**Impact of Immediate Treatment on Acute Pulmonary Embolism in Patients with Hemodynamic Instability**

**ABSTRACT**

**Aims:** This systematic review aims to evaluate the clinical outcomes, mortality, and safety profile of immediate therapeutic interventions—including systemic thrombolysis, surgical embolectomy, and catheter-directed therapies—for acute pulmonary embolism (APE) in adult patients presenting with hemodynamic instability. It also assesses the timing of interventions and outcomes across specific subgroups, such as elderly and comorbid patients.

**Study Design:** Systematic literature review.

**Place and Duration of Study:** Databases searched (PubMed, SciELO, LILACS, BVS, MEDLINE) between January 2014 and April 2024.

**Methodology:** The review followed PRISMA guidelines. Studies published from 2014 to 2024 were included if they evaluated immediate treatment strategies in adult patients with high-risk APE and hemodynamic instability. Eligible study designs included randomized clinical trials, cohort studies, and multicenter analyses. Data extraction and quality assessment (using the Newcastle-Ottawa Scale and Cochrane RoB 2.0 tool) were performed independently by two reviewers.

**Results:** Of 487 studies identified, 32 met all inclusion criteria, encompassing 2,761 patients. Systemic thrombolysis showed a significant reduction in mortality and faster hemodynamic stabilization compared to anticoagulation alone, but with an increased risk of major bleeding, particularly intracranial hemorrhage. Surgical and catheter-directed embolectomy demonstrated similar efficacy to thrombolysis, with potentially fewer bleeding complications in high-risk subgroups. Early intervention (within 2 hours of diagnosis) was consistently associated with better outcomes.

**Conclusion:** Immediate reperfusion therapy is essential for improving survival and reducing complications in high-risk APE patients with hemodynamic instability. While thrombolysis remains the first-line treatment, embolectomy represents a safe and effective alternative when thrombolysis is contraindicated. Further randomized, multicenter trials are needed to optimize patient stratification and refine therapeutic algorithms tailored to comorbid and elderly populations.

1. **INTRODUCTION**

Acute pulmonary embolism (APE) is defined as the sudden obstruction of one or more pulmonary arteries, typically caused by thrombotic emboli originating from the deep venous system, especially from the lower limbs (1). This obstruction impairs pulmonary circulation and disrupts the ventilation-perfusion ratio, resulting in hypoxemia, increased pulmonary vascular resistance, and, in severe cases, acute right ventricular overload (2).

Clinically, APE presents with a wide range of manifestations depending on the extent of embolic burden and the patient's baseline cardiopulmonary condition. The most frequent symptoms include sudden-onset dyspnea, pleuritic chest pain, tachycardia, tachypnea, anxiety, cough, sweating, and occasionally hemoptysis (3). In more severe cases, systemic arterial hypotension, syncope, or even sudden cardiac arrest may occur (4). Diagnosis requires high clinical suspicion and is confirmed through imaging such as pulmonary CT angiography, ventilation-perfusion scintigraphy, or echocardiography in unstable patients (5).

APE with hemodynamic instability—also referred to as massive PE—is characterized by systolic blood pressure below 90 mmHg for at least 15 minutes, a ≥40 mmHg drop from baseline, or obstructive shock with signs of hypoperfusion (6). This condition suggests significant pulmonary arterial obstruction, leading to right ventricular dysfunction and a markedly increased risk of mortality (7). The presence of hemodynamic instability is a clear indication for immediate therapeutic intervention, such as systemic thrombolysis, surgical embolectomy, or catheter-directed procedures, aiming to promptly restore pulmonary perfusion and prevent cardiovascular collapse (8).

Immediate treatment in high-risk cases is deemed critical due to the imminent threat of death from circulatory failure. The abrupt increase in pulmonary arterial pressure imposes an acute afterload on the right ventricle, leading to its dilation and dysfunction, with consequent decline in cardiac output. Without effective intervention within the first hours, this scenario may rapidly evolve into obstructive shock and cardiac arrest (9).

Clinical studies and international guidelines indicate that mortality from hemodynamically unstable APE may exceed 50% in the absence of reperfusion strategies, whereas early thrombolytic therapy can reduce this risk by up to 50% (10). The narrow therapeutic window underscores the importance of rapid diagnosis and immediate initiation of treatment, particularly systemic thrombolysis, which enables swift restoration of pulmonary blood flow and reversal of right ventricular dysfunction (11). Delays in treatment are associated not only with increased mortality but also with serious complications such as chronic thromboembolic pulmonary hypertension and multiorgan failure (12). Therefore, both hospital and prehospital protocols should be structured to rapidly assess eligibility for reperfusion therapies, minimizing the time between diagnosis and intervention (13).

Despite advancements in diagnostics and therapeutic options, significant knowledge gaps and clinical controversies persist, warranting the present systematic review. One major uncertainty involves the ideal treatment in cases where thrombolysis is contraindicated or ineffective, and surgical or catheter-based embolectomy is not widely available or standardized across healthcare centers (14). Moreover, although current guidelines recommend immediate thrombolysis in high-risk cases, real-world data reveal that this strategy is frequently underutilized—either due to concerns about bleeding complications or diagnostic uncertainty in critical scenarios (15). This reflects a disconnect between evidence-based recommendations and clinical practice, exacerbated by the heterogeneity of existing studies, many of which include small sample sizes and diverse outcome definitions (16).

Another unresolved issue is the optimal timing for intervention and the clinical impact of slight variations in the interval between diagnosis and treatment initiation. The literature remains limited in terms of direct comparisons between reperfusion strategies (systemic thrombolysis vs. surgical or catheter embolectomy), especially in subgroups such as the elderly, cancer patients, or individuals with cardiovascular comorbidities (17). In light of these uncertainties, this systematic review aims to answer the following question:

"What is the impact of immediate treatment of acute pulmonary embolism in patients with hemodynamic instability in terms of mortality, complications, and relevant clinical outcomes, considering different therapeutic strategies?"

This analysis is based on studies comparing thrombolysis, embolectomy, and anticoagulation alone in high-risk APE patients, with special attention to intervention timing, treatment safety, and efficacy across different clinical profiles. The goal is to support a more standardized clinical approach in one of the most critical scenarios in emergency medicine.

1. **MATERIAL AND METHODS**

**Review Design**

This is a systematic literature review conducted in accordance with the principles established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The objective was to collect, analyze, and synthesize the available evidence regarding the efficacy and safety of immediate treatment for acute pulmonary embolism (APE) in patients with hemodynamic instability. The search, selection, and data extraction processes were performed independently by two reviewers, with disagreements resolved by consensus.

**PICO Question**

The central research question was structured according to the PICO framework (Population, Intervention, Comparator, Outcomes):

* P (Population): Adult patients diagnosed with acute pulmonary embolism (APE) with associated hemodynamic instability
* I (Intervention): Immediate treatment with systemic thrombolysis, surgical embolectomy, or catheter-directed therapy
* C (Comparator): Anticoagulation alone or delayed treatment
* O (Outcomes): Mortality, hemodynamic stabilization, hemorrhagic complications, length of hospital stay, adverse events

PICO Question: What is the impact of immediate treatment compared to anticoagulation alone on clinical outcomes (mortality, hemodynamic stabilization, and complications) in high-risk APE patients with hemodynamic instability?

**Inclusion Criteria**

Studies were included if they met the following criteria:

* Evaluated adult patients diagnosed with APE and hemodynamic instability
* Compared systemic thrombolysis, surgical or catheter-based embolectomy with anticoagulation alone
* Reported clinical outcomes such as mortality, hemodynamic stabilization, major bleeding, length of hospital stay, or complications
* Published in the last 10 years (2014–2024)
* Full-text available through PubMed, SciELO, LILACS, BVS, and Medline
* Written in English, Portuguese, or Spanish

**Exclusion Criteria**

The following studies were excluded:

* Studies evaluating APE without hemodynamic instability
* Narrative reviews, case reports, letters to the editor, or papers without primary clinical data
* Duplicates across databases
* Studies that did not allow extraction of data specific to high-risk subgroups
* Trials with inadequate methodology or inconsistent data

**Data Sources and Search Strategy**

A systematic search was conducted across the following electronic databases: PubMed, SciELO, LILACS, BVS (Virtual Health Library), and Medline, targeting studies published between January 2014 and April 2024. Controlled vocabulary (DeCS/MeSH) and their Portuguese equivalents were used, along with free-text terms combined with Boolean operators.

**Key search terms included:**

*Pulmonary embolism, acute pulmonary embolism, hemodynamic instability, massive PE, thrombolysis, catheter embolectomy, surgical embolectomy, anticoagulation, mortality, bleeding, intracranial hemorrhage, treatment outcomes.*

The typical search strategy was:

(“pulmonary embolism” OR “acute pulmonary embolism”) AND (“hemodynamic instability” OR “massive PE”) AND (“thrombolysis” OR “embolectomy” OR “anticoagulation”) AND (“mortality” OR “bleeding” OR “outcomes”)

Filters were applied for language (Portuguese, English, and Spanish), full-text availability, and publication date (last 10 years).

**Study Selection Process**

After the initial search, all results were exported to an Excel spreadsheet and screened for duplicates. Two independent reviewers conducted the **title and abstract screening** based on predefined eligibility criteria. Potentially relevant studies were retrieved in full text for a second, detailed review.

Disagreements between reviewers were resolved by consulting a third researcher.

**Quality Assessment and Risk of Bias**

The methodological quality of the included studies was assessed using validated tools according to study design:

* For randomized clinical trials (RCTs), the Cochrane Risk of Bias 2.0 (RoB 2) tool was applied, evaluating domains such as randomization, allocation concealment, blinding, incomplete data, and selective outcome reporting.
* For observational studies (cohorts and retrospective analyses), the Newcastle-Ottawa Scale (NOS) was used, assessing participant selection, group comparability, and outcome evaluation.

Each study was independently assessed by two reviewers. Any discrepancies were resolved through consensus or adjudicated by a third reviewer.

The results of this assessment were used to inform the critical analysis of the findings and are presented descriptively in the results and discussion sections.

1. **RESULTS**

Table 1 – Study Selection Flow

| Review Stage | Number of Studies |
| --- | --- |
| Studies identified in databases | 487 |
| After removal of duplicates | 315 |
| Titles/abstracts screened | 315 |
| Full-text articles assessed for eligibility | 54 |
| Studies included in final analysis | 32 |

*Source: authors (2025).*

Table 2 – Characteristics of Included Studies

| Characteristic | Description |
| --- | --- |
| Study types | Randomized clinical trials, retrospective cohorts, multicenter analyses |
| Publication period | 2014 to 2024 |
| Target population | Patients with high-risk APE and hemodynamic instability |
| Interventions assessed | Systemic thrombolysis, surgical embolectomy, catheter embolectomy, anticoagulation alone |
| Primary outcomes | Mortality, hemodynamic stabilization, intracranial hemorrhage |
| Secondary outcomes | Length of hospital stay, intensive care support, chronic pulmonary complications |

*Source: authors (2025).*

Table 3 – Summary of Clinical Evidence

| Topic Assessed | Main Conclusions |
| --- | --- |
| Efficacy of immediate thrombolysis | Reduction in mortality and improvement in right ventricular function |
| Alternatives to thrombolysis | Surgical or catheter embolectomy effective and safe, with comparable mortality |
| Special subgroups | Higher risk of major bleeding; catheter-directed thrombolysis may be safer |
| Importance of intervention timing | Early intervention (within 2 hours of diagnosis) improves stabilization and reduces mortality |

*Source: authors (2025).*

**Effects of Immediate Thrombolysis on Mortality, Hemodynamic Stabilization, and Bleeding Risk**

The use of immediate systemic thrombolysis in patients with acute pulmonary embolism (PE) and hemodynamic instability has been extensively studied as a reperfusion strategy with the potential to positively impact clinical outcomes. Compared to anticoagulation alone, several studies suggest that thrombolysis may reduce mortality in high-risk patients. For instance, a retrospective study conducted at a reference center with 32 high-risk PE patients observed that those undergoing thrombolysis or embolectomy had higher survival rates (54%) compared to those receiving only anticoagulation (40%), although this difference was not statistically significant (p = 0.2), possibly due to the small sample size. Other evidence supports the superiority of thrombolysis in situations of shock or circulatory collapse, reinforcing its recommendation in international guidelines as the first choice in cases of hemodynamic instability.

Beyond its potential impact on mortality, thrombolysis promotes faster recovery of hemodynamic parameters, such as reduced pulmonary vascular resistance, improved right ventricular function, and relief of symptoms related to cardiac overload. These effects positively influence clinical stabilization, reducing the need for vasopressor and ventilatory support and contributing to earlier recovery in intensive care units. The rapid action of fibrinolytics on the central thrombus improves pulmonary perfusion more efficiently than anticoagulation alone, especially within the first 24 to 48 hours of the condition.

However, the main limitation of thrombolysis remains the increased risk of hemorrhagic complications. In the aforementioned study, patients undergoing thrombolysis had a higher bleeding rate (35%) compared to the anticoagulation-only group (17%). This risk includes serious events such as intracranial hemorrhage, necessitating careful evaluation of absolute and relative contraindications before initiating treatment. Alternative strategies, such as low-dose or catheter-directed thrombolysis, are being explored to maintain reperfusion efficacy with a lower bleeding risk. A promising example is the HI-PEITHO trial, which investigates catheter-directed thrombolysis combined with standard anticoagulation compared to anticoagulation alone, focusing on outcomes like mortality, hemodynamic instability, and hemorrhagic complications.

Therefore, while immediate thrombolysis carries risks, its use remains a high-impact clinical approach in cases of PE with hemodynamic instability, particularly when appropriately and individually indicated.

**Comparison Between Embolectomy and Thrombolysis in High-Risk PE Patients**

Various therapeutic approaches have been evaluated for managing acute pulmonary embolism (PE) with hemodynamic instability, especially in patients with contraindications to thrombolysis or therapeutic failure. Embolectomy, whether surgical or catheter-based, emerges as a promising alternative, though questions remain regarding its comparative efficacy and safety relative to systemic thrombolysis.

Generally, thrombolysis remains the first-line treatment in high-risk PE cases due to its effectiveness in reversing cardiogenic shock and persistent arterial hypotension, as well as its strong recommendation in international guidelines. However, both surgical and catheter-based embolectomy have proven effective in contexts where thrombolysis is contraindicated or ineffective, allowing rapid restoration of pulmonary flow with significant reductions in hospital mortality.

Studies indicate that hospital mortality in patients undergoing surgical embolectomy is similar to that of thrombolysis but with fewer pulmonary sequelae, such as ventilation-perfusion mismatch and impaired pulmonary diffusion, suggesting better long-term functional outcomes. Additionally, a recent national analysis comparing thrombolysis and catheter embolectomy found no statistically significant differences in in-hospital mortality, hemorrhagic events (including intracranial), or length of stay, suggesting that both strategies are viable in centers with appropriate expertise and infrastructure.

Embolectomy also yields favorable results even in extremely adverse clinical contexts, such as patients with prior intracranial hemorrhage or formal contraindications to anticoagulation, demonstrating an acceptable safety profile in these high-risk subgroups.

Therefore, while thrombolysis remains the preferred approach, embolectomy—especially when performed in specialized centers—proves to be an effective and safe alternative in specific clinical scenarios, with the potential for better pulmonary outcomes and comparable mortality rates. Therapeutic decisions should consider the individual clinical condition, formal contraindications, local availability, and the multidisciplinary team's experience.

**Side Effects and Risk of Severe Bleeding Associated with Immediate Thrombolysis**

Immediate treatment of acute pulmonary embolism (PE) with systemic thrombolysis is associated with significant side effects, the most notable being the risk of major bleeding. The most feared complication is intracranial hemorrhage (ICH), which can be fatal or result in permanent neurological sequelae.

Studies show that the rate of major bleeding with thrombolysis varies between 9% and 24%, depending on the studied population, age, comorbidities, and the dose of thrombolytic used. A comprehensive meta-analysis found that thrombolysis was associated with a significantly increased risk of major bleeding compared to anticoagulation alone (odds ratio of 2.91), with an incidence of intracranial hemorrhage ranging between 1.5% and 3%.

In a study involving patients with intermediate-risk PE, thrombolysis with tenecteplase resulted in major bleeding in 11.5% of patients and intracranial hemorrhage in 2% of cases. These data are particularly relevant when extrapolated to high-risk patients, who, in addition to the baseline hemorrhagic risk, often present with hemodynamic instability, require vasopressors, and have other critical conditions that may exacerbate the treatment's safety profile.

Non-hemorrhagic side effects of thrombolysis include transient hypotension, rare allergic reactions, nausea, and arrhythmias, especially during the reperfusion phase. However, the risk of bleeding, particularly intracranial, represents the greatest challenge in therapeutic decision-making, necessitating individualized risk-benefit assessments.

Thus, while thrombolysis is an effective strategy in reducing mortality and improving hemodynamics in high-risk PE patients, its use requires caution, especially in the elderly, patients with poorly controlled hypertension, or those with a history of previous bleeding.

**Impact of Time Between Diagnosis and Intervention on Mortality and Hemodynamic Stabilization**

The time elapsed between the diagnosis of high-risk acute pulmonary embolism (PE) and the initiation of reperfusion therapy is a critical prognostic factor for patient survival and hemodynamic stabilization. Evidence demonstrates that treatment delays are directly associated with unfavorable clinical outcomes, including higher in-hospital mortality and lower rates of hemodynamic response.

A multicenter analysis found that patients who received thrombolysis within the first two hours after diagnosis had significantly lower hospital mortality rates and higher chances of early hemodynamic stabilization compared to those who initiated thrombolysis after this interval. These findings support the notion that, similar to the established concept in acute myocardial infarction, "time is right ventricle."

Furthermore, delayed interventions in patients with hemodynamic instability tend to be less effective in reversing circulatory collapse and are associated with increased intensive care unit stays and prolonged need for vasopressor and ventilatory support. The efficacy of thrombolysis is closely linked to the rapid clearance of the pulmonary vascular bed, which reduces right ventricular afterload and improves systemic perfusion. Delays in this process contribute to the progression of obstructive shock and increase the risk of multiorgan failure.

For these reasons, current guidelines recommend that once the diagnosis of PE with hemodynamic instability is confirmed, reperfusion treatment should be initiated immediately, ideally in emergency or intensive care settings with continuous monitoring. Structuring hospital protocols that prioritize rapid diagnostic confirmation and immediate access to thrombolytics or embolectomy, when indicated, is essential to improve clinical outcomes in this critical population.

**Response to Interventions and Risk of Complications in Special Subgroups: Elderly and Patients with Comorbidities**

Specific subgroups of patients with acute pulmonary embolism (PE), such as the elderly, individuals with cancer, or those with heart disease, exhibit distinct responses to therapeutic interventions and have a higher risk of complications, particularly related to systemic thrombolysis.

Patients with active cancer or cardiovascular comorbidities have a significantly increased risk of mortality and serious hemorrhagic events when undergoing thrombolysis. A multicenter study demonstrated that the presence of these comorbidities was associated with a higher risk of major bleeding and intracranial hemorrhage, as well as worse overall clinical outcomes, even after adjusting for age and PE severity.

In the elderly, the risk of intracranial hemorrhage can be two to three times higher than in younger adults, necessitating even more cautious evaluation of systemic thrombolysis indications. In such cases, alternatives like catheter embolectomy or low-dose directed thrombolysis have been proposed as safe and effective strategies, especially when performed in centers experienced in endovascular therapy.

Additionally, patients with pre-existing cardiac dysfunction, such as ventricular insufficiency or chronic pulmonary hypertension, tend to have a more limited hemodynamic response to thrombolytic reperfusion. This is due to coexisting factors that impair cardiac output recovery, even after pulmonary vascular bed clearance. In these scenarios, the risk-benefit ratio of systemic thrombolysis must be carefully considered, and alternative therapies gain prominence.

Therefore, managing these subgroups should be individualized, taking into account the clinical profile, presence of comorbidities, and potential bleeding risk. Strategies such as catheter-directed thrombolysis, mechanical embolectomy, or even anticoagulation alone, in cases of absolute contraindication, may be safer and still effective.

1. **DISCUSSION**

**Effectiveness of Immediate Interventions**

The results of this systematic review reinforce that immediate interventions—particularly systemic thrombolysis—have a direct and significant impact on reducing mortality and achieving hemodynamic stabilization in patients with high-risk acute pulmonary embolism (PE). When administered promptly after diagnosis, thrombolysis substantially reduces in-hospital mortality and improves right ventricular function, directly contributing to the reversal of obstructive shock (18–22). These benefits also translate into shorter hospital stays and reduced need for intensive care support (21,22).

Additionally, the time between diagnosis and initiation of reperfusion emerged as a prognostic determinant. The shorter this interval, the better the clinical outcomes—highlighting the need for streamlined care pathways both in the hospital and pre-hospital settings (30,31).

**Comparison with Current Guidelines**

The findings of this review align with the latest guidelines, such as those from the European Society of Cardiology (ESC), which recommend immediate thrombolysis as the first-line treatment for patients with PE and hemodynamic instability, unless absolute contraindications are present (6,10,19,33). ESC guidelines classify this intervention as Class I, Level B recommendation, reinforcing the scientific basis for its use in critical scenarios.

The effectiveness of alternative strategies, such as surgical or catheter-based embolectomy, was also confirmed, showing mortality rates comparable to thrombolysis and favorable safety profiles in specialized centers (24–26). These interventions—also recognized in current guidelines—are especially relevant when thrombolysis is contraindicated or unavailable (8,13,27).

**Limitations of Included Studies**

Despite the robustness of some findings, this review identified important methodological limitations in the analyzed studies. Most were retrospective cohorts or observational studies with small sample sizes, lack of randomization, and heterogeneity in diagnostic criteria and outcome measures (33). These issues hinder generalizability and introduce potential selection, confounding, and reporting biases.

Moreover, vulnerable populations—such as frail elderly, patients with cancer, hematologic disorders, or those receiving palliative care—were underrepresented. Although some studies included these groups, the data remain insufficient for strong conclusions (32,33).

**Clinical Implications**

The clinical relevance of these findings is particularly notable in emergency and intensive care settings. The confirmation of immediate thrombolysis efficacy and the critical role of time-to-treatment should prompt the implementation of rapid response protocols, involving coordination among emergency, cardiology, radiology, and intensive care teams. These protocols must ensure not only early diagnosis but also the safe and immediate initiation of reperfusion therapy (30,31).

Identifying subgroups at higher risk of hemorrhagic complications—such as elderly patients and those with comorbidities—also underscores the need for personalized approaches. Interventions like catheter-directed thrombolysis or mechanical embolectomy, which show lower bleeding risks, should be considered first-line options in these contexts (26,33).

**Recommendations for Future Research**

In light of the identified gaps, we recommend conducting randomized, multicenter clinical trials with robust sample sizes comparing systemic thrombolysis, catheter-based embolectomy, and anticoagulation alone. It is especially important that these studies include vulnerable subgroups and use standardized diagnostic criteria and outcome measures to enhance the comparability and applicability of the results.

1. **CONCLUSION**

Based on the evidence gathered in this systematic review, it is concluded that immediate intervention in cases of acute pulmonary embolism (PE) with hemodynamic instability is essential for reducing mortality and achieving effective hemodynamic recovery. Systemic thrombolysis, when administered within the first hours after diagnosis, remains the strategy with the greatest clinical impact, provided there are no absolute contraindications. Its effect on pulmonary perfusion and right ventricular function is well documented, justifying its prioritized recommendation in both national and international guidelines.

However, thrombolysis carries a significant risk of hemorrhagic complications, particularly intracranial bleeding, especially in elderly patients and those with relevant comorbidities. In such cases, alternative approaches such as catheter-based or surgical embolectomy emerge as effective and safer options, particularly when performed in centers with appropriate technical expertise. Catheter-directed thrombolysis using reduced doses of fibrinolytics also appears promising for higher-risk subgroups, although it still lacks robust comparative studies.

Despite therapeutic advances, significant knowledge gaps remain that require further investigation. The lack of randomized clinical trials directly comparing different reperfusion strategies, as well as the scarcity of specific data for vulnerable populations—such as cancer patients, frail elderly individuals, and those with partial contraindications to thrombolysis—limits the personalization of treatment. Furthermore, the long-term effects of therapies on quality of life, thromboembolic recurrence, and chronic pulmonary hypertension remain poorly understood.

Therefore, institutional policies that prioritize the early identification of high-risk PE, the implementation of streamlined clinical protocols, and the encouragement of multicenter clinical research to address unresolved questions are strongly recommended. Only with high-quality data will it be possible to improve decision-making and ensure effective and safe treatment for all patient profiles.

**COMPETING INTERESTS DISCLAIMER:**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

**Disclaimer (Artificial intelligence)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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