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Addressing the rising trend of high-risk pulmonary embolism mortality: Clinical and research priorities

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Abstract

Deaths from high-risk pulmonary embolism (PE) appear to have increased in the last decade. Modifiable risks contributing to this worrisome trend present opportunities for physicians, researchers, and healthcare policymakers to reduce excess mortality. Emerging advanced therapies for PE appear promising, although we lack clear insight as to the magnitude of potential benefit and which patient subgroup(s) should receive them. Treatment and outcome disparities attributable to social determinants of health demand new healthcare delivery policy. In this article, we examine current PE epidemiology, suggest quality improvement and healthcare policy initiatives, and discuss relevant ongoing clinical trials aimed at addressing excess PE mortality.

Keywords

Pulmonary embolism, quality improvement, health care disparities, systemic thrombolysis, catheter directed thrombolysis

Introduction

Although overall mortality in pulmonary embolism (PE) is low and mortality in non-high-risk PE appears to have stabilized,[1,2] mortality from high-risk PE may be increasing in the US (figure 1).[3] While non-modifiable trends may contribute, we must prioritize specific clinical and research initiatives to decrease excess PE mortality.

The 2019 European Society of Cardiology guidelines risk stratify patients with acute PE according to risk of 30-day mortality based upon hemodynamic stability, clinical parameters and comorbidities (e.g. PE Severity Index [PESI] class), and the presence/absence of radiographic and biochemical right ventricular dysfunction (RVD). High-risk PE is characterized by hemodynamic instability defined as cardiac arrest, obstructive shock, or persistent hypotension (systolic blood pressure <90mmHg) not explained by alternative etiologies. Intermediate-risk patients belong to PESI class III-V and are further stratified into intermediate-low-risk (RVD *or* elevated troponin) and intermediate-high-risk (RVD *and* elevated troponin).[4] Most PE-related deaths occur in patients who present with high and intermediate-high-risk PE and improving the management of these two groups offers the greatest potential to decrease mortality.[5] Clinical and research initiatives should prioritize improved understanding of PE mortality trends, better adherence to guideline-directed management of high-risk PE, and the validation of advanced therapies for patients with intermediate-risk PE.

An increasing PE-related mortality trend

High-risk PE mortality appears to have risen by 93.5% between 1999 and 2019 in the US (absolute age-adjusted mortality rate in 1999: 2.70 [95%CI 2.64-2.76] vs 2019: 3.59 [95%CI 3.56-3.63]).[3] Large European studies report a decrease in overall PE-related mortality over a similar time period, but did not stratify their reported mortality analysis by PE risk.[4] Thus, it remains unclear if an increase in high-risk PE mortality may be simultaneously occurring in Europe.[6,7] Epidemiological data from the US reveal geographic, racial, age, and sex disparities in the age-adjusted mortality rate due to PE, suggesting that this increased risk may be modifiable.[2,3,6,8] Farmakis and Zghouzi recently demonstrated socioeconomic and geographic disparities in accessing advanced PE therapies (systemic thrombolysis, catheter-directed thrombolysis [CDT], thrombectomy, extracorporeal membrane oxygenation) in large US populations.[9] Increased PE mortality in younger US patients is paradoxical.[6,8,10] Suggested explanations include an increasing prevalence of obesity,[11] gastrointestinal cancers,[8,12] behavioral risk factors[8], health care inequalities,[3,9] as well as US medical care price inflation.[6]

Other factors may contribute to an increase in overall high-risk PE mortality. First, an increasing burden of cardiopulmonary disease in an aging population yields patients with more comorbidities at time of diagnosis.[8] Second, deaths previously described as “unexplained” may increasingly be attributed to PE due to heightened awareness and improved diagnostic strategies, creating a misleading upward trend in high-risk PE mortality.[3] Epidemiological methods of determining PE mortality that are based upon death certificate data may also have limitations that introduce error.[13] Third, the SARS-CoV-2 pandemic has increased global PE incidence and may be further contributing to PE-related mortality.[14,15] Fourth, high-risk PE

patients may be significantly undertreated with regards to systemic thrombolysis and presumptive anticoagulation prior to diagnostic confirmation.[16-18]

Improving outcomes for patients with high-risk PE

Rapid and appropriate anticoagulation of patients with high-risk PE has received a Class IC level of evidence from the European Society of Cardiology (ESC).[4] Although this practice is standard-of-care, adherence is often suboptimal.[4,19,20] Prompt anticoagulation has been associated with reduced risks of mortality, recurrent venous thromboembolic disease, and progression to hemodynamic instability in several retrospective studies.[21-23] However, underutilization of presumptive anticoagulation has been documented across all PE risk strata[18,24-26] and, presumably, affects high-risk patients differentially.[26] Randomized controlled trials of presumptive anticoagulation, qualitative studies of emergency physicians' PE management behaviors, and implementation trials addressing identified knowledge and practice gaps are needed.

All major guidelines concur: patients with high-risk PE should receive systemic thrombolysis in the absence of contraindications, although the evidence supporting this recommendation is weak and optimal dosing is unknown.[4,27-30] Nonetheless, several reports demonstrate systemic thrombolysis underutilization in eligible patients.[16,17,31,32] Approximately 4% of patients with acute, symptomatic PE are hemodynamically unstable and physicians may be unfamiliar with clinical practice guidelines for managing this small subset of patients.[4,33] While no definitive explanation exists for underutilization of systemic thrombolysis in eligible high-risk patients, it is

possible that physicians may fear iatrogenic major bleeding. This concern may be magnified in patients who lacked confirmatory imaging for PE at the time of treatment consideration.

High-risk patients might also benefit from other treatments such as catheter-directed therapies. The recently-published FLAME study reported a low mortality in high-risk patients treated with catheter-directed mechanical thrombectomy, although this small study was non-randomized.[34] Nonetheless, percutaneous catheter-directed treatments should be considered for high-risk patients who have failed systemic thrombolysis or have contraindications to it although high-quality evidence is lacking (ESC Class IIA level C evidence).[4]

New organizational and research priorities may increase the treatment of eligible patients with systemic thrombolysis and anticoagulation. Comprehensive clinical practice guidelines for reperfusion that are endorsed by national, regional, and local physician organizations are needed. Trials of reduced-dose systemic thrombolysis may improve compliance with guideline-directed recommendations by making the practice more acceptable to physicians.[35-37] Increasing the appropriate use of systemic thrombolysis may improve geographic and socioeconomic disparities in accessing advanced PE treatment as it is readily available at most hospitals.[3,38]

PE Response Teams (PERTs) are multi-disciplinary rapid response organizations that provide individualized treatment plans for all patients with acute PE in all stages of the clinical course.[39] The formation of PERTs is recommended with ESC Class IIa Level C evidence and more robust clinical evidence is needed.[4] One systematic review found PERTs were associated with increased use of advanced therapies and were broadly supported among physicians who

manage patients with acute PE.[39] PERT consultation delivered by telemedicine could be offered to medically underserved areas to address disparities in advanced therapy utilization.[9] Financial incentives to create PERTs should be initiated and research investigating the effect of PERTs on patient outcomes, length of hospital stay, and total hospital expenditures may provide needed financial justification.[40]

Improving outcomes for patients with intermediate-high-risk PE

In-hospital mortality of patients admitted for acute intermediate-high-risk PE is a considerable 1-5%.[41-43] The optimal treatment of this patient subgroup is unclear, and we lack reliable methods for deciding which intermediate-high-risk patient will become hemodynamically unstable. Blood pressure, biomarkers and echocardiographic findings alone are insufficient to risk stratify this subgroup, as some patients who are initially normotensive will experience hemodynamic instability requiring rescue reperfusion, vasopressors, intubation, or cardiopulmonary resuscitation.[4] Besides the ESC classification, prediction scores might also be helpful to identify acute PE patients who may benefit from reperfusion treatment. The Bova score is a prospectively validated risk stratification tool for predicting 30-day PE-related complications in normotensive patients.[44] Risk scores such as CAPE and PE SCORE may also be useful to identify patients at risk for short-term adverse events.[45-47] However, none of these scores has been validated in PE management studies and more evidence is needed before physicians can base reperfusion decision-making upon them.

Inappropriate anticoagulation choice may be a barrier to optimizing outcomes. Consensus guidelines recommend low molecular weight heparin or fondaparinux for hemodynamically

stable patients,[4] however some studies indicate that most will receive unfractionated heparin.[32,48] This is problematic as patients receiving unfractionated heparin may spend excess time outside of the therapeutic range owing to heparin's unpredictable pharmacokinetic profile as well as its complex dosing and monitoring requirements.[21,32,49-51] Deleterious effects of sub-therapeutic and supra-therapeutic anticoagulation in acute PE make other pharmacologic anticoagulation strategies a potential better choice in intermediate-risk PE.[52,53]

Efforts to expand the indication for systemic thrombolysis to include intermediate-risk patients were curtailed by the results of the PEITHO study.[42] The PEITHO investigators found that the modest clinical benefits in reducing hemodynamic decompensation associated with systemic thrombolysis were outweighed by an increased risk of intracranial hemorrhage.[42] However, a renewed interest in systemic thrombolysis in the intermediate-risk subgroup has been driven by: (1) reduced-dose systemic thrombolysis strategies that may minimize bleeding risk;[35-37] and (2) a *post-hoc* analysis of the PEITHO data suggesting a higher risk subgroup that may be more likely to benefit from reperfusion.[54] Future studies are needed to clarify optimal thrombolytic dosing as well as to determine if it is beneficial in a subset of intermediate-high-risk patients.

Several anticipated randomized controlled trials are currently investigating advanced PE treatments compared to anticoagulation alone. The PEITHO3 trial is investigating reduced-dose systemic thrombolysis using alteplase (0.6mg/kg) in intermediate-high-risk patients who also have at least 1 of the following criteria: (1) systolic blood pressure ≤110 mmHg for ≥15 minutes, (2) respiratory rate >20 respirations per minute or oxygen saturation <90% on room air, or (3) a history of congestive heart failure.[36,55] The HI-PEITHO trial is examining the safety and efficacy

of CDT in a population of intermediate-high-risk patients. The study is ensuring a clinically ill cohort by requiring that enrolled patients meet 2 of 3 additional criteria: (1) heart rate ≥100 beats per minute, (2) systolic blood pressure ≤110 mmHg, or (3) respiratory rate >20 respirations per minute or oxygen saturation <90% on room air.[56,57] PE-TRACT will evaluate CDT or mechanical thrombectomy plus anticoagulation compared with anticoagulation alone in intermediate-high-risk patients with a proximal pulmonary arterial clot.[58] The PEERLESS study will use a randomized, controlled study design to evaluate the performance of catheter-directed mechanical thrombectomy compared with any commercially available CDT therapy.[59] Future high-quality studies comparing systemic thrombolysis to catheter directed therapies would increase the generalizability of these reperfusion treatments to the high-risk patient population and help guide reperfusion decision making.

Conclusions

Although overall mortality of non-high-risk PE appears stable, high-risk PE mortality appears to be increasing in the US. Knowledge and practice gaps in high- and intermediate-risk PE management exist. Robust implementation efforts are needed to improve acute PE management and resolve treatment disparities. Further research efforts should work to refine risk stratification of intermediate-risk patients and examine reperfusion strategies in intermediate-high-risk PE.

Figure 1 reprinted from Thrombosis Research, Zuin M, Bikdeli B, Davies J, et al. Contemporary trends in mortality related to high-risk pulmonary embolism in US from 1999 to 2019, page 75, Copyright (2023), with permission from Elsevier.

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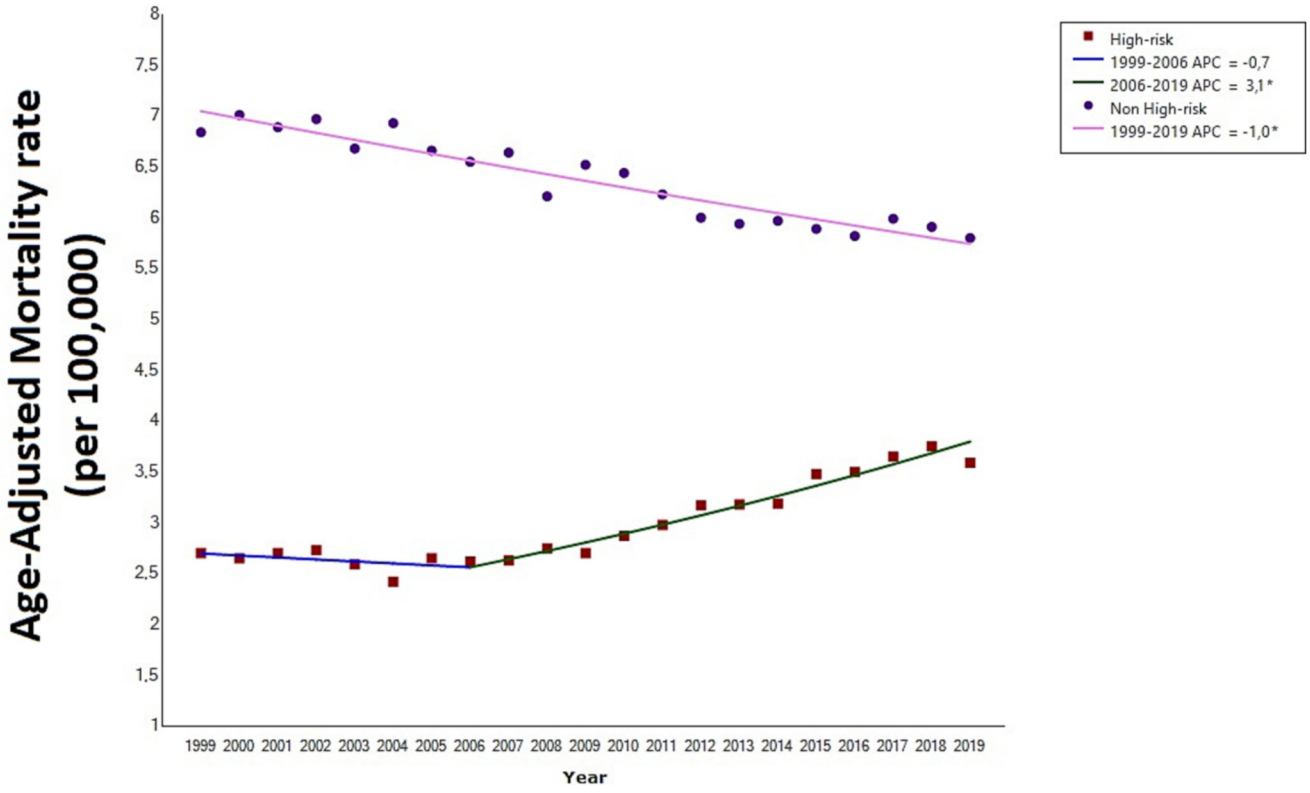

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