A seven-year single-center experience on AngioJet rheolytic thrombectomy in patients with pulmonary embolism at high risk and intermediate-high risk

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Abstract

Objective: AngioJet rheolytic thrombectomy (ART) has been used as a catheter-based treatment for acute pulmonary embolism (PE). In this study, based on our 7-year experience with ART in patients with PE, we evaluated the efficacy and safety outcomes of ART.

Methods: Our study is based on retrospective evaluation of 56 patients with high- and intermediate-high-risk PE, with an average age of 62 years [interquartile range (IQR) 50–73 years] who underwent ART.

Results: High and intermediate-high risks were noted in 21.4% and 78.6% of the patients, respectively. The ART duration was 304 (IQR: 246–468) seconds. Measures of obstruction, right to left ventricle diameter ratio, right to left atrial diameter ratio, and pulmonary arterial pressures were improved ($p<0.001$ for all). During the hospital stay, acute renal failure, major and minor bleeding, and mortality rates were 37.5%, 7.1%, 12.5%, and 8.9%, respectively. Aging related to post-procedural nephropathy while high-risk status was associated with in-hospital mortality ($p=0.006$) and long-term mortality.

Conclusion: ART resulted in significant and clinically relevant improvements in the pulmonary arterial thrombotic burden, right ventricle strain, and hemodynamics in patients with PE at high and intermediate-high risk. Aging increased the risk of post-procedural nephropathy, whereas baseline high-risk status predicted in-hospital and long-term mortality.

Keywords: pulmonary embolism, thrombectomy, mechanical thrombolysis, angioJet rheolytic thrombectomy

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Introduction

Acute pulmonary embolism (PE) has been documented as the third most frequent lethal cardiovascular disease in the Western World (1, 2). Acute-onset hemodynamic instability owing to 30% to 50% thrombotic obliteration of the pulmonary arterial (PA) vessels and right ventricle (RV) strain manifested by RV diameter to left ventricle diameter ratio (RV/LVr) either assessed by echocardiography (Echo) or computed tomography (CT) has been documented to predict clinical worsening even in the low-risk status (1-3). The European Society of Cardiology/European Respiratory Society (ESC/ERS) 2014 and 2019 PE guidelines have recommended an updated acute phase treatment strategy based on the definition of high, intermediate-high, intermediate-low, and low-risk groups (1, 2). Patients at high-risk (HR) status have been considered to require urgent primary pharmacological (or alternatively, surgical, or interventional) reperfusion therapies (1, 2). Moreover, for patients who develop hemodynamic instability, rescue thrombolytic treatment (TT) has also been recommended; and catheter directed treatments (CDT) as an alternative to rescue TT should be considered (2). However, systemic TT has been documented to improve RV

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HIGHLIGHTS

- Although AngioJet rheolytic thrombectomy (ART) has been a black box warning as a treatment method for acute pulmonary embolism (PE), optimal duration and efficacy remain to be determined.
- This largest single-center study on ART performed in patients with PE at intermediate-high and high risk has resulted in significant improvements in obstructive burden and hemodynamics. High-risk status is related to early and long-term mortality.
- ART may be considered in patients with PE and with multiple comorbidities and a tendency to bleed.

dysfunction and hemodynamic status at the expense of the increased risk of major bleeding events, including intracranial hemorrhage (1-5).

Among the several CDT systems, only three devices have been approved by the Food and Drug Administration (FDA) (6-9). Experience with other CDT systems in sub-massive or massive PE has been based on off-label utilization in anecdotal case reports, small retrospective series comprising highly selected patient groups, and systematic reviews or meta-analyses of heterogeneous datasets (10-13). Only one of these, an ultrasound-assisted thrombolysis technology, EkoSonic® Endovascular System (Boston Scientific Corporation, USA), was tested in randomized clinical trials (7, 8, 14) and has been reported to facilitate thrombolysis with reduced lytic dosages, which leads to lowered bleeding risk in patients with PE at high and intermediate-high-risk (IHR) status (7, 8, 14-17).

The AngioJet rheolytic thrombectomy (ART) (Possis Medical, Minneapolis, Minnesota, USA) system is a widely used CDT device that uses high pressure and circumferential saline jet expulsions at the catheter tip (2,500 psi or 1.7–107 Pa) to create a local low-pressure zone via Bernoulli's principle of fluid dynamics to entrain, fragment, and aspirate thrombi even if the catheter is positioned several millimeters away from the occlusive clot. Moreover, the on-the-wire design of ART permits aspiration thrombectomy procedures along all the subsegmentary pulmonary artery branches selected (18-25). ART seems to be an efficacious CDT device in terms of thrombus fragmentation/aspiration, as well as improvement of clinical measures in massive and sub-massive PE (18-25). However, the mortality rate in unstable settings remains high, and a controversy exists regarding the safety of ART (18-28).

In this study, we aimed to evaluate our 7-year experience with ART in patients with PE at HR or IHR and to assess predictors of efficacy and safety outcomes following this CDT.

Methods

Our study population included 56 patients [average age 62 years, interquartile range (IQR) 50–73 years, 24 (46.9%) women of 710 patients] referred to our tertiary cardiovascular center with a diagnosis of acute PE and who underwent ART treatment with various indications from October 2012 to November 2020. The patients were evaluated retrospectively. The systematic work-up for an initial diagnosis of acute PE, and risk stratification comprising the multidetector contrast-enhanced CT angiography and Echo assessments, PE severity indexes, and biomarker evaluation have been based on the criteria recommended by the ESC/ERS 2014 and 2019 PE guidelines (1, 2). Inclusion criteria were acute symptomatic PE confirmed by CT with thrombus located in at least one main or proximal lower lobe PA and the presence of high bleeding risk for full-dose TT because of recent major trauma, bone fractures, major surgery, or hemodynamic and/or clinical instability. The baseline risk status was HR or IHR in all the included patients. Lower extremity venous Doppler ultrasound was also available for all the patients.

The use of ART as a treatment option for acute PE was approved by the National Ministry of Health, and all the patients were reimbursed by the National Social Security Authority. Moreover, the eligibility criteria for ART were defined by the institutional review board, and the appropriateness of this treatment for each patient was discussed by a multidisciplinary teamwork. Following the approval of ART treatment by this team, written informed consent was obtained from all the patients before the initiation of ART. The study complied with the Declaration of Helsinki, and the study protocol was approved by the Institutional Ethics Committee.

Right heart catheterization, pulmonary angiography, and ART procedure

Only the femoral venous route with a 6-French (F) sheath was used, and arterial puncture was avoided. A 6F multipurpose catheter was used for initial PA pressure measurements and selective angiograms. The selective placements of the multipurpose catheter were followed by exchange with a 6F sheathless catheter over a 0.35-inch hydrophilic guidewire. The ART catheter was connected to the aspiration system and advanced to the proximity of the occluded pulmonary artery over the guidewire. The fragmentation/aspiration sequences were activated for 15 to 20 seconds with manual antegrade advancements throughout the thrombotic obstruction under fluoroscopic guidance and were repeated until satisfactory reperfusion was achieved. In cases of patients in whom sinus bradycardia and/or atrioventricular conduction disturbances occurred immediately at the moment of system activation, ART was deactivated for 30 to 60 seconds until the recovery of normal sinus rhythm.

Local intrapulmonary infusion of adjuvant recombinant tissue-type plasminogen activator (t-PA) was also used in cases of patients with massive thrombotic occlusions threatening the perfusion of large pulmonary territories. Intravenous heparin was started after termination of the ART procedure, and the aim was to keep the activated partial thromboplastin time around 60 seconds. In cases of patients with acute-onset heparin-induced thrombopenia, fondaparinux or rivaroxaban

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were preferred. In accordance with currently available PE practice guidelines, a minimum of 6 months of anticoagulant therapy with warfarin, rivaroxaban, apixaban, or edoxaban was recommended.

Chest CT pulmonary angiography

Images were acquired before and 3 to 4 days after the ART procedure using a 64-slice helical CT scanner (Toshiba Aquilion 64™, Toshiba Medical Systems Corp., Tokyo, Japan) with angiographic contrast material (Omnipaque 350), and the stored images were evaluated. A validated CT score for pulmonary arterial occlusion proposed by Qanadli et al. (29) [Qanadli score (QS)], RV/LVr, right atrial to left atrial diameter ratio (RA/LAr), and main, left, and right pulmonary arterial diameters were measured from CT images as reported previously (15-17).

Efficacy measures

Improvements in the measures of pressure overload and RV function, including RV/LVr, RA/LAr, QS, and pulmonary arterial diameters quantitated by CT; longitudinal RV function measures including tricuspid annular plenary systolic excursion (TAPSE); tissue velocity assessed by echocardiography; and pulmonary arterial systolic and mean pressure estimates were used as surrogates for acute efficacy of ART compared with baseline.

Safety measures

Safety outcomes included minor and non-fatal major bleeding and all-cause mortality during the in-hospital period following ART. Long-term follow-up data were also included in the analysis for mortality and bleeding outcomes. Major bleeding was defined as overt bleeding associated with a fall in the hemoglobin level of at least 2.0 g/dL or with the transfusion of 2 units of packed red blood cells or involvement of a critical site. A clinically overt bleeding not fulfilling the criteria for a major bleeding was classified as a minor bleeding (30). The post-procedural nephropathy (PPN) was evaluated in patients using the criterion of an increase of 0.5 mg/dL in plasma creatinine levels or a 25% increase in basal creatinine within 72 hours after the procedure recommended by the European urogenital radiology community (31). Because of its retrospective nature, informed consent was not required to participate in the study.

Statistical analysis

The Shapiro-Wilk test was used to determine whether the distribution of variables was normal. We preferred to use median IQR for continuous variables. Non-normally distributed continuous variables were presented as median and IQR (quartile I to quartile 3). Normally distributed variables were presented as mean ± standard deviation. The Mann-Whitney U test was used to compare the two independent groups. Categorical variables were presented as counts and percentages. Categorical variables were compared using the chi-squared test and Fisher exact test as appropriate. In addition, echocardiographic, CT, and vital measures before and after ART were compared for all the patients using the Wilcoxon test. The survival curves were constructed using the Kaplan-Meier method, and groups were compared using the log-rank test.

Dependent variables were the RV/LV ratio, QS, and pulmonary artery systolic pressure (PASP) change.

Post-procedural nephropathy

As a rule of thumb, there should be at least 10 patients with an outcome in relation to the degrees of freedom of the predictors included in the model (outcome/degrees of freedom n=10). In our PPN model, 4 predictors were identified, whereas outcomes (PPN) were present in 21 patients (21/4=5.25). Therefore, multivariate logistic regression analysis was used to evaluate the association between CIN and 4 candidate predictors of overfitting risk. Our regression model includes predictor variables such as age, contrast volume, QS, and baseline creatinine. All statistical analyses were performed using "rms," "Hmisc," "survminer," "survival," and "ggplot2" packages with R version 4.01 (R Project, Vienna, Austria).

Results

A total of 56 patients with PE with IHR or HR status were treated with ART. Patient characteristics, comorbidities, and treatment patterns are presented in Table 1. Baseline risk statuses were IHR or HR in 78.6% and 21.4% of the patients, respectively. The median time delays from symptoms to ART treatment and from ART to post-procedural CT acquisition were 3.5 (2–5.25) and 5 (4–6) days, respectively. Moreover, ART was performed after the failure of systemic t-PA or ultrasound-assisted thrombolysis in 5 patients, and CT measures obtained after termination of t-PA infusion were used as baseline reference for assessing the efficacy of ART in these cases. Absolute or relative contraindications for t-PA, including active bleeding from esophageal varices, recent or active major bleeding, in-hospital PE immediately after major surgery, and intracranial metastasis or bleeding were noted in 10 (83.3%) patients at HR and in 20 (45.4%) patients at IHR (Table 1).

The system catheters were successfully placed in all the patients. Unilateral and bilateral ART treatments were needed in 22 (39.3%), and 34 (60.7%) patients, respectively. Bilateral ART treatments were needed in 33.3% of the patients at high-risk and 68.2% of the patients at intermediate-high risk. Overall, the ART activation duration was 304 (246–468) seconds. Adjuvant t-PA was used in 19 (33.9%) patients, and the lytic dosage was 15 mg (10–20). The tPA was given intravenously to 9 patients; the median intravenous dose was 27.5 mg for both groups, and the median infusion duration was 6 hours for IHR and 2 hours for HR patients. Mechanical ventilation and extracorporeal membrane oxygenation (ECMO) were needed in 5 and 2 patients, respectively (Table 1). Treatment characteristics were comparable between patients at HR and IHR. All the clinical, echo, and CT measures of RV systolic strain and dysfunction, QS, and PA pressure estimates were significantly improved after ART (Fig. 1, Table 2). Comparison of improvements in these measures

Table 1. Baseline clinical and laboratory characteristics of 56 patients treated with ART

Variables	All	IHR (n=44)	HR (n=12)	*P*-value
Age (years)	62 (50–73)	66 (50.8–73.3)	56 (36.3–62)	0.097
Male sex, n (%)	32 (57.1%)	22 (50%)	10 (83.3%)	0.039
Diabetes mellitus, n (%)	15 (26.8%)	12 (27.3%)	3 (25%)	0.875
Hypertension, n (%)	24 (42.9%)	21 (47.7%)	3 (25%)	0.158
Atrial fibrillation, n (%)	3 (5.4%)	3(6.8%)	–	0.999
Syncope	25 (44.6%)	17 (38.6%)	8 (66.7%)	0.083
Chronic obstructive lung disease, n (%)	5 (8.9%)	4 (9.1%)	1 (8.3%)	0.999
Previous coronary artery disease, n (%)	11 (19.6%)	8 (18.2%)	3 (25%)	0.598
Previous pulmonary embolism, n (%)	7 (12.5%)	5 (11.4%)	2 (16.7%)	0.622
Presence of deep vein thrombosis, n (%)	37 (66.1%)	29 (65.9%)	8 (66.7%)	0.999
Possible secondary causes, n (%)				
Malignancy	15 (26.8%)	12 (27.3%)	3 (25%)	0.999
Orthopedic surgery/fractures	7 (12.5%)	8 (13.6%)	1 (8.3%)	0.999
Previous stroke history	6 (10.7%)	4 (9.1%)	2 (16.7%)	0.599
Prolong traveling	3 (5.4%)	3 (6.8%)	–	0.999
Postoperative status	17 (30.4%)	10 (22.7%)	7 (58.3%)	0.043
Thrombophilia	2 (3.6%)	2 (4.5%)	–	0.999
Immobility	3 (55.4%)	22(50%)	9 (75%)	0.191
Pulmonary infarction, n (%)	5 (16.7%)	2 (9.1%)	3 (37.5%)	0.102
Pleural effusion, n (%)	6 (20%)	3 (13.6%)	3 (37.5%)	0.300
Baseline vital signs				
Heart rate/min	112 (103–125)	110 (100–120)	132 (122–143)	<0.001
Systolic blood pressure, mm Hg	127 (104–136)	132 (119–136)	90.5(88–92.8)	<0.001
Diastolic blood pressure, mm Hg	71 (60–81)	79 (69.3–83.3)	56.5 (50–60)	<0.001
Oxygen saturation, %	88 (84.8–91.3)	88.5 (85–92)	85.5 (79–87.5)	0.032
Baseline laboratory variables				
Troponin, ng/mL	0.12 (0.06–0.36)	0.1 (0.06–0.25)	0.23 (0.09–0.59)	0.209
D–Dimer, U/mL	7 (3.4–14.4)	5.03 (2.98–11.7)	17.9 (9.35–20)	0.011
C–reactive protein	3.78 (2.0–10.4)	3.46 (1.93–7.47)	12.3 (4.84–18.7)	0.034
Symptom duration (days)	5 (2.0–5.25)	4 (2.0–5.25)	2.5 (1.75–5.50)	0.413
PESI	117 (97.8–129)	106 (88.3–125)	135 (120–151)	0.003
PESI Class	4 (3–5)	4 (3–4.25)	5 (4–5)	0.002
Simplified PESI	2 (1–2.25)	2 (1–2)	3 (2.75–3)	<0.001
Absolute or relative contraindications to thrombolytic	30 (53.6%)	20 (45.4%)	10 (83.3%)	0.001
Intracranial bleeding	4 (7.1%)	2 (4.5%)	2 (16.7%)	0.191
Active bleeding	3 (5.36%)	2 (4.5%)	1 (8.3%)	0.515
Recent major bleeding	3 (5.36%)	3 (6.8%)	–	0.999
Recent major surgery	9 (16%)	9 (20.4%)	5 (41.7%)	0.134
Recent head trauma	4 (7.14%)	3 (6.8%)	1 (8.3%)	0.999
Intracranial metastasis	1 (1.78%)	1 (2.27%)	1 (8.3)	0.999

ART - AngioJet rheolytic thrombectomy, HR - high-risk, IHR - intermediate-high risk, PESI - pulmonary embolism severity indices

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Table 2. Echocardiographic, CT, and vital measures before and after ART

Variables	Before ART	After ART	Mean change	*P*-value
PASP (mm Hg)	56.7±14.3	40.2±13.4	16.4	<0.001
RV/LV ratio	1.33±0.24	0.92±0.18	0.41	<0.001
RA/LA ratio	1.39±0.40	0.95±0.17	0.44	<0.001
TAPSE (cm)	1.75±0.34	2.17±0.36	-0.42	<0.001
ST (cm/sec)	10.68±2.22	13.46±1.99	-2.77	<0.001
QS	24.2±6.23	11.92±6.89	12.27	<0.001
Main PA diameter (mm)	28.16±8.17	27.75±4.51	0.41	<0.001
Heart rate (bpm)	110.5±17.1	84.2±11.5	26.1	<0.001
Systolic blood pressure (mm Hg)	123.3±21.1	123.2±14.4	0.1	0.865
Oxygen saturation (%)	87.7±5.3	94.5±2.5	-6.8	<0.001
Shock index	0.93±0.27	0.69±0.13	0.23	<0.001
Modified shock index	0.01±0.003	0.007±0.001	0.003	<0.001

ART - AngioJet rheolytic thrombectomy, PA - pulmonary artery, PASP - pulmonary arterial systolic pressure, RV - right ventricle, LV - left ventricle, RV/LV - right ventricle to left ventricle diameter ratio, RA/LA - right atrial to left atrial diameter ratio, TAPSE - tricuspid annular planary systolic excursion, ST - tricuspid annular systolic velocity on tissue Doppler, QS - Qanadli score

Table 3. Comparisons of age and risk groups for percent and absolute changes in the measures of efficacy

Change in measures	<65 years	>65 years	*P*-value	IHR	HR	*P*-value
RV/LV diameter ratio (%)	30.9 (0.20–0.42)	26.7 (21.3–32)	0.255	30.5 (21.4–40.9)	24.4 (15.9–30.4)	0.163
RV/LV diameter ratio (absolute)	0.41 (0.24–0.61)	0.33 (0.25–0.42)	0.173	0.40 (0.26–0.55)	0.30 (0.17–0.44)	0.273
PASP (%)	33.3 (17.5–45.0)	30.0 (17.4–42.7)	0.895	30 (16.7–40.0)	45.0 (19.4–47.3)	0.173
PASP (absolute, mm Hg)	15 (7–25)	17 (11–28.5)	0.335	15.0 (10–22.8)	26 (10.0–29.0)	0.213
QS (%)	59.3 (38.7–75)	53.6 (26.7–62.5)	0.234	50.8 (31.8–68.2)	61.3 (57.1–70.5)	0.194
QS (absolute)	14 (9–18)	11 (5–15.8)	0.112	11 (7.5–15.5)	18.5 (11.8–21.5)	0.015

IHR - intermediate-high risk, HR - high risk, PASP - pulmonary arterial systolic pressure, RV - right ventricle, LV - left ventricle, RV/LV - right ventricle to left ventricle diameter ratio, RA/LA - right atrial to left atrial diameter ratio, TAPSE - tricuspid annular planary systolic excursion, ST - tricuspid annular systolic velocity on tissue Doppler, QS - Qanadli score

between HR versus IHR subgroups, and older versus younger age groups according to the cut-off limit of 65 years is given in Table 3.

Transient bradyarrhythmia's spontaneously terminating immediately after deactivation of ART were noted in 18 (32.1%) of patients and were comparable between risk groups (Table 4). Gross hemoglobinuria following ART was uniformly observed. However, hemoglobinuria recovered within 24 hours in all the patients with saline over hydration. Transient renal failure was noted in 22 (39.3%) patients regardless of the risk groups (Table 4). Penalized logistic regression revealed that age was the only independent predictor of post-procedural nephropathy [age 50–73, odds ratio (OR) 2.12 (1.05–4.24), 95% confidence interval (CI) 1.05–4.24, p=0.034] (Table 5).

During a hospital stay of a median of 13 (IQR 9–17) days, 5 (8.9%) patients died; and intracranial and unresolved severe PE were associated with mortality in 1 (1.8%) and 4 (7.1%) patients, respectively (Table 4). ECMO was needed in 2 of the 4 of these mortal cases. Non-fatal major bleeding was documented in 4 (7.1%) patients and included intracranial, hemoptysis, and gastrointestinal bleeding in 1, 1, and 2 episodes, respectively. Minor bleeding events were noted in 7 (12.5%) patients; and groin hematoma, hemoptysis, hematuria, hemorrhoidal, and menstrual bleeding were observed in 1, 3, 1, 1, and 1 episode, respectively. HR versus IHR statuses were associated with higher in-hospital mortality (33.3% versus 2.3%, p=0.006), whereas major or minor bleeding rates were comparable (p=0.999 and p=0.325, respectively) (Table 4).

The 3 criteria were defined for assessment of clinical efficacy as follows; systolic blood pressure ≥110 mm Hg, pulse O_2 saturation >90% at discharge, and absence of in-hospital mortality and major bleeding; systolic blood pressure ≥100 mm Hg, O_2 saturation >90% at discharge, and absence of in-hospital mortality and major bleeding; and only O_2 saturation >90 at discharge. According to these definitions, the efficacy rates were 66.1%, 71.5%, and 84%, respectively.

Heparin-induced thrombocytopenia occurred in 2 patients, and fondaparinux was used in these patients. Post-discharge follow-up data based on periodic clinical and telephone controls for a median of 1,258 (425–1,698 days) was available for all the patients. The Kaplan-Meier survival curves and log-rank tests revealed that long-term event-free survival probability seemed to be associated with IHR status, but not with aging (Fig. 2 and 3).

Table 4. Characteristics of ART, adjuvant thrombolytic regimen, and complications in HR and IHR groups

Measures	Total	IHR (n=44)	HR (n=12)	*P*-value
Treatment regimens				
Bilateral ART, n (%)	34 (60.7%)	30 (68.2%)	4 (33.3%)	0.044
ART activation duration (seconds)	304 (246–468)	300 (246–443)	348 (274–480)	0.663
Need for adjuvant t-PA via catheter (%)	19 (33.9)	16 (36.3%)	3 (25%)	0.732
Intraprocedural total t-PA dose	15 (10–20)	14 (10–20)	20 (15–21.3)	0.245
IV t–PA dose	27.5 (18.8–63.8)	25 (0–50)	60 (42.5–80)	0.301
ECMO need	2 (3.6%)	0	2 (8.3%)	0.999
Transient bradycardia and/or atrioventricular block	18 (32%)	13 (29.5%)	5 (41.7%)	0.494
Peri-procedural nephropathy	22 (39.3%)	20 (45.5%)	2 (16.7%)	0.101
Transient hemodialysis need	1 (1.8%)	1 (2.2%)	–	0.999
Major bleeding	4 (7.1%)	3 (6.8%)	1 (8.3%)	0.999
Minor bleeding	7 (12.5%)	7 (15.9%)	–	0.325
In-hospital mortality	5 (8.4%)	1 (2.3%)	4 (33.3%)	0.006
Median hospital stay (days)	13 (9–17)	14 (10–19)	8 (3.5–13.5)	0.012

ART - AngioJet rheolytic thrombectomy, IHR - intermediate-high risk, HR - high risk, t-PA - tissue-type plasminogen activator, ECMO - extracorporeal membrane oxygenation

Table 5. Penalized multivariable logistic regression for prediction post-procedural nephropathy

Variables	OR (95% CI)	*P*-value
Baseline creatinine (from 0.65 to 0.96), mg/dL	0.64 (0.33–1.21)	0.177
QS (20 to 28)	0.89 (0.45–1.75)	0.744
Age (50 to 73), years	2.12 (1.05–4.24)	0.034
Contrast volume (98 to 184), mL	1.04 (0.50–2.22)	0.912

ART - AngioJet rheolytic thrombectomy, CI - confidence interval, OR - odds ratio, QS - Qanadli score

Discussion

This study, based on our 7-year experience with ART in patients with acute PE at HR and IHR, represents the largest single-center data for this percutaneous PE treatment system. Although ART was associated with significant improvements in pulmonary arterial obstruction, right heart strain, and hemodynamics, bleeding and mortality risks were not negligible. Fatal bleeding and unresolved PE accounted for 20% and 80% of in-hospital deaths, respectively. Aging related to transient nephropathy after ART with HR status predicted higher in-hospital mortality and long-term mortality.

The idea of risk-adjusted PE treatment strategies providing the benefits of efficacy outcomes with a low bleeding risk has remained an unmet need for at least four decades (1-13). The vast majority of data regarding the efficacy and safety concerns of CDTs has been derived from registries and pooled analyses of case series, which could suffer from publication bias. None of these provided robust evidence (based on conflicting results of efficacy and safety issues of CDTs, except two currently available CDT systems having FDA approval) (10-13) for the superiority of one CDT over others in sub-massive or massive PE (7-9). A meta-analysis of earlier CDT studies showed an 86.5% overall clinical success rate with 7.9% and 2.4% pooled rates of minor and major procedural complications, respectively (10).

The most frequently reported complications of ART are transient bradyarrhythmia's and asystole, which are considered to be secondary to hemolysis followed by adenosine release occurring at activation bursts (27, 28). However, short bursts (usually less than 10 pulses at a time) with intervals of 20–30 seconds between activations usually allow for clearance of compounds such as adenosine and recovery of normal sinus rhythm (27, 28). Another controversial issue, the potential for local thermal injury related to ART, was investigated in human saphenous vein segments mounted in an *ex vivo* perfusion system (26). Continuous ART for 4 minutes and pulsed ART for eight cycles of 30 seconds, followed by 10 seconds of deactivation, were reported to produce a mean 7.61°C and 7.31°C increase in temperature above baseline, with mean maximum temperatures of 44.11°C and 43.81°C, respectively (26). In comparison to those in untreated segments, ART resulted in a significant intima/media thinning with a reduction in intact endothelium and an increase in staining for heat shock protein 90 expression with immunohistology staining (26). These results seem to be consistent with a potential risk for local thermal injury with/or without

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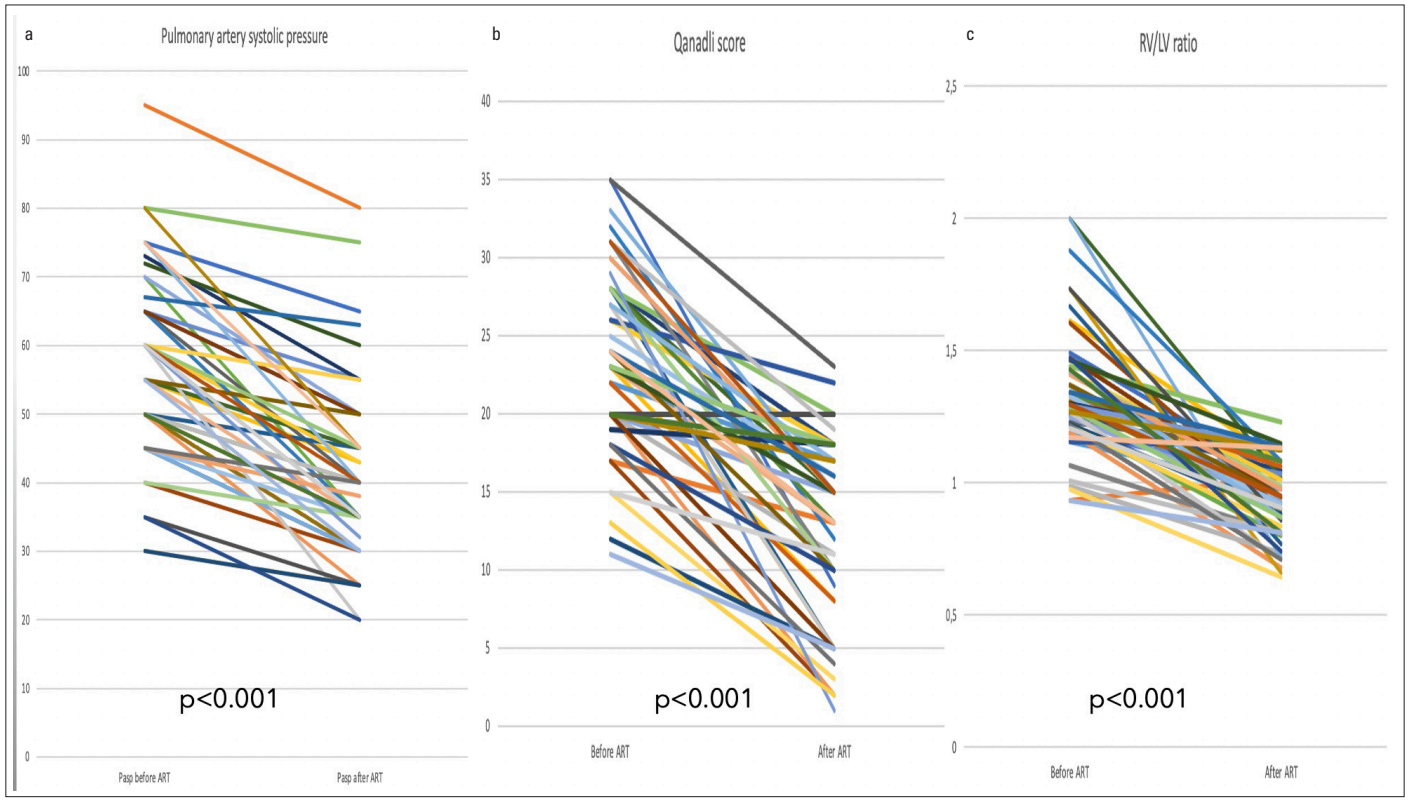

Figure 1. Individual changes in pulmonary arterial systolic pressure, Qanadli score, and right ventricle to left ventricle diameter ratio

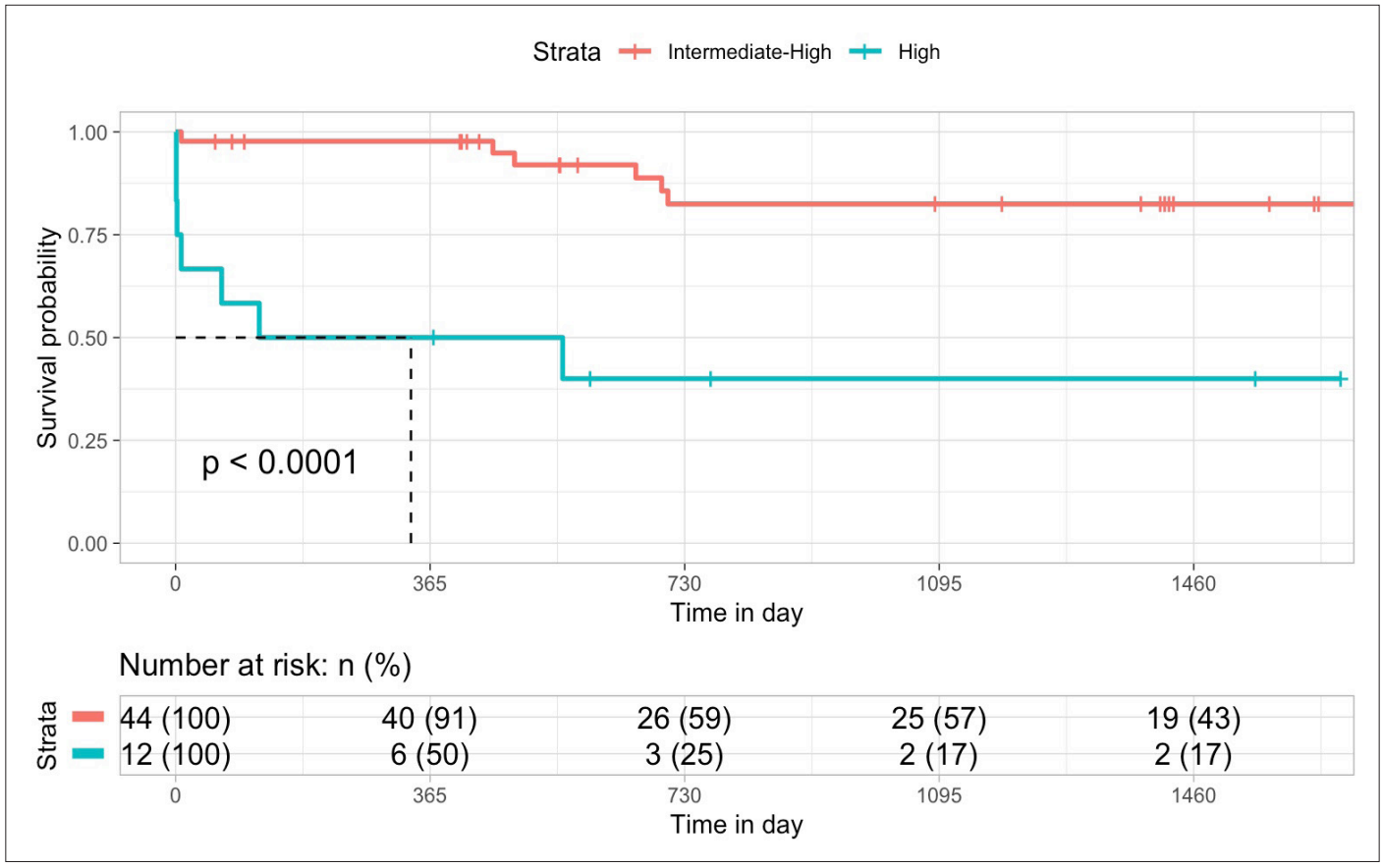

Figure 2. Comparison of patients at high-risk versus intermediate-high-risk status by Kaplan-Meier survival estimates

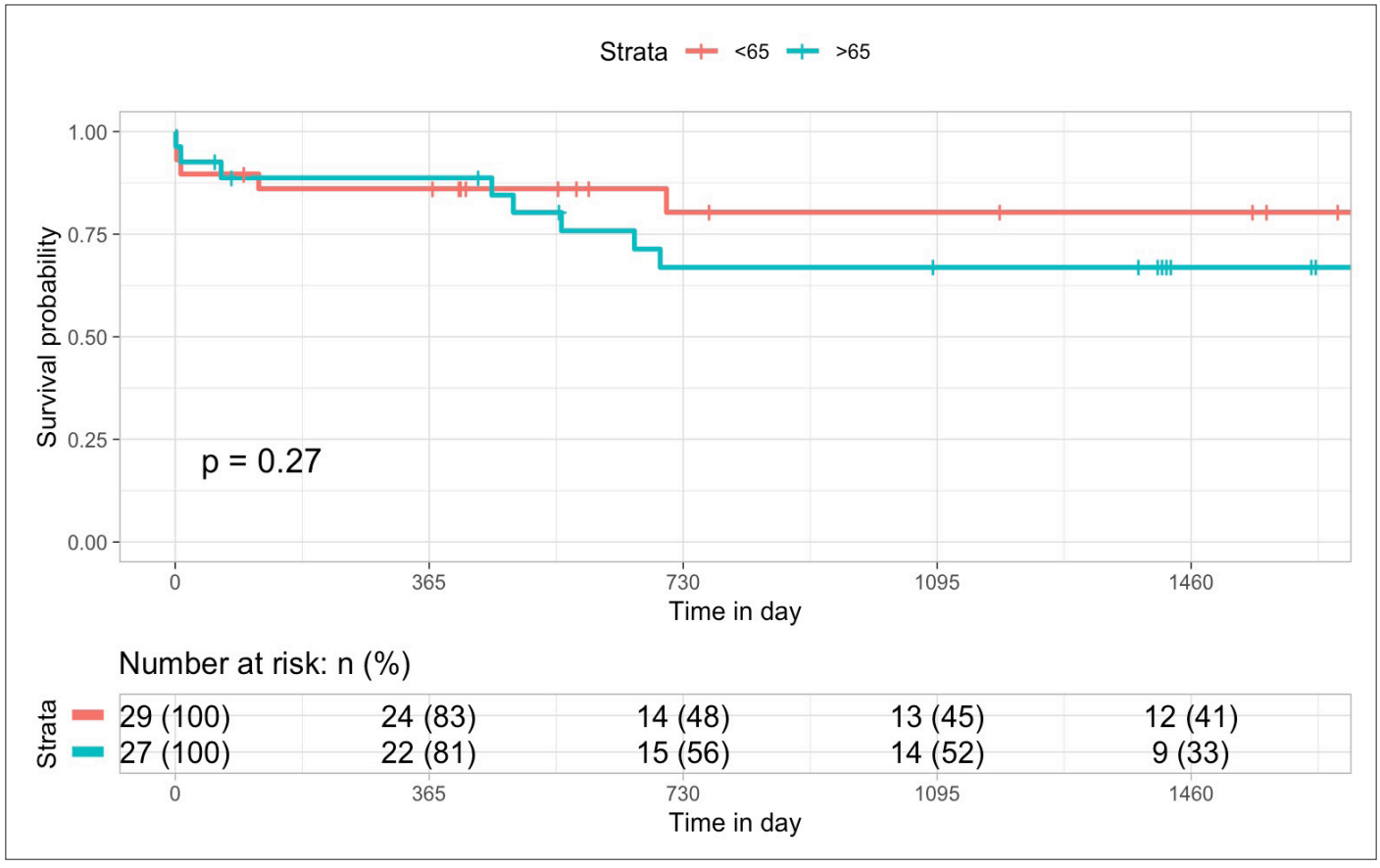

Figure 3. Comparison of age groups (<65 versus >65 years) by Kaplan-Meier survival estimates

mechanical damage in the treated vessel segments, especially in cases of longer activation durations (26).

Additional concerns related to hemolysis are the occurrence of severe hyperkalemia and hemoglobinuria (22-25, 28). Hyperkalemia may exacerbate the electrical instability, and hemoglobinuria may cause acute deterioration of kidney function in these patients already at risk because of hemodynamic instability and contrast utilization for diagnostic computed tomography angiographic evaluation and selective pulmonary arterial injections during the ART procedure (22-25, 28).

In an early meta-analysis of 68 patients treated with ART, the rates of major and minor complications and procedure-related deaths were 28% and 40%, and 7.35%, respectively (10). More importantly, 76% of all major complications were reported to be attributable to ART, and the authors concluded that this device should not be used as the initial mechanical treatment in future CDT protocols for patients with acute massive PE (10). Accordingly, the FDA has issued a black box warning on the commercially available ART device label pertaining to its use in patients with acute PE. In another meta-analysis of 14 studies that included a total of 197 patients with PE, rates of technical and/or clinical success in massive and sub-massive PE groups were 86.8% and 94.3% and in-hospital mortality was 23.7% and 13.2%, respectively. A total of 22 device-related major and minor complications were observed in 15.7% of the patients.

A recently published single-center ART study, which included 44 patients with acute PE in total (21 HR and 23 IHR), provided robust data for efficacy and safety concerns of this CDT system (25). The mean duration of overall ART activation runs was 156.6±59.1 seconds (ranging from 78 to 280 seconds), and adjunctive local urokinase was used in 90.9% of them (25). ART resulted in significant improvement in clinical, hemodynamic, and angiographic parameters, including perfusion, obstruction, and total Miller indexes, and IHR versus HR PE was associated with more obvious improvements in shock index, pulse oximetric percent saturation, and angiographic parameters and a significantly shorter stay in the intensive care unit (25). The in-hospital mortality rate was 13.6% and was significantly associated with HR status or shock. Renal failure requiring hemodialysis was observed in 13.6% of the patients and more frequently in patients at HR (25). The Echo showed a significant decrease in the PA mean pressure with improvement or normalization in right ventricular function, and CT pulmonary angiography revealed that the majority of the central and lobar arteries were clot free at the sixth month post-procedural assessment (25). Compared with this study, the duration of ART activation was markedly longer (median 304 seconds), and either the percent adjuvant t-PA (33.9%) or the median lytic dose was 15 mg (10–20) were lower in our series, including multiple comorbidities. Although post-procedural nephropathy was observed in 39.3% of our patients after ART, one-session dialysis was required in only 1

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(1.8%) patient, and all the patients recovered with saline over hydration. Older age, but not risk status or duration of ART activation, was related to acute nephropathy.

In another ART series that included 32 patients with massive (71.9%) or submassive (28.1%) PE, technical success was reported to be 100%, and 96.9% of them survived till discharge (24). Improvements in RV strain and pulmonary arterial pressure were achieved in all the survivors within 48 hours of the ART. Post-discharge four-week echo and CT assessments showed normalization of RV strain and pulmonary pressure measures in all the patients and complete resolution of thrombus in 79.3% of patients (24).

Study limitations

The retrospective nature of the analysis and operator-driven decisions for the total duration of ART activation runs and adjuvant lytic regimen were the main limitations of this study. Comparison with a heparin alone arm in the IHR group and with a fixed dose intravenous t-PA alone arm in the HR group might provide more relevant data in terms of efficacy and safety outcomes of ART therapies. Moreover, compared with the currently approved ultrasound-assisted thrombolysis system concomitant with different t-PA regimens as tested in a randomized trial (14), efficacy and safety concerns of ART in a randomized fashion might provide valuable data for IHR and HR PE groups.

Conclusion

Our experience showed that ART was associated with clinically relevant improvements in the measures of pulmonary arterial obstruction, RV strain, and hemodynamics in patients with PE at HR and IHR. Aging increased the risk of renal failure, whereas baseline HR status predicted in-hospital and long-term mortality. These results seem to suggest the need for reappraisal of the use of ART in patients with PE.

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