Several echocardiographic indices\textsuperscript{1–11} have been proposed to be prognostically important in patients with pulmonary hypertension (PH). Most indices have been derived from single-center studies involving heterogeneous cohorts of patients with different etiologies of PH and limited number of patients. Recent PH guidelines\textsuperscript{1,2} suggest that a tricuspid annular plane systolic excursion (TAPSE) $<15$ mm and the presence of a pericardial effusion (PEf) are associated with poor prognosis. Right atrial pressure (RAP) has also been shown to be a negative prognostic marker for idiopathic pulmonary arterial hypertension (PAH).\textsuperscript{12–15} However, there has not been a systematic study to date in patients with primary PH, which examines echocardiographic and hemodynamic indices as prognostic markers of survival separately in PAH and chronic thromboembolic pulmonary hypertensive disease (CTEPH). Therefore, the aim of this study was a systematic longitudinal assessment of echocardiographic and invasive hemodynamic measures in a large patient cohort with primary PH to model survival.

See Clinical Perspective
January 2002 and December 2011 were prospectively recruited for the study. Patients had a comprehensive transthoracic echocardiogram and invasive hemodynamic assessments, before commencing medical treatment.

Echocardiographic measurements were performed in accordance with the British, European, and American guidelines for echocardiographic assessment of PH.1,2,10–27 All patients also underwent left and right heart catheterization. Diagnostic criteria for precapillary PH were based on the current European guidelines,1 which included a combination of invasive hemodynamic measures (mean pulmonary arterial pressure ≥25 mm Hg at rest, pulmonary arterial wedge pressure ≤15 mm Hg and pulmonary vascular resistance (PVR)>3 Wood units).1,2 and echocardiographic parameters such as tricuspid regurgitant (TR) velocity ≥2.6 m/s for patients below the age of 60 years or ≥2.9 m/s when older than 60 years or ≥2.8 m/s in obese patients (body mass index ≥30).2,10 The differentiation between PAH and CTEPH was made using ventilation–perfusion and computed tomographic scans of the lungs to exclude thromboembolic disease.1,2

The most important echocardiographic measurements and the methodology of acquisition are described in Figure 1.

Exclusion Criteria
Patients were excluded if they had postcapillary PH because of (1) mitral and aortic valve disease, atrial tumors, congenital heart disease, myocardial disease, pulmonary vein compression, disproportional lung disease primarily (restrictive and obstructive types) resulting in PH, transplant recipients or patients who received an endarterectomy because of an acute reduction of pulmonary pressures, significant cardiac arrhythmias including ventricular arrhythmias, and fast (nonrate controlled) atrial fibrillation, free flow TR, significant uncontrolled essential hypertension, and pulmonary capillary wedge pressure >15 mm Hg. Patients with a positive va- soreactivity study3 were also excluded from the study because of a favorable reversible prognosis.

Patient Follow-Up
The follow-up was through regular clinic visits every 6 months according to the PH center’s protocol except for patients with clinical deterioration who are assessed earlier.2,12

Data Collection
All patients were assessed for symptoms of heart failure based on the World Health Organization (WHO) classification system for heart failure on admission and during the follow-up visit. Mortality data were obtained from the medical records and confirmed with the National Registry of Births, Deaths, and Marriages.

Echocardiography
All echocardiograms were performed using Philips iE33 and Sonos 7500 ultrasound machines (Andover, MA). Measurements were performed offline on the index study and the most recent echocardiogram during the follow-up period. All echoes were analyzed by an observer blinded to the clinical history and patients outcomes. A range of echocardiographic parameters18–25 was measured by 1 observer (J.G.). Intraobserver variability was assessed for all echocardiographic parameters on a 100 patients randomly sampled from the population. An average of 3 consecutive cardiac cycles was presented and relevant parameters indexed for heart rate and body surface area. Severity of TR, right ventricular (RV) and PA dilatation were analyzed as categorical variables. Patients with TR were classified as 2 groups based on severity: trivial-mild and moderate–severe. TR was assessed visually based on the color Doppler flow disturbance in systole localized to the area adjacent to the valve closure plane.9,10 Intraobserver variability was assessed in 100 patients randomly sampled from the 777 patients. The majority of the echocardiographic parameters showed low intraobserver variability. RV fractional area change (FAC) and RV myocardial performance index (MPI) had a moderate degree of variability (RV FAC: ICC, 0.72; P=0.04; mean bias, 8.4%; SD of bias, 5.6% and RV MPI: ICC, 0.69; P=0.02; mean bias, 0.23; SD of bias, 0.15), whereas PVR showed a higher variability consistent with lower reproducibility (PVR: ICC, 0.64; P=0.025; mean bias, 8 and SD of bias, 3.2).

Baseline Invasive Hemodynamic Data
Invasive hemodynamic measurements1–4 were obtained before the initiation of treatment and included systolic, diastolic and mean systemic arterial pressure, mean pulmonary arterial systolic pressure, PVR, mean pulmonary capillary wedge pressure, mean RAP, and cardiac index (CI). Right heart catheterizations that were performed included a fluid challenge,12,13 to unmask any diastolic heart failure.

Statistical Analysis
Categorical variables, expressed as numbers and percentages, were compared by χ2 test, whereas continuous data, expressed as means±SD, were compared using Welch 2-sample t test or Mann–Whitney test, as appropriate. Shapiro–Wilk test was performed to evaluate the distribution of the continuous variables.

Estimations of the risk of death were performed using Cox proportional-hazard models by univariable and multivariable analysis.18 The end point was cardiovascular-related death, which was observed in 195 patients (25.1%). Potential predictors of death were identified initially by univariable analyses, and then entered in a stepwise procedure into a multivariable model, with cutoff set to a significance level of 0.05. In addition, variables that had clinical relevance in predicting survival based on previous studies in patients with PAH were also included. Variables that measure the same phenomenon (eg, TR velocity and invasive systolic pulmonary arterial pressure) or obviously interdependent covariates were not entered simultaneously into the multivariable models. Initially, clinical and echocardiographic variables were selected and then hemodynamic variables that express the severity of the disease were included.

Time-dependent receiver-operating characteristic curves were used for evaluating the accuracy of the echocardiographic and hemodynamic variables to predict death.18 The cutoff points were chosen as the values that maximizes (sensitivity+specificity) for each time. Survival analysis was assessed using the Kaplan–Meier method. Nonadjusted comparison of time to the death was based on the log-rank test. Statistical analysis was performed using the Statistical Package for Social Sciences for Windows, version 18.0 (SPSS Inc, Chicago, IL), and R software, version 2.15.1 (R foundation for statistical computing, Vienna, Austria).

The study was approved by an Institutional Review Committee and that the subjects gave informed consent.

Results
There were 1329 patients who presented to the PH clinic between 2002 and 2011. Of those, 230 patients were excluded because of postcapillary PH and 176 patients were excluded because of disproportional lung disease. Eleven patients were excluded because of inadequate quality echocardiography studies, whereas 19 did not have a definite diagnosis. Finally, a further 116 patients were excluded because they underwent transplant or endarterectomies. The final cohort comprised 777 patients with precapillary PH. Of those, 514 (66.1%) were women, mean age was 42±11.3 years. Two hundred eighty-seven patients (37%) had controlled systemic hypertension; 28% hypercholesterolemia; 23% diabetes mellitus type 2; and 3% chronic renal disease. At the time of enrollment, 68 patients (9%) were current smokers and 277 (36%) were ex-smokers.

The mean pulmonary arterial systolic pressure was 78.2±21.5 mm Hg. The baseline hemodynamic data are described in Table 1.
**Functional Class**

Patients were also assessed for symptoms of PH during all clinic visits. At baseline, 157 patients were in WHO class II (20.2%), 385 patients in WHO class III (49.5%), and 235 patients in WHO class IV (30.3%). At the last visit, defined as the visit before death or the last available, 98 (12.6%)
patients were in WHO functional class II, 304 patients (39.1%) in functional class III, and 375 (48.2%) patients in WHO class IV.

**Treatment**

Therapy was instituted according to current European Guidelines. Of the 777 patients, 380 patients (48.9%) were started on bosentan, 213 patients (27.4%) on sildenafil, and 184 patients (23.7%) on prostanoid infusion. Five hundred seventy-four patients (73.8%) required a change in therapy during the follow-up period.

**Survival in the Overall Population (PAH and CTEPH)**

Univariable analysis revealed that, severity of TR, RV MPI, RV FAC, pulmonary artery dilatation, left ventricular eccentricity index, CI, invasive RAP, and the presence of PEf were all significant predictors of mortality (Table 2). Female sex was also a negative prognostic marker.

Multivariable analysis revealed that moderate or severe TR RV MPI, the presence of PEf, high PVR, and RAP were all independent echocardiographic predictors of mortality (Table 2), whereas patients with high CI had better survival. Figure 2 shows the Kaplan–Meier curves for the 6 highly significant parameters from the multivariable analysis.

Patients were considered as high risk based on the presence of one of the following: moderate or severe TR, a raised PVR ≥8.5 dyn/s per cm−5, evidence of PEf, MPI ≥0.64, a low CI ≤3.0 L/min/m², or a raised RAP ≥12 mm Hg.

**Sub Analysis of Patients With PAH**

There were 572 patients classified as having PAH of whom 130 (22.7%) died: 256 patients (44.7%) had PAH related to connective tissue disease, 208 patients (36.4%) were described as idiopathic PAH, 56 patients (9.7%) had porto-PH, 52 patients (9%) had PAH related to shunts and 1 patient (0.17%) HIV-related PAH.

Univariable time-dependent analysis (Table 3) demonstrated that TR severity, RV MPI, end-diastolic left ventricular eccentricity index, and the presence of PEf were the most significant predictors of poor outcome. When hemodynamic data were included in the multivariable model (Table 3), high PVR and RAP remained as significant predictors of mortality, whereas a low CI was the strongest predictor of poor survival (TR severity, RV FAC, pulmonary artery dilatation, the presence of PEf, high PVR, and low CI were all predictors of mortality). Therefore, RV FAC, PA dilatation, the severity of TR, and PEf were independent echocardiographic predictors of survival, even after adjustment for hemodynamic parameters, including CI, PVR, and RAP.

**Sub Group Analysis of Patients With CTEPH**

Sixty-five of 205 (31.7%) patients with CTEPH died. TR severity, RV MPI, and the presence of PEf were the most significant prognostic indicators (Table 4). High PVR and RAP and a low CI were markers of poor survival (Table 4). In the multivariable model, the RV MPI was the strongest predictor of mortality. High CI and a high TR velocity were related to a better survival (Table 4). Similarly to the subset of patients with PAH, RAP remained as an important predictor of death. Figure 3 shows the Kaplan–Meier survival curve for both the groups (PAH and CTEPH).

**Discussion**

This study constitutes a large longitudinal survival study cohort of patients with precapillary PH with an overall incidence of 6.1 deaths per 100 patient-years, and highlights the prognostic value of echocardiographic and hemodynamic indices in patients with precapillary PH. The strongest predictors of mortality were severity of TR, RV FAC, presence of PEf, PVR, RAP, and a low CI. When PAH and CTEPH patients were analyzed separately, TR severity remained the most important prognostic marker. A high TR velocity was associated with better survival (P<0.019; hazard ratio, 0.613) in the CTEPH group compared with patients with PAH, which may indicate differences in the pathophysiological and natural course between PAH and CTEPH disease.

**Differences in Pathophysiology: PAH Versus CTEPH**

There was a difference in survival between PAH and CTEPH (Figure 2) with CTEPH patients having a worse survival. The survival curve in our study is comparable to Ling et al’s whose cohort comprised patients <50 years of age showing a reduced mortality after an initial period of high mortality rate. However, our overall patient cohort was larger and younger (42±11.3), which may explain the somewhat earlier plateau in mortality. PAH is characterized by a gradual increase of PVR, which leads into RV dilatation, hypertrophy, pressure, and volume overload, whereas CTEPH is characterized by more sudden changes on the pulmonary vascular bed. CTEPH disease leads into significant reduction of RV CO, which in the acute setting, may result in lower TR velocities. Conversely, a higher TR velocity may reflect greater CO and may indicate a better prognosis for the patients with CTEPH.

**Echocardiographic Indices as Prognostic Markers**

PEf was previously associated with poor prognosis in patients with PH. We also found that PEf was associated with poor survival (hazard ratio, 1.679 in our cohort). Other studies, however, suggest that PEf is not a good prognostic marker in the early stages of PH. It is possible that
a PEf in severe PH may act as a protective and compensatory mechanism of RV physiology because a PEf may allow adaptation to the changes in ventricular remodeling. Although TAPSE has been suggested by the recent European and American guidelines as a surrogate marker of poor prognosis in PH, in this study TAPSE failed to predict mortality. TAPSE is a measure of RV longitudinal function and is volume-dependent. In our study, the subset of the patients with PH, particularly those with WHO class III–IV disease at baseline (a total of 620 patients—79.7%), were likely to have dilated RVs with severely impaired systolic function and significant TR, which may result in pseudo normalization of TAPSE and, therefore, falsely normal results, accounting for the lack of predictive value for survival in our study.

Previous reports have identified left ventricular eccentricity index as a prognostic marker for patients with PH. Because a PEf may allow adaptation to the changes in ventricular remodeling. Although TAPSE has been suggested by the recent European and American guidelines as a surrogate marker of poor prognosis in PH, in this study TAPSE failed to predict mortality. TAPSE is a measure of RV longitudinal function and is volume-dependent. In our study, the subset of the patients with PH, particularly those with WHO class III–IV disease at baseline (a total of 620 patients—79.7%), were likely to have dilated RVs with severely impaired systolic function and significant TR, which may result in pseudo normalization of TAPSE and, therefore, falsely normal results, accounting for the lack of predictive value for survival in our study.

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Table 2. Cox Proportional-Hazards Analysis for Modeling Mortality in the Overall Population

<table>
<thead>
<tr>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% Confidence Interval)</td>
</tr>
<tr>
<td>Women</td>
<td>1.68 (1.21–2.34)</td>
</tr>
<tr>
<td>CTEPH</td>
<td>1.42 (1.05–1.91)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.37 (0.26–0.52)</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.43 (0.27–0.69)</td>
</tr>
<tr>
<td>PA dilatation</td>
<td>4.84 (2.48–9.44)</td>
</tr>
<tr>
<td>TR velocity, m/s</td>
<td>1.38 (1.16–1.65)</td>
</tr>
<tr>
<td>Moderate–severe TR</td>
<td>14.76 (10.73–20.31)</td>
</tr>
<tr>
<td>RV estimation function</td>
<td>1.63 (1.47–1.82)</td>
</tr>
<tr>
<td>RV dilatation</td>
<td>3.77 (2.38–5.99)</td>
</tr>
<tr>
<td>RV FAC, %</td>
<td>0.94 (0.92–0.96)</td>
</tr>
<tr>
<td>PEf</td>
<td>3.46 (2.61–4.58)</td>
</tr>
<tr>
<td>EID</td>
<td>4.15 (2.49–6.88)</td>
</tr>
<tr>
<td>EIS</td>
<td>2.59 (2.03–3.29)</td>
</tr>
<tr>
<td>MPI</td>
<td>10.54 (6.23–17.64)</td>
</tr>
<tr>
<td>TAPSE, mm</td>
<td>0.936 (0.90–0.97)</td>
</tr>
<tr>
<td>RA volume, mL/m²</td>
<td>1.005 (1.003–1.007)</td>
</tr>
<tr>
<td>IVC diameter, mm</td>
<td>1.05 (1.009–1.088)</td>
</tr>
<tr>
<td>IVRT, ms</td>
<td>1.013 (1.007–1.019)</td>
</tr>
<tr>
<td>RV AT, ms</td>
<td>0.99 (0.983–0.997)</td>
</tr>
<tr>
<td>Hemodynamic data</td>
<td></td>
</tr>
<tr>
<td>RAP, mmHg</td>
<td>1.14 (1.11–1.17)</td>
</tr>
<tr>
<td>PASP, mmHg</td>
<td>1.009 (1.003–1.014)</td>
</tr>
<tr>
<td>PVR, dyn/s per cm⁻⁵</td>
<td>1.32 (1.28–1.37)</td>
</tr>
<tr>
<td>CI, L/min per m²</td>
<td>0.19 (0.15–0.23)</td>
</tr>
</tbody>
</table>

Data are expressed as the mean value±SD or number (percentage) of patients. CI indicates cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; E/A ratio, mitral inflow ratio; EID, left ventricular eccentricity index in end diastole; EIS, left ventricular eccentricity index in end systole; FAC, fractional area change; HR, hazard ratio; IVC, inferior vena cava; IVRT, isovolumic relaxation time; LA, left atrial; MPI, myocardial performance index; PA, pulmonary artery; PASP, pulmonary arterial systolic pressure; PEf, pericardial effusion; PVR, pulmonary vascular resistance; RA, right atrial; RAP, RA pressure; RV, right ventricular estimation (composite score of function); RVOT AT, RV outflow tract acceleration time; RVSP, RV systolic pressure; TAPSE, tricuspid annular plane systolic excursion; and TR, tricuspid regurgitant.

index in end diastole) in the univariable model but not in the multivariable model.

Another suggested measure of potential prognostic significance is the RV MPI, which is a composite index of systolic and diastolic RV functions. One study of idiopathic patients with PH reported an RV MPI of >0.88 to be predictive of survival. In our study, RV MPI ≥0.64 predicted reduced survival with a lower cutoff value compared with the previous studies, possibly because of the higher number of patients. Furthermore, RV FAC proved to be one of the strongest predictors of mortality, in our study. Although RV FAC added value in the prediction of survival, it is an indirect measure of RV ejection fraction and has a few limitations, that is, a pseudo normalization of RV FAC when the RV is volume overloaded, exclusion of significant portions of the RV such as the RV outflow tract as measurements are made in the apical 4 chamber view, and decreased accuracy and reproducibility because of suboptimal endocardial definition.

In our study, only indirect measurements of RV function, such as RV FAC, TAPSE, and RV MPI used. RV ejection fraction...
fraction was not used as this measure had a low reproducible rate using 2-dimensional echocardiography.

The creation of a prognostic risk score for patients with PH combining all the echocardiographic parameters may have better predictive value than single echocardiographic measures. Our study proved that RV dysfunction, TR severity, low CI, and raised RAP were associated with poor survival for both PAH and CTEPH patients. Subsequently, we demonstrated that high-risk patients were characterized by the presence of one of the following indices: moderate or severe TR, MPI ≥0.64, evidence of PEf, raised PVR ≥8.5 dyn·s·cm⁻⁵, a low CI ≤3.0 L/min per m², and a raised RAP ≥12 mmHg. Therefore, a combination of the different echocardiographic variables in the form of a risk score may potentially provide a better tool for the assessment of prognosis, particularly where a single echocardiographic measure fails.

Figure 2. Kaplan–Meier plots for 6 echocardiographic indices. CI indicates cardiac index; MPI, myocardial performance index; PVR, pulmonary vascular resistance; RAP, right atrial pressure; and TR, tricuspid regurgitation.
Risk Factors of Survival
Age, sex, 6-minute walking distance (6MWD) and cardiac output/CI are commonly linked to prognosis.\textsuperscript{1,4,5} In the Bologna PAH experience, age and sex were important risk factors in some clinical subgroups but not all, whereas cardiac output was not identified as a risk factor, in contrast with the French registry.\textsuperscript{30} In this study, we found that a CI $>$3.0 L/min per m$^2$ was associated with a good outcome.

Assessment of Confounding Factors
Data from the sildenafil PAH development program indicate that heart rate at baseline, and systemic pulse pressure at follow-up, were predictive of long-term outcomes.\textsuperscript{23,37–39} Consistent with previous studies,\textsuperscript{10} patients with high CI had a better survival (hazard ratio , 0.155; confidence interval, 0.152–0.225; $P$ <0.001).

Hemodynamic Parameters
Hemodynamic variables at baseline (eg, elevated mean RAP, mean pulmonary artery pressure, and reduced CI) were prognostic predictors\textsuperscript{23,37–39} Consistent with previous studies,\textsuperscript{10} patients with high CI had a better survival (hazard ratio , 0.155; confidence interval, 0.152–0.225; $P$ <0.001).

In our study, high PVR and RAP and a low CI were negative prognostic markers for survival for both PAH and CTEPH patients. PVR has long been accepted, as a measure of RV afterload that has been predictive of mortality in previous series.\textsuperscript{40–44} RAP and CI have been established as important
indicators for survival in population with PAH.\textsuperscript{43–45} CI is largely controlled by venous return, which is determined by the difference between mean systemic venous pressure and RAP. Several authors\textsuperscript{45,46} have suggested that RAP is a dependent variable, whereas venous return an independent variable because RAP decreased when cardiac output increases.

In our study, pulmonary capillary wedge pressure was not predictive of mortality and could possibly be explained by the fact that all patients had a capillary wedge pressure <15 mm Hg. It may be that capillary wedge pressure plays a more important role in postcapillary PH when >15 mm Hg.

In a recent study by Fine et al,\textsuperscript{47} the authors used RV strain parameters to predict survival in a mixed population of patients with precapillary, postcapillary, or suspected PH while our study used established echocardiographic parameters in a homogenous cohort with precapillary PH (PAH and CTEPH).

In their study, the severity of TR was not considered while 25% of the population did not have PH. Our follow-up was also >3× longer (57.7 versus 16.5 months). Nevertheless, our findings agree with Fine et al\textsuperscript{47} in that echocardiography has additional prognostic importance over hemodynamic parameters.

The presence of moderate or severe TR, raised PVR ≥8.5 dyn/s per cm\textsuperscript{-5}, PEf, MPI ≥0.64, a low CI ≤3.0 L/min per m\textsuperscript{2}, and a raised RAP ≥12 mm Hg were the most significant indices of increased mortality during 1733±768 days of follow-up.

Clinical Implications

Our study aimed to identify the most significant echocardiographic and hemodynamic indices associated with survival in precapillary PH patients. The risk assessment comprised by any of the 6 echocardiographic and hemodynamic parameters described may be used for assessing prognosis and follow-up of such patients and help to identify those who are at high risk to institute more aggressive therapies.

Limitations of the Study

While the aim of the study was to stratify echocardiographic and hemodynamic indices, which may predict survival in precapillary PH patients, the impact of treatment was not
assessed. All patients, however, were assessed after initiation of optimal medical therapy following current guidelines and adjusted accordingly so that it can be reasonably assumed that echocardiographic predictors of survival were prognostic independently of treatment. Evaluation of pulmonary vascular capacitance would probably be more sensitive in looking at changes in the medium and large pulmonary vasculature. However, because of the large number of patients within our cohort, it was not practical to do so, hence this was not evaluated in this cohort.

Conclusions

In a large group of precapillary PH patients, patients with worse prognosis have (1) moderate to severe TR, (2) raised CI (3) PVR ≥ 2.85 dyn·s/cm², (4) evidence of PEF, (5) MPI ≥ 0.64, (5) low CI ≤ 3.0 L/min per m², and (6) raised RAP ≥ 12 mmHg. In addition, patients with CTEPH had worse prognosis when compared with patients with PAH. The identification of predictors of poor survival in patients with PH may be fundamental in management and risk stratification.

Sources of Funding

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Disclosures

None.

References


In this study, we looked at the prognostic value of echocardiographic and hemodynamic measures in a large cohort of patients with precapillary pulmonary hypertension before and after initiation of treatment. A range of clinical and echocardiographic measures including indices of right and left heart geometry and function were collected and stored on a database to assess predictors of survival. Invasive hemodynamic data including pulmonary artery pressure, pulmonary vascular resistance, capillary wedge pressure, and cardiac index were also obtained at baseline in all patients. Outcome was defined as mortality because of cardiovascular-related death. We concluded that right ventricular dysfunction, moderate–severe tricuspid regurgitation, low cardiac index, and raised right atrial pressure were associated with poor survival for both pulmonary arterial hypertension and chronic thromboembolic disease patients. In a large precapillary pulmonary hypertensive population, the severity of tricuspid regurgitation, myocardial performance index, presence of pericardial effusion, pulmonary vascular resistance, cardiac index, and right atrial pressure may be used to stratify risk of death.
Echocardiographic and Hemodynamic Predictors of Survival in Precapillary Pulmonary Hypertension: Seven-Year Follow-Up

Julia Grapsa, Maria Carmo Pereira Nunes, Timothy C. Tan, Ines Zimbarra Cabrita, Taryn Coulter, Benjamin C.F. Smith, David Dawson, J. Simon R. Gibbs and Petros Nihoyannopoulos

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