

# Intra-aortic Balloon Pump Therapy for Anterior ST-elevation Myocardial Infarction with Cardiogenic Shock: An Observational Cohort Study

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## Research article

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# Abstract

**Background** As a mechanical circulatory assistance, intra-aortic balloon pump (IABP) has been widely used for cardiogenic shock (CS), although recent clinical trials questioned its impact on acute myocardial infarction patients, nothing is hitherto known on the contribution of IABP to CS patients after anterior wall infarction. The aim of this study was to investigate the efficacy and safety of IABP therapy in patients presenting with anterior ST-elevation myocardial infarction (STEMI) complicated by CS. **Methods** We conducted a retrospective study of 215 consecutive patients presenting with CS after STEMI in the anterior wall between January 2006 and August 2017, including 125 patients in the IABP group and 90 patients in the control group. **Results** At 30 days, 60 (48.0%) patients in the IABP group and 58 (64.4%) patients in the control group had died ( $P=0.017$ ). The Kaplan-Meier survival curves showed the cumulative survival rate in the IABP group was consistently higher than control group ( $P=0.009$  by Log-Rank test). Nevertheless, IABP increased the occurrence of thrombocytopenia (21.6% vs. 2.2%,  $P<0.001$ ) and lower limb complications (20.0% vs. 2.2%,  $P<0.001$ ) at the same time. Subgroup analyses by Cox regression showed a better trend of prognoses in patients aged less than 60 years old ( $HR=0.49$ , 95%  $CI=0.26-0.91$ ,  $P=0.025$ ), male ( $HR=0.53$ , 95%  $CI=0.34-0.83$ ,  $P=0.005$ ), no history of hypertension ( $HR=0.47$ , 95%  $CI=0.26-0.87$ ,  $P=0.017$ ) and systolic blood pressure less than 80 mm Hg ( $HR=0.40$ , 95%  $CI=0.22-0.73$ ,  $P=0.009$ ). At 12-month follow-up, all-cause mortality in the IABP group was obviously lower than the control group (52.5% vs. 74.1%,  $P=0.002$ ), there were no significant differences in other adverse cardiovascular events ( $P=1.000$ ). **Conclusions** The combination of IABP use is associated with reduced 30-day and 12-month mortality in patients with anterior STEMI complicated by CS, though thrombocytopenia and lower limb complications are frequently observed.

## Introduction

Cardiogenic shock (CS) accounts for only 5.2%-8.9% of the patients with acute myocardial infarction (AMI), while its mortality reaches 41.2%-52.1%<sup>[1-8]</sup>. Over the past 30 years, although a strategy of early revascularization was carried out, CS has still been the leading cause of death in AMI patients.

Intra-aortic balloon pump (IABP) has been commonly used in CS for its hemodynamic support since 1968<sup>[9]</sup>. However, recent studies questioned its impact on clinical prognosis. A randomized controlled trial (known as IABP-SHOCK II trial) including 600 patients was conducted at 37 German centers in 2012, which found no survival benefit for IABP support both in short and long term even if early revascularization was planned<sup>[10-12]</sup>. Based mainly on the evidence of IABP-SHOCK II trial and relevant meta-analyses<sup>[13-15]</sup>, IABP therapy was downgraded to Class IIa (Level of Evidence B) and Class III (Level of Evidence B) recommendation in U.S. and European guidelines respectively regarding the treatment of AMI patients with CS<sup>[16,17]</sup>. Although IABP has been challenged a lot recently, we still sought to find a specific group of CS patients applicable for IABP implantation.

We noticed that the anterior ST-elevation myocardial infarction (STEMI) subpopulation of IABP-SHOCK II trial had lower 30-day mortality in IABP group (35.4% vs. 43.7%,  $RR=0.81$ , 95%  $CI=0.58-1.13$ ). It was of

great clinical importance to have mortality decreased by 8.3% in patients with cardiogenic shock even if no statistical difference was observed. For high-risk patients presenting with CS after anterior wall infarction, a critical risk factor is severe left ventricular (LV) dysfunction. As a mechanical circulatory assistance, IABP inflates during diastole period, subsequently augments diastolic blood pressure and coronary perfusion. Early in the systole period, IABP reduces LV wall tension and myocardial oxygen consumption by decreasing LV afterload[18]. These positive effects underlie an increase in cardiac output, which means IABP insertion may have more favorable influences on anterior STEMI, theoretically. To the best of our knowledge, there are indeed numbers of studies available for IABP and CS, but none of them focuses on the anterior STEMI. The present study aims to investigate whether IABP counterpulsation would lead to better outcomes in STEMI patients in the anterior wall complicated by CS.

## Methods

### 2.1. Study population

A total of 665 consecutive individuals diagnosed with STEMI complicated by CS from January 2006 to August 2017 were retrospectively reviewed, 348 (52.3%) of which presented as anterior STEMI. We excluded patients with symptom onset to admission >24 hours, age >90 years, malignancies or other serious diseases (life expectancy <1 year), prophylactic use before the percutaneous coronary intervention (PCI), implantation during and after coronary artery bypass graft (CABG) and incomplete clinical data. Finally, 215 cases were selected and analyzed.

### 2.2. Methods

Patients who underwent IABP implantation were enrolled in the IABP group and others acted as the control group. We compared the demographic characteristics, clinical features and mortality rates of the two groups. The short-term prognosis was evaluated by all-cause mortality at 30 days. Kaplan–Meier survival curves showed the cumulative survival rate throughout the first 30 days, with the Log-Rank test used for the comparison. Subgroup analyses were performed by Cox regression model in subgroups defined according to gender, age (<60 or  $\geq$ 60 years), history of hypertension, diabetes, treatment strategies (conservative treatment, thrombolysis and emergency PCI), systolic blood pressure (SBP) before IABP placement (<80 or  $\geq$ 80 mm Hg). We also used the incidence of in-hospital adverse events to assess the safety of IABP. Long-term prognosis was compared by all-cause mortality and other adverse cardiovascular events after follow-up for 12 months through telephone calls.

### 2.3. Definitions

Myocardial infarction was defined according to the third universal definition of myocardial infarction<sup>[19]</sup>. Based on the above, anterior ST-elevation myocardial infarction was defined as ST segment elevation  $\geq$ 0.2 mV in two or more contiguous precordial leads<sup>[20]</sup>.

The definition of cardiogenic shock was SBP <90 mm Hg for  $\geq 30$  minutes or needed catecholamines to maintain SBP  $\geq 90$  mm Hg, with evidence of impaired endorgan perfusion (at least one of the following: altered mental status; cold, clammy skin and extremities; oliguria; serum lactate  $>2$  mmol/L)<sup>[10]</sup>.

The term reinfarction was used for an AMI that occurred within 28 days of an incident or recurrent myocardial infarction<sup>[19]</sup>.

Bleeding was defined according to Bleeding Academic Research Consortium (BARC)<sup>[21]</sup>. A mild or moderate bleeding was under type 3 and severe bleeding was above or equal to type 3.

By definition, acquired thrombocytopenia was platelet count reduced 50% from the baseline or  $<100 \times 10^9$  /L.

The definition of lower limb complications included hemorrhage and hematoma of puncture site, pseudoaneurysm, arteriovenous fistula, lower limb ischemia caused by atherosclerotic plaque or thrombosis.

## 2.4. Statistical analysis

Statistical analysis was performed using SPSS software V.22.0 (SPSS Inc., Chicago, IL, USA). For continuous variables, the normality of distribution was tested by one-sample Kolmogorov-Smirnov test. Normal variables were expressed as mean  $\pm$  standard deviation (SD) and compared by independent Student's t test, while non-normal variables were presented as median (interquartile range) and Wilcoxon signed-rank test was used. The frequency of categorical variables was assessed by Chi-square test or Fisher's exact test. Cumulative survival rate throughout the first 30 days was recorded using Kaplan-Meier plots and compared by the Log-Rank test. Forest graph showed the outcome of subgroup analyses which performed by Cox regression model. A value of  $P < 0.05$  was considered significant.

## Results

The final study cohort consisted of 148 males (68.8%) and 67 females (31.2%) with a mean age of 61 (52.00, 70.00) years. As depicted in Table 1, baseline characteristics were similar between the IABP group (n=125) and the control group (n=90). There were no statistically significant differences in blood pressure, heart rate, left ventricular ejection fraction, mechanical complications and in-hospital medications (Table 2).

Notably, significant difference in all-cause mortality at 30 days was observed ( $P=0.017$ ), 48.0% in the IABP group and 64.4% in the control group respectively. Kaplan-Meier survival curves (Figure 1) also exhibited a consistently higher cumulative survival rate in patients who received IABP therapy ( $P=0.009$  by Log-Rank test). Treatments for STEMI differed a lot ( $P < 0.001$ ). The rates of conservative treatment and thrombolytic therapy in the IABP versus control group were 32.8% vs. 52.2% and 8.0% vs. 18.9%, respectively. Patients in the IABP group were more often treated with emergency PCI (59.2% vs. 28.9%).

For in-hospital events detailed in Table 3, patients were more likely to get thrombocytopenia (21.6% vs. 2.2%,  $P < 0.001$ ) and lower limb complications (20.0% vs. 2.2%,  $P < 0.001$ ) because of the IABP insertion. As intuitively shown in the forest plot (Figure 2), subgroup analyses revealed a better trend of prognosis in patients aged less than 60 years old (HR=0.49, 95% CI=0.26-0.91,  $P=0.025$ ), male (HR=0.53, 95% CI=0.34-0.83,  $P=0.005$ ), no history of hypertension (HR=0.47, 95% CI=0.26-0.87,  $P=0.017$ ) and systolic blood pressure less than 80 mm Hg (HR=0.40, 95% CI=0.22-0.73,  $P=0.009$ ). Thrombolytic therapy might reduce mortality with IABP implantation but had no statistical difference. It was less prone to use IABP in patients who underwent emergency PCI.

12-month clinical follow-up was completed in 81 patients among 97 survivors (83.5%). At 12 months, 62 of 118 (52.5%) patients in the IABP group and 60 of 81 (74.1%) in the control group died, the all-cause mortality differed significantly between the two groups ( $P=0.002$ ), which was consistent with the observation from 30 days. Other cardiovascular events during the follow-up were summarized in Table 4. The incidence of non-fatal myocardial infarction between the two groups was similar, with no significant differences in the target vessel revascularization and stroke as well.

## Discussion

What's novel about our study was that we targeted at high-risk patients presenting with cardiogenic shock after anterior wall infarction in the "real world". Because of the presumed causal relationship mentioned in the introduction, LV dysfunction is the main cause of cardiogenic shock in this subpopulation, which corresponds with the mechanical principle of IABP. Therefore, we raised a reasonable hypothesis that IABP therapy was associated with enhanced survival rate when used for patients with anterior STEMI, as a supplement to current randomized controlled trials.

For STEMI patients suffer from CS, prognoses are strongly affected by therapeutic strategies which contain conservative treatment, thrombolysis and emergency PCI. A consensus exists that patients who receive only conservative drugs as their therapy have an advantage of elevated hemodynamic parameters and lowered mortality when IABP is applied<sup>[22]</sup>. Besides, patients receiving thrombolysis show superior survival in combination with IABP use. GUSTO-I trial demonstrated that decreased mortality at 12 months (57% vs. 67%,  $P = 0.04$ ) was paralleled by IABP implantation following thrombolytic therapy<sup>[23]</sup>, same conclusions were obtained in the subsequent TACTICS and NRMI-2 trials<sup>[24,25]</sup>. The mechanism is, at least partially, based on the synergistic action between thrombolytic agent and IABP. On the contrary, the research evidence did not favor the clinical utility of IABP in patients underwent emergency PCI with or without stent implantation. IABP-SHOCK II trial elucidated that the use of IABP did not significantly reduce 30-day mortality (39.7% vs. 41.3%, RR=0.96, 95% CI=0.79-1.17,  $P=0.69$ ), in addition, considerable supports for this result were provided by 12-month (52% vs. 61%, RR=1.01, 95% CI=0.86-1.18,  $P=0.91$ ) and 6-year follow-up (66.3% vs. 67.0%, RR=0.99, 95% CI=0.88-1.11,  $P=0.98$ )<sup>[11-13]</sup>. It is quite intelligible that IABP helps to increase the coronary perfusion pressure and improve LV compliance for its mechanical circulatory support, nevertheless, the absolute rise in cardiac output (0.5 L/min) is so modest that it is insufficient to reduce mortality on the basis of the revascularization.

Subgroup analyses in our study implied that there was a trend toward better prognoses in patients aged less than 60 years, male and with no history of hypertension. One logical explanation would be the quick recovery from the low cardiac output owing to a good general condition. Moreover, IABP therapy conferred better clinical benefits on those SBP less than 80 mm Hg, potentially due to the limited effects on patients with normal or slightly decreased SBP.

It is worthwhile to mention that safety issues during the counterpulsation cannot be neglected. The overall incidence of IABP post-interventional complications was reported to be 29%<sup>[26]</sup>, including thrombocytopenia, bleeding, lower limb ischemia, thrombosis, vascular injury and balloon burst. As the most common complication, thrombocytopenia occurred in 20% of cases in our study. The induction of heparin<sup>[27,28]</sup> or glycoprotein IIb/IIIa receptor antagonist<sup>[29,30]</sup> is responsible for thrombocytopenia, along with the mechanical destroy of platelets by IABP counterpulsation in synchrony with the cardiac cycle. Given that the severity and duration of thrombocytopenia presents a notable positive correlation with the utility time, IABP is supposed to be removed as soon as possible after stabilized condition. Furthermore, hemorrhage and hematoma of puncture site, pseudoaneurysm and lower limb ischemia are frequently observed after IABP insertion. In this case, appropriate balloon is of particular value for prevention, while skin color, temperature and dorsalis pedis artery pulse should also be under close observation.

However, there are still several problems remaining to be settled, one of which is the optimal order of IABP insertion and emergency PCI. Existing data illustrated that patients supported preoperatively by IABP had better coronary perfusion, whereas early insertion also resulted in myocardial injury for the delay of door-to-balloon time<sup>[31,32]</sup>. Another question is about the exact role of left ventricular assist devices (LVADs), such as Impella system and Tandem Heart. Despite improvements in hemodynamics and metabolic parameters<sup>[33-35]</sup>, current evidence showed LVADs failed to reduce mortality in comparison with IABP<sup>[34-37]</sup>, mainly driven by an excess of related complications. As a result, more trials containing larger numbers of patients should be performed to evaluate the influence of LVADs on patient survival, with long-term follow-up.

Our research had a number of limitations. First, this was a single-center study that might weaken the statistical power. In addition, as a retrospective study, whether to implant IABP and the application timing of IABP were not only decided by treating physicians, but also depended on the family members and their economic situation. Finally, events during the 12-month follow-up were not completely accurate because there was a potential recall bias according to the long follow-up time.

## Conclusions

In general, we provided a theoretical basis for the clinical utility of IABP therapy, which could reduce 30-day and 12-month mortality in patients with anterior STEMI complicated by CS while increasing the risk of thrombocytopenia or lower limb complications at the same time.

## Abbreviations

**ACEI:** angiotensin converting enzyme inhibitor

**AMI:** acute myocardial infarction

**ARB:** angiotensin receptor blocker

**BARC:** bleeding academic research consortium

**CABG:** coronary artery bypass graft

**CRF:** chronic renal failure

**CS:** cardiogenic shock

**DBP:** diastolic blood pressure

**DM:** diabetes mellitus

**ECMO:** extracorporeal membrane oxygenation

**HR:** heart rate

**IABP:** intra-aortic balloon pump

**LV:** left ventricular

**LVADs:** left ventricular assist devices

**LVEF:** left ventricular ejection fraction

**MBP:** mean blood pressure

**MI:** myocardial infarction

**MODS:** multiple organ dysfunction syndrome

**PCI:** percutaneous coronary intervention

**PDA:** peripheral arterial disease

**SBP:** systolic blood pressure

**Scr:** serum creatinine

**SD:** standard deviation

**STEMI:** ST-elevation myocardial infarction

**TVR:** target vessel revascularization

## **Declarations**

### **Ethics approval and consent to participate**

This study was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University and obtained the informed consent of all the patients.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Authors' contributions**

SL conceived of the presented idea and substantively revised the manuscript. KZ as the first author contributed to the study design, data acquisition, data analysis and took the lead in writing the manuscript. JD helped in study design and data acquisition. JT, KC, YY, LC, ZQ, YZ contributed to the data acquisition and analysis. All the authors have read and approved the final manuscript.

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### **Authors' information**

Prof. Shuzheng Lyu is the chief physician and the director of Department of Internal Medicine in Beijing AnZhen Hospital affiliated to Capital Medical University, which is one of the largest cardiovascular centers in the world with annual percutaneous coronary intervention (PCI) more than 15000. As a famous

cardiologist, Prof. Lyu is a true pioneer who performed the first emergency percutaneous transluminal coronary angioplasty (PTCA) in 1991 in China and made remarkable achievements in the PCI of complex coronary artery disease such as chronic total occlusive (CTO), unprotected left main coronary artery disease and bifurcation lesions (total PCI > 20000). The success rate for the treatment of CTO is as high as 90%, taking a leading position in the world. Prof. Lyu also has rich clinical experience in the rescue of refractory heart disease with the support of intra-aortic balloon pump (IABP).

Prof. Lyu has published more than 100 papers and is the associate editor for “Chinese Journal of Cardiology”, “Chinese Journal of Evidence-based Cardiovascular Medicine” and “Journal of Cardiovascular and Pulmonary Diseases”. He undertook numbers of national research projects (including Key Projects in the National Science and Technology Pillar Program during the 12th Five-Year Plan Period) and was awarded “National Prize for Science and Technology Progress”, “the Capital Labor Medal” and “State Council special allowance”.

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## Tables

**Table 1. Baseline characteristics between the two groups [n (%), M(Q<sub>R</sub>)]**

Characteristics	IABP (n=125)	Control (n=90)	P Value
Age/ year	60.00 (52.00, 68.00)	62.50 (52.00, 72.00)	0.244
Male sex	90 (72.0)	58 (64.4)	0.238
Current smoking	42 (33.6)	32 (35.6)	0.766
Past history			
Hypertension	83 (66.4)	54 (60.0)	0.336
DM	48 (38.4)	26 (28.9)	0.148
Hypercholesterolemia	51 (40.8)	29 (32.2)	0.199
Prior MI	27 (21.6)	16 (17.8)	0.489
Prior PCI	20 (16.0)	11 (12.2)	0.437
Prior bypass surgery	2 (1.6)	1 (1.1)	0.763
Prior stroke	19 (15.2)	15 (16.7)	0.771
Known PDA	2 (1.6)	2 (2.2)	0.739
CRF	8 (6.4)	9 (10.0)	0.335

Abbreviations: DM: diabetes mellitus; MI: myocardial infarction; PCI: percutaneous coronary intervention; PDA: peripheral arterial disease; CRF: chronic renal failure.

**Table 2. Clinical presentations and treatments [  $\bar{x} \pm s$ , n (%), M(Q<sub>R</sub>) ]**

Variables	IABP (n=125)	Control (n=90)	P Value
SBP/mm Hg	84.50 (78.00, 90.00)	80.0 (77.75, 95.00)	0.934
DBP/mm Hg	55.00 (47.25, 60.00)	55.50 (47.50, 60.00)	0.871
MBP/mm Hg	63.33 (56.67, 70.00)	65.00 (57.92, 71.67)	0.806
HR/(beats/min)	94.88 ± 27.88	94.55 ± 27.73	0.934
Sign of impaired organ perfusion			
Altered mental status	97 (77.6)	68 (75.6)	0.726
Cold, clammy skin and extremities	77 (61.6)	51 (56.7)	0.467
Oliguria	38 (30.4)	27 (30.0)	0.950
Serum lactate >2 mmol/L	48 (38.4)	34 (37.8)	0.926
Serum lactate/(mmol/L)	2.60 (1.70, 4.55)	2.70 (1.90, 5.70)	0.592
Scr/(μmol/L)	88.30 (75.10, 133.98)	95.25 (68.56, 144.50)	0.924
LVEF/%	38.00 (32.00, 45.00)	37.00 (30.00, 47.50)	0.908
Mechanical complications			0.738
Ventricular septal rupture	5 (4.0)	3 (3.3)	
Free wall rupture	3 (2.4)	2 (2.2)	
Papillary muscle rupture	1 (0.8)	0 (0.0)	
Resuscitation before randomization	15 (12.0)	6 (6.7)	0.194
Medications in-hospital			
Catecholamines	76 (60.8)	49 (54.4)	0.351
Aspirin	121 (96.8)	88 (97.8)	0.992
Clopidogrel	122 (97.6)	88 (97.8)	1.000
ACEI/ARB	46 (36.8)	25 (27.8)	0.165
β-blocker	48 (38.4)	26 (28.9)	0.148
Calcium channel blocker	2 (1.6)	3 (3.3)	0.709
Diuretics	57 (45.6)	36 (40.0)	0.414
Long acting nitrates	65 (52.0)	41 (45.6)	0.351
Inotropic agents	80 (64)	53 (58.9)	0.447
Use of ECMO	6 (4.8)	1 (1.1)	0.265

Abbreviations: SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure; HR: Heart rate; Scr: Serum creatinine; LVEF: Left ventricular ejection fraction; PCI: Percutaneous coronary intervention; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ECMO: Extracorporeal membrane oxygenation.

**Table 3. Short-term prognosis of the two groups [n (%)]**

Outcomes	IABP (n=125)	Control (n=90)	P Value
All-cause mortality at 30 days	60 (48.0)	58 (64.4)	0.017*
Treatment strategies			<0.001***
Conservative treatment	41 (32.8)	47 (52.2)	
Thrombolysis	10 (8.0)	17 (18.9)	
Emergency PCI	74 (59.2)	26 (28.9)	
In-hospital events			
Reinfarction	11 (8.8)	3 (3.3)	0.109
Stroke			0.400
Hemorrhagic	1 (0.8)	0 (0.0)	
Ischemic	3 (2.4)	6 (6.7)	
Bleeding			1.000
BARC type ≥3	4 (3.2)	4 (4.4)	
BARC type <3	12 (9.6)	11 (12.2)	
MODS	48 (38.4)	30 (33.3)	0.446
Sepsis	31 (24.8)	20 (22.2)	0.661
Thrombocytopenia	27 (21.6)	2 (2.2)	<0.001***
Lower limb complications	25 (20.0)	2 (2.2)	<0.001***

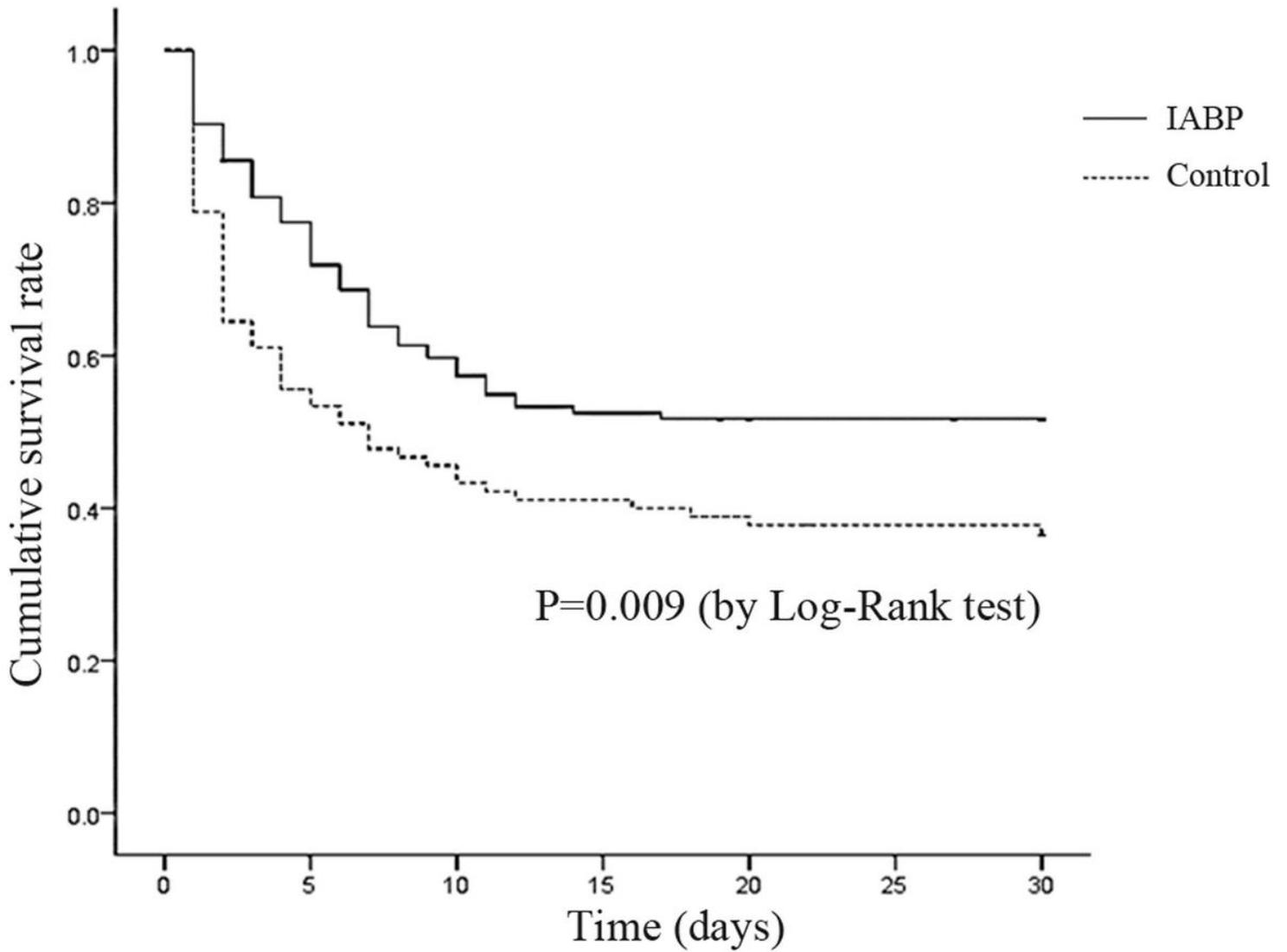
Abbreviations: BARC: Bleeding academic research consortium; MODS: Multiple organ dysfunction syndrome. \* P<0.05, \*\*\*P<0.001.

**Table 4. Clinical follow-up at 12 months [n/N (%)]**

Outcomes	IABP group	Control group	P Value
All-cause mortality	62/118 (52.5%)	60/81 (74.1%)	0.002**
Cardiac mortality	61/118 (51.7%)	60/81 (74.1%)	0.001**
Non-cardiac mortality	1/118 (0.8%)	0/81 (0%)	1.000
Other events in 1-year survivors	10/56 (17.9%)	4/21 (19.0%)	1.000
Non-fatal MI	1/56 (1.8%)	1/21(4.8%)	0.474
TVR	8/56 (14.3%)	3/21(14.3%)	1.000
Stroke	1/56 (1.8%)	0/21(0.0%)	1.000

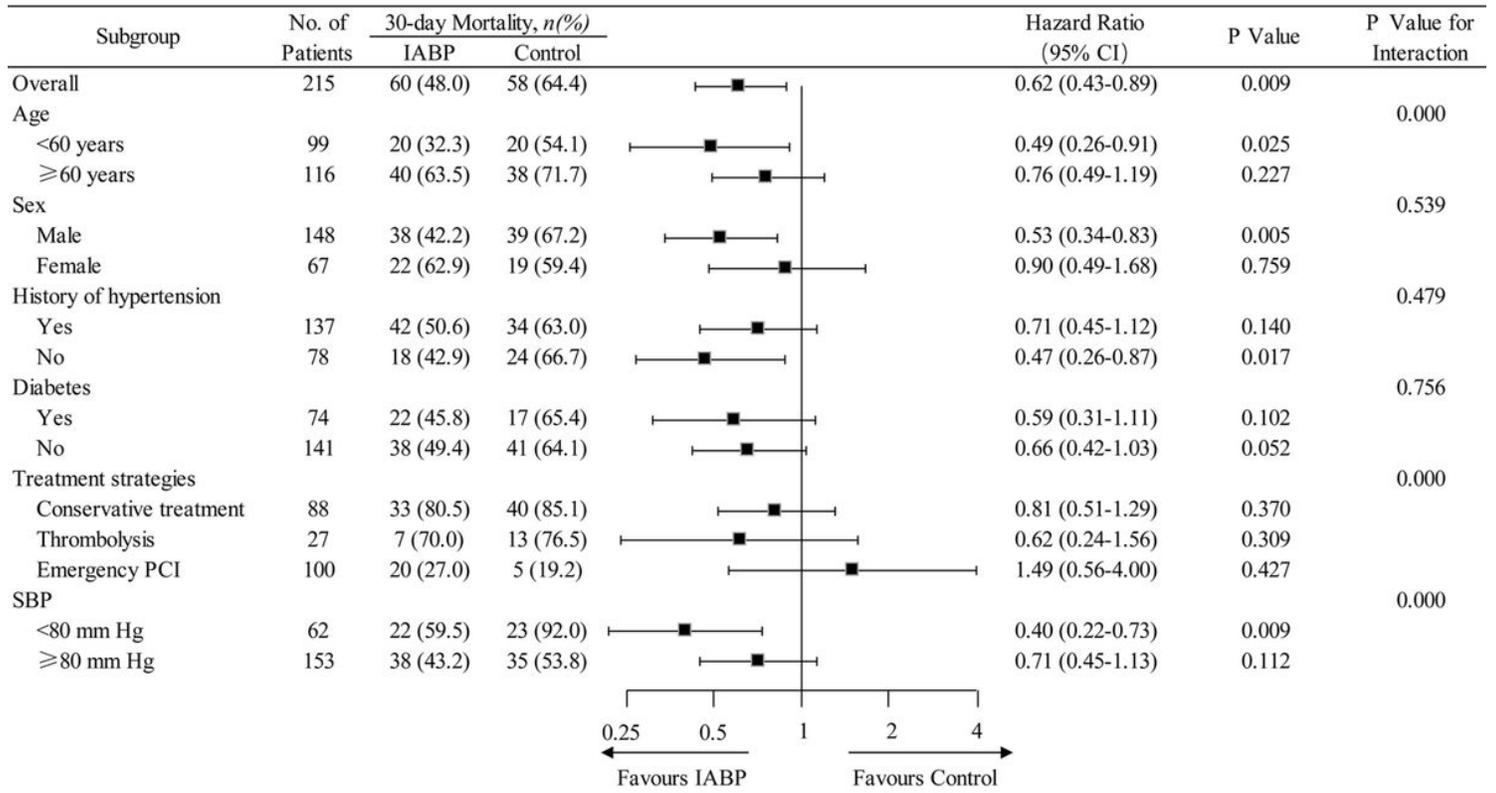
There were 7 lost to follow-up in the IABP group and 9 in the control group at 12 months.

## Figures



**Figure 1**

Kaplan-Meier curves for cumulative survival rates through 30 days Cumulative survival rates throughout the first 30 days were shown in survival curves. Event rates represented Kaplan-Meier estimates. Solid line: IABP group; Dotted line: control group; IABP: intra-aortic balloon pump.



**Figure 2**

Subgroup analyses with 30-day follow-up The forest plot showed the hazard ratio and 95% confidence intervals for defined subgroups. Included are follow-up data for all patients after 30 days. Abbreviations: SBP: Systolic blood pressure; PCI: percutaneous coronary intervention; IABP: intra-aortic balloon pump.