Effect of antithrombin III among patients with disseminated intravascular coagulation in obstetrics: a nationwide observational study in Japan

Yudai Iwasaki, MD[1], Hiroyuki Ohbe, MD, MPH[2], Daisuke Shigemi, MD, MPH[2], Kiyohide Fushimi, MD, PhD[3], Hideo Yasunaga, MD, PhD[2]

1 Department of Anesthesiology and Perioperative Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan
2 Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
3 Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, 1-5-45 Yushima, Bunkyo-ku, Tokyo 1138510, Japan

Correspondence to:
Hiroyuki Ohbe
Department of Clinical Epidemiology and Health Economics, School of Public Health, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 1130033, Japan
Email: hohbey@gmail.com
Tel: +81-3-5841-1887; Fax: +81-3-5841-1888

Short running title: Antithrombin III for DIC in obstetrics

Abstract

Objective: Pregnant women may develop disseminated intravascular coagulation (DIC), possibly resulting in massive maternal haemorrhage and perinatal death. The Japan guideline recommends use of antithrombin III (ATIII) for DIC in obstetrics; however, its effect remains uncertain. The present study therefore aimed to investigate the effect of ATIII for DIC patients in obstetrics, using a national inpatient database in Japan.

Design: Nationwide observational study

Setting: Japan

Population: We used the Diagnosis Procedure Combination inpatient database to identify patients who delivered at hospital and were diagnosed with DIC from July 2010 to March 2018.

Methods: Propensity score matching analyses were performed to compare in-hospital maternal mortality and hysterectomy during hospitalization between users and non-users of ATIII on the day of delivery.

Main Outcome Measures: In-hospital mortality, hysterectomy

Results: A total of 9,920 patients were enrolled, including 4,329 patients (44%) who used ATIII and 5,511 patients (56%) who did not use ATIII. One-to-one propensity score matching created 3290 pairs. In-hospital maternal mortality did not differ significantly between the propensity-matched groups (0.3% in the ATIII group vs. 0.5% in the control group; odds

ratio, 0.73; 95% confidence interval, 0.35–1.54). Patients in the ATIII group, compared with those in the control group, had a significantly lower proportion of receiving hysterectomy during hospitalization (5.3% vs. 8.7%; difference, -2.9%; 95% confidence interval, -4.2 to -1.6%).

Conclusions: The present study did not show mortality-reducing effect of ATIII for patients with DIC in obstetrics. ATIII may have clinical benefit in terms of reduction in receiving hysterectomy.

Funding

This work was supported by grants from the Ministry of Health, Labour and Welfare, Japan (19AA2007 and 20AA2005) and the Ministry of Education, Culture, Sports, Science and Technology, Japan (20H03907).

Keywords: disseminated intravascular coagulation, obstetrics, antithrombin III, propensity score matching

Introduction

Disseminated intravascular coagulation (DIC) is a severe coagulopathic condition which presents widespread thrombosis in microvessels, consumption of clotting factors, and haemorrhagic tendency caused by various diseases [1]. Complications in pregnant women (such as placental abruption or amniotic fluid embolism) can induce endothelial dysfunction, activation of platelet and coagulation system, and consumption of coagulation factors, resulting in DIC [2]. DIC can cause uncontrollable maternal haemorrhage and is one of the leading causes of death in pregnant women [2,3].

In Japan, several approaches have been applied for the treatment of DIC in obstetrics. In addition to a termination of pregnancy and supportive care, Japanese Society of Thrombosis and Hemostasis guideline recommends use of antithrombin III (ATIII) for DIC patients in obstetrics based on expert opinion [4]. Consequently, ATIII have been widely administered for DIC patients in obstetrics in Japan[5] [6].

However, the effect of ATIII for DIC patients in obstetrics is unknown. One randomized controlled trial for DIC patients in obstetrics reported that ATIII decreased organ failure score and DIC score compared with gabexate mesylate [7]. Two small randomised controlled studies for patients with severe preeclampsia showed that ATIII improved maternal symptoms and coagulation parameters [8,9]. A previous meta-analysis of ATIII use for critically ill patients

concluded that there were insufficient data about ATIII use for DIC patients in obstetrics;[10] thus, clinical benefit of anticoagulant therapy for DIC in obstetrics remains unclear [11]. Therefore, this study aimed to investigate the effect of ATIII for DIC patients in obstetrics, using a national inpatient database in Japan.

Methods

Data source

The study design was a retrospective cohort study using routinely collected data, and the reporting of this study conforms to the RECORD statement [12]. We used the Japanese Diagnosis Procedure Combination inpatient database, which includes discharge abstracts and administrative claims data from more than 1200 acute-care hospitals, which account for about half of all acute admissions in Japan. The database includes the following data: age; sex; smoking history; body weight; body height; level of consciousness at admission; ambulance use; planned or emergency admission; diagnoses recorded according to the International Classification of Diseases Tenth Revision (ICD-10) codes and written in Japanese text; procedures recorded according to the Japanese medical procedure codes; prescriptions; drug administration; discharge status, pregnancy status (pregnant or not), gestational age at admission, and delivery during hospitalization [13 14]. Because the diagnostic records are linked to a payment system, attending physicians must report objective evidence for their diagnoses

for purposes of treatment cost reimbursement [15]. A validation study of the database suggested the sensitivity and specificity of diagnosis for DIC were 35.8% and 98.2%, respectively [16]. The Institutional Review Board of the University of Tokyo approved this study (approval number 3501-3; December 2017). Because all data were de-identified, the requirement for patient informed consent was waived.

Study population

Using the database from July 1st, 2010 through March 31th, 2018, we identified all patients who delivered at hospital and were diagnosed with DIC (ICD-10 code: D65 O450 O460 O723) during the same hospitalization. We defined patients who received caesarean section (Japanese medical procedure codes: K898) or other delivery related procedures (K891 K892 K893 K894 K895 K896 K897 K900 K901 K900-2 K902 K903 K904 K905 K908) as patients who delivered at hospital. We excluded the following patients: (i) older than 50 years old; (ii) at the second or subsequent admission with a delivery and diagnosis of DIC during the study period; (iii) died on the day of delivery; and (iv) discharged on the day of delivery.

Group assignment

Patients who received ATIII on the day of delivery were defined as the ATIII group, and the remaining patients were defined as the control group.

Covariates and outcomes

Covariates included age, smoking history (non-smoker, current/past smoker, unknown), body mass index at admission, Japan Coma Scale at admission [17], ambulance use, introduction from another hospital, planned or emergency admission, teaching hospital, gestational age at admission, underlying conditions for DIC, caesarean section, anaesthesia during the delivery, intensive care unit admission on the day of delivery, and supportive therapies on the day of delivery. The body mass index was categorized as <18.5, 18.5–24.9, 25.0–29.9, or ≥30.0 kg/ m^2, or missing data. Japan Coma Scale status was categorized as alert, confusion, somnolence, and coma. Japan Coma Scale status has been shown to be well correlated with the Glasgow Coma Scale score [17]. Gestational age at admission was categorized as extremely preterm (<28 weeks), very preterm (28–<32 weeks), moderate to late preterm (32–<37 weeks), term (37–<42 weeks), or post-term (≥42 weeks) [18]. We included the following underlying conditions for DIC: oedema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium (ICD-10 code: O10-O16); multiple gestation (O30); maternal care for fetal abnormality, damage, or problems (O35 O36); placenta praevia (O44); placental abruption (O45); atonic postpartum haemorrhage （O721）; and amniotic fluid embolism (O881). The primary outcome was in-hospital maternal mortality. Secondary outcomes were hysterectomy during hospitalization, transcatheter arterial embolization during hospitalization, total transfusion volume within 28 day of delivery (including red blood cell, fresh frozen plasma, and platelet), length of hospital stay, and total hospitalization costs.

Statistical analysis

A propensity score matching method was applied to compare outcomes between ATIII and control groups [19,20]. A multivariable logistic regression model was employed to predict the propensity scores of the patients receiving ATIII on the day of delivery, using all the covariates presented in **Supplemental Table 1** as predictor variables. One-to-one nearest-neighbour matching without replacement was then performed for the estimated propensity scores of the patients using a caliper width set at 20% of the standard deviation for the propensity scores [19,20]. Distributions of propensity scores before and after matching are presented in **Supplemental Figure S1** and **Supplemental Figure S2**. To assess the performance of the matching, the covariates before and after propensity score matching were compared using absolute standardized differences [21]. Absolute standardized differences ≤10% were regarded as denoting negligible imbalances between the ATIII and control groups [21]. We conducted propensity score matching using the STATA module of PSMATCH2 software provided by Leuven and Sianesi [22].

After propensity score matching, we used a generalized estimating equation approach for comparisons of the primary and secondary outcomes, accompanied by cluster-robust standard errors with hospitals used as the cluster variable [23]. Differences and their 95% confidence

intervals were obtained by generalized estimating equation regression models with identity link function.

We conducted two sensitivity analyses to confirm the robustness of the main results by applying different models: namely, an inverse probability of treatment weighting (IPTW) and an instrumental variable analysis. In the IPTW, we calculated a stabilized average treatment effect weight, which can maintain the sample size of original data and provides more precise interval estimations of the variance of the main effect and controls type I error compared with non-stabilized IPTW[19 24]. We used a weighted generalized linear model to compare the primary and secondary outcomes, accompanied by cluster-robust standard errors that treated individual hospitals as clusters.

Propensity score methods cannot remove hidden biases caused by unmeasured confounders. We therefore conducted an instrumental variable analysis as a confirmatory analysis. In a properly executed instrumental variable analysis, instrumental variables approximate random assignment of patients to a treatment group analogous to a randomized clinical trial [25,26]. In the present study, hospitals' preference of ATIII was chosen as the instrumental variable. Hospitals' preference of ATIII was defined as the number of patients who received ATIII on the day of delivery divided by the number of eligible patients in each hospital. To assess the validity of treatment preference of hospitals as an instrumental variable, we confirmed that treatment preference of hospitals was highly correlated with patients' receiving ATIII on the

day of delivery (F statistic >10). We also examined whether the covariates and outcomes were associated with hospitals' preference for ATIII (**Supplementary Table 2**). We used a two-stage residual inclusion estimation framework for instrumental variable analysis [27]. All instrumental variable analyses were performed using robust standard errors.

Categorical variables were described as numbers and percentages. Continuous variables were presented as the mean and standard deviation. All reported *p*-values were two-sided; values for which $p<0.05$ were inferred as significant. All analyses were conducted using software STATA/MP 16.0 (Stata Corp. College Station, TX, USA).

Funding

This work was supported by grants from the Ministry of Health, Labour and Welfare, Japan (19AA2007 and 20AA2005) and the Ministry of Education, Culture, Sports, Science and Technology, Japan (20H03907). These awarded grants did not include external peer review for scientific quality.

Results

A total of 9,840 patients were enrolled in the analyses. Of these, 4,329 patients (44%) were assigned to the ATIII group and 5,511 patients (56%) were assigned to the control group (**Figure 1**).

Supplemental Table 1 shows the baseline characteristics of the unmatched and propensity score-matched cohorts. In the unmatched cohort, patients in the ATIII group were more likely to be hospitalized in a teaching hospital, to have an atonic postpartum haemorrhage, to undergo general anaesthesia, to be admitted to the intensive care unit, and to receive vasopressor and transfusions, compared with the control group. One-to-one propensity score matching created 3,290 matched pairs. After propensity score matching, patients' characteristics were well balanced between the two groups.

Table 1 shows the outcomes in the unmatched and propensity score-matched cohorts. After propensity score matching, there was no significant difference in in-hospital maternal mortality (0.3% in the ATIII group vs. 0.4% in the control group; difference, 0.0%; 95% confidence interval, -0.3 to 0.3%). Patients in the ATIII group, compared with those in the control group, were less likely to undergo hysterectomy during hospitalization (5.3% vs. 8.7%; difference, -2.9%; 95% confidence interval, -4.2 to -1.6%). There were no significant differences in the transcatheter arterial embolization during hospitalization and length of hospital stay. Patients in the ATIII group, compared with those in the control group, had significantly higher volume of total transfusion volume within 28 days of delivery and higher healthcare costs.

Two sensitivity analyses (IPTW and instrumental variable analyses) showed similar results to the main analysis (**Table 2** and **Table 3**). In the instrumental variable analysis, hospitals' preference for ATIII was highly associated with administration of ATIII (F statistic = 1,896).

Discussion

Main findings

In this nationwide observational study using propensity score and instrumental variable analyses, ATIII use among patients with DIC in obstetrics was not significantly associated with reduced in-hospital maternal mortality, but was significantly associated with a lower proportion of receiving hysterectomy during hospitalization.

Strengths and Limitations

This study has several limitations. First, we used a real-world database, and thus, the decisions to start ATIII were made by individual clinicians according to their own criteria. However, the decision to start ATIII in itself may be a marker of disease severity, and thus, the treatment allocation was not random, possibly leading to confounding by indication. We attempted to control for this confounding by propensity score matching analyses, but were unable to control for possible unmeasured variables. Second, we could not obtain data of bleeding amount related to the delivery. The bleeding amount can be associated with disease severity and transfusion volume, and this unmeasured confounder might have biased our

results. Therefore, we conducted the instrumental variable analyses and results of these analyses were similar to those of the main analyses. Third, because of data unavailability, we were not able to use any scoring systems for DIC. Fourth, some obstetricians may not hesitate to perform a hysterectomy to control massive bleeding, while others may control massive bleeding by transfusion and ATIII administration. Therefore, the results of the present study might be due to differences in strategies for obstetric haemorrhage.

Interpretation

The results of our study suggest that use of ATIII may not affect maternal mortality. In previous studies, the numbers of patients were too small to evaluate the effect of ATIII on the maternal mortality for DIC patients in obstetrics [6,7]. Although one of the strengths in this study was a large number of participants, it would be difficult to show the effect of ATIII on maternal death, given the very low maternal mortality rate in obstetric DIC patients.

In contrast, ATIII use was associated with a lower proportion of hysterectomy. There are two possible mechanisms. One is early recovery from catastrophe of coagulation function by ATIII supplementation. Antithrombin forms thrombin-antithrombin complexes and contributes to decreased thrombin formation[28]. Thus, healthy people with sufficient antithrombin can maintain balances between coagulation and anticoagulation. However, in patients with obstetric DIC, balance between coagulation and anticoagulation can be collapsed and substantial coagulation and anticoagulant factors are consumed[29]. Supplemental

ATIII may thus be effective to correct catastrophe of coagulation function. Second is the anti-inflammatory effect of ATIII. Experimental studies showed that ATIII directly reduced the emission of proinflammatory cytokines [30,31], which may work to protect organs and avoid hysterectomy.

Conclusion

Among patients with DIC in obstetrics, ATIII may not reduce maternal mortality but reduce hysterectomy during hospitalization. Further randomized studies are warranted to confirm our findings.

Disclosure of Interests

The authors declare that they have no conflicts of interest.

Contribution to Authorship

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by HO and DS. The first draft of the manuscript was written by YI and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Details of Ethics Approval

The Institutional Review Board of the University of Tokyo approved this study (approval number 3501-3; December 2017). Because all data were de-identified, the requirement for patient informed consent was waived.

References

1. Singh B, Hanson AC, Alhurani R, Wang S, Herasevich V, Cartin-Ceba R, et al. Trends in the incidence and outcomes of disseminated intravascular coagulation in critically ill patients (2004-2010): a population-based study. Chest. 2013;143(5):1235-42. doi:10.1378/chest.12-2112
2. Erez O, Mastrolia SA, Thachil J. Disseminated intravascular coagulation in pregnancy: insights in pathophysiology, diagnosis and management. Am J Obstet Gynecol. 2015;213(4):452-63. doi:10.1016/j.ajog.2015.03.054
3. Rattray DD, O'Connell CM, Baskett TF. Acute disseminated intravascular coagulation in obstetrics: A tertiary centre population review (1980 to 2009). J Obstet Gynaecol Canada. 2012;34(4):341-7. doi:10.1016/S1701-2163(16)35214-8
4. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. J Intensive Care. 2014;2(1):15. doi:10.1186/2052-0492-2-15
5. Minakami H, Maeda T, Fujii T, Hamada H, Iitsuka Y, Itakura A, et al. Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and

Japan Association of Obstetricians and Gynecologists (JAOG) 2014 edition. J Obstet Gynaecol Res. 2014;40(6):1469-99. doi:10.1111/jog.12419

6. Kawaguchi R, Matsumoto K, Akira S, Ishitani K, Iwasaku K, Ueda Y, et al. Guidelines for office gynecology in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2017 edition. J Obstet Gynaecol Res. 2019;45(4):766-86. doi:10.1111/jog.13831

7. Maki M, Terao T, Ikenoue T, Takemura T, Sekiba K, Shirakawa K, et al. Clinical evaluation of antithrombin III concentrate (BI 6.013) for disseminated intravascular coagulation in obstetrics. Well-controlled multicenter trial. Gynecol Obstet Invest. 1987;23(4):230-40. doi:10.1159/000298866

8. Antithrombin therapy for severe preeclampsia: results of a double-blind, randomized, placebo-controlled trial. BI51.017 Study Group - PubMed. [cited 2020 Aug 1]. Available from: https://pubmed.ncbi.nlm.nih.gov/11057854/

9. Sameshima H, Kodama Y, Ikenoue T, Kajiwara Y. Antithrombin improves fetal condition in women with severe pre-eclampsia before 32 weeks of gestation; a randomized, double-blind, placebo-controlled trial. J Obstet Gynaecol Res. 2008;34(1):34-9. doi:10.1111/j.1447-0756.2007.00677.x

10. Allingstrup M, Wetterslev J, Ravn FB, Møller AM, Afshari A. Antithrombin III for critically ill patients. Cochrane Database Syst Rev. 2016;2:CD005370. doi:10.1002/14651858.CD005370.pub3

11. Rabinovich A, Abdul-Kadir R, Thachil J, Iba T, Othman M, Erez O. DIC in obstetrics: Diagnostic score, highlights in management, and international registry-communication from the DIC and Women's Health SSCs of the International Society of Thrombosis and Haemostasis. J Thromb Haemost. 2019;17(9):1562-6. doi:10.1111/jth.14523

12. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015;12(10):e1001885. doi:10.1371/journal.pmed.1001885

13. Shigemi D, Aso S, Yasunaga H. Inappropriate use of ritodrine hydrochloride for threatened preterm birth in Japan: a retrospective cohort study using a national inpatient database. BMC Pregnancy Childbirth. 2019;19(1):204. doi:10.1186/s12884-019-2352-1

14. Shigemi D, Ishimaru M, Matsui H, Fushimi K, Yasunaga H. Suicide Attempts Among Pregnant and Postpartum Women in Japan: A Nationwide Retrospective Cohort Study. J Clin Psychiatry. 2020;81(3):19m12993. doi:10.4088/JCP.19m12993

15. Yasunaga H. Real World Data in Japan: Chapter II The Diagnosis Procedure Combination Database. Ann Clin Epidemiol. 2019;1(3):76-9. doi:10.37737/ace.1.3_76

16. Yamana H, Horiguchi H, Fushimi K, Yasunaga H. Comparison of Procedure-Based and Diagnosis-Based Identifications of Severe Sepsis and Disseminated Intravascular Coagulation in Administrative Data. J Epidemiol. 2016;26(10):530-7. doi:10.2188/jea.JE20150286

17. Shigematsu K, Nakano H, Watanabe Y. The eye response test alone is sufficient to predict stroke outcome--reintroduction of Japan Coma Scale: a cohort study. BMJ Open. 2013;3(4):e002736. doi:10.1136/bmjopen-2013-002736

18. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: A systematic analysis and implications. Lancet. 2012;379(9832):2162-72. doi:10.1016/S0140-6736(12)60820-4

19. Griswold ME, Localio AR, Mulrow C. Propensity score adjustment with multilevel data: setting your sites on decreasing selection bias. Ann Intern Med. 2010;152(6):393-5. doi:10.7326/0003-4819-152-6-201003160-00010

20. The bias due to incomplete matching - PubMed. [cited 2020 Aug 8]. Available from: https://pubmed.ncbi.nlm.nih.gov/4005368/.

21. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083-107. doi:10.1002/sim.3697

22. Leuven E, Sianesi B. psmatch2. [cited 2020 Aug 8]. Available from: https://www.ifs.org.uk/publications/2684.

23. Marginal modeling of nonnested multilevel data using standard software - PubMed. [cited 2020 Aug 8]. Available from: https://pubmed.ncbi.nlm.nih.gov/17121864/.

24. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol. 2008;168(6):656-64. doi:10.1093/aje/kwn164

25. Baiocchi M, Cheng J, Small DS. Instrumental variable methods for causal inference. Stat Med. 2014;33(13):2297-340. doi:10.1002/sim.6128

26. Garabedian LF, Chu P, Toh S, Zaslavsky AM, Soumerai SB. Potential bias of instrumental variable analyses for observational comparative effectiveness research. Ann Intern Med. 2014;161(2):131-8. doi:10.7326/M13-1887

27. Terza JV, Basu A, Rathouz PJ. Two-stage residual inclusion estimation: addressing endogeneity in health econometric modeling. J Health Econ. 2008;27(3):531-43. doi:10.1016/j.jhealeco.2007.09.009

28. Mammen EF. Antithrombin: its physiological importance and role in DIC. Semin Thromb Hemost. 1998;24(1):19-25. doi:10.1055/s-2007-995819

29. Kobayashi T, Terao T, Maki M, Ikenoue T. Diagnosis and management of acute obstetrical DIC. Semin Thromb Hemost. 2001;27(2):161-7. doi:10.1055/s-2001-14076

30. Fourrier F, Jourdain M, Tournoys A, Gosset P, Mangalaboyi J, Chopin C. Effects of a combined antithrombin III and protein C supplementation in porcine acute endotoxic shock. Shock. 1998;10(5):364-70. doi:10.1097/00024382-199811000-00010

31. Gray E, Thomas S, Mistry Y, Poole S. Inhibition of tissue factor and cytokine release. Haemostasis. 1996;26 Suppl 1:92-5. doi:10.1159/000217247

Figure captions

Figure 1. Patient flow chart

DIC, disseminated intravascular coagulation

Supplemental Figure S1. Distributions of propensity scores before matching

Supplemental Figure S2. Distributions of propensity scores after matching

Table 1. Outcomes in the unmatched cohort and the propensity score-matched cohort

Outcomes	Unmatched cohort		Propensity score-matched cohort			
	ATIII (n=4,329)	Control (n=5,511)	ATIII (n=3,290)	Control (n=3,290)	Difference (95% confidence interval)	P-value
In-hospital maternal mortality, n (%)	13 (0.3)	20 (0.4)	11 (0.3)	12 (0.4)	0.0 (-0.3 to 0.3)	0.83
Hysterectomy, n (%)	360 (8.3)	326 (5.9)	176 (5.3)	286 (8.7)	-2.9 (-4.2 to -1.6)	<0.001
Transcatheter arterial embolization, n (%)	316 (7.3)	236 (4.3)	172 (5.2)	188 (5.7)	-0.2 (-1.3 to 1.0)	0.75
Total transfusion volume, ml, mean (SD)	2317 (3105)	1277 (2374)	1814 (2785)	1862 (2589)	185 (30 to 341)	0.020
Length of hospital stay, days, mean (SD)	16.3 (17.0)	15.6 (18.0)	15.5 (17.3)	15.5 (17.8)	-0.4 (-1.4 to 0.7)	0.49
Hospitalization cost, USD, mean (SD)	14342 (9172)	11452 (9149)	13216 (8602)	12557 (9097)	914 (392 to 1435)	0.001

ATIII, antithrombin III; SD, standard deviation; USD, United States dollar

Table 2. Results of inverse probability of treatment weighting analyses

Outcomes	Difference (95% confidence interval)	P-value
In-hospital maternal mortality, n (%)	-0.1 (-0.3 to 1.0)	0.27
Hysterectomy, n (%)	-2.3 (-3.5 to -1.1)	<0.001
Transcatheter arterial embolization, n (%)	-0.3 (-1.2 to 0.7)	0.56
Total transfusion volume, ml, mean (SD)	-6 (-119 to 107)	0.92
Length of hospital stay, days, mean (SD)	0.6 (-0.2 to 1.3)	0.16
Hospitalization costs, USD, mean (SD)	977 (601 to 1352)	<0.001

SD, standard deviation; USD, United States dollar

Table 3. Results of instrumental variable analyses

Outcomes	Difference (95% confidence interval)	P-value
In-hospital maternal mortality, n (%)	0.2 (-0.3 to 0.7)	0.46

Hysterectomy, n (%)	-4.1 (-6.2 to -2.0)	<0.001
Transcatheter arterial embolization, n (%)	-0.9 (-2.8 to 1.0)	0.37
Total transfusion volume, ml, mean (SD)	68 (-112 to 248)	0.46
Length of hospital stay, days, mean (SD)	0.6 (-0.6 to 1.8)	0.34
Hospitalization costs, USD, mean (SD)	690 (102 to 1278)	0.021

SD, standard deviation; USD, United States dollar