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REVIEW ARTICLE

Pulmonary embolism response teams: Changing the paradigm in the care for acute pulmonary embolism

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Abstract

Pulmonary embolism response teams (PERTs) have emerged as a multidisciplinary, multispecialty team of experts in the care of highly complex symptomatic acute pulmonary embolism (PE), with a centralized unique activation process, providing rapid multimodality assessment and risk stratification, formulating the best individualized diagnostic and therapeutic approach, streamlining the care in challenging clinical case scenarios (e.g., intermediate–high risk and high-risk PE), and facilitating the implementation of the recommended therapeutic strategies on time. PERTs are currently changing how complex acute PE cases are approached. The structure, organization, and function of a given PERT may vary from hospital to hospital, depending on local expertise, specific resources, and infrastructure for a given academic hospital center. Current emerging data demonstrate the value of PERTs in improving time to PE diagnosis; shorter time to initiation of anticoagulation reducing hospital length of stay; increasing use of advanced therapies without an increase in bleeding; and in some reports, decreasing mortality. Importantly, PERTs are positively impacting outcomes by changing the paradigm of care for acute PE through global adoption by the healthcare community.

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KEYWORDS
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1 | INTRODUCTION AND SCOPE OF THE PROBLEM

Acute pulmonary embolism (PE) represents the third most common cause of cardiovascular death globally, behind myocardial infarction and stroke. Accounting for approximately 100 000 deaths across the United States each year, PE is associated with significant morbidity and mortality.[1] Unlike other medical problems, the management of acute PE does not belong to one specialty. Instead, it can involve many different medical and surgical specialties. Furthermore, diagnosis, risk stratification, triage, and treatment vary depending on hospital resources and the experience and expertise of healthcare providers. Currently, there is no standardized, consistent, systematic approach in the therapeutic decision-making process for complex cases of acute PE, particularly for patients suffering from intermediate–high and high-risk PE.[2]

This lack of standards and robust scientific evidence was the impetus behind the pulmonary embolism response teams (PERT), starting in 2012 at the Massachusetts General Hospital (MGH) in Boston.[3] Shortly after MGH created and publicized its PERT, other university-based and community-based hospitals built their own institutional PERTs. Fortunately, the therapeutic armamentarium for the treatment of PE has evolved beyond systemic anticoagulation alone. It now includes systemic thrombolysis, catheter-directed therapies, surgical pulmonary embolectomy (SPE), and mechanical circulatory support systems like extracorporeal membrane oxygenation (ECMO). These therapeutic advances appeared to have evolved in parallel with the creation of PERTs, and together have become tools in treating challenging PE cases.[2,3] In May 2015, the PERT Consortium was created, whose purpose is to "serve the general public by undertaking activities to advance the status of PE care and promote research in the treatment of PE" (https://pertconsortium.org/about/). Since its inception, the PERT Consortium has more than 100 hospitals/institutions registered, and it has grown beyond the United States to include sites in Australia, Brazil, China, Japan, as well as several countries in Europe (i.e., Spain, Ireland, Poland, and the Netherlands).[4]

2 | STRUCTURE, FUNCTION, AND RATIONALE FOR PERTs

PERTs represent an innovative and effective way to perform early and appropriate risk stratification, and a therapeutic approach in a multidisciplinary fashion. The primary objective is to improve outcomes and survival in challenging patients with complex clinical scenarios.[5] PERT members vary by institution and involve several specialists leveraging local knowledge and technical expertise in acute PE.[6,7] One of the main goals of PERTs is to use this multidisciplinary decision-making process to determine the best therapeutic plan for each patient. It is important to emphasize that the structure of PERTs will vary from hospital to hospital, and there is no defined or specific number of team members. PERTs come in multiple "shapes and sizes." In some hospitals, there may be two to four members within a given PERT, whereas in more prominent academic centers, that number may range between six and twelve members. However, a PERT leader must orchestrate and moderate discussion of challenging case scenarios among participants, and ideally, a skilled interventionalist on the team. PERT team members may include specialists from cardiology, interventional cardiology, pulmonary/critical care medicine, hematology, vascular surgery, vascular medicine, and interventional radiology with some variability across hospitals.[2–7] The emergent activation/consultation of a PERT can occur virtually in any section of the hospital, and sometimes can come from an outside facility. For the latter scenario, a well-structured inter-hospital transfer plan must be carefully executed to safely transfer a patient without significant clinical deterioration or worsening hemodynamic instability in the process.[8,9] PERT providers must obtain pertinent clinical history, imaging, and laboratory data as quickly as possible. Subsequently, in a multidisciplinary manner, the PERT team will use this data to make the best therapeutic decisions on managing complex PE cases. This timing of PERTs may vary and depends on the complexity and urgency of the situation.[9] The PERT model streamlines care in the setting of acute complex PE cases, facilitating rapid, effective, and efficient multidisciplinary communication, allowing for fast hospital-specific mobilization of local resources for a given patient, positively impacting the morbidity and mortality of this life-threatening condition.[6,7] Figure 1 illustrates a schematic flow diagram showing the criteria for activation, dynamics, organization, functionality, and fundamental roles of PERT members during the care of complex acute PE. Table 1 illustrates diverse PERTs' multispecialty members potentially involved in the care of acute PE.

3 | THERAPEUTIC TOOLS AVAILABLE FOR PERTs

Systemic anticoagulation with either subcutaneous low molecular weight heparin (LMWH) or intravenous (IV) unfractionated heparin (UFH) should be initiated as soon as an acute PE is suspected even before confirmation by imaging modalities if suspicion is high and the bleeding risk is considered low or acceptable. Current clinical practice guidelines from the 2019 acute PE European Society of Cardiology (ESC)/European Respiratory Society (ERS) and the latest

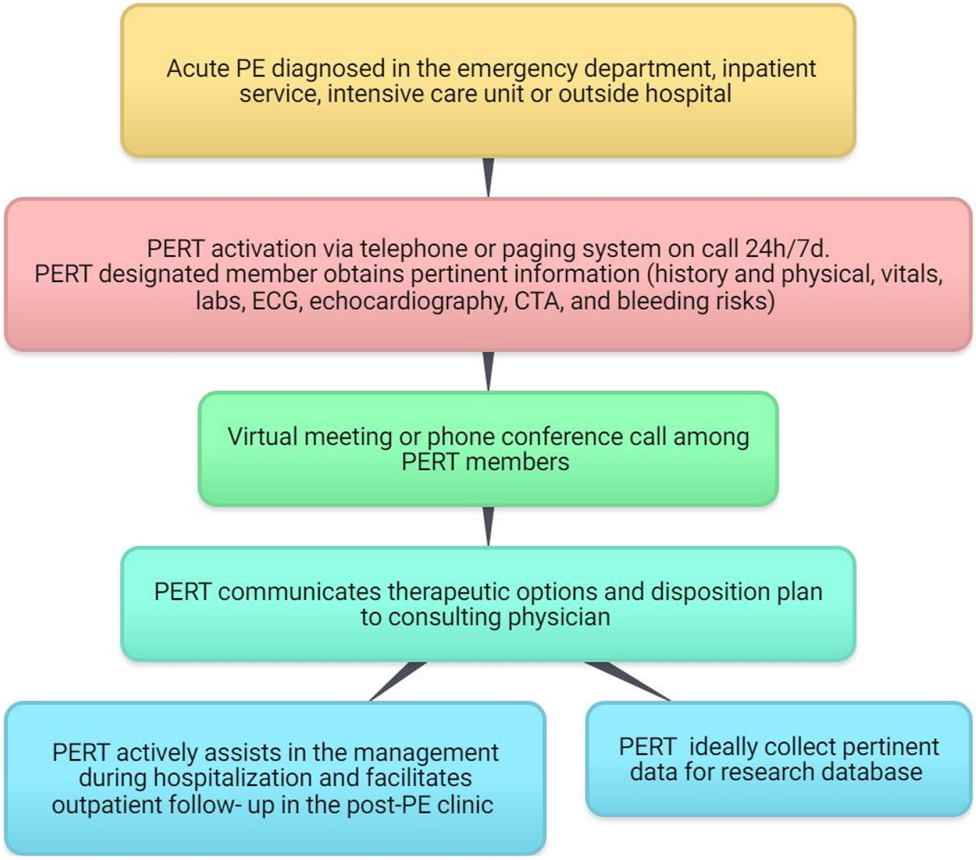

FIGURE 1 Schematic flow diagram showing the criteria for activation, dynamics, organization, functionality, and fundamental roles of PERT members during the care of complex acute PE. Adapted from Porres-Aguilar et al.[2] CTA, computed tomography angiogram; ECG, electrocardiogram; PE, pulmonary embolism; PERT, pulmonary embolism response team.

TABLE 1 Mnemonics of medical and surgical specialties that may be involved in pulmonary embolism response teams (PERTs)

Hospitalist/internist or family medicine (primary care team)
- ***P***ulmonary/critical care
- ***E***ndovascular specialist (e.g., interventional cardiology and emergency medicine)
- ***R***adiology (diagnostic and interventional)
- ***T***hrombosis specialist (e.g., hematology, cardiology, or vascular medicine)
- ***S***urgery (e.g., cardiothoracic and vascular)

Note: Inpatient pharmacists with expertise in antithrombotic therapies, and specialized thrombosis inpatient nurses could also be part of PERTs; however, depending on specific needs, and local resources available for every institution or hospital for a given PERT, members may vary. PERTs can be inclusive beyond the specialties mentioned above.

PERT consortium statement recommend the use of LMWH as initial therapy for acute PE, particularly for intermediate–low and low-risk acute PE, and if no immediate interventions are planned to be performed.[10,11] Support for using LMWH is further demonstrated in a recent retrospective analysis of 505 patients with acute PE treated with UFH (either bolus + infusion or infusion alone) where more than half of the patients failed to achieve any therapeutic activated partial thromboplastin time (APTT) level within 24 h of UFH initiation.[12] If there are concerns for hemorrhagic complications, intravenous UFH may be a better option due to its shorter half-life, ability to adjust the dose in a short time, and its easy reversibility with protamine sulfate. Additionally, if systemic thrombolysis (ST) is strongly considered, UFH may be the preferred agent.[10,11]

The use of ST may be considered in high-risk (massive) acute PE and no absolute contraindications; the ESC/ERS acute PE 2019 guidelines give a Class-I recommendation for the use of ST in high-risk PE.[10] However, ST in patients with intermediate–high risk PE patients remains controversial and continues to be investigated.[13] The PEITHO-3 (NCT04430569) is an ongoing randomized, placebo-controlled, double-blind, multicenter, multinational trial with long-term follow-up to compare the efficacy and safety of a reduced-dose systemic IV alteplase regimen with standard heparin anticoagulation. The study will enroll 659 intermediate–high-risk PE patients. The primary efficacy outcome is the composite of all-cause death, hemodynamic collapse, or venous thromboembolism (VTE) recurrence within 30 days of randomization.[13]

Catheter-directed therapies (CDT) such as catheter-directed thrombectomy with suction/maceration, aspiration, and/or fragmentation with mechanical thrombectomy, and catheter-directed thrombolysis with or without ultrasound facilitation are therapeutic options that may be considered in patients with indications for advanced therapies, especially in those with higher hemorrhagic risks

or with absolute or relative contraindications to ST, respectively.[14] Unfortunately, these endovascular percutaneous techniques may not be available in all hospitals, and their use is contingent upon local expertise and resources.

SPE is recommended for high-risk acute PE if there is an absolute contraindication to ST or if ST and/or CDT has failed. SPE may also be considered in the setting of intracardiac thrombi in transit.[15]

In selected hemodynamically unstable high-risk acute PE patients, the use of ECMO has shown benefits while waiting for definitive intervention. ECMO offers the potential to stabilize severely decompensated acute PE patients with impending right ventricular failure, refractory hypoxemia, or cardiac arrest.[14] The veno-arterial configuration (VA-ECMO) can be utilized as a bridge to more advanced reperfusion strategies such as CDT, SPE, or as a protocolized, stand-alone therapeutic strategy in high-risk PE patients who are not ideal candidates for advanced reperfusion therapies, and has demonstrated a reduction in mortality.[16,17]

Inferior vena cava (IVC) filters should be reserved for patients with acute PE who have contraindications to anticoagulation.[18] Under particular and challenging circumstances, such as in those with a history of multiple recurrent VTE despite being adequately anticoagulated, IVC filters may also be considered.[18] PERTs may be helpful in deciding which patients may benefit from advanced therapies by balancing the paucity of robust studies with technological advancements with multiple endovascular devices that could potentially be useful in appropriately selected patients. Figure 2 illustrates PERT indicators for activation and guides potential therapeutic options for patients with acute complex PE.

4 | PUBLISHED OUTCOMES WITH PERTs

There are more than 100 indexed articles in PubMed/National Library of Medicine/Medline databases about PERTs, reflecting that this approach is relatively novel and evolving, but an extremely passionate topic within the world of VTE. The MGH reported their first observational, descriptive analysis of the initial 30-month experience with PERTs in 2016.[19] In that paper, there were 394 PERT activations, with a sustained increase of 16% every 6 months after the creation of the team, confirming the rapid adoption of the PERT model. The most common therapeutic modality recommended by the MGH PERT at that time was systemic anticoagulation (69%), followed by CDT (9%) and ST (5%).[19] These initial findings were provocative and, since then, have sparked numerous additional descriptive, retrospective, and comparative analyses by other PERT institutions.[20,21]

Wright et al. conducted an observational analysis of 137 patients before PERT implementation between 2014–2015 and 231 patients after PERT implementation. The primary outcome was 6-month mortality. PERT was associated with a sustained reduction in mortality through 6 months (6-month mortality rates of 14% post-PERT vs. 24% pre-PERT, unadjusted hazard ratio [HR] of 0.57, relative risk ratio [RRR] of 43%, $p = .025$). Additionally, there was a reduced length of stay following PERT implementation (9.1 vs. 6.5 days, $p = .007$), concluding that performance of PERTs had a sustained reduction in 6-month mortality, particularly for patients with high-risk acute PE.[22] There were few limitations in this study; as it was observational, there was inherent risk for biases; the number of patients was significantly higher in the post-PERT implementation; greater use of echocardiography and

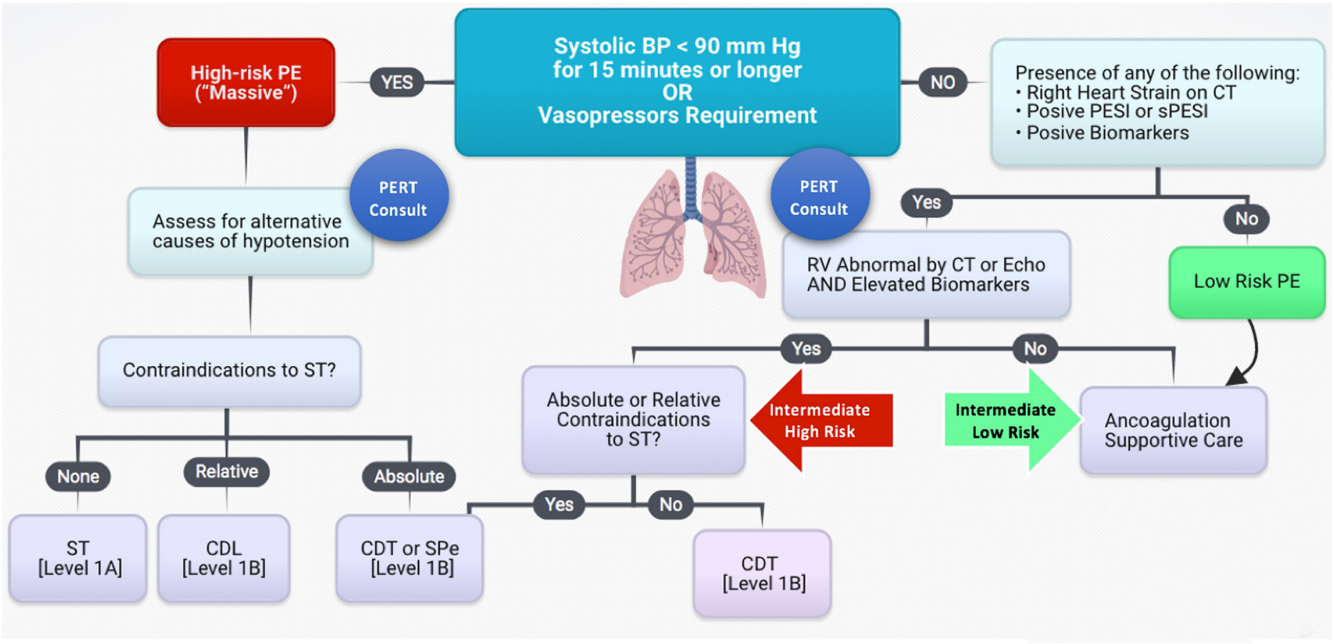

FIGURE 2 PERT indicators for activation and guide for potential therapeutic options in patients with acute complex PE. Adapted and modified from Rivera-Lebron et al.[11] BP, blood pressure; CDT, catheter-directed therapies; CT, computed tomography; PE, pulmonary embolism; PESI, pulmonary embolism severity index; RV, right ventricle; SPE, surgical pulmonary embolectomy; ST, systemic thrombolysis; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

biomarkers were used compared to pre-PERT performance, identifying more patients with intermediate-risk PE in the post-PERT implementation; and investigators were not able to adjudicate causes of death, and differences in complications from acute PE.[22]

Carroll et al. performed a retrospective comparative analysis in pre-PERT and post-PERT eras, evaluating in-hospital acute PE-related mortality for 3 years pre-PERT and 3-years post-PERT implementation. Of the 2042 patients included in the analysis, 165 (14.2%) were associated with PERT activations, there was no difference in PE-related mortality between the two time periods (2.6% pre-PERT implementation vs. 2.9% post-PERT implementation, $p = .89$);[23] however, IVC filters utilization decreased in the post-PERT era (10.7% pre-PERT implementation vs. 6.9% post-PERT implementation, $p = .002$).[23]

Chaudhury et al. evaluated 769 patients from the Cleveland Clinic and found that post-PERT implementation patients had lower rates of major or clinically relevant nonmajor bleeding (17.0% vs. 8.3%, $p = .002$), shorter time-to-therapeutic systemic anticoagulation (16.3 h vs. 12.6 h, $p = .009$), as well as decreased use of IVC filters (22.2% vs. 16.4%, $p = .004$). Importantly, there was a significant decrease in 30-day/inpatient mortality (8.5% vs. 4.7%, $p = .03$). These differences in outcomes were more pronounced in the intermediate and high-risk acute PE subgroups (mortality 10.0% vs. 5.3%, $p = .02$).[24]

Araszkiewicz et al. recently described the first Polish PERT initiative results in 690 unique PERT activations. Most PERT activations were generated in patients with intermediate–high risk PE (42.9%), whereas high-risk PE occurred in 10% of patients. Systemic anticoagulation alone was delivered to 80.3% of patients and 23.3% of patients received at least one advanced therapy: CDT (11.3%), ST (5.3%), SPE (2.4%), IVC filter placement (3.7%), and ECMO (0.6%). In-hospital mortality in the whole study group was 5.1%. This European study emphasized the significant variation in PERTs between institutions, particularly from the organizational and operational points of view, with an acceptable mortality rate overall.[25]

Jerjes-Sánchez et al. created and described their first PERT in Mexico, the PREVENTION team. Such a multidisciplinary team may be activated with acute complex proximal extensive deep vein thromboses, with the primary objective to cover the full clinical spectrum of VTE, providing fast identification and rapid institution of best therapies for patients with high-risk features. Ideally within the first 60–90 min post-PERT consult activation, the team must come up with a solid therapeutic recommendation by consensus, mainly if ST or CDT are considered, because time is of essence for right ventricular ischemia/infarction, thrombus resistance, and limb salvage as well as preventing long-term complications like post-thrombotic syndrome, chronic thromboembolic disease, chronic thromboembolic pulmonary hypertension, and post-PE syndrome.[26]

In a nationwide survey performed in China, Wang et al.[27] showed that only one fourth of hospitals had a fully functional PERT program. In contrast, the majority of PERTs were partially operating, and under development, emphasizing the urgent need of further studying PERT outcomes in China. More recently, the Chinese PERT Alliance published its first consensus document highlighting PERTs, the incorporation of international PERT practice, the promotion of PERTs, and the standardization of PERT centers.[28] Table 2 summarizes studies regarding clinical outcomes and the impact of diverse PERTs.

TABLE 2 Studies summarizing clinical outcomes and impact of diverse PERT activations

Study	Number of patients	Outcomes
Kabrhel et al.[19]	394 PERT activations	69% of patients received AC CDT in 9%, ST in 5%
Wright et al.[22]	137 pre/post-PERT	↓6 months mortality rate; ↓ LOS
Carroll et al.[23]	2042 pre/post-PERT	↑ Risk stratification assessment by cardiac biomarkers and TTE. ↓ IVC filters use. No difference in mortality
Chaudhury et al.[24]	769 pre/post-PERT	↓ Rate of bleeding; ↓ Time-to-therapeutic AC; ↓ IVC filters; ↓ 30-day mortality
Araszkiewicz et al.[25]	690 PERT Activations	ST alone in 80.3% of patients 23.3% received advanced therapy: CDT 11.3%, ST 5.3% SPE in 2.4% and ECMO in 0.6%
Annabathula et al.[34]	530 pre/post-PERT	↓ In-hospital mortality; ↓ LOS; ↓ total cost of care
Myc et al.[35]	554 patients	↓ All-cause mortality. Improved outcomes compared to patients who did not receive PERT

Abbreviations: AC, anticoagulation; CDT, catheter-directed therapies; ECMO, extracorporeal membrane oxygenation; IVC, inferior vena cava; LOS, length of stay; PERT, pulmonary embolism response team; SPE, surgical pulmonary embolectomy; ST, systemic thrombolysis; TTE, transthoracic echocardiography.

5 | ROLE OF PERTs DURING THE COVID-19 PANDEMIC

It is well known now that contracting the novel coronavirus disease 2019 (COVID-19) represents a significant hypercoagulable risk factor for VTE development, particularly in hospitalized patients with moderate and severe forms of COVID-19.[29] The development of acute PE/VTE associated with or complicated by COVID-19 represents a unique and challenging clinical scenario. However, PERT members play an essential role by providing adequate, evidence-based guidance and showing the best therapeutic strategies for challenging and complex cases of COVID-19–associated VTE. Therefore, PERTs must assist and proactively address important aspects of this severe complication. Recently, a brief perspective and opinion paper by Porres-Aguilar et al.[30,31] and a recent PERT consortium informative position statement document by Rosovsky et al., published in 2020, address this clinical scenario and propose critical points for optimal patient care of complex acute VTE in the setting of COVID-19.[32] We believe that a team-based approach like PERTs for clinical decision making, and coordination of care, have been critical during the pandemic. For instance, PERTs can play a role when suspecting acute PE in a complicated and challenging patient. Multiple national and international collaborations among clinical researchers, societal clinical practice guidelines, and statement documents have been published to guide VTE prophylaxis in COVID-19 patients and many have been coauthored by PERT leaders, to ultimately improve the care of hospitalized patients with COVID-19.[32,33]

6 | COST EFFECTIVENESS OF PERTs

Available data suggest that implementing a PERT improves the quality of life and cost of care, resulting in improved value. This may be due to more timely identification and risk stratification leading to earlier interventions and streamlined decision making, leading to better outcomes and shorter length of stay in the hospital.[34] Myc et al. performed a retrospective analysis, evaluating patient-centered outcomes and cost effectiveness of PERTs in 554 patients, focusing on 6-month survival, hospital length of stay, hospital-related costs, 30-day readmission rates, and in-hospital bleeding rates; all-cause mortality was significantly and consistently decreased after the inception of a designated PERT, without incurring additional hospital costs or protracting length of stay. Moreover, there was no significant rise in in-hospital bleeding events.[35] PERTs improved patient outcomes compared to patients who did not receive PERT activation during the same period.[35]

7 | FUTURE PERSPECTIVES AND CONCLUSIONS

PERTs may elevate the care of patients with PE and have demonstrated improvement in quality metrics such as reductions in time to diagnose acute PE, prompt utilization of therapeutic anticoagulation, and reductions in length of stay. Since its inception, the PERT Consortium has offered guidance on how to improve the care of PE patients, such as treatment of PE patients during COVID and, more recently, how to treat PE patients in rural settings. The PERT Consortium recently developed a position paper on transferring patients from a remote rural-based hospital to a centralized institution with higher volume and more resources available.[8] Furthermore, the PERT Consortium has an ongoing prospective multinational registry, addressing knowledge gaps around quality of care, achieving excellence and optimal care in complex cases of acute PE, and evaluating the efficacy and efficiency of PERTs.

Many other diseases have centers of excellence (COE) which have been recently defined as organizational design, personnel, servicescape design, readily available cutting-edge advanced medical therapies, marketing, and financial impact.[35] PERTs already fulfill many of these features, and creating COE may be the next step in their evolution.[36,37]

PERTs represent a concept and a continuously evolving process under dynamic changes. There has been widespread adoption of PERTs, with increased activation, utilization, and input since their inception almost a decade ago; however, more data in the form of national and international registries and randomized trials are needed to demonstrate a true net clinical benefit of PERTs. In addition, studies are needed to address improving morbidity and mortality in acute PE and minimizing major and fatal bleeding complications. The ESC/ERS acute PE 2019 guidelines on managing intermediate–high and high-risk acute PE patients currently recommend the potential utilization of designated PERTs if available as a class II-A recommendation.[10]

As PERTs continue to evolve rapidly, these dynamic changes may facilitate the implementation of clinical research, particularly on how PERTs can impact appropriate utilization of therapeutic tools available for a given complex acute PE patient. Areas of interest include exploration and description of the current performance of PERTs including major and fatal bleeding events, particularly in patients chronically taking oral anticoagulation therapies for acute PE. Perhaps a so-called "hemostatic PERT" may be of equipoise while investigating such catastrophic complications; equally important are objective evaluations, quality metrics, descriptive data, and research to describe the performance on how efficient and productive PERTs can be while risk-stratifying and predicting early major bleeding events in-hospital. Thus, PERTs can offer valuable clinical implications while reaching consensus on which therapeutic strategy may be best for a given complex acute PE patient. Given the complexity of post-acute PE syndrome, PERT multidisciplinary clinics may be needed to perform continuity of care in the outpatient setting, and to monitor and manage these patients, particularly the subset of patients at high risk for the development of chronic thromboembolic disease and/or chronic thromboembolic pulmonary hypertension.[26] However, this is still an unmet goal for PERTs, but at the same time, a potential area of interest that requires further exploratory research.

The PERT process is currently changing our clinical practice. More education and awareness are essential for rapid acceptance

and adoption worldwide. Despite the challenging of designing and performing a prospective randomized clinical trial evaluating the benefits/risks of interventions executed by PERTs, we believe PERTs will continue to change the paradigm in the care of acute PE, achieving excellence in such care, with full adoption by clinical-practice guidelines globally.

AUTHOR CONTRIBUTIONS

MPA, RPR, BRL, SK, DM, JAA, DJ, and CJS all contributed substantially to deserve coauthorship, in all aspects including: conceiving the idea of the work, data collection, data analysis, interpretation, drafting the manuscript, critical revision for important intellectual content, and approval of the final version of such manuscript for consideration of publication.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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