary vascular resistance. Compl.: compliance. Ees/Ea: End-systolic elastance / pulmonary arterial elastance. CO: Cardiac output.

Table 3. Probability of developing post transplantation right ventricular failure according to quartiles of TAPSE/PSP

Quartile	TAPSE/PSP ratio	Probability of RV failure	OR (95% CI)
1st quartile	0-0.23	65%	23 (2.3-235)
2nd quartile	0.24-0.28	45%	5.2 (0.5-54)
3rd quartile	0.29-0.45	20%	2.1(0.17-27)
4th° quartile	0.45-1	10%	Reference

TAPSE: Tricuspid annular plane systolic excursion. PSP: Pulmonary systolic pressure.

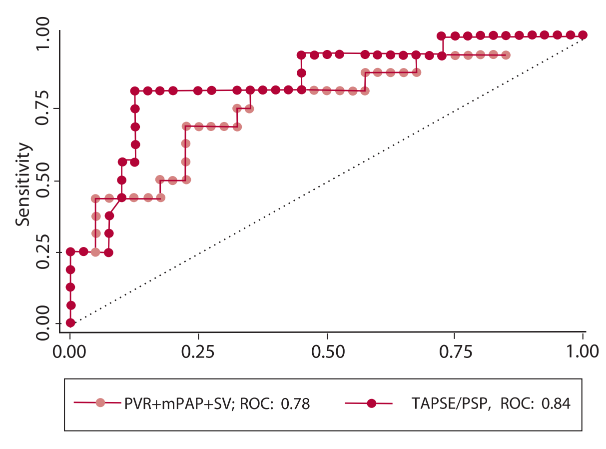


Fig. 1. Area under the ROC curve of a model composed of PVR, mPAP and CO measured in an invasive manner compared with the area under the ROC curve of ultrasound measured TAPSE/PSP

function parameter and a hemodynamic parameter influenced by PVR could predict the development of RV failure after heart transplantation. Maybe the better TAPSE/PSP performance over PSP, mPAP or PVR should not be a surprise. What turned out to be a finding was that TAPSE/PSP had a better predictive capacity than the end-systolic elastance/arterial elastance ratio and the calculation of pulmonary artery compliance.

End- systolic elastance (Ees) represents the ventricular inotropic state and is not affected by preload, afterload, or heart rate (13), while arterial elastance (Ea) is a parameter that groups all afterload components including mean vascular resistance, impedance and systolic and diastolic intervals. (14) The equation that determines Ea was simplified and validated by Kelly et al. as Ea=end-systolic pressure (ESP)/SV ratio. (15) The result of this ratio shares the same units (mmHg/ml) as Ees, which in turn is represented by the ratio Ees=ESP/end-systolic volume (ESV). Simplifying mathematical terms we have that Ees/Ea=SV/ESV, giving an equation that reflects ventricular-arterial coupling.

$$1)\ Ees = \frac{ESP}{ESV} \quad 2)\ Ea = \frac{ESP}{SV} \quad 3)\ \frac{Ees}{Ea} = \frac{SV}{ESV}$$

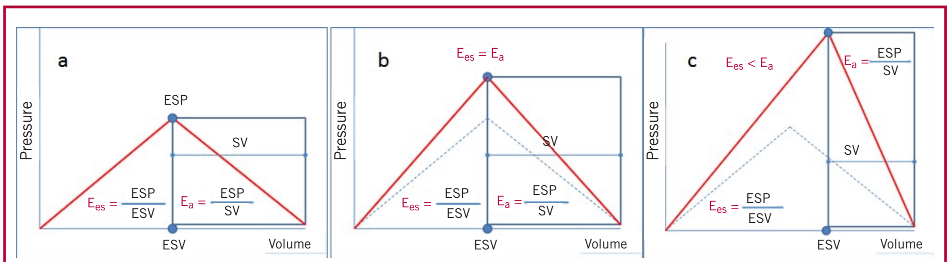
As afterload increases, Ees will increase in order to compensate for the increase in Ea. The arterial ventricular unit remains coupled as long as the Ees/Ea ratio is close to 1. If afterload continues to rise, the Ees/Ea ratio decreases and ventricular-arterial uncoupling occurs (16) (Figure 2). In this sense, our results are in line with those of Vanderpool et al. who showed that the Ee/Ea ratio derived from volume measurements obtained by magnetic resonance imaging or computed tomography was a predictor of survival in patients with PHT but not when it was estimated from invasive measurements. (16)

The TAPSE/PSP ratio showed a good degree of correlation with pulmonary vascular compliance. This would be attributable to the fact that compliance arises from the ratio between SV and pulse pressure, both variables measured directly by catheterization and subjected to technical issues and mathematical assumptions. This correlation supports the hypothesis that TAPSE/PSP would be an echocardiographic surrogate of pulmonary vascular remodeling and the ensuing decrease in the vascular bed compliance. This is particularly interesting in the light of a recently published work by Palazzini et al. in which they observed that the compliance of the pulmonary artery is a risk marker for mortality in patients with heart failure and PHT. (17) Although this observation does not allow to draw conclusions, it opens a field of research for a relatively unexplored variable which is obtained in a simple, reproducible and non-invasive way. (12)

Limitations

The single center and retrospective nature of the study is one of the limitations of this work. This resulted in the non-simultaneous performance of echocardiographic and hemodynamic measurements, added to the fact that not all the patients had the necessary echocardiographic measurements to be included in the analysis. The latter, together with the small number of fatal events, prevented reaching statistical

Fig. 2. Ventricular-arterial coupling



a) Ventricular-arterial coupling Ees=Ea. b) Increasing afterload (Ea) there is a proportional increase in contractility (Ees). c) Additional afterload increase cannot be compensated by contractility leading to ventricular-arterial uncoupling. Ea: Pulmonary arterial elastance; Ees: End-systolic elastance; ESP: End-systolic pressure. ESV: End-systolic volume .SV: Stroke volume.

significance between the TAPSE/PSP ratio and mortality. This forces to extrapolate the conclusions from a less robust endpoint such as RV failure. However, this last limitation is mitigated by the evidence that the patients who were classified within the group that presented RV failure, required longer support and evidenced a tendency towards higher mortality.

CONCLUSIONS

The estimation of RV arterial coupling through the TAPSE/PSP ratio showed better discrimination and calibration to predict postoperative RV failure than classical hemodynamic variables in adult patients undergoing orthotopic heart transplantation. A TAPSE/PSP ratio of 0.26 was the value with the best prognostic performance. Due to the limitations of this work, it would be very important to validate these findings prospectively in a larger cohort.

Conflicts of interests

None declared.
(See authors' conflicts of interest forms on the web/Supplementary material).

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