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A pulmonary embolism response team (PERT) approach: initial experience from the Cleveland Clinic

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Abstract
Management of intermediate and high risk acute pulmonary embolism (PE) is challenging. The role of multidisciplinary teams for the care of these patients is emerging. Herein, we report our experience with a pulmonary embolism response team (PERT). We conducted a retrospective chart review on all patients admitted to the Cleveland Clinic main campus who required activation of the (PERT) from October 1, 2014 to September 1, 2016. We extracted data pertaining to clinical presentation, bleeding complications, and pre- and post-discharge imaging. Patients were classified as low, intermediate or high risk PE. Descriptive and continuous variables were collected and analyzed. There were 134 PERT activations. PE was confirmed by CT-PA in 118 patients. Fifteen (13%) patients were classified as low risk, 80 (68%) intermediate risk PE and 23 (19%) high risk PE. Fourteen (12%) patients were treated with catheter directed rtPA, 6 (5%) received full dose (100 mg rtPA), 16 (13%) received systemic half-dose (50 mg rtPA), 6 (5%) underwent a surgical embolectomy and 4 (3%) underwent mechanical thrombectomy. 65 (55%) patients received anticoagulation only, and 8 (7%) patients were managed conservatively without any anticoagulation or advanced therapy. 11 (9%) patients died while during the hospitalization. Fourteen patients had major bleeding events. There were no bleeding events among patients who received systemic low dose or full dose rtPA. A multidisciplinary approach to cases of intermediate risk and high risk PE can be implemented successfully. We saw a relatively low rate of bleeding events with use of rtPA.

Keywords Pulmonary embolism · PERT · Thrombolysis · Anticoagulation

Highlights

- A multidisciplinary team approach to intermediate and high risk PE patients can be implemented successfully
- The majority of patients were treated with anticoagulation alone
- The multidisciplinary approach allowed for the identification of patients in whom the use of systemic thrombolysis is associated with a low rate of bleeding complications

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Introduction

Pulmonary embolism (PE) is associated with significant morbidity and mortality. PE is associated with about 200,000 deaths in the United States annually [1]. It is also an expensive illness to diagnose and treat [2]. Different options are now available in the management of PE. These include anticoagulation, systemic thrombolysis (full dose or half dose), catheter-directed therapy (thrombolysis and/or mechanical thrombectomy) and surgical embolectomy [3–5]. Over the last few years, pulmonary embolism response teams (PERT) have gained traction nationwide. They have been modeled on other successful rapid response teams such as those for ST-segment elevation myocardial infarction and stroke. Recently, a PE consortium was also formed [6]. The rationale behind the formation of these response teams is to allow for prompt coordination between different medical specialties and promote engagement of experts in order to circumvent a paralysis of time sensitive decision making in the absence of standardized clinical guidelines and algorithms. Importantly, such teams allow for the rapid implementation of the recommended treatment approach. The ultimate goal of these response teams is to improve the morbidity and mortality associated with PE and to reduce complications. PE response teams are of particular importance in patients with intermediate risk PE since they represent a group of clinically unique patients in which the risks and benefits of anticoagulation versus advanced interventions (such as recombinant tissue plasminogen activator (rtPA), catheter directed thrombolysis, mechanical thrombectomy, surgical embolectomy, extracorporeal membrane oxygenation (ECMO), and IVC filter placement) can vary considerably, even amongst existing society guidelines [3].

Methods

The Cleveland Clinic PERT was created in October 2014 and consists of specialists from vascular medicine, pulmonary and critical care, interventional radiology, interventional cardiology, cardio-thoracic surgery, pharmacy, hematology, and internal medicine.

Data collection

The Institutional Review Board (IRB) approved data collection and analysis (Study 16–282). This is a retrospective study and data was collected on patients from October 2014 until September 2016. All consecutive patients in the PERT registry at the Cleveland Clinic during this time frame were part of the study. Variables collected included patient demographics, medications, comorbid illnesses, PE risk factors, history of deep venous thrombosis (DVT) and PE, results of diagnostic tests such as biomarkers, electrocardiography, echocardiographic, computer tomographic imaging and where applicable ventilation perfusion imaging at the time of PERT activation, and bleeding complications. After PERT activation, these patients were followed for the rest of their hospital stay and treatment outcomes were closely monitored. Patients were also asked to follow up in the vascular medicine clinic after discharge, and as needed in the pulmonary medicine clinic.

Activation process

To activate the PERT team, referring physicians are required to page the "2-PERT" pager (Fig. 1). This pager is carried by a physician team member at all times. During the day it is carried by a vascular medicine fellow and overnight it is carried by a critical care fellow. On receiving the page, the physician quickly responds and gathers relevant clinical information including type and extent of PE, diagnostic imaging data, severity indices, and bleeding risk factors, and communicates with the primary team to complete any pending clinical, lab, or imaging workup. The entire PERT is then notified via page, text message and email and an online Skype® business meeting is planned immediately. PERT members may then view radiographic, echocardiogram and venous ultrasound images live via the screen share feature on a conference call. If computer access is not available, members may dial in via phone. A group discussion ensues and consensus opinion is reached upon in regards to the preferred therapeutic intervention. The PERT's recommendations are conveyed to the primary team, the patient and the patient's family. If agreed upon by the primary team and the patient (or patient's medical proxy), the PERT team immediately helps to mobilize resources such as activation of the interventional laboratory, institution of extracorporeal membrane oxygenation, or activation of the operating room theater. The PERT has no leader and decisions are based on majority consensus opinion. The patients are followed by the vascular medicine consult service for the rest of their hospitalization. Follow up in the outpatient vascular medicine clinic is also set up prior to discharge. When needed for persistent symptoms, patients may also be referred to the pulmonary clinic.

Diagnosis and PE classification

PE was confirmed by CT pulmonary angiography (CT-PA) or a high probability ventilation-perfusion scan (V/Q) in patients with a high suspicion of PE. Once confirmed, PE patients were then classified into high risk, intermediate risk or low risk based on the European Society of

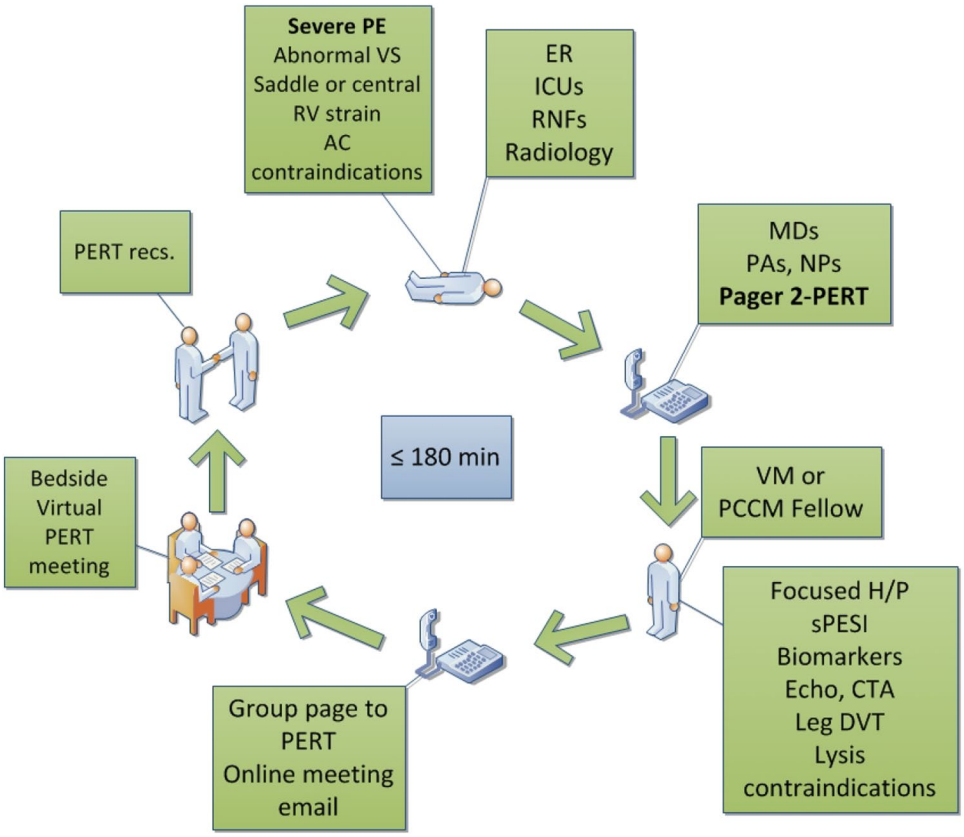

Fig. 1 PERT activation process

Cardiology guidelines [3]. High risk PE was defined as PE presenting with sustained hypotension (systolic blood pressure less than 90 mmHg) or cardiac arrest. Intermediate risk PE was defined as normotensive PE with a simplified pulmonary embolism severity index (sPESI) greater than ≥ 1 and evidence of new right ventricular strain on echocardiogram and CT imaging and/or biomarker evidence of right ventricular strain (elevated troponin and/or NT-proBNP). PE's were classified as low risk if they did not meet the criteria of high risk or intermediate risk.

Treatment

Therapeutic interventions recommended by the PERT included anticoagulation, no anticoagulation, full dose systemic thrombolysis with recombinant tissue plasminogen activator (100 mg rtPA over a 2 h period), half dose systemic thrombolysis (50 mg rtPA over a 2 h period), catheter directed thrombolysis, mechanical thrombectomy or surgical embolectomy. The PERT also made decisions regarding inferior vena cava (IVC) filter placement and the need for extracorporeal membrane oxygenation (ECMO).

Outcomes

Outcomes included all-cause mortality during hospital stay, major bleeding complications as defined by the International Society of Thrombosis and Hemostasis (ISTH) criteria, which include a drop in hemoglobin greater than 2 g/dL, requirement of blood transfusion, or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome [7].

Results

There were 140 unique PERT activations. Out of these, PE was confirmed by CT-pulmonary angiography or V/Q imaging in 118 patients. We will describe the characteristics and outcomes of these 118 patients (Table 1). The mean patient age was 59.7 ± 15 years (range 22–89 years) and over half of them were male (56%). About one quarter had a history of malignancy (23.2%), 18 patients (16.1%) had recent surgery in the last 8 weeks, 7 (6.3%) were on anticoagulation prior to presentation, 16 (14.2%) had a history of obstructive lung

Table 1 Study population: 118 confirmed PE patients out of 140 PERT activations

	Value (n = 118)
Age (years)	60 ± 14
Male gender	65 (55)
Recent surgery	19 (16.1)
History of DVT	29 (24.5)
History of PE	14 (11.8)
History of malignancy	26 (22.0)
History of diabetes	41 (35.5)
History of COPD	15 (12.7)
Anticoagulation prior to admission	8 (6.7)
Previous IVC filter	11 (9.3)
Right heart strain by EKG	33 (34.7)
Right heart strain by CT Imaging	64 (54.2)
Right heart strain by Echocardiography	81 (68.6)

Data presented as mean ± SD or number (%), as appropriate

disease, 13 (11.6%) had a history of prior PE, 27 (24.1%) had a prior DVT and ten patients (8.9%) had previously received an IVC filter. Other baseline characteristics can be seen in Table 1. There was evidence of right heart strain in 33 (34.7%), 63 (56.2%) and 78 (69.6%) patients by EKG, CT and echocardiography respectively.

Types of PE

The majority of pulmonary embolisms in our cohort were intermediate risk, 80 (68%). 23 (19%) patients had high risk PE and 15 (13%) had low risk pulmonary embolism (Fig. 2). In terms of location, 48 (41%) were saddle emboli, 47 (4%) were in the main pulmonary arteries, 17 (14%) were in the lobar arteries and 6 (5%) were in the segmental arteries. A lower extremity DVT was present in 84 (71%) patients.

Types of therapy

More than half of the patients (55%) evaluated by the team were treated with anticoagulation alone (Tables 2 and 3). About one-third of patients (30%) received some form of rtPA: systemic full dose thrombolysis (n = 6, 5%), systemic half dose (n = 16, 13%), and catheter-directed thrombolysis (n = 14, 12%). Mechanical thombectomy (n = 4, 3%) and surgical embolectomy (n = 6, 5%) were performed in a minority of patients. Five of the six patients who underwent surgical embolectomy had an intra-cardiac clot and three of these patients underwent concomitant closure of a patent foramen ovale (PFO). One patient underwent both mechanical thrombectomy and surgical embolectomy. An IVC filter was inserted in 34 patients (29%).

All-cause mortality

All-cause mortality at 30 days was 9% (11 deaths). Figure 2 and Table 4 shows mortality according to PE severity and type of therapy received respectively. There were seven, three, and one deaths at 30 days amongst patients who had high, intermediate and low risk pulmonary embolisms respectively (Table 4). Of these fatalities, four (3%) specifically resulted from hemodynamic collapse as consequence of PE. The remaining seven deaths (6%) were in

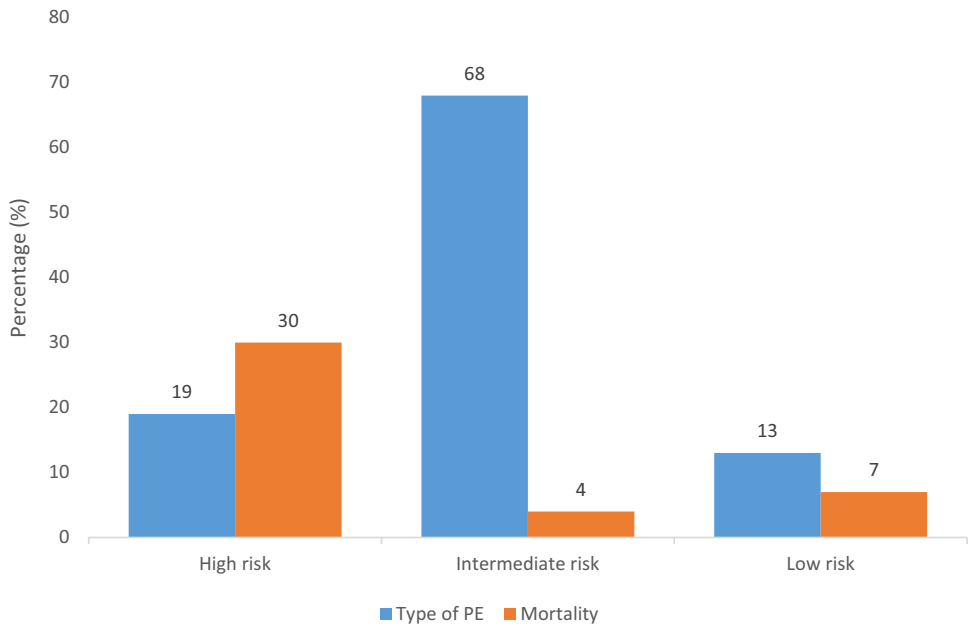

Fig. 2 Classification of PE and all-cause mortality

Table 2 Implemented therapies and mortality based on type of therapy

	Type of therapy Number (%)	Mortality Number (%)
Anticoagulation only	65 (55)	6/65 (9)
Systemic half dose rtPA	16 (13)	0/16 (0)
Catheter directed rtPA	14 (12)	2/14 (14)
No anticoagulation	8 (7)	0/16 (0)
Systemic full dose rtPA	6 (5)	1/6 (17)
Surgical Embolectomy	6 (5)	1/6 (17)
Mechanical Thrombectomy	4 (3)	1/4 (25)

Table 3 Therapies in intermediate and high risk PE

Type of therapy	High risk PE (n = 23)	Intermediate risk PE (n = 80)
Systemic full dose rtPA	3 (14)	3 (4)
Systemic half dose rtPA	4 (18)	13 (16)
Catheter directed rtPA	7 (32)	7 (9)
Mechanical Thrombectomy	3 (14)	1 (1)
Surgical Embolectomy	2 (9)	4 (5)
Anticoagulation only	4 (18)	44 (55)
No anticoagulation	0	9 (12)

Bleeding complications

Major bleeding occurred in 15 patients (12.7%). The majority of the bleeding events [12] were in patients who received only anticoagulation versus three events in patients who received catheter directed thrombolysis (Table 5). The most frequent bleeding complications were gastrointestinal bleeding [3], followed by intramuscular hematomas [3], followed by intracranial hemorrhage [2], hematuria [2], hemoptysis [2], hemorrhagic pericardial effusion with tamponade [1] and vaginal bleeding [1]. There were no bleeding complications amongst patients who received systemic thrombolysis.

Discussion

In the absence of robust data, decision making for high risk and intermediate risk PE remains an ongoing challenge [8]. To streamline our therapeutic approaches, the PERT was created with the goal of bringing together experts from different specialties with the common goal of improving patient outcomes in a manner that is safe, evidence driven, and efficient [9]. Kabrhel et all recently described the first PERT model at Massachusetts General Hospital along with their initial outcomes [10]. Many patients transitioned to comfort care measures given their underlying comorbid diseases. There was one death in the low risk PE group (terminal malignancy and the patient was transitioned to hospice). Six of the eleven deaths were in patients who received only anticoagulation. One who received systemic full dose thrombolysis died and two patients who received catheter directed thrombolysis died. There were no deaths in the group of patients who received systemic half dose thrombolysis.

Table 4 Table of deaths in patients with pulmonary embolism

	Severity	Treatment	Mechanism of death	Comments
1	Massive	Mechanical thrombectomy	Transitioned to comfort care	
2	Massive	Catheter directed rtPA	Transitioned to comfort care	
3	Intermediate	Anticoagulation only	PEA arrest	
4	Intermediate	Anticoagulation only	PEA arrest	Concomitant septic shock
5	Massive	Anticoagulation only	Transitioned to comfort care	
6	Massive	Cather directed rtPA	Ventricular fibrillation	Active malignancy
7	Low risk	Anticoagulation only	Transitioned to comfort care	Active malignancy
8	Intermediate	Anticoagulation only	Transitioned to comfort care	Active malignancy
9	Massive	Anticoagulation only	Transitioned to comfort care	Active malignancy
10	Massive	Full dose rtPA	PEA arrest	
11	Massive	Surgical embolectomy	Transitioned to comfort care	Intracranial hemorrhage

Table 5 Major bleeding according to therapy

Type of therapy	Number (%)
Anticoagulation only	11/65 (17)
Catheter directed thrombolysis	3/14 (21)
Systemic rtPA—full dose	0 (0)
Systemic rtPA—half dose	0 (0)

other hospitals across the country have started to adapt similar models. In fact, there is now a National PERT Consortium which consists of more than 180 teams (personal communication from Chris Kabrhel). This consortium aims to work in conjunction to standardize PE management and share data in an effort to further high-quality research in PE [6, 11].

The creation of the PERT has been very well received at our institution. Upon its inception, efforts were made to educate house staff and attending physicians with regards to its utility, purpose, and scope. The PERT pager is physically carried at all times at our institution. On a 24 h basis, members of the team join a PERT conference call when it is convened. We maintain uniformity in terms of our data collection, risk stratification, and research methods with use of standardized PERT templates for documentation in the electronic medical record and an algorithm which allows us to standardize care and facilitate care at the bedside.

With the advent of PERT, there was concern that there may be 'over activation' in the case of low risk PE's. In our cohort, of 118 patients, 15 (13%) were classified as low risk PE's. It must be noted that the truest utility of a PERT would be in cases of high risk and intermediate risk PE. A multidisciplinary complex approach is typically not needed for low risk PE, as these patients require anticoagulation alone, and some can be managed without inpatient admission [12]. Institutional efforts at having criteria for PERT activation and dissemination of this amongst house staff and physicians can help mitigate the problem of over activation. It should also be noted that our PERT serves as a consult team which means that treatment decisions, including use of thrombolytics, are ultimately made by the primary team. However, in our experience, the PERT's recommendations are always welcomed by the primary team, as the PERT is now recognized as an expert multidisciplinary PE team in our institution. Importantly, primary providers particularly value the efficient manner with which complex therapeutic approaches are implemented thanks to the multidisciplinary nature of the PERT.

As mentioned previously, the rationale behind development of PERT teams is to improve patient outcomes in a manner that is safe, evidence driven, and efficient. As data becomes available from various PERT programs across the country, it will be important to see if development of these response teams has an effect on patient mortality when compared to previous years when PERT was not an available resource.

Historically, the usage of thrombolysis for severe PE has been limited given the lack of standardized guidelines. In our cohort, we used advanced therapies (thrombolysis, mechanical thrombectomy, and surgery) in 44 (37%) of patients. We believe that the advent of PERT and the PERT Consortium will eventually result in greater understanding (through emerging data and shared experiences) as to when advanced therapies for PE should be used in patients with intermediate-risk PE. At present, it is still to be determined whether increased usage of these therapies leads to an overall survival benefit and reduction in long term complications. Furthermore, complex advanced therapies such as catheter-directed thrombolysis may not always be necessary in patients with intermediate risk PE. Note that 55% of our patients were treated with anticoagulation alone, and we observed a low PE-related mortality of 3%. More specifically, in intermediate risk PE patients, we observed a PE-related mortality of 1% (1 PE related death caused by hemodynamic collapse out of 80 patients with intermediate risk PE). This is congruent with the experience of other PERT teams, such as the MGH team PERT where about 69% of their patients were also treated with anticoagulation alone. Interestingly, our more recent experience (unpublished data) shows that only 3 (4%) of 71 patients treated in 2017 underwent catheter-directed thrombolysis. It will be interesting to see how our and other PE response teams evolve over time in terms of management strategies.

One of the hesitancies behind the lack of widespread thrombolytic usage has been the fear of bleeding complications. We concur with conclusions reached by Kabrhel et al. that bleeding complications were overall lower than previously described in the literature [10]. This may in part be due to newer innovations in thrombolytic therapies such as catheter directed thrombolysis, more rigorous monitoring of bleeding profiles while on thrombolytic therapy, and standardized protocols. Another interesting observation was the lack of major bleeding and mortality in patients who received 100 mg of systemic rtPA. This is of particular interest as data from prior studies at our own medical center have suggested that patients with full dose systemic rtPA may have major bleeding rates as high as 45% [13]. It is thus interesting to note the lack of bleeding with systemic rtPA in our study. It is possible that the multi-disciplinary and multi-professional approach of the PERT and selection of the correct patient population to receive thrombolysis depicted the lower rate of major bleeding. In moving to catheter directed therapies we must not forget the utility of systemic rtPA as the relative efficacy of catheter-directed thrombolysis versus systemic rtPA remains to be determined. We also noted that a sizable proportion of patients fell into the "grey zone" where either anticoagulation or thrombolysis may have been chosen as the treatment modality. In these cases, individualized decisions were made keeping co-morbidities such as malignancy, overall prognosis, and patient preferences in mind. When anticoagulation is selected as the recommended treatment plan, there is generally a discussion to determine a back-up plan to enact if the patient's condition worsens.

An important aspect of our PERT is efficient resource utilization and identification of individuals with expertise in

particular procedures such as surgical embolectomy, catheter directed thrombolysis and mechanical thrombectomy. Another consideration from our experience is the use of surgical embolectomy for intermediate risk PE. Four of the six surgical embolectomy cases were performed in patients with intermediate risk PE. Historically, surgical embolectomy has been performed for high risk PE. There is increasing data that shows that this life saving procedure may have a greater role in patients with intermediate risk PE as well, specifically if their bleeding risk with thrombolytic therapy is judged to be excessive [14].

This study has several limitations. First, this is a retrospective review of our PERT registry. Retrospective data is not always complete and attempts are made to clarify details with clinical providers when needed. To date, no prospective clinical trials have been done to confirm a long term mortality benefit from the utilization of PERT; however, with the growing interest in this team based approach to PE management, such studies can be expected in the future. Second, although this was a single center study, we believe that our results will be comparable to other academic centers with similar facilities. Third, there are limitations within the PERT model itself. Notably, not every member of the PERT can see and talk to the patient. While we are able to share clinical, radiographic and echocardiographic data via computer screen mirroring, several members will never actually interact with the patient. However, this virtual assessment does allow teams to make therapeutic decisions in a shorter duration of time. With the creation of PERT S', it is expected that further studies to help guide the future of PE therapy will become available.

Conclusions

We report the initial outcomes of our pulmonary embolism response team representing multiple specialties with the unified goal of improving outcomes for patients with PE, and collecting data to guide future care of these complex cases.

Author Contributions JM and GH had full access to the data and take responsibility for the integrity of the data and content of the manuscript. JM, IH, DS, AG, NE, DH, NFM,MG, DJ, MS, ST, SB, MM, MS, JB, and GH contributed substantially to the study design, interpretation of results and writing of this manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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