Relationship between the volume of cases and in-hospital mortality in patients with cardiogenic shock receiving short-term mechanical circulatory support

Takashi Araki, MD,[1] Toru Kondo, MD, PhD,[1, 2*] Takahiro Imaizumi, MD, PhD,[3, 4] Yoko Sumita,[5] Michikazu Nakai, PhD,[5] Akihito Tanaka, MD, PhD,[1] Takahiro Okumura, MD, PhD,[1] Mingming Yang,[2,6] MD, PhD, Jawad H.Butt, MD,[2,7] Mark C.Petrie, MB, ChB,[2] Toyoaki Murohara, MD, PhD[1]

[1] Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[2] British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, UK

[3] Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

[4] Department of Advanced Medicine, Nagoya University Hospital, Nagoya, Japan

[5] Department of Medical and Health Information Management, National Cerebral and Cardiovascular Center, Suita, Japan

[6] Department of Cardiology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China

[7] Department of Cardiology, Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark

Short title: Volume and outcome in cardiogenic shock on MCS

*** Corresponding author:** Toru Kondo, MD, PhD.

Department of Cardiology, Nagoya University Graduate School of Medicine.
Address: 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan.
Tel: +81-52-744-2147
Fax: +81-52-744-2210
E-mail: toru.k0927@med.nagoya-u.ac.jp

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Abstract

***Background*:** We examined the relationship between annual case volume at each hospital and outcome in cardiogenic shock (CS) patients receiving mechanical circulatory support (MCS) devices.

***Methods*:** This cross-sectional study used the Japanese nationwide database to identify patients receiving short-term MCS for CS between April 2012 and March 2020. Of 65,837 patients, three sub-cohorts were created; the intra-aortic balloon pump (IABP) alone (n=48,643), the extracorporeal membrane oxygenation (ECMO) (n=16,871), and the Impella cohorts (n=696).

Results: The median annual case volume was 13.5 (7.4–22.1) in the IABP alone cohort, 6.4 (3.4-11.0) in the ECMO cohort, and 7.5 (4.0–10.7) in the Impella cohort. The highest quintile for the volume of cases in the IABP alone and ECMO had the lowest in-hospital mortality (IABP alone, 25.1% in quintile 1 vs. 15.2% in quintile 5; ECMO, 73.7% in quintile 1 in 67.4% in quintile 5). Adjusted ORs for in-hospital mortality decreased as case volume increased (IABP alone, 0.63 [0.58–0.68] in quintile 5; ECMO, 0.73 [0.65–0.82] in quintile 5, with the lowest quintile as reference) but did not decrease significantly in the Impella (0.90 [0.58–1.39] in tertile 3, with the lowest tertile as reference). In the continuous models with the case volume as a continuous variable, adjusted ORs for in-hospital mortality decreased to 28 IABP cases/year and 12 ECMO/cases/year. They did not decrease or became almost flat above that.

***Conclusions*:** Higher volumes of IABP and ECMO are associated with a lower mortality. There is an upper limit to the decline. Centralizing patients with refractory CS in a particular hospital might improve patient outcomes in each region.

Key words: cardiogenic shock, intra-aortic balloon pumping, extracorporeal membrane oxygenation, mortality, high-volume hospital

Background

Cardiogenic shock (CS) is a fatal condition caused by cardiac dysfunction due to various causes.[1–3] Short-term mechanical circulatory supports (MCS) are indicated for cases with refractory CS despite optimization volume status and using inotropes/vasodilators.[1–3] Intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO) have been widely used as short-term MCS devices in clinical practice, and Impella became available recently.[4–6] These devices can improve tissue hypoperfusion by increasing blood flow and resolving the metabolic derangements associated with CS;[7,8] however, some patients on short-term MCS devices experience serious complications, sometimes fatal. Thus, implementing appropriate MCS devices for suitable candidates at the optimal time is required.[1–3,8] Furthermore, while managing patients on MCS devices, device and drug management to maintain stable hemodynamics, simultaneous cardiac (such as percutaneous coronary intervention) and non-cardiac procedures, weaning decision-making, and implementing the next treatment step (such as heart transplantation) in cases refractory to these management are required.[1–3,7,8] Considering them, it can be assumed that the case volume at each hospital, which relates to the hospitals' and MCS teams' experience and care processes,[9] is likely to be associated with outcomes.

Previous studies revealed that the in-hospital mortality decreased as the volume of cases increased among patients with AMI who underwent IABP placement, and similar results were observed in patients who received VA-ECMO or Impella.[9–13] These results imply a learning MCS management curve for each hospital; however, it is unclear whether it is still true after device management guidelines become widespread.[1,2] Furthermore, the volume of cases above which in-hospital mortality decreases remain to be determined. Recently, the regional integrated Hub-and-spoke care CS systems have been advocated to centralize resources and expertise and improve CS prognosis,[1,7,14–17] and the answer to these

questions would provide relevant evidence for a condition which should be required for a Hub hospital.

Therefore, using the nationwide JROAD-DPC registry (Japanese Registry of All Cardiac and Vascular Diseases-Diagnosis Procedure Combination) in Japan, we described the differences in characteristics of patients receiving short-term MCS for CS according to MCS case volume (or cases of each MCS device type), examined the relationship between outcomes, including in-hospital mortality and case volume, and explored whether there is an upper limit to this relationship.

Methods

Data sources

This retrospective cross-sectional study used the JROAD-DPC database. The JROAD-DPC database is a nationwide medical database with information on cardiovascular disease hospitalization, created by combining JROAD and DPC data, launched by the Japanese Society of Cardiology (JCS).[18] The JROAD database is derived from a national survey to evaluate the clinical activity, which covered most JCS-certified teaching hospitals in Japan with cardiovascular beds. JCS-certified teaching hospitals are classified into two categories; Class A JCS-certified teaching hospitals need more than 2 JCS board-certified cardiologists and 30 cardiovascular beds, and class B need more than 1 JCS board-certified cardiologist and 15 cardiovascular beds.[18] DPC is a mixed patient classification system linked to payments at acute-care hospitals in Japan.[19] The JROAD-DPC database includes patient demographics, International Classification of Diseases-based diagnoses, Tenth Revision (ICD-10) codes, devices, therapeutic procedures, discharge status, length of hospital stay, and hospitalization costs. Of the 1,553 hospitals that participated in the JROAD survey, 1,243

were JROAD-DPC-eligible hospitals that adopted the DPC system, and 1,086 provided DPC data to the Japanese Society of Cardiology between April 2012 and March 2020. Following the principles of the Declaration of Helsinki, the ethics committee approved the study protocol (Nagoya University Graduate School of Medicine ethics committee, approval number: 2021-0065). However, informed consent was waived because individual-specific information was not included, and all the data had been anonymized.

Study population

We included patients ≥ 18 years who received short-term MCS, including IABP, ECMO, or Impella, on emergency admission. Patients using inotropes but not using short-term MCS were not included. We excluded patients without diagnoses based on the following ICD-10 codes, reflecting the potential CS cause, in "main diagnosis," "admission-precipitating diagnosis," "most resource-consuming diagnosis," or "second most resource-consuming diagnosis" of DPC disease classification: AMI, I21.x; HF, I50.x; valvular disease, A52.0, I05.x-I08.x, I09.1, I09.8, I34.x-I39.x, Q23.0-Q23.3, Z95.2-Z95.4; fulminant myocarditis (FM), I40, I41; ventricular arrhythmia, I470, I472, I490; pulmonary embolism (PE), I26.0, I26.9. If a patient had multiple ICD-10 codes with AMI, HF, valvular disease, FM, arrhythmia, or PE, the priority order was FM, PE, AMI, valvular disease, HF, and then arrhythmia based on the diagnostic specificity considering the opinions of several cardiologists. The accuracy of ICD-10 codes in identifying AMI, HF, valvular disease, and PE has been previously validated with high specificity and sensitivity.[20–22] Furthermore, patients who started MCS on or after the day of cardiac surgery were excluded as post-cardiotomy.

Analyzed cohort according to the type of MCS used, and volume of cases

Analysis was performed on three sub-cohorts based on the MCS type used; IABP alone, ECMO (ECMO alone, ECMO+IABP, ECMO+Impella), Impella (Impella alone, ECMO+Impella), and a cohort including all patients (all MCS cases). Patients with ECMO+Impella overlapped in the ECMO and Impella cohorts. Patients who received IABP and Impella were regarded as Impella cases. The MCS devices used were identified from the device supplies and procedural codes recorded. The volume of cases in each cohort was determined using the average of annual cases at each hospital; the volume of IABP alone cases was the average of IABP alone cases; the volume of ECMO cases was the average of ECMO alone, ECMO+IABP, and ECMO+Impella cases; the volume of Impella cases was the average of Impella alone and ECMO+Impella cases; the volume of all MCS cases was the average of all MCS cases; For instance, if 100 MCS cases are encountered in eight years, the volume of all MCS cases is 12.5.

Health care system in Japan

All people living in Japan are required by law to have health insurance. Depending on family income and the age of the insured person, part of the medical costs is covered by the patient and the rest by the insurer or government. Patients are free to choose their doctors and facilities and are not denied coverage.

Outcome

In-hospital mortality, length of hospital stay, MCS support duration, and hospitalization costs were evaluated in this study. The latter three outcomes were presented for patients discharged alive and dead, separately. Hospitalization costs were converted to US dollars at the current exchange rate (1 US dollar = 140 Japanese yen).

Statistical analysis

Patient characteristics were described and compared according to the quintile categories in the volume of the IABP alone, the ECMO, all MCS cohorts, and the tertile categories in the volume of the Impella cohort. Continuous variables were expressed as mean±standard deviation or median (interquartile ranges), and categorical variables were expressed as frequencies (percentages). Continuous variables were compared using the Jonckheere–Terpstra trend test, and binary variables were compared using the Cochran-Armitage trend test.

The multivariable logistic regression models were constructed to compute the odds ratios (OR) with 95% confidence intervals (CI) for in-hospital mortality according to the quintile or tertile categories of the volume of cases with quintile 1 or tertile 1 as reference. The models were adjusted for age, sex, body mass index, chronic kidney disease, diabetes mellitus, cardiopulmonary resuscitation (on or before the MCS introduction date), intubation, right heart catheterization, causes of CS (AMI, HF, valvular disease, FM, arrhythmia, or PE), and era (2012–2013, 2014–2015, 2016–2017, 2018–2019 except for the Impella cohort). The use of IABP or Impella was also used for adjustment for the ECMO cohort; the use of ECMO for the Impella cohort; the use of IABP, ECMO, and Impella for the all MCS cohort. We did not include renal replacement therapy and cardiac surgery for adjustment in the multivariable models because these procedures were performed at a median of two and three days later than MCS initiation, respectively. Since there were co-linearities between the volume of cases and the number of hospital beds, and the number of certificated cardiologists (some had >0.50), those variables were also not used for adjustment in the main models; but the models including those variables were shown as sensitivity analysis. In addition, the continuous trends for unadjusted and adjusted ORs according to the volume of cases were depicted using a restricted cubic spline with 1 case/year as reference. Kernel density plots expressed the case

volume distribution in each cohort. The continuous relationships between the volume of cases and the in-hospital mortality were also modelled using the modified Poisson regression models and depicted using a restricted cubic spline.[23] In each restricted cubic spline, five knots were applied for the IABP alone, ECMO, and all MCS cohorts and three for the Impella cohort. Some variables were missing (age <0.1%; body mass index 12.8%); therefore, multiple imputations by chained equations were conducted to impute them. After obtaining twenty imputed datasets, the estimates of each dataset analysis were integrated with Rubin's rule.

As a sensitivity analysis, the continuous relationships between the volume of cases and the in-hospital mortality were evaluated in patients with AMI.

Finally, statistical significance was set at $P < 0.05$. All statistical analyses were performed using Stata/MP 16.1 (Stata Corp., College Station, TX, USA).

Results

The JROAD-DPC database contained 9,825,635 health records from 1,086 hospitals between April 2012 and March 2020. Overall, 114,874 patients ≥ 18 years received short-term MCS during hospitalization. We excluded 18,282 patients with non-emergent admissions, 24,402 patients without the disease diagnosed as a potential cause of CS, and 6,353 patients with postcardiotomy. The remaining 65,837 patients from 927 hospitals were the all MCS cohort. In addition, based on the MCS type used, the other three cohorts of IABP alone, ECMO, and Impella were created (**Supplemental Figure 1**).

Baseline Characteristics according to the volume of cases at each hospital

Baseline characteristics according to the quintile categories of number of cases at each hospital for the IABP alone cohort and ECMO cohort are presented in **Table 1-2**. The mean age was 70.5 years in the IABP alone cohort and 64.7 years in the ECMO cohort, and 74.0% and 74.7% were male, respectively. Each hospital's median volume of annual cases was 13.5 (7.4–22.1) in the IABP alone cohort and 6.4 (3.4-11.0) in the ECMO cohort. In both cohorts, the difference in age according to the quintile categories was small, while the proportion of male and body mass index were similar. In the higher quintile group, cardiopulmonary resuscitation was less frequently performed in the IABP alone cohort; however, it was similarly performed across the quintile categories in the ECMO cohort. In both cohorts, right heart catheterization was more frequently performed in the higher quintile category, and percutaneous intervention for AMI patients was similarly performed across the quintile categories. Regarding the cause of CS, AMI was the leading cause, and its prevalence was lower in the higher quintile group (IABP alone cohort, 85.7% in quintile 1, 80.3% in quintile 5; ECMO cohort, 64.9% in quintile 1, 57.9% in quintile 5) in both cohort, while HF was higher (10.3% in quintile 1, 13.3% in quintile 5) in the IABP alone cohort and arrhythmia was higher (6.5% in quintile 1, 16.4% in quintile 5) in the ECMO cohort. As the quintile category increased, the number of certificated cardiologists significantly increased in both cohorts. The baseline characteristics according to the quintile categories of number of cases at each hospital for the Impella cohort are presented in **Supplemental Table 1**. The median volume of annual cases in each hospital was 7.5 (4.0–10.7). By contrast to the IABP alone and ECMO cohort, the AMI rate as a cause of CS increased with an increase in quintile categories (59.7% in quintile 1 and 79.0% in quintile 3) in the Impella cohort. In all MCS cohort, the median volume of annual cases in each hospital was 19.1 (10.6–31.4). The patient background of the MCS cohort showed similar trends to the IABP alone cohort, because the

MCS cohort is mainly made up of patients from the IABP alone cohort (**Supplemental Table 2**).

Patient outcomes according to the quintile or tertile categories in the volume of cases

Crude in-hospital mortality was 69.9% in the ECMO cohort and 19.5% in the IABP alone cohort; it decreased as the quintile categories increased (IABP alone cohort, 25.1% in quintile 1, 15.2% in quintile 5; ECMO cohort, 73.7% in quintile 1, 67.4% in quintile 5) (**Table 3A-B**). On the other hand, in the Impella cohort, there was no significant trend in in-hospital mortality across the tertile groups (44.3% in tertile 1, 45.8% in tertile 3) (**Table 3C**). In the all MCS cohort, crude in-hospital mortality decreased with an increase in the quintile categories (34.1% in quintile 1, 29.0% in quintile 5) (**Table 3D**). In the IABP alone and ECMO cohorts, length of hospital stay and MCS duration in patients discharged alive did not meaningfully differ according to the quintile categories, while hospitalization costs were higher. On the other hand, in the Impella cohort, there were no significant trends in length of hospital stay and MCS duration in patients discharged alive, and hospitalization costs. Trends in outcomes in all cohort were similar to those of the IABP cohort.

Multivariable analysis for in-hospital mortality according to the quintiles or tertiles of short-term MCS volume

In the IABP alone cohort, adjusted ORs for in-hospital mortality decreased as the quintile category increased (0.63 [0.58–0.68] in quintile 5 with a tertile 1 as reference) (**Figure 1**). Similar trends were observed in the ECMO alone (0.73 [0.65–0.82] in quintile 5 with a quintile 1 as reference) and all MCS cohorts (0.68 [0.64–0.73] in quintile 5 with a quintile 1 as reference). In the Impella cohort, the odds ratios were lower than 1.0 in the tertile 2 and tertile 3 categories but was not significantly different. In the models adjusted for the number

of hospital beds and the number of certificated cardiologists, the number of cases had similar odds ratios to the models not adjusted for them (**Supplementary Table 3**). In-hospital mortality according to the decile categories in the volume of cases is presented in **Supplemental Figure 2**.

Continuous relationship between ORs for in-hospital mortality and the volume of cases

The continuous relationship between adjusted ORs for in-hospital mortality and the volume of cases, with the Kernel density of the annual number of cases, for each cohort is illustrated in **Figure 2A-D**. In the IABP alone cohort, the ORs decreased to 28 cases/year, and gradually increased above that (**Figure 2A**). In the ECMO, the ORs sharply decreased to approximately 5 cases/year, and there seemed to be a gradual decline to approximately 12 cases/year; however, it almost plateaued above the trend (**Figure 2B**). In the Impella cohort, the ORs decreased as the volume of cases increased; nonetheless, the 95% CI straddled 1.0 (**Figure 2C**). In the all MCS cohort, the ORs decreased to 35 cases/year and gradually increased above that (**Figure 2D**). In the IABP alone cohort, hospitals with ≥ 28 IABP alone cases/year were 3.6 % (33/924 hospitals) including 15.5% patients of this cohort. In the ECMO cohort, hospitals with ≥ 5 ECMO cases/year were 23.1% (167/723 hospitals), including 61.0% patients, and hospitals with ≥ 12 ECMO cases/year were 4.7% (34/723 hospitals), including 20.9% patients. In the all MCS cohort, hospitals with ≥ 35 MCS cases/year were 18.2 % (38/927 hospitals) including 4.1% patients of this cohort. The continuous relationship between unadjusted ORs and the volume of cases is illustrated in **Supplemental Figure 3A-D.** Regarding sensitivity analysis, the continuous relationship between unadjusted and adjusted ORs and the volume of cases in the patients with AMI is presented in **Supplemental Figures 4A-C and 5A-C**.

Continuous relationship between the volume of cases and in-hospital mortality

The continuous relationships between the volume of cases and in-hospital mortality for each cohort are depicted in **Figure 3A-D**. In the IABP alone cohort, there was a sharp decrease in in-hospital mortality to 30 cases/year; hospitals with ≥ 30 IABP alone cases/year were 13.9 % (27/924 hospitals) including 2.9% patients of this cohort. Above that point, the increasing trend was gradual (**Figure 3A**). On the other hand, in the ECMO cohort, a sharp decrease in in-hospital mortality to approximately 5 cases/year and a gradual decrease to about 12 cases/year were observed, and a gradual increase above that (**Figure 3B**). In the Impella cohort, in-hospital mortality was slightly lower in the higher volume ranges but almost flat (**Figure 3C**). In the all MCS cohort, in-hospital mortality continued to decrease gradually (**Figure 3D**). Regarding sensitivity analyses, the continuous relationships between the volume of cases and in-hospital mortality in patients with AMI are presented in **Supplementary Figure 6A-C**.

Discussion

Our nationwide dataset of over 65,000 patients with CS who received short-term MCS described the patients' differences according to the volume of cases at each hospital (each MCS device type or for all MCS) and its relationship with in-hospital mortality. There were no clinically significant differences in length of hospital stay and MCS duration in patients discharged alive according to the volume of cases; however, more costs were incurred as the volume of cases increased. There was a significant difference in in-hospital mortality between quintiles 1 and 5 of the volume of cases, with a 10% difference in the IABP alone cohort and a 6% difference in the ECMO cohort. In the multivariable models, as the volume of cases increased, the risk of in-hospital mortality decreased in the IABP alone and ECMO

cohort; nonetheless, there was an upper limit to the decline, above which it remained constant or increased slightly. Trends in all MCS cohort were similar to ones in the IABP alone cohort. In the Impella cohort, adjusted ORs seemed to decrease as the volume of cases increased; however, there were no significant differences due to low power by small sample size.

Our negative volume-outcome relationship is consistent with previous studies.[9–12] However, the relationship between the volume and outcome presented a J-curve in adjusted models for the IABP alone cohort or all MCS, which was unexpected. This result might have been influenced by unadjusted confounders, such as a selection bias that used IABP in more severe cases in the higher volume hospitals. Otherwise, it means there is likely a "sweet spot" below which outcomes suffer and above which outcomes suffer (likely due to the different indications of MCS for patients with CS). Nevertheless, the number of hospitals above the inflection point of the IABP alone or all MCS cohort were considerably low, 3.6% and 4.1% of all the hospitals, respectively. Furthermore, in-hospital mortality at hospitals above this inflection point remained better than quintiles 1–3 and almost comparable to quintile 4. In other words, the relationship between better prognosis and increasing volume may be generally valid when considering the volume of cases of IABP alone or all MCS; but, this is worth exploring in more detail in the future. Regarding ECMO, the volume-outcome relationship has disappeared over time in some patient populations (pediatric), depending on the rapid expansion and innovation in available MCS technology;[9] however, the volume-outcome relationship persisted in our study, including recent patients on MCS.

Patients above these inflextion points corresponded to quintile 4-5 of the IABP alone or ECMO cohort. Those patients had less AMI and received more right heart catheterization. Interestingly, in the IABP cohort, those had higher rates of renal replacement therapy and

CABG, which means those received more invasive treatments, but those received a lower rate of intubation, which is thought to be associated with complications.

The volume-outcome relationship is explained by organizational structure and care process differences, including personnel knowledge and expertise, staffing intensity, equipment, multidisciplinary team dynamics, protocols, and order sets.[9] In our study, a higher number of hospitals correlated with more frequent right heart catheterization utilization, which may reflect the "organizational structure and care processes". Recent studies have reported that careful mechanical monitoring with the right heart catheterization was associated with a better prognosis,[24,25] which could partially explain the difference in the better crude in-hospital mortality at a higher volume of cases in our study.

The relationship between volume and outcomes is driven by the circle of two mechanisms, "selective referral" and "practice makes perfect";[9,26–28] that is, the volume at a hospital increases through "selective referrals" to hospitals reputed to have good outcomes, and in "practice makes perfect", increased experience improves performance and thereby outcomes. Several recent statements recommend utilizing high-volume CS referral hospitals in a hub-and-spoke model to centralize resources and expertise best.[1,5,12] The circle of two mechanisms can provide better patient outcomes for a hub hospital and reduce human and financial resources.[15] In a previous report, approximately 30% of hospitals were hub hospitals, with 68.3% of all patients treated there.[15] It may be challenging to compare and interpret the numbers with this previous report simply; notwithstanding, our study observed a volume-outcome relationship with the volume of IABP cases observed in at least 96.4% of all hospitals included (84.5% of all patients) and ECMO cases in at least 95.4% of all hospitals included (79.6% of all patients) in the multivariable model, suggesting that even among hub hospitals, in-hospital mortality differs according to the volume of cases. Therefore, the disorganization of hub hospitals in a small area would worsen patient outcomes by disrupting

this cycle. Furthermore, the volume of cases at each hospital can be a surrogate indicator of whether the hospital is suitable as a hub hospital. Obviously, the volume is not the only requirement for a hub hospital; however, in-hospital mortality continued to decrease as the volume of cases at each hospital increased, in the multivariable model; at least up to 28 cases/year for IABP alone, and approximately 12 cases/year for ECMO, and 35 cases/year for all MCS. Centralizing patients with refractory cardiogenic shock by transport system to a specific hospital can increase the volume of cases in this specific hospital, which may contribute to increasing experience and improving treatment quality so far. Consequently, patient outcomes in each region might improve. However, our results also highlighted the issue when centralizing patients into high-volume centers. That is cost; the higher the volume of cases, the higher the cost. Appropriate allocation of resources based on an accurate prediction of prognosis will be the next challenge.

Finally, there are several matters to be attended to on how to generalize the absolute volume of cases in each hospital to each healthcare system. First, we included patients with CS, but some reports included all patients receiving MCS regardless of the reasons, which resulted in a lower volume of cases in our data.[13,15,29] Thus, it is necessary to consider who was included in the calculation in the volume of cases. Second, the number of hospitals per capita and shock transfer systems vary by region, suggesting that the distribution of the absolute volume of cases and this threshold may differ depending on the region. Finally, Impella was only approved in 2017 and had to meet institutional criteria for use in Japan; thus, data on Impella will need to be evaluated in the future, again.

Our study had several limitations. First, although we used a large nationwide dataset confirmed by doctors and should be highly reliable, some data codes such as products, procedures, comorbidities, and complications may have been based on medical claims and assigned a different identification. Second, laboratory data, physiological tests, and

hemodynamic data were unavailable. Consequently, our multivariable analysis may not have fully adjusted for all potential prognostic variables. Third, we cannot determine whether the mechanism of the negative volume-outcome relationship is due to experience or differences in the hospital equipment, the presence and dynamics of the shock team, and treatment strategies, including the decision to use an MCS device, which are associated with the volume of cases at each hospital.[2,7,8,14,17,29,30]

Conclusion

In a large nationwide database with over 65,000 cases, higher volumes of cases for MCS or each MCS device are associated with a better prognosis. Additionally, there is an upper limit to the decline, above which in-hospital mortality remains constant or increases slightly. Thus, the volume of cases at each hospital is an important indicator for better prognosis in patients with CS receiving MCS. Centralizing patients with refractory cardiogenic shock by transport system to a particular hospital may improve patient outcomes in each region.

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Reference

1. van Diepen S, Katz JN, Albert NM, et al. Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation.* 2017; 136: e232–e268.
2. Chioncel O, Parissis J, Mebazaa A, et al. Epidemiology, pathophysiology and contemporary management of cardiogenic shock - a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2020; 22: 1315–1341.
3. Reyentovich A, Barghash MH, Hochman JS. Management of refractory cardiogenic shock. *Nat Rev Cardiol.* 2016; 13 :481–92.
4. Shah M, Patnaik S, Patel B, et al. Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. *Clin Res Cardiol.* 2018; 107: 287–303.
5. Lang CN, Kaier K, Zotzmann V, et al. Cardiogenic shock: incidence, survival and mechanical circulatory support usage 2007-2017-insights from a national registry. *Clin Res Cardiol.* 2021; 110: 1421–1430.
6. Schrage B, Becher PM, Goßling A, et al. Temporal trends in incidence, causes, use of mechanical circulatory support and mortality in cardiogenic shock. *ESC Heart Fail.* 2021; 8: 1295–1303.
7. Geller BJ, Sinha SS, Kapur NK, et al. Escalating and De-escalating Temporary Mechanical Circulatory Support in Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation.* 2022; 146: e50–e68.
8. Balthazar T, Vandenbriele C, Verbrugge FH, et al. Managing Patients With Short-Term Mechanical Circulatory Support: JACC Review Topic of the Week. *J Am Coll Cardiol.* 2021; 77: 1243–1256.

9. Barbaro RP, Odetola FO, Kidwell KM, et al.Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med.* 2015; 191: 894–901.
10. Becher PM, Goßling A, Schrage B, et al. Procedural volume and outcomes in patients undergoing VA-ECMO support. *Crit Care.* 2020; 24: 291.
11. Chen EW, Canto JG, Parsons LS, et al. Relation between hospital intra-aortic balloon counterpulsation volume and mortality in acute myocardial infarction complicated by cardiogenic shock. *Circulation.* 2003; 108: 951–7.
12. O'Neill WW, Grines C, Schreiber T, et al. Analysis of outcomes for 15,259 US patients with acute myocardial infarction cardiogenic shock (AMICS) supported with the Impella device. *Am Heart J.* 2018; 202: 33–38.
13. Shaefi S, O'Gara B, Kociol RD, et al. Effect of cardiogenic shock hospital volume on mortality in patients with cardiogenic shock. *J Am Heart Assoc.* 2015; 4: e001462.
14. Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2018; 20: 1505–1535.
15. Lu DY, Adelsheimer A, Chan K, et al. Impact of hospital transfer to hubs on outcomes of cardiogenic shock in the real world. *Eur J Heart Fail.* 2021; 23: 1927–1937.
16. Baumwol J. "I Need Help"-A mnemonic to aid timely referral in advanced heart failure. *J Heart Lung Transplant.* 2017; 36: 593–594.
17. Helman DN, Morales DL, Edwards NM, et al. Left ventricular assist device bridge-to-transplant network improves survival after failed cardiotomy. *Ann Thorac Surg.* 1999; 68: 1187–94.

18. Yasuda S, Nakao K, Nishimura K, et al. The Current Status of Cardiovascular Medicine in Japan- Analysis of a Large Number of Health Records From a Nationwide Claim-Based Database, JROAD-DPC. *Circ J.* 2016; 80: 2327–2335.
19. Yasunaga H, Ide H, Imamura T, et al. Impact of the Japanese Diagnosis Procedure Combination-based Payment System on cardiovascular medicine-related costs. *Int Heart J.* 2005; 46: 855–66.
20. Nakai M, Iwanaga Y, Sumita Y, et al. Validation of Acute Myocardial Infarction and Heart Failure Diagnoses in Hospitalized Patients With the Nationwide Claim-Based JROAD-DPC Database. *Circ Rep.* 2021; 3: 131–136.
21. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care.* 2005; 43: 1130–9.
22. Alotaibi GS, Wu C, Senthilselvan A, et al. The validity of ICD codes coupled with imaging procedure codes for identifying acute venous thromboembolism using administrative data. *Vasc Med.* 2015; 20: 364–8.
23. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* 2004; 159: 702–6.
24. Chow JY, Vadakken ME, Whitlock RP, et al. Pulmonary artery catheterization in patients with cardiogenic shock: a systematic review and meta-analysis. *Can J Anaesth.* 2021; 68: 1611–1629.
25. Saxena A, Garan AR, Kapur NK, et al. Value of Hemodynamic Monitoring in Patients With Cardiogenic Shock Undergoing Mechanical Circulatory Support. *Circulation.* 2020; 141: 1184–1197.
26. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA.* 2011; 306: 1659–68.

27. Allareddy V, Ward MM, Wehby GL, et al. The connection between selective referrals for radical cystectomy and radical prostatectomy and volume-outcome effects: an instrumental variables analysis. *Am J Med Qual.* 2012; 27: 434–40.
28. Bryner B, Cooley E, Copenhaver W, et al. Two decades' experience with interfacility transport on extracorporeal membrane oxygenation. *Ann Thorac Surg.* 2014; 98: 1363–70.
29. Papolos AI, Kenigsberg BB, Berg DD, et al. Management and Outcomes of Cardiogenic Shock in Cardiac ICUs With Versus Without Shock Teams. *J Am Coll Cardiol.* 2021; 78: 1309–1317.
30. Moghaddam N, van Diepen S, So D, et al. Cardiogenic shock teams and centres: a contemporary review of multidisciplinary care for cardiogenic shock. *ESC Heart Fail.* 2021; 8: 988–998.

Figure 1. In-hospital mortality according to the quintiles or tertiles of short term MCS volume.

In the IABP alone, ECMO and all MCS cohorts, patients were divided into quintile categories. In the Impella cohort, patients were divided into tertile categories. Adjusted odds ratios for in-hospital mortality for each category are presented with the lowest group as a reference.
ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support.

Figure 2. Continuous relationship between adjusted odds ratios for in-hospital mortality and the volume of cases.

Continuous relationship between adjusted odds ratio for in-hospital mortality and the volume of cases in the IABP alone cohort (A), ECMO cohort (B), Impella cohort (C), and all MCS cohort (D). A hospital with 1 case/year for each cohort was used as reference. The solid red line reveals a continuous odd ratio, and the interrupted red lines on either side illustrate the 95% confidence interval.
Below 98 percentiles of the volume of cases in each cohort were depicted.
The model was adjusted for age category, sex, body mass index category, chronic kidney disease, diabetes mellitus, cardiopulmonary resuscitation (on or before the date when MCS was introduced), intubation, right heart catheterization, causes of CS (AMI, HF, FM, arrhythmia, or PE), and era (2012–2013, 2014–2015, 2016–2017, 2018–2019).
Kernel density estimation was drawn as the black line to express the case volume distribution.

AMI, acute myocardial infarction; CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; FM, fulminant myocarditis; HF, heart failure; IABP, intra-aortic balloon pump; and MCS, mechanical circulatory support and PE, pulmonary embolism.

Figure 3. Continuous relationship between in-hospital mortality and the volume of cases.

Continuous relationship between in-hospital mortality and the volume of cases in the IABP alone cohort (A), ECMO cohort (B), Impella cohort (C), and all MCS cohort (D). The solid red line illustrates a continuous in-hospital mortality (%), and the interrupted red lines on either side reveal the 95% confidence interval.
Below 98 percentiles of the volume of cases in each cohort were depicted.
ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; PE, pulmonary embolism.

Table 1. Patient characteristics in hospitals according to the quintiles of IABP alone volume.

	Quintile 1 (-6.3 cases/year) N=9,700	Quintile 2 (6.4-10.8 cases/year) N=9,556	Quintile 3 (10.9-16.1 cases/year) N=9,704	Quintile 4 (16.2-23.5 cases/year) N=9,818	Quintile 5 (23.6- cases/year) N=9,865	p for trend
IABP alone, cases/year	4.4 (3.2-5.4)	8.6 (7.4-9.8)	13.4 (12.1-14.9)	19.8 (18.1-22.1)	31.8 (28.2-38.4)	<0.001
Age, years *	71.0±12.3	70.9±12.6	70.3±12.5	70.0±12.5	70.5±12.5	<0.001
Age groups, no. (%)						
18-49	623 (6.4)	630 (6.6)	666 (6.9)	727 (7.4)	648 (6.6)	0.17
50-59	1,037 (10.7)	1,056 (11.1)	1,165 (12.0)	1,163 (11.8)	1,188 (12.0)	0.001
60-69	2,359 (24.3)	2,280 (23.9)	2,405 (24.8)	2,484 (25.3)	2,359 (23.9)	0.66
70-79	3,054 (31.5)	2,966 (31.0)	2,934 (30.2)	2,997 (30.5)	3,041 (30.8)	0.22
80-	2,627 (27.1)	2,624 (27.5)	2,533 (26.1)	2,447 (24.9)	2,629 (26.6)	0.017
Male sex, no. (%)	7,091 (73.1)	7,045 (73.7)	7,301 (75.2)	7,316 (74.5)	7,224 (73.2)	0.47
Body mass index, kg/m^2 †	23.5±3.9	23.4±3.9	23.5±3.9	23.5±3.9	23.4±6.6	0.049
Body mass index categories, no. (%)						
<18.5	664 (8.0)	741 (8.7)	673 (7.6)	722 (8.0)	788 (8.7)	0.34
>=18.5 and <25.0	5,075 (61.0)	5,222 (61.1)	5,492 (62.1)	5,576 (62.0)	5,545 (61.4)	0.28
>=25.0 and <30.0	2,118 (25.4)	2,129 (24.9)	2,177 (24.6)	2,190 (24.3)	2,199 (24.4)	0.064
>=30.0	468 (5.6)	457 (5.3)	503 (5.7)	509 (5.7)	496 (5.5)	0.94
Chronic kidney disease, no. (%)	825 (8.5)	863 (9.0)	882 (9.1)	926 (9.4)	935 (9.5)	0.011
Diabetes Mellitus, no. (%)	3,123 (32.2)	3,125 (32.7)	3,131 (32.3)	3,371 (34.3)	3,218 (32.6)	0.10
Cause of CS, no. (%)						
AMI	8,310 (85.7)	7,965 (83.4)	8,031 (82.8)	8,116 (82.7)	7,918 (80.3)	<0.001
HF	997 (10.3)	1,128 (11.8)	1,107 (11.4)	1,139 (11.6)	1,308 (13.3)	<0.001
Valvular disease	124 (1.3)	199 (2.1)	262 (2.7)	269 (2.7)	310 (3.1)	<0.001
FM	137 (1.4)	97 (1.0)	125 (1.3)	98 (1.0)	119 (1.2)	0.21
Arrhythmia	119 (1.2)	154 (1.6)	172 (1.8)	185 (1.9)	206 (2.1)	<0.001
PE	13 (0.1)	13 (0.1)	7 (0.1)	11 (0.1)	4 (0.0)	0.036
Procedure, no. (%)						
Cardiopulmonary resuscitation ‡	1,257 (13.0)	961 (10.1)	988 (10.2)	801 (8.2)	657 (6.7)	<0.001
Intubation	4,979 (51.3)	4,755 (49.8)	4,958 (51.1)	4,783 (48.7)	4,204 (42.6)	<0.001

Right heart catheterization	3,189 (32.9)	3,561 (37.3)	4,435 (45.7)	4,273 (43.5)	5,161 (52.3)	<0.001
Renal replacement therapy	540 (5.6)	548 (5.7)	598 (6.2)	631 (6.4)	721 (7.3)	<0.001
PCI in AMI	7,491 (90.1)	7,242 (90.9)	7,226 (90.0)	7,381 (90.9)	7,191 (90.8)	0.18
CABG in AMI	332 (4.0)	459 (5.8)	611 (7.6)	533 (6.6)	578 (7.3)	<0.001
Number of hospital beds, no. §	360.0 (288.0-478.0)	433.0 (326.0-600.0)	520.0 (396.0-684.0)	584.0 (490.0-689.0)	606.0 (450.0-789.0)	<0.001
Hospital type. (%) ||						
Class A JCS-certified teaching hospitals	8,398 (86.6)	8,774 (91.8)	9,481 (97.7)	9,818 (100.0)	9,865 (100.0)	<0.001
Class B JCS-certified teaching hospitals	1,123 (11.6)	737 (7.7)	211 (2.2)	0 (0.0)	0 (0.0)	<0.001
Others	179 (1.8)	45 (0.5)	12 (0.1)	0 (0.0)	0 (0.0)	<0.001
Number of certificated cardiologists, no. #	4.0 (3.0-5.0)	5.0 (3.0-7.0)	6.0 (4.0-9.0)	6.0 (4.0-11.0)	9.0 (6.0-13.0)	<0.001
Era, no. (%)						
2012-13	2,030 (20.9)	1,847 (19.3)	2,143 (22.1)	2,405 (24.5)	2,021 (20.5)	0.001
2014-15	2,345 (24.2)	2,358 (24.7)	2,432 (25.1)	2,367 (24.1)	2,480 (25.1)	0.32
2016-17	2,678 (27.6)	2,619 (27.4)	2,686 (27.7)	2,621 (26.7)	2,759 (28.0)	0.99
2018-19	2,647 (27.3)	2,732 (28.6)	2,443 (25.2)	2,425 (24.7)	2,605 (26.4)	<0.001

Data excluding missing data are presented as mean±standard deviation, median (interquartile range) or number (percentage).
* One patient was described as being aged 121 so was regarded as missing data.
† Height recorded as less than 50 cm and weight recorded as less than 20 kg or 600 kg were regarded as missing data. There were 4,899 missing data.
‡ On or before the date when MCS was introduced.
§ The number of beds was missing in 4 cases.
|| Class A JCS-certified teaching hospitals need more than 2 JCS board-certified cardiologists and 30 cardiovascular beds, and class B need more than 1 JCS board-certified cardiologist and 15 cardiovascular beds.
The number of certificated cardiologists was missing in 45 cases.
AMI indicates acute myocardial infarction; CABG, coronary artery bypass graft; CS, cardiogenic shock; FM, fulminant myocarditis; HF, heart failure; PCI, percutaneous coronary intervention and PE, pulmonary embolism.

Table 2. Patient characteristics in hospitals according to the quintiles of ECMO volume.

	Quintile 1 (-2.8 cases/year) N=3,285	Quintile 2 (2.9-5.0 cases/year) N=3,395	Quintile 3 (5.1-8.0 cases/year) N=3,437	Quintile 4 (8.1-12.0 cases/year) N=3,319	Quintile 5 (12.1- cases/year) N=3,435	p for trend
ECMO, cases/year	1.9 (1.2-2.4)	3.8 (3.4-4.3)	6.4 (5.6-7.0)	9.9 (8.9-10.8)	14.1 (13.4-15.9)	<0.001
Age, years	65.8±14.1	65.2±14.1	63.7±14.5	63.5±14.1	65.2±14.4	<0.001
Age groups, no. (%)						
18-49	454 (13.8)	485 (14.3)	627 (18.2)	578 (17.4)	528 (15.4)	0.002
50-59	520 (15.8)	558 (16.4)	520 (15.1)	575 (17.3)	562 (16.4)	0.34
60-69	861 (26.2)	904 (26.6)	953 (27.7)	895 (27.0)	892 (26.0)	0.93
70-79	912 (27.8)	933 (27.5)	917 (26.7)	899 (27.1)	924 (26.9)	0.38
80-	538 (16.4)	515 (15.2)	420 (12.2)	372 (11.2)	529 (15.4)	0.003
Male sex, no. (%)	2,422 (73.7)	2,523 (74.3)	2,564 (74.6)	2,538 (76.5)	2,558 (74.5)	0.13
Body mass index, kg/m^2 *	24.2±5.9	24.1±4.4	24.3±5.9	24.1±4.4	24.1±5.0	0.51
Body mass index categories, no. (%)						
<18.5	156 (6.2)	173 (6.4)	199 (7.2)	183 (7.0)	218 (7.8)	0.012
>=18.5 and <25.0	1,455 (57.4)	1,567 (58.1)	1,541 (55.7)	1,475 (56.6)	1,584 (56.7)	0.32
>=25.0 and <30.0	713 (28.1)	732 (27.2)	782 (28.3)	714 (27.4)	745 (26.7)	0.32
>=30.0	211 (8.3)	224 (8.3)	243 (8.8)	236 (9.0)	248 (8.9)	0.29
Chronic kidney disease, no. (%)	273 (8.3)	262 (7.7)	305 (8.9)	230 (6.9)	308 (9.0)	0.69
Diabetes Mellitus, no. (%)	724 (22.0)	682 (20.1)	647 (18.8)	621 (18.7)	520 (15.1)	<0.001
Cause of CS, no. (%)						
AMI	2,133 (64.9)	2,214 (65.2)	2,068 (60.2)	1,972 (59.4)	1,989 (57.9)	<0.001
HF	287 (8.7)	288 (8.5)	278 (8.1)	297 (8.9)	307 (8.9)	0.56
Valvular disease	73 (2.2)	120 (3.5)	138 (4.0)	103 (3.1)	158 (4.6)	<0.001
FM	285 (8.7)	223 (6.6)	209 (6.1)	188 (5.7)	170 (4.9)	<0.001
Arrhythmia	214 (6.5)	316 (9.3)	475 (13.8)	532 (16.0)	564 (16.4)	<0.001
PE	293 (8.9)	234 (6.9)	269 (7.8)	227 (6.8)	247 (7.2)	0.017
Procedure, no. (%)						
Cardiopulmonary resuscitation †	1,633 (49.7)	1,630 (48.0)	1,751 (50.9)	1,725 (52.0)	1,692 (49.3)	0.27
Intubation	2,848 (86.7)	2,964 (87.3)	2,979 (86.7)	2,880 (86.8)	2,985 (86.9)	0.94

Right heart catherterization	1,349 (41.1)	1,731 (51.0)	1,885 (54.8)	1,645 (49.6)	1,859 (54.1)	<0.001
Renal replacement therapy	253 (7.7)	229 (6.7)	263 (7.7)	264 (8.0)	240 (7.0)	0.87
PCI in AMI	1,869 (87.6)	1,927 (87.0)	1,801 (87.1)	1,720 (87.2)	1,745 (87.7)	0.87
CABG in AMI	39 (1.8)	59 (2.7)	37 (1.8)	50 (2.5)	30 (1.5)	0.43
Concomitant use of MCS device, no. (%)						
ECMO alone	737 (22.4)	724 (21.3)	753 (21.9)	787 (23.7)	872 (25.4)	<0.001
ECMO+IABP	2,528 (77.0)	2,616 (77.1)	2,584 (75.2)	2,449 (73.8)	2,448 (71.3)	<0.001
ECMO+Impella	20 (0.6)	55 (1.6)	100 (2.9)	83 (2.5)	115 (3.3)	<0.001
Impella 2.5/CP ‡	17 (85.0)	44 (80.0)	92 (92.0)	72 (86.7)	95 (82.6)	<0.001
Impella 5.0 ‡	3 (15.0)	11 (20.0)	8 (8.0)	11 (13.3)	20 (17.4)	0.001
Number of hospital beds, no. §	406.0 (307.0-532.0)	510.0 (394.0-637.0)	592.0 (450.0-751.0)	651.0 (574.0-804.0)	628.0 (409.0-901.0)	<0.001
Hospital type. (%) ‖						
Class A JCS-certified teaching hospitals	3,069 (93.4)	3,220 (94.8)	3,401 (99.0)	3,319 (100.0)	3,435 (100.0)	<0.001
Class B JCS-certified teaching hospitals	184 (5.6)	175 (5.2)	36 (1.0)	0 (0.0)	0 (0.0)	<0.001
Others	32 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
Number of certificated cardiologists, no. #	4.0 (3.0-6.0)	6.0 (4.0-9.0)	7.0 (5.0-12.0)	9.0 (6.0-14.0)	11.0 (6.0-18.0)	<0.001
Era, no. (%)						
2012-13	548 (16.7)	597 (17.6)	557 (16.2)	579 (17.4)	562 (16.4)	0.69
2014-15	679 (20.7)	734 (21.6)	806 (23.5)	750 (22.6)	751 (21.9)	0.15
2016-17	952 (29.0)	953 (28.1)	907 (26.4)	950 (28.6)	958 (27.9)	0.51
2018-19	1,106 (33.7)	1,111 (32.7)	1,167 (34.0)	1,040 (31.3)	1,164 (33.9)	0.74

Data excluding missing data are presented as mean±standard deviation, median (interquartile range) or number (percentage).
Impella cases also overlap in the Impella cohort.
* Height recorded as less than 50 cm and weight recorded as less than 20 kg or 600 kg were regarded as missing data. There were 3,472 missing data.
† On or before the date when MCS was introduced.
‡ Patients for whom an artificial vessel was used when initial Impella device was implanted were regarded as using Impella 5.0, and the remaining patients were regarded as using Impella 2.5/CP.
§ The number of beds was missing in 1 cases.

|| Class A JCS-certified teaching hospitals need more than 2 JCS board-certified cardiologists and 30 cardiovascular beds, and class B need more than 1 JCS board-certified cardiologist and 15 cardiovascular beds.
The number of certificated cardiologist was missing in 22 cases.
AMI indicates acute myocardial infarction; CABG, coronary artery bypass graft; CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; FM, fulminant myocarditis; HF, heart failure; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention and PE, pulmonary embolism.

Table 3. Patient outcome according to the quintile or tertile categories in the volume of cases.

A) IABP alone cohort

	Quintile 1 (-6.3 cases/year) N=9,700	**Quintile 2 (6.4-10.8 cases/year) N=9,556**	**Quintile 3 (10.9-16.1 cases/year) N=9,704**	**Quintile 4 (16.2-23.5 cases/year) N=9,818**	**Quintile 5 (23.6- cases/year) N=9,865**	**p for trend**
In-hospital death, %	2,431 (25.1)	1,999 (20.9)	1,919 (19.8)	1,614 (16.4)	1,504 (15.2)	<0.001
Length of hospital stay, days	20.0 (11.0-32.0)	21.0 (14.0-33.0)	20.0 (13.0-32.0)	20.0 (14.0-31.0)	20.0 (14.0-32.0)	<0.001
in patients discharged alive	22.0 (15.0-35.0)	22.0 (16.0-35.0)	22.0 (15.0-34.0)	21.0 (15.0-32.0)	21.0 (15.0-32.0)	<0.001
in patients discharged dead	5.0 (2.0-18.0)	8.0 (2.0-24.0)	9.0 (2.0-24.0)	10.0 (3.0-26.0)	12.5 (3.0-29.0)	<0.001
Duration of MCS, days	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-5.0)	<0.001
in patients discharged alive	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-5.0)	<0.001
in patients discharged dead	2.0 (1.0-4.0)	3.0 (2.0-5.0)	3.0 (2.0-6.0)	3.0 (2.0-6.0)	4.0 (2.0-7.0)	<0.001
Hospitalization costs, thousand US dollars	20.9 (14.9-29.5)	23.2 (17.2-32.6)	23.5 (17.3-33.7)	23.3 (17.4-32.9)	24.9 (18.9-35.1)	<0.001
in patients discharged alive	22.3 (16.7-30.3)	23.9 (18.1-32.8)	24.1 (18.4-33.9)	23.5 (18.0-32.8)	24.9 (19.3-34.7)	<0.001
in patients discharged dead	15.1 (10.6-25.4)	19.0 (12.1-31.6)	19.3 (12.6-32.6)	21.0 (13.6-33.4)	24.3 (15.1-37.3)	<0.001

B) ECMO cohort

	Quintile 1 (-2.8 cases/year) N=3,285	**Quintile 2 (2.9-5.0 cases/year) N=3,395**	**Quintile 3 (5.1-8.0 cases/year) N=3,437**	**Quintile 4 (8.1-12.0 cases/year) N=3,319**	**Quintile 5 (12.1- cases/year) N=3,435**	**p for trend**
In-hospital death, %	2,422 (73.7)	2,378 (70.0)	2,379 (69.2)	2,296 (69.2)	2,315 (67.4)	<0.001
Length of hospital stay, days	6.0 (2.0-24.0)	9.0 (2.0-30.0)	10.0 (2.0-31.0)	10.0 (3.0-33.0)	12.0 (3.0-33.0)	<0.001
in patients discharged alive	37.0 (19.0-61.0)	40.0 (24.0-63.0)	39.0 (25.0-58.0)	41.0 (26.0-61.0)	38.0 (24.0-59.0)	0.019
in patients discharged dead	4.0 (2.0-11.0)	4.0 (2.0-12.0)	4.0 (2.0-13.0)	4.0 (2.0-13.0)	4.0 (2.0-14.0)	<0.001

Duration of MCS, days	3.0 (2.0-6.0)	3.0 (2.0-7.0)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	4.0 (2.0-7.0)	<0.001
in patients discharged alive	4.0 (3.0-7.0)	5.0 (3.0-7.0)	4.0 (3.0-7.0)	5.0 (3.0-7.0)	5.0 (3.0-7.0)	0.12
in patients discharged dead	2.0 (1.0-5.0)	3.0 (1.0-6.0)	3.0 (2.0-6.0)	3.0 (2.0-7.0)	3.0 (2.0-7.0)	<0.001
Hospitalization costs, thousand US dollars	21.3 (13.5-36.4)	25.5 (15.3-43.0)	27.1 (16.3-44.0)	27.1 (15.4-44.7)	28.9 (16.4-47.2)	<0.001
in patients discharged alive	35.9 (24.0-49.9)	41.1 (29.8-56.8)	41.6 (30.0-58.2)	43.2 (31.6-60.4)	44.0 (32.2-61.3)	<0.001
in patients discharged dead	17.9 (12.1-28.6)	19.9 (13.0-34.0)	21.1 (13.3-34.7)	19.8 (12.6-34.5)	21.6 (13.2-36.6)	<0.001

C) Impella cohort

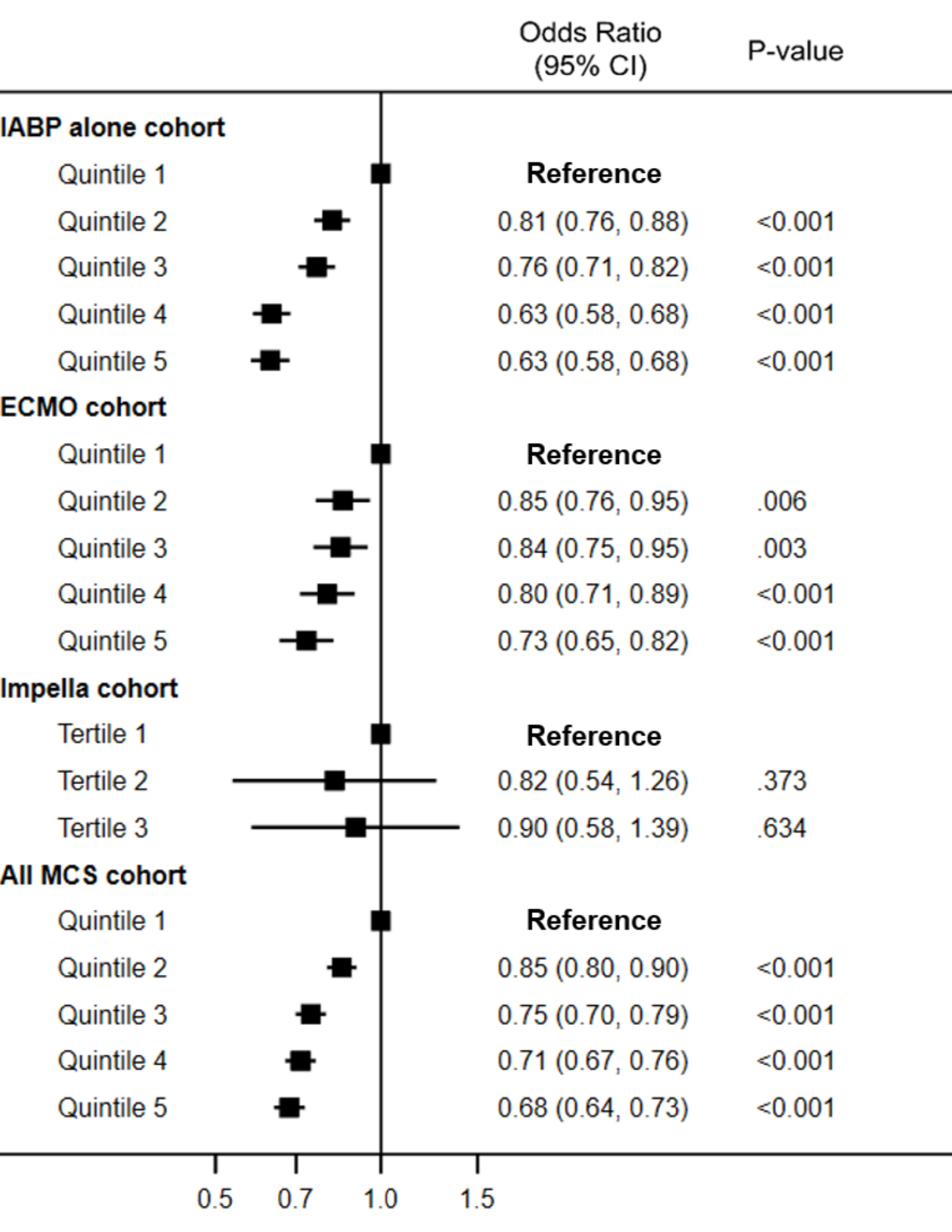
	Quintile 1 (-4.50 cases/year) N=201	**Quintile 2 (4.51-9.00 cases/year) N=257**	**Quintile 3 (9.01- cases/year) N=238**	**p for trend**
In-hospital death, %	89 (44.3)	102 (39.7)	109 (45.8)	0.70
Length of hospital stay, days	25.0 (14.0-42.0)	24.0 (14.0-46.0)	24.0 (12.0-50.0)	0.99
in patients discharged alive	34.5 (20.5-54.5)	32.0 (20.0-59.0)	37.0 (21.0-65.0)	0.26
in patients discharged dead	14.0 (4.0-31.0)	11.0 (4.0-24.0)	13.0 (4.0-24.0)	0.64
Duration of MCS, days	6.0 (3.0-11.0)	6.0 (3.0-11.0)	5.0 (3.0-10.0)	0.17
in patients discharged alive	5.0 (3.0-8.0)	6.0 (3.0-9.0)	4.0 (2.0-7.0)	0.12
in patients discharged dead	8.0 (3.0-16.0)	8.0 (4.0-14.0)	8.0 (3.0-15.0)	0.51
Hospitalization costs, thousand US dollars	56.1 (40.4-77.7)	53.2 (41.8-76.4)	54.3 (40.9-70.9)	0.67
in patients discharged alive	53.7 (41.9-70.8)	53.1 (42.2-73.1)	51.8 (40.7-67.6)	0.60
in patients discharged dead	61.8 (36.8-84.7)	54.4 (40.4-79.9)	56.2 (41.6-73.4)	0.86

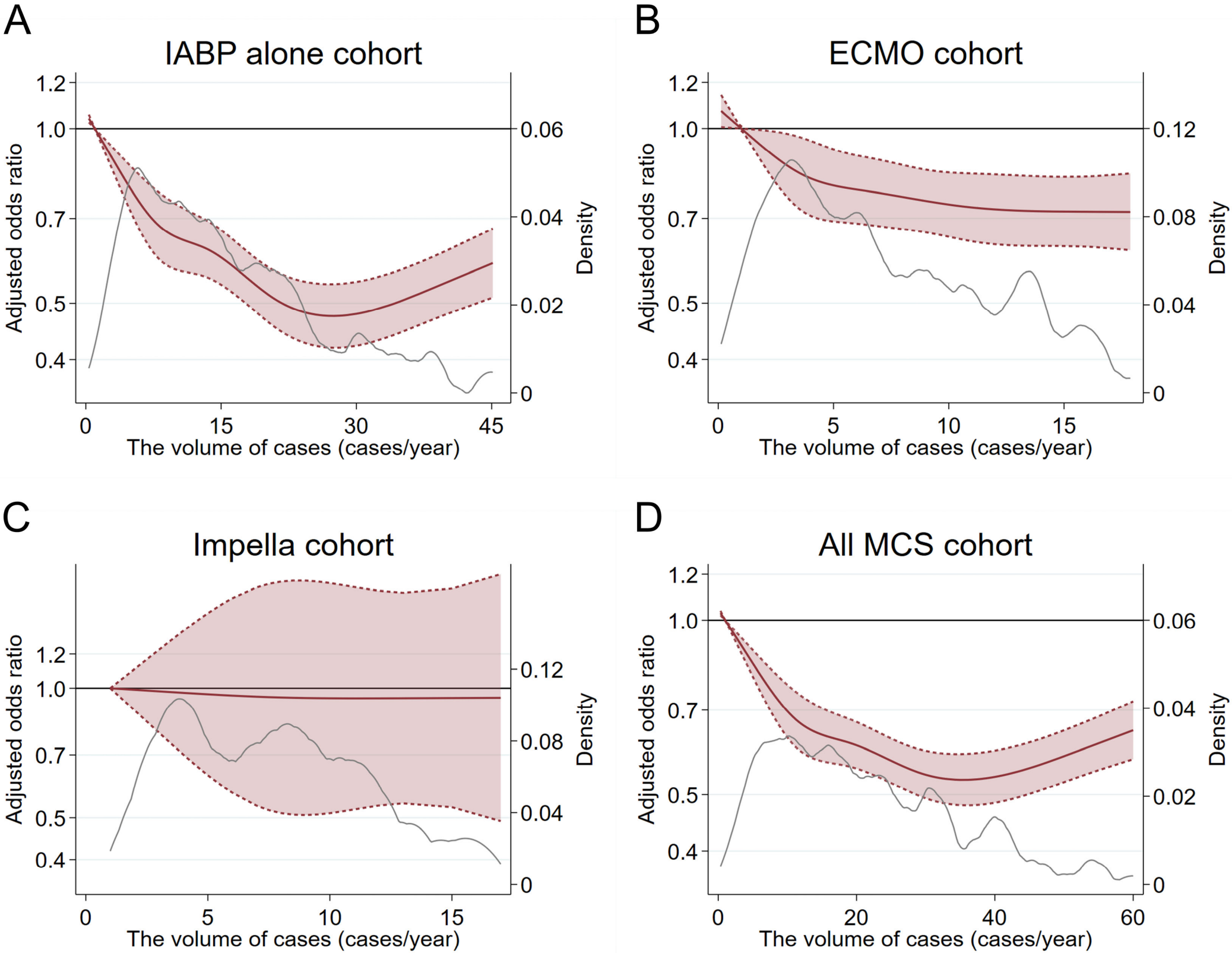
D) All MCS cohort

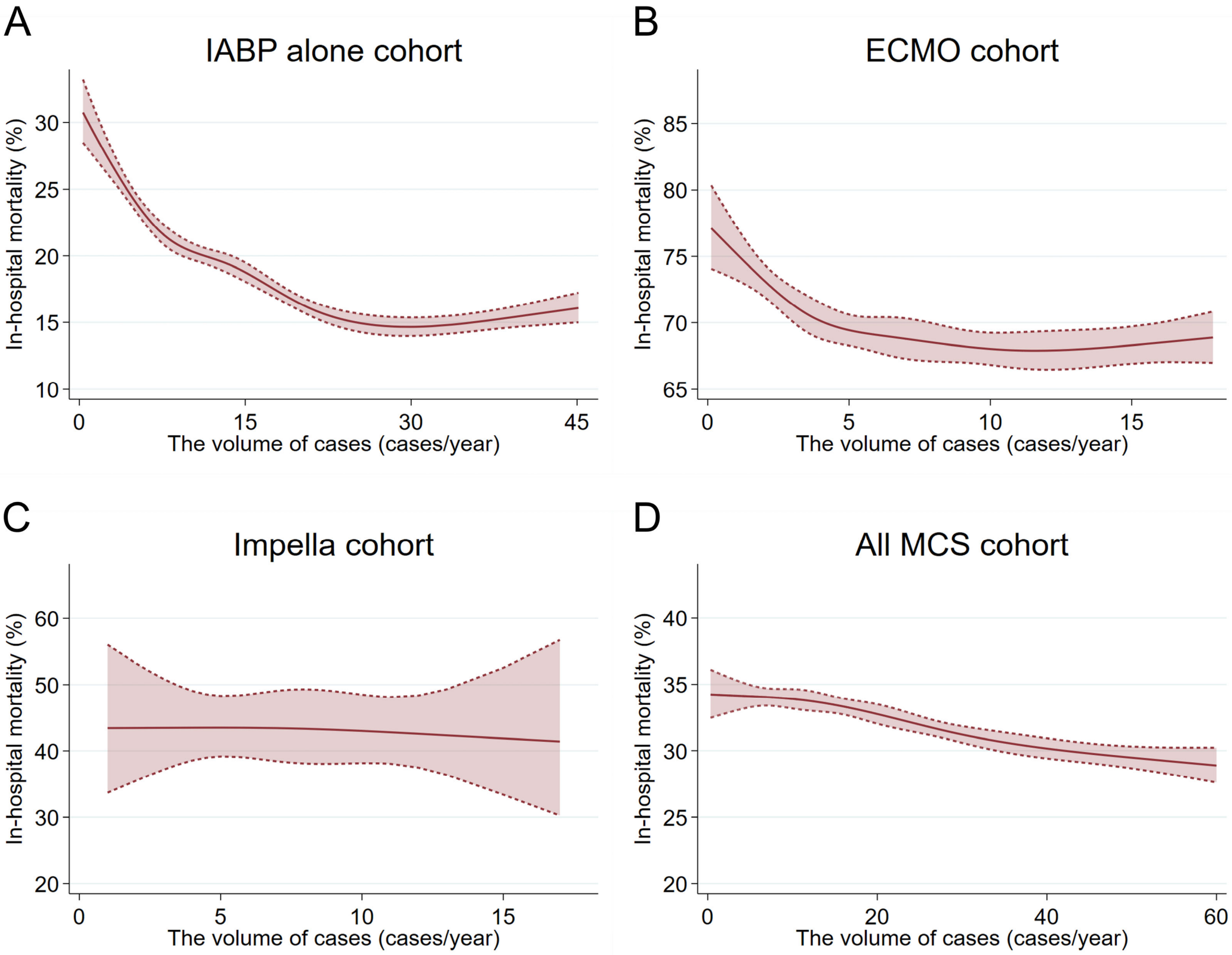
	Quintile 1	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**	**p for trend**

	(-8.9 cases/year) N=13,018	(9.0-15.5 cases/year) N=13,213	(15.6-23.1 cases/year) N=12,958	(23.2-32.5 cases/year) N=13,116	(32.6- cases/year) N=13,532	
In-hospital death, %	4,442 (34.1)	4,475 (33.9)	4,185 (32.3)	4,304 (32.8)	3,927 (29.0)	<0.001
Length of hospital stay, days	18.0 (6.0-31.0)	19.0 (9.0-32.0)	19.0 (10.0-32.0)	19.0 (10.0-32.0)	19.0 (12.0-33.0)	<0.001
in patients discharged alive	23.0 (15.0-37.0)	23.0 (16.0-37.0)	23.0 (15.0-38.0)	23.0 (16.0-37.0)	22.0 (16.0-36.0)	0.85
in patients discharged dead	4.0 (2.0-15.0)	5.0 (2.0-17.0)	5.0 (2.0-18.0)	6.0 (2.0-18.0)	7.0 (2.0-21.0)	<0.001
Duration of MCS, days	3.0 (2.0-4.0)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	<0.001
in patients discharged alive	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	<0.001
in patients discharged dead	2.0 (1.0-5.0)	3.0 (1.0-6.0)	3.0 (2.0-6.0)	3.0 (2.0-6.0)	4.0 (2.0-7.0)	<0.001
Hospitalization costs, thousand US dollars	20.6 (14.5-30.0)	23.1 (16.5-34.5)	24.3 (17.2-36.1)	24.8 (17.6-37.0)	25.9 (18.6-38.7)	<0.001
in patients discharged alive	22.6 (16.8-31.2)	24.5 (18.2-35.2)	25.6 (19.0-37.0)	26.1 (19.4-38.0)	26.5 (19.8-38.9)	<0.001
in patients discharged dead	16.0 (10.8-26.1)	19.2 (12.4-32.2)	20.2 (13.0-33.3)	21.1 (13.3-34.2)	23.2 (14.3-38.1)	<0.001

Data excluding missing data are presented as median (interquartile range).
Abbreviations are the same as in Table 1.


Odds Ratio (95% CI)
P-value
IABP alone cohort
Quintile 1
Reference
Quintile 2
0.81 (0.76, 0.88)
<0.001
Quintile 3
0.76 (0.71, 0.82)
<0.001
Quintile 4
0.63 (0.58, 0.68)
<0.001
Quintile 5
0.63 (0.58, 0.68)
<0.001
ECMO cohort
Quintile 1
Reference
Quintile 2
0.85 (0.76, 0.95)
.006
Quintile 3
0.84 (0.75, 0.95)
.003
Quintile 4
0.80 (0.71, 0.89)
<0.001
Quintile 5
0.73 (0.65, 0.82)
<0.001
Impella cohort
Tertile 1
Reference
Tertile 2
0.82 (0.54, 1.26)
.373
Tertile 3
0.90 (0.58, 1.39)
.634
All MCS cohort
Quintile 1
Reference
Quintile 2
0.85 (0.80, 0.90)
<0.001
Quintile 3
0.75 (0.70, 0.79)
<0.001
Quintile 4
0.71 (0.67, 0.76)
<0.001
Quintile 5
0.68 (0.64, 0.73)
<0.001
0.5
0.7
1.0
1.5


A
IABP alone cohort
Adjusted odds ratio
1.2
1.0
0.7
0.5
0.4
0.06
0.04
0.02
0
Density
0
15
30
45
The volume of cases (cases/year)
B
ECMO cohort
Adjusted odds ratio
1.2
1.0
0.7
0.5
0.4
0.12
0.08
0.04
0
Density
0
5
10
15
The volume of cases (cases/year)
C
Impella cohort
Adjusted odds ratio
1.2
1.0
0.7
0.5
0.4
0.12
0.08
0.04
0
Density
0
5
10
15
The volume of cases (cases/year)
D
All MCS cohort
Adjusted odds ratio
1.2
1.0
0.7
0.5
0.4
0.06
0.04
0.02
0
Density
0
20
40
60
The volume of cases (cases/year)


A
IABP alone cohort
In-hospital mortality (%)
10
15
20
25
30
0
15
30
45
The volume of cases (cases/year)
B
ECMO cohort
In-hospital mortality (%)
65
70
75
80
85
0
5
10
15
The volume of cases (cases/year)
C
Impella cohort
In-hospital mortality (%)
20
30
40
50
60
0
5
10
15
The volume of cases (cases/year)
D
All MCS cohort
In-hospital mortality (%)
20
25
30
35
40
0
20
40
60
The volume of cases (cases/year)