Role of Clinical and Echocardiographic Findings in Patients with Acute Pulmonary Embolism: Prediction of Adverse Outcomes and Mortality in 180 Days

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Received: 2 April 2020
Accepted: 27 October 2020

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INTRODUCTION

Pulmonary embolism (PE) can be a possible mortal cardiopulmonary disease. Its mortality rate can be 5% in clinically stable patients to higher than 30% in those with hemodynamic instability (1,2). Patients with PE have a variety of clinical presentations and outcomes, thereby requiring different severities of clinical care; therefore, risk stratification for adverse outcomes is essential to make appropriate care choices (3-5). Patients with a high probability of facing an adverse outcome require intensive care; however, early hospital discharge or even home treatment would be appropriate for patients with a
predicted low risk of an adverse outcome (6,7). Severe PE is related to right ventricular dysfunction (RVD) and increased pulmonary arterial pressure (PAP) in echocardiography that can be used as predictive factors of adverse outcomes and mortality in patients with acute PE (7).

Computed tomography angiography (CTA) has provided the opportunity for the noninvasive diagnosis of acute PE. This method allows detecting clots in pulmonary arteries (PA) (8). The role of embolic burden evaluated by CTA as an indication of clinical outcomes is of some debate (9). Some studies (10) have investigated the accuracy of computed tomography (CT) scoring systems for PA clot load, and other studies have revealed CT findings for RVD (11,12); however, few studies have assessed the relationship between clot load score and clinical outcomes (11-14). With this background in mind, this retrospective study was performed on patients with acute PE to evaluate the prognostic value of various clinical, echocardiographic, and pulmonary artery obstruction index (PAOI) findings for adverse outcomes and long-term mortality.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the Institutional Ethics Committee of Shahid Beheshti University of Medical Sciences. Informed consent was waived. Adult inpatients and outpatients within 2015-2017 were reviewed in this study. The inclusion criteria were pulmonary computed tomography angiography (PCTA) positivity for arterial PE, availability of patient medical records, and a follow-up of at least 6 months. The exclusion criteria were cardiogenic shock and chronic PE (15).

Clinical Outcomes

The patients were classified into five groups according to clinical outcomes. Group 1 included patients who faced an adverse outcome, specified as a serious clinical condition, including the infusion of vasopressors, respiratory failure or undergoing mechanical ventilation, or cardiopulmonary resuscitation (15,16). Group 2 comprised patients who expired in 30 days of their PE diagnosis. Group 3 consisted of patients who expired within 30-90 days. Group 4 included patients who expired within 90-180 days. Group 5 consisted of patients who survived and did not experience any adverse outcome, which was named the “others” group (15). In the present study, a patient was assumed to have expired due to PE-related causes if a) death certificate or medical records mentioned PE as a cause of death or b) respiratory failure, cardiopulmonary arrest, or shock caused death in the absence of other cardiopulmonary diseases (15,17,18).

Covariate Collection

Details on patient demographics (i.e., age and gender), comorbidities (e.g., malignancy, ischemic heart disease [IHD], chronic obstructive pulmonary disease, pulmonary hypertension, and diabetes mellitus), symptoms (i.e., chest pain and dyspnea), length of both hospital and intensive care unit (ICU) stays, and the need for mechanical ventilation were gathered from medical records (19).

The patients were considered to have chronic heart failure (CHF) if they had documented heart failure and received medication (11). The pulmonary embolism severity index (PESI) was obtained by summing each patient’s age (year), gender (male, 10 points), comorbidities (i.e., cancer [30 points], CHF [10 points], and chronic lung disease [10 points]), pulse rate of ≥ 110/min (20 points), systolic blood pressure of < 100 mmHg (30 points), respiratory rate of ≥ 30/min (20 points), temperature of < 36 °C (20 points), altered mental status (60 points), and arterial oxygen saturation of < 90% (20 points). Each patient’s score corresponded to several risk classes, including a score of ≤ 65 as class I (very low risk), 66-85 as class II (low risk), 86-105 as class III (intermediate risk), 106-125 as class IV (high risk), and > 125 as class V (very high risk) (20).

PCTA Examination

All PCTA examinations were performed using a 64-slice multidetector CT scanner (Brilliance CT scanner, Philips Healthcare, USA) at a single hospital. The images were acquired at a slice thickness of 0.9 mm and
reconstructed at 0.5-mm slice intervals, following intravenous injection of 120 mL iodinated contrast media (iodixanol; Visipaque 320 mg) within 5-6 mL/s timed by bolus tracking at the main PA. The helical CT criterion used to diagnose PE was the detection of a nonocclusive endoluminal thrombus (i.e., central filling defect completely or partially outlined by contrast agent) or complete occlusion by a thrombus in normal-sized or enlarged vessels (10,15). The images were reviewed by a radiologist who was reporting thoracic CT scans for 6 years and was blinded to the clinical history (15,21).

**Degree of Vascular Obstruction**

The scoring system described by Qanadli et al. was used to calculate the vascular obstruction index (10). The PAOI scores were categorized into five classes of ≤ 8 (class I), 8-16 (class II), 16-24 (class III), 24-32 (class IV), and 32-40 (class V) (15).

**Echocardiographic Evaluation**

The patients’ clinical documents were examined to perform a transthoracic echocardiogram within 24 h of PE diagnosis. The patient was assumed to have echocardiographic RVD if there were at least two of several conditions, namely the right ventricle dilatation, right ventricle appearing larger than the left ventricle, or systolic pulmonary artery pressure over 30 mmHg (16,22).

**Six-Month Follow-up**

The patients’ deaths up to 6 months after the diagnosis of PE were registered and evaluated by an independent committee. This committee determined if a patient’s death should definitely or most probably be attributed to PE or other causes (14).

**Statistical Analysis**

The Kolmogorov-Smirnov test was used to evaluate the normality of continuous variables. The data characterized by a normal distribution, such as the PESI, are stated as mean±standard deviation. Parameters with an abnormal distribution are mentioned as the median (first-third interquartile range). The analysis of variance or the Kruskal-Wallis test was used to compare the groups, and the Chi-square test was applied to compare discrete variables. The Spearman’s Rho and Pearson’s correlation tests were used to determine the correlation between variables (23). For the determination of cut-off PAOI values for detecting adverse outcomes and mortality, receiver operating characteristic plots were analyzed, and the area under the curve was calculated.

The threshold value for which sensitivity equaled specificity was calculated for measurements with an Az value that was significantly different from 0.5. For the identification of predictors of adverse outcomes, multiple logistic regression analysis was used for variables with the p-values of < 0.05 in univariate analysis. Statistical analysis was performed using SPSS software (version 24).

**RESULTS**

A total of 104 patients, 52 (50%) of whom were male, were entered in the present study. The mean patient age was 62.5 (range: 48-74) years. Demographic and clinical characteristics are summarized in table 1. In this study, 16 patients experienced an adverse outcome. Over a period of 6 months, there were 17 deaths. According to the Independent Adjudication Committee, death could have been related to PE in all cases. Additionally, 10, 5, and 2 deaths occurred within 30, 30-90, and 90-180 days of PE diagnosis during the follow-up period. A total of 47 patients (45%) were younger than 60 years of age, 34 of whom were in the “others” group (those who survived without having any adverse outcome). Out of the remaining patients, nine subjects experienced an adverse outcome, and four subjects died. The significant difference between the groups was observed as p < 0.001.

A total of 14 patients (13%) had malignancy, the rate of whom was highest in the groups of patients who expired within 30-90 and 90-180 days (80% and 50%; p=0.036). The most frequent presentation was dyspnea (89%), which was significantly higher in the groups of patients who died within 30, 30-90, and 90-180 days, compared to that in the adverse outcome and “others” groups (100% vs. 87%; p<0.001). Furthermore, the mean PAOI was 10.5 (range: 4-20).
The adverse outcome group had the highest PAOI (21; range: 19-25) in comparison to the groups of patients who died within 30 days (3; range: 2-15), 30-90 days (10; range: 6-15), and the “others” group (8.5; range: 4-17); however, the p-value of 0.146 was not statistically significant. The Pearson’s correlation and Spearman’s Rho test were performed to detect any correlations between the PAOI/PAOI class and other variables (Table 2). Spearman’s correlation coefficients were highest between PAP and PA clot load and lower the PESI, and PA clot load.

**Predictors of Outcomes at 6 Months**

The findings of univariate logistic regression analysis showed that a significant baseline predictor of adverse...
outcomes was the PESI (OR=1.018; \( P=0.031 \)), and a predictor of death in 30 days of PE diagnosis was the mean ICU stay (OR=1.180; \( P=0.016 \)). The results showed that having IHD (OR=0.150; \( P=0.009 \)), HF (OR=0.135; \( P=0.015 \)), MI (OR=0.114; \( P=0.029 \)), or a history of kidney transplantation (OR=0.037; \( P=0.010 \)) were related to a decreased risk of death in 30 days. The predictors of mortality within 30-90 days were the PESI (OR=1.041; \( P=0.009 \)) and the time to diagnosis (OR=1.130; \( P=0.044 \)). The PAOI showed no significant association with any of the groups \((P>0.05)\). Based on the multivariate logistic regression analysis, the mean ICU stay (OR=1.202; \( P=0.036 \)), predicted mortality within 30 days, and a history of kidney transplantation (OR=0.011; \( P=0.002 \)) were associated with a decreased risk of death in 30 days of PE diagnosis (Tables 3 and 4).

Table 2. Correlation between PA clot load and other variables

| Variables                                      | PAOI/PAOI class | \( P \) value |
|------------------------------------------------|-----------------|--------------|
| Clinical characteristic, N (%)                |                 |              |
| Age                                           | -0.097          | 0.326        |
| Age <60 years                                  | 0.144           | 0.144        |
| Male gender                                   | -0.097          | 0.326        |
| Comorbid disease, N (%)                        |                 |              |
| Ischemic heart disease                         | -0.155          | 0.117        |
| Congestive heart failure                       | -0.12           | 0.223        |
| Myocardial infarction                          | 0.047           | 0.638        |
| Chronic obstructive pulmonary disease          | -0.068          | 0.491        |
| Diabetes mellitus                              | -0.088          | 0.376        |
| Hypertension                                   | -0.064          | 0.517        |
| Hyperlipidemia                                 | 0.098           | 0.324        |
| Any renal disease                              | 0.157           | 0.113        |
| Kidney transplantation history                 | 0.092           | 0.353        |
| Malignancy                                     | -0.019          | 0.849        |
| Coagulopathy                                   | 0.01            | 0.924        |
| Pulmonary hypertension                         | 0.158           | 0.109        |
| Echocardiography findings                      |                 |              |
| Pulmonary artery pressure                      | 0.306           | 0.002        |
| \( PAP\geq30 \)                                | 0.180           | 0.067        |
| Right ventricular systolic dysfunction         | 0.259           | 0.008        |
| Clinical symptoms and signs at presentation, N (%) |             |              |
| Chest pain                                     | 0.195           | 0.048        |
| Dyspnea                                        | 0.028           | 0.781        |
| Syncope                                        | 0.124           | 0.208        |
| Hemoptysis                                     | -0.041          | 0.677        |
| Heart rate>100/min                             | 0.208           | 0.034        |
| \( O_2 \) saturation                           | -0.169          | 0.086        |
| \( O_2 \) saturation<90%                      | 0.466           | <0.001       |
| \( PAO_2 <60\% \)                              | 0.358           | <0.001       |
| Pulmonary embolism severity index              | 0.235           | 0.017        |
| Length of hospital stay, days                  | -0.160          | 0.104        |
| Length of ICU stay, days                       | -0.129          | 0.191        |
| Mechanical ventilation                         | -0.175          | 0.076        |
| Time to diagnosis of PTE                       | -0.077          | 0.44         |

Correlation coefficients were calculated by using the Pearson correlation coefficients and Spearman’s rho correlation coefficients.

\( PAOI \), pulmonary artery obstruction index
Table 3. Predictors of adverse outcome and mortality in 30 days of 104 patients with acute pulmonary embolism

| Risk factor      | Adverse outcome |          |          | Death< 30 days |          |          |
|------------------|-----------------|----------|----------|----------------|----------|----------|
|                  | Univariable     | Multivariable | Multivariable | Univariable | Multivariable | Multivariable |
|                  | OR(95% CI) P value | OR(95% CI) P value | OR(95% CI) P value | OR(95% CI) P value | OR(95% CI) P value | OR(95% CI) P value |
| Age , per year   | 1.0(0.97-1.03) 0.873 | - | - | 1.04(0.99-1.09) 0.092 | - | - |
| Male gender      | 1.11(0.45-2.73) 0.81 | - | - | 2.13(0.5-9.02) 0.304 | - | - |
| Malignancy       | 1.18(3.4-6.4) 0.806 | - | - | - | - | - |
| PAOI             | 1.01(0.96-1.06) 0.694 | - | - | 0.9(0.8-1.01) 0.077 | - | - |
| IHD              | 0.68(0.23-2.01) 0.489 | - | - | 0.15(0.03-0.62) 0.009 | 0.23(0.03-1.52) 0.130 | - |
| HF               | 0.35(0.08-1.44) 0.147 | - | - | 0.13(0.02-0.67) 0.015 | 0.2(0.02-1.76) 0.150 | - |
| MI               | 0.45(0.07-2.88) 0.402 | - | - | 0.11(0.01-0.8) 0.029 | 0.29(0.02-3.64) 0.341 | - |
| COPD             | 1.62(0.18-14.57) 0.666 | - | - | - | - | - |
| DM               | 0.86(0.27-2.68) 0.797 | - | - | 0.4(0.09-1.79) 0.233 | - | - |
| HTN              | 1.64(0.65-4.16) 0.292 | - | - | 0.3(0.09-1.6) 0.189 | - | - |
| Kidney trans     | - | - | - | 0.037(0.003-0.463) 0.010 | 0.011(0.001-0.204) 0.002 | - |
| PESI             | 1.01(0.00-1.03) 0.031 | - | - | 0.1(0.01-3.03) 0.321 | - | - |
| RVSD             | 0.75(0.3-1.88) 0.55 | - | - | 0.96(0.24-3.82) 0.962 | - | - |
| Length of ICU stay, days | 2.0(1.44-3.02) <0.001 | - | - | 1.18(1.03-1.35) 0.016 | 1.20(1.01-1.42) 0.036 | - |
| Time to diagnosis of PTE | 0.97(0.89-1.06) 0.583 | - | - | 1.04(0.94-1.17) 0.387 | - | - |

*Only variables found to significantly predict adverse outcome or mortality in 30 days by univariable analysis were entered in the multivariable model.

Table 4. Predictors of mortality in 30-90 days and 90-180 days in 104 patients with pulmonary embolism

| Risk factor | Death 30-90 days |          |          | Death 90-180 days |          |          |
|-------------|-----------------|----------|----------|-----------------|----------|----------|
|             | Univariable     | Multivariable | Multivariable | Univariable | Multivariable | Multivariable |
|             | OR(95% CI) P value | OR(95% CI) P value | OR(95% CI) P value | OR(95% CI) P value | OR(95% CI) P value | OR(95% CI) P value |
| Age , per year | 1.00(0.95-1.06) 0.756 | - | - | 1.10(0.91-1.32) 0.304 | - | - |
| Male gender | 1.25(0.2-7.81) 0.811 | - | - | - | - | - |
| Malignancy | 0.028(0.003-0.276) 0.002 | - | - | - | - | - |
| PAOI | 0.98(0.88-1.09) 0.765 | - | - | 1.12(0.88-1.43) 0.326 | - | - |
| IHD | 0.95(0.1-8.99) 0.964 | - | - | - | - | - |
| HF | 0.35(0.03-3.53) 0.375 | - | - | - | - | - |
| COPD | 0.06(0.00-0.491) 0.008 | - | - | - | - | - |
| HTN | 3.47(0.37-3.21) 0.273 | - | - | - | - | - |
| Kidney trans | 0.08(0.00-1.1) 0.06 | - | - | - | - | - |
| PESI | 1.04(1.01-1.07) 0.009 | 0.98(0.91-1.05) 0.64 | 1.017(0.95-1.08) 0.585 | - | - |
| RVSD | 5.2(0.56-48.3) 0.14 | - | - | - | - | - |
| Length of ICU stay, days | 0.98(0.76-1.28) 0.935 | - | - | 0.002 0.997 | - | - |
| Time to diagnosis of PTE | 1.13(1.00-1.27) 0.044 | 1.13(0.92-1.38) 0.227 | 1.02(0.72-1.42) 0.910 | - | - |

*Only variables found to significantly predict adverse outcome or mortality in 30 days by univariable analysis were entered in the multivariable model.

The PAOI, PESI, PAP, mean hospital stay, mean ICU stay, and time to diagnosis were assessed for their ability to predict survival. The Az value was higher than 0.5 for the mean ICU stay in the group of patients who expired within 30 days (P=0.006). This study also detected Az values of 0.837 (P=0.011) for the PESI and 0.793 (P=0.028) for the mean hospital stay in the group of patients who expired within 30-90 days. The Az value for the PAOI as a predictor of mortality within 90-180 days was 0.691; however, it was not significant (P=0.075). Regarding the factors for which the Az values were significantly higher than 0.5, table 5 lists the threshold values for which sensitivity equaled specificity. Moreover, it was observed that the PAOI with a threshold value of 7 (Az=0.649; P=0.009) can predict RVSD (Table 6).
Table 5. Performance of CT and Echocardiography and clinical measurements for discrimination of Survivors from Non-survivors (each mortality group), as indicated by Receiver Operating Characteristic Curves

| Measurement                  | Adverse outcome | Death<30 days | Death 30-90 days | Death 90-180 days | Threshold value ** | Sensitivity Equals Specificity (%) |
|------------------------------|-----------------|---------------|------------------|------------------|-------------------|-----------------------------------|
| PAOI                         | Value*          | Az value      | p value          | Az value          | Az value          | p value                           |
| 0.489(0.363,0.615)           | 0.856           | 0.281(0.107,0.454) | 0.023           | 0.491(0.325,0.657) | 0.945             | 0.691(0.490,0.893)              |
| PAP                          | Value           | Az value      | p value          | Az value          | Az value          | p value                           |
| 0.474(0.352,0.595)           | 0.665           | 0.426(0.219,0.632) | 0.440           | 0.576(0.330,0.821) | 0.569             | 0.461(0.001,1.000)             |
| PESI                         | Value           | Az value      | p value          | Az value          | Az value          | p value                           |
| 0.271(0.170,0.372)           | <0.001          | 0.687(0.525,0.849) | 0.053           | 0.837(0.686,0.989) | 0.011             | 0.792(0.708,0.875)             |
| Length of hospital stay, days| Value           | Az value      | p value          | Az value          | Az value          | p value                           |
| 0.232(0.215,0.450)           | 0.006           | 0.634(0.419,0.848) | 0.166           | 0.793(0.684,0.902) | 0.028             | 0.769(0.530,1)                 |
| Length of ICU stay, days     | Value           | Az value      | p value          | Az value          | Az value          | p value                           |
| 0.208(0.100,0.316)           | <0.001          | 0.766(0.596,0.937) | 0.006           | 0.499(0.240,0.758) | 0.994             | 0.672(0.230,1)                 |
| Time to diagnosis of PTE     | Value           | Az value      | p value          | Az value          | Az value          | p value                           |
| 0.508(0.380,0.633)           | 0.917           | 0.545(0.319,0.771) | 0.643           | 0.673(0.416,0.930) | 0.194             | 0.475(0.257,0.694)             |

Az values were calculated and tested for difference from 0.5. For Az values that showed difference from 0.5, threshold values were calculated for which sensitivity equaled specificity.

*Data in parentheses are 95% confidence intervals.

**NA = not applicable.

Table 6. Performance of PAOI for discrimination of patients with RVSD or PAP>30 mmHg or being in specific PESI class from other patients with pulmonary embolism that do not have these characteristics

| PESI Class | Az value | Value* | P value | Threshold value** | Sensitivity equals specificity (%)** |
|------------|----------|--------|---------|-------------------|-------------------------------------|
| RVSD       | Value    | 0.649(0.541,0.756) | 0.009 | 7                 | 71                                |
| PAP>30mmHg | Value    | 0.573(0.449,0.697) | 0.306 | NA                | NA                                |
| PESI I     | Value    | 0.266(0.161,0.371) | 0.002 | NA                | NA                                |
| PESI II    | Value    | 0.559(0.427,0.692) | 0.356 | NA                | NA                                |
| PESI III   | Value    | 0.544(0.421,0.666) | 0.484 | NA                | NA                                |
| PESI IV    | Value    | 0.612(0.456,0.767) | 0.157 | NA                | NA                                |
| PESI V     | Value    | 0.468(0.327,0.608) | 0.718 | NA                | NA                                |

Az values were calculated and tested for difference from 0.5. For Az values that showed difference from 0.5, threshold values were calculated for which sensitivity equaled specificity.

*Data in parentheses are 95% confidence intervals.

**NA = not applicable.

**DISCUSSION**

The present study assessed the prognostic value of various clinical, echocardiographic, and PCTA factors in patients who had acute PE. The findings of the current study are not in favor of the hypothesis that a higher PAOI score in multidetector computed tomography predicts a higher 6-month mortality rate or a higher rate of adverse outcomes. These findings are similar to the findings of a study performed by Heyer et al. (24), who could not find any association between PA clot load and mortality rate; however, contrary to the results of the present study, a correlation was observed between the PAOI and adverse outcomes, such as ICU admission.
The findings of the current study confirm those of a previous study (25), in which there was no correlation between the PAOI and adverse clinical outcomes. It was not possible to demonstrate that the PAOI is a predictor of 30-day mortality, which is similar to the results reported by Oz et al. (26). On the other hand, based on four previous studies (13,14,21,27), the score obtained with the system assessed by Qanadli et al. (10) can be a predictor of survival; the median scores were 10%, 32%, 36.5%, and 52%, respectively, reflecting differences in the study populations.

George et al. (19) reported that CHF and malignancy could be independent predictors of PE-related 30-day mortality. The present study demonstrated that IHD, HF, and MI were accompanied by a lower risk of death in 30 days using univariate analysis; however, this was not significant in multivariate analysis. Sakhuj a et al. (28) studied the prevalence and outcomes of PE in donor kidney recipients and stated that transplant patients with PE have excellent outcomes. Similarly, the present study indicated that a history of kidney transplantation was independently associated with a lower occurrence of death in 30 days; therefore, due to the lower number of kidney transplanted patients in this study that could show bias, a larger sample size is needed to confirm these results.

Most previous studies have observed that the PAOI is significantly correlated with RVDS (10,14). Selimoglu Sen et al. (21) stated that a PAOI of 23.75% or higher leads to an increased risk of RVD; however, the present study showed a threshold value of 7%. Moreover, the present study demonstrated a significant correlation between the PESI, HR of >100 beats per minute, chest pain, hypoxia, and PAP with the PAOI/PAOI class.

In the present study, the patients who died were classified under three groups, including those who died within 30, 30-90, and 90-180 days of PE diagnosis, with a cut-off point of 98 for the PESI. The patients with higher scores had a significantly increased risk of death within 30-90 days; however, these results are in conflict with those reported by Polo Friz et al. (29), who showed that the ability of the simplified pulmonary embolism severity index (sPESI) to predict PE mortality within 90 days was low. This contradiction may be a result of different ages within the populations in the aforementioned study (median: 77; range: 16-99 years) in which 77.7% of the subjects were under 65 years of age; nevertheless, the patients of the current study were younger (median: 62.5; range: 48-74; 55% of the patients >60 years). Moreover, Friz et al. calculated the sPESI; nevertheless, this study calculated the PESI (29).

In this study, it was shown that a mean ICU stay of 1 day or longer carried an increased risk of death within 30 days, and a mean hospital stay longer than 13 days increased the mortality rate within 30-90 days. In the present study, the difference in the mean hospital stay among the groups was significant; however, Choi et al. (20) observed no significant difference in the length of hospital stay between the adverse outcomes and low-risk groups.

The current study has some limitations. Firstly, the PAOI (median: 10.5; range: 4-20) is low. Secondly, the impact of PE-specific therapy on the clinical outcome was not considered. Thirdly, the small group size (death: <30 days; death: 30-90 days; death: 90-180 days; adverse outcome) may bias the results.

CONCLUSION

In conclusion, it was observed that a history of kidney transplantation might be independently accompanied by a lower occurrence of death in 30 days. Moreover, there was a significant correlation between the PESI, HR of >100 beats per minute, chest pain, hypoxia, and PAP with the PAOI/PAOI class. A larger multicenter study may demonstrate the value of various clinical, echocardiographic, and helical PCTA findings as a risk stratification tool in patients with PE.

Conflict of interest disclosure

The authors declare that there are not conflicts of interest.
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