staffing, improvement of professional staffing remains an important policy issue in Japan [17].

In the present study, we hypothesized that better staffing of physicians and nurses, even in the extremely low end observed in Japan, is independently associated with better postoperative early outcomes following cancer surgery, irrespective of hospital volume. To prove this hypothesis, we used a national inpatient database in Japan, and performed multivariate analyses to confirm the relation between physician/nurse staffing and operative outcomes, adjusting for hospital volume as well as patient characteristics. Regarding outcome measures, we used the "failure to rescue"—mortality among patients with postoperative complications—because how successfully hospitals rescue patients from surgical complications may be a sensitive indicator for evaluating quality of surgical care [18,19].

A better understanding of the relationship between professional staffing and outcomes may lead to health policy innovation for more efficient resource allocation to increase the benefit to cancer surgical patients. We discuss the implications of our results that could be useful for health policy decision makers in any country.

Methods

Data source

We used the Diagnosis Procedure Combination (DPC) database and the Survey of Medical Institutions data. The DPC is a case-mix patient classification system, launched in 2002 by the Ministry of Health, Labour and Welfare of Japan, and is linked with a lump-sum per-diem payment system. All the 82 university hospitals are obliged to adopt the DPC system, but participation by other community hospitals, private or public, is voluntary. Participating hospitals included 855 in 2008, covering approximately 2.9 million inpatients, or approximately 40% of all acute care inpatient hospitalizations in Japan. For this study, we used the data of 2007 and 2008 that included 5.85 million discharge cases.

The DPC system mandates participating hospitals to have electronic submission of claim bills and some clinical data of all the patients discharged between July 1 and December 31 each year, and a copy of the submitted data was collected for research purposes by the research group. The database includes the following: patients' age and sex; main diagnoses, pre-existing comorbidities, and post-admission complications coded by the International Classification of Disease and Related Health Problems, 10th Revision (ICD-10) codes; and surgical procedures coded by the Japanese original surgical coding system, which is comparable with the ICD, 9th Revision, Clinical Modification (ICD-9-CM) codes. The data also include discharge status [20,21]. In the DPC database, complications that occurred after admission are clearly differentiated from comorbidities that were already present at admission. To optimize the accuracy of the recorded diagnoses, physicians in charge are obliged to record the diagnoses with reference to medical charts.

The Survey of Medical Institutions is a census of hospitals in Japan, conducted every 3 years. The survey data contains structural information such as the number of beds, the number of full-time employed physicians, and the number of nurses in full-time equivalent. We linked the data to the DPC database using hospital identifiers as a linkage key. Because of the anonymous nature of the data, the requirement for informed consent was waived. Study approval was obtained from the Institutional Review Board in the University of Occupational and Environmental Health.

Patient selection

We identified patients who had undergone elective cancer surgery including (i) lung lobectomy for lung cancer (excluding pneumonectomy), (ii) esophagectomy for esophageal cancer, (iii) gastrectomy for gastric cancer, (iv) colorectal cancer surgery (including colectomy for colon cancer and anterior resection or abdominoperineal resection for rectal cancer), (v) hepatectomy for hepatic cancer, or (vi) pancreatectomy for pancreatic cancer. These six surgeries are major oncological surgeries, which generally have a higher operative mortality than other procedures in general and thoracic surgery [3-5]. Those who underwent two or more cancer surgeries during one hospitalization were excluded.

Preoperative comorbidities included diabetes mellitus (ICD 10 codes, E10-E14), hypertension (I10-I15), cardiac diseases (I20-I25, ischemic heart diseases; I30-I52, other forms of heart diseases), cerebrovascular disease (I60-I69), chronic lung diseases (J40-J47), liver cirrhosis (K74), and chronic renal failure (N18). Based on Quan's protocol [22], each ICD-10 code of comorbidity was converted into a score, and was summed up for each patient to calculate a Charlson Comorbidity Index (CCI).

Professional staffing and hospital volume

In Japan, there are two types of nursing licenses, including a registered nurse and practical nurse, but there is no mid-level provider's license, such as a physician assistant or nurse practitioner. Using the Survey of Medical Institutions data, we estimated the number of physicians per 100 beds (physician-to-bed ratio, PBR) and the number of nurses per 100 beds (nurse-to-bed ratio, NBR) for each hospital. Our data included the number of all the full-time employed physicians, including residents and attending physicians. The number of nurses included the full-time equivalent numbers of all the licensed nurses, but did not include the number of non-licensed providers, such as nurse aids. PBR and NBR are considered to be correlated and the problem of multicollinearity could occur if these two continuous variables were included in a multivariate model. To avoid this problem, PBR and NBR were combined into a single categorical variable including the following four groups: (i) Group A (*below* median PBR and *below* median NBR), (ii) Group B (*below* median PBR and *above* median NBR), (iii) Group C (*above* median PBR and *below* median NBR), and (iv) Group D (*above* median PBR and *above* median NBR).

Hospital volume was defined as the number of each surgical procedure performed annually at each hospital, and was categorized into tertiles (low-, medium-, and high-volume), with approximately equal numbers of patients in each group.

Outcomes

The outcome measurements included postoperative complications, inhospital mortality and failure to rescue (FTR). Postoperative complications included surgical site infection (T793, T814), peritonitis (K65), sepsis (A40, A41), respiratory complications (pneumonia [J12-J18], postprocedural respiratory disorders [J95] or respiratory failure [J96]), pulmonary embolism (I26), cardiac events (acute coronary events [I21-I24] or heart failure [I50]), stroke (cerebral infarction or hemorrhage [I60-I64]), and acute renal failure (N17).

FTR was defined as the proportion of inhospital death cases among those who had experienced a postoperative complication [18,19]. Therefore, FTR identifies whether the patient is successfully rescued from the complication. An underlying assumption of the FTR theory is that complications reflect patient severity, and the rescue of patients with complications depends on quick identification and aggressive treatment of complications [18,19]. There is ongoing controversy on how FTR should be calculated, because previous FTR studies have used different sets of complications. Silber's original FTR used a comprehensive set of complications, but several modified FTRs have used limited definitions. For example, a "nurse sensitive" definition only included six complications (pneumonia, shock, gastrointestinal bleeding, cardiac arrest, sepsis and deep venous thrombosis) [18]. Our original set of complications comprised common complications in general and thoracic surgery. We excluded rare complications in general and thoracic surgery, which were involved in Silber's definition, such as gangrene, amputation, decubitus ulcers, orthopedic complications and compartment syndromes.

Data analyses

Patient characteristics were summarized by four categories of physician/nurse staffing. We performed univariate comparisons of explanatory variables using a χ^2 test or an analysis of variance as appropriate. Inhospital mortality, postoperative complication rates, and FTRs were compared across physician/nurse staffing categories. Multivariate analyses were then performed to model the concurrent effects of potentially influential factors (age, sex, CCI, hospital volume, and physician/nurse staffing) on the outcomes using multi-level logistic regression analyses. Data were structured hierarchically into two levels: hospitals and patients. We accounted for clustering of outcomes within hospitals using mixed effects models. This approach is commonly used instead of basic regression approaches because outcomes of patients in the same hospital may be correlated, thus violating independence assumptions made by traditional regression procedures [23,24]. The threshold for significance was a p value <0.05. All statistical analyses were conducted using SAS ver. 9.2 (SAS Institute, Cary, NC, US).

Results

A total of 131,394 eligible patients were identified. Hospital volume categories (low, medium and high) were determined to be ≤51, 52–106, and ≥107 per year for lung lobectomy (n = 21,639); ≤9, 10–26, and ≥27 for esophagectomy (n = 3,917); ≤47, 48–93, and ≥94 for gastrectomy (n = 35,978); ≤66, 67–119, and ≥120 for colorectal surgery (n = 51,878); ≤22, 23–58, and ≥59 for hepatectomy (n = 10,921); and ≤13, 14–29, and ≥30 for pancreatectomy (n = 7,061).

Table 1 shows that the proportions of patients in the low-, medium- and high-volume groups were almost equal (33.6%, 33.0% and 33.4%, respectively). Lower volume hospitals were more likely to have a lower PBR and NBR. The median PBR was 19.7 (interquartile range, 14.6–27.3) per 100 beds and the median NBR was 77.0 (68.2–86.1) per 100 beds. These numbers were used as cutoff points to categorize physician/nurse staffing into four categories. The mean age was highest in Group A. Patients in Groups C and D had higher rates of several comorbidities. Consequently, CCI was higher among patients in Groups C and D than in those in Groups A and B.

Table 1 Patient characteristics

	Total	Group A: low PBR, low NBR	Group B: low PBR, high NBR	Group C: high PBR, low NBR	Group D: high PBR, high NBR	p
Number of patients	131,394	44,758	21,705	22,837	42,094	
Age (average±SD, years)	67.8±11.5	69.0±11.0	68.4±11.2	66.5±11.8	66.8±11.7	<0.001
Sex (males,%)	62.8	62.4	62.1	62.9	63.5	0.001
Preoperative comorbidities (%)						
Hypertension	17.5	16.2	15.9	19.2	18.7	<0.001
Diabetes mellitus	13.6	13.1	12.6	14.4	14.3	<0.001
Cardiovascular diseases	94.0	94.3	94.7	94.0	93.1	<0.001
Chronic lung diseases	4.9	4.1	3.9	5.2	6.1	<0.001
Liver cirrhosis	1.6	1.2	1.3	2.0	1.8	<0.001
Chronic renal failure	0.70	0.71	0.58	0.80	0.71	0.055
Cerebrovascular diseases	0.48	0.55	0.43	0.43	0.47	0.061
Charlson Comorbidity Index (%)						
0-2	61.2	64.3	63.4	59.2	57.8	<0.001
3-5	26.6	24.2	24.6	27.9	29.5	
6-	12.2	11.5	12.0	12.9	12.7	
Hospital volume						
Low	33.6%	58.2%	37.0%	16.3%	15.1%	<0.001
Medium	33.0%	27.0%	37.4%	35.1%	36.0%	
High	33.4%	14.8%	25.6%	48.6%	49.0%	

PBR, physician-to bed ratio (low, <19.7 physicians per 100 beds; high, ≥19.7); NBR, nurse-to-bed ratio (low, <77.0 nurses per 100 beds; high, ≥77.0)

Overall, postoperative complications were observed among 3.8% of patients for surgical site infection, 3.1% for sepsis, 3.1% for respiratory complications, 2.6% for peritonitis, 1.9% for cardiac events, 1.0% for acute renal failure, 0.86% for stroke, and 0.20% for pulmonary embolism. In total, 15.2% of all patients had at least one complication. Overall inhospital mortality was 1.8% and the FTR rate was 11.9%.

Figure 1 illustrates the rates of inhospital mortality, postoperative complications, and FTR by the four categories of physician/nurse staffing. Patients with a higher PBR showed lower morality, complication rates, and FTR rates.

Figure 1 Relationship between physician/nurse staffing and cancer surgical outcomes.
PBR, physician-to bed ratio (low, <19.7 physicians per 100 beds; high, ≥19.7); NBR, nurse-to-bed ratio (low, <77.0 nurses per 100 beds; high, ≥77.0)

Table 2 shows the results of logistic regression analysis for FTR. Even after adjustment for patients' conditions and hospital volume, FTR rates were significantly different between Groups A and D (odds ratio, 0.76 [95% confidence interval, 0.63–0.90]; p = 0.002), but not between Groups A and B (0.94 [0.78–1.13]; p = 0.505) or between Groups A and C (0.91 [0.73–1.13]; p = 0.379). Group D showed a relatively lower FTR rate than Group C, but this was not significant (0.83 [0.66–1.05]; p = 0.128).

Table 2 Logistic regression analysis for failure to rescue

	odds ratio	95% confidence interval			p
Age (10-year age increase)	1.50	1.43	-	1.57	<0.001
Sex (Female vs. male)	0.79	0.72	-	0.88	<0.001
Charlson Comorbidity Index	1.03	1.01	-	1.05	0.002
Hospital volume					
Low	1.00				
Medium	0.89	0.79	-	1.01	0.077
High	0.62	0.53	-	0.73	<0.001
Physician and nurse staffing					
Group A (low PBR, low NBR)	1.00				
Group B (low PBR, high NBR)	0.94	0.78	-	1.13	0.505
Group C (high PBR, low NBR)	0.91	0.73	-	1.13	0.379
Group D (high PBR, high NBR)	0.76	0.63	-	0.90	0.002

PBR, physician-to bed ratio (low, <19.7 physicians per 100 beds; high, ≥19.7); NBR, nurse-to-bed ratio (low, <77.0 nurses per 100 beds; high, ≥77.0)

When we conducted a similar analysis on inhospital mortality, Group D showed a significantly lower mortality compared with Group A (0.82 [0.71–0.95]; $p = 0.009$), while postoperative complication rates were not different among the groups (1.01 [0.90–1.13]; $p = 0.918$ for Group D vs. Group A).

Table 3 shows the results of post-hoc analyses of FTR rates in the four physician/nurse staffing groups by the types of surgery. FTR was significantly related to physician/nurse staffing in lung lobectomy, esophagectomy, gastrectomy, colorectal surgery, and pancreatectomy.

Table 3 Failure to rescue in the four physician/nurse staffing groups for each surgery

				FTR (%)					
	N	Inhospital mortality (%)	Postoperative complications(%)	Total	Group A: low PBR, low NBR	Group B: low PBR, high NBR	Group C: high PBR, low NBR	Group D: high PBR, high NBR	p
Lung lobectomy	21,639	0.92	10.2	9.0	15.3	12.9	7.9	5.9	<0.001
Esophagectomy	3,917	4.14	26.3	15.7	21.8	18.7	10.9	13.8	0.001
Gastrectomy	35,978	1.43	13.1	10.9	13.8	10.9	10.7	7.3	<0.001
Colorectal surgery	51,878	2.06	15.8	13.0	14.2	14.3	12.2	10.6	<0.001
Hepatectomy	10,921	2.49	17.4	14.3	17.3	14.3	11.8	14.0	0.061
Pancreatectomy	7,061	2.48	27.8	8.9	12.5	9.0	7.6	6.6	0.001

PBR, physician-to bed ratio (low, <19.7 physicians per 100 beds; high, ≥19.7); NBR, nurse-to-bed ratio (low, <77.0 nurses per 100 beds; high, ≥77.0)

Discussion

The present study examined the association between cancer surgical outcomes and physician/nurse staffing in relation to hospital volume, using a nationwide administrative database. After adjustment for hospital volume, the FTR rate in the high-PBR-high-NBR group was significantly lower than that in the low-PBR-low-NBR group.

The inverse relationship between better professional staffing and hospital mortality in the present study is consistent with findings in previous studies [10-16]. Few studies have taken into account both professional staffing and hospital volume to evaluate surgical outcomes [13]. Our study revealed that better physician and nurse staffing were independently associated with a lower FTR in general and thoracic cancer surgery, irrespective of hospital volume.

Previously reported volume-outcome relationships may be partly explained by professional staffing. In this context, recent debate on hospital volume as an indicator of quality of care needs careful reconsideration in terms of allocation of a suitable number of qualified physicians and nurses as a structural basis for quality of care.

Volume-outcome relationships have mainly been explained by the "practice-makes-perfect" theory, and case accumulation has been enhanced based on this theory. In fact, growing interest in these relationships has bolstered relevant policy changes, including migration of cancer surgery to high-volume hospitals [25,26]. However, there is ongoing controversy regarding such policy; if patients are directed to higher volume institutions, the increased volume will overwhelm the resources of such institutions, thereby rendering these procedures even less accessible [27].

In accordance with our results, case accumulation should be accompanied by a suitable increase in medical staff. Concentration of physicians and nurses is considered necessary for hospitals regardless of size and case volume.

Efficient resource allocation for improving cancer surgical management is a common healthcare policy issue in any advanced nation. Japan is facing a super-aged society and weakened economy, which threatens the sustainability of the publish health insurance system. Physician shortage is an unsolved problem in Japan; the number of surgeons (including general and thoracic surgeons) is gradually decreasing from 28,425 in 1996 to 26,995 in 2008 [28]. Geographically, 2,522 surgical centers are distributed to an inhabited area of 121,000 km^2 in Japan (2.1 centers/100 km^2), as of 2008. A total of 44,010 cancer surgeries were performed in September 2008, and the mean number of cancer surgeries was calculated to be only 17.5 per hospital per month [2]. Therefore, healthcare resource allocation regarding cancer surgery in Japan is characterized as a large number of small hospitals with low case volume.

Based on our results, we speculate that consolidation of surgical centers and simultaneous reallocation of human resources could lead to better outcomes after cancer surgery, particularly in general and thoracic surgery. Migration of medical professions to high volume hospitals is considered essential. This approach should be implemented through the shutdown of low-volume surgical units, even if it will result in increased travel distance for cancer patients.

The Japanese Association of Thoracic Surgery has already initiated an attempt for regionalization of cardiac surgery by restricting its certification criteria for training institutions in 2005. This restriction has required several certified centers in the same regions to consolidate, resulting in an improvement in outcome and a slight decrease in accessibility to cardiac surgeries [29]. Unlike cardiac surgery, most cancer surgeries are elective; therefore, increased patient travel distance for cancer surgery could have less negative effect on health outcomes. Therefore, consolidation of cancer surgical centers may lead to improvement of outcomes that could compensate for a decreased accessibility to surgical care.

Several limitations should be acknowledged. First, we used the number of physicians per bed as an indicator for intensity of physician services, but further knowledge of individual physician characteristics, such as surgeon volume and training status (residents/fellows/board-certified physicians), and nurse characteristics, such as nurse education and the nurse work environment [14] could refine our approach. Second, other important outcomes including recurrence, long-term survival, and subsequent health resource consumption were not investigated in the present study because of data availability. Third, hospitals in the DPC database are not representative of all hospitals in Japan. Specifically, a low participation rate of very small hospitals in the DPC system skews the population being evaluated, and this might have resulted in underestimation of overall mortality. Fourth, the DPC database is an administrative claim database, and recorded diagnoses in such databases are less well validated than those in planned prospective cohorts or registries. Postoperative complications might have been underestimated due to underreporting. Because the DPC database includes only inpatient data, 30-day mortality was not available. Lastly, due to a novel author-derived definition of FTR, results may not compare directly with previously-published work.

Conclusion

Well-staffed hospitals confer a benefit for patients in terms of reduced FTR. Our results suggest that consolidation of surgical centers together with a concentrated allocation of medical professionals may improve the quality of surgical care for cancer.

Competing interests

The authors have no competing interests.

Authors' contributions

HY and HH1 conceived the study concept and study design. HY and HH2 performed compilation and synthesis of the data. HY and HM carried out statistical analyses. SM supervised the DPC research project. All authors participated in interpretation of the results and writing of the report, and approved the final version.

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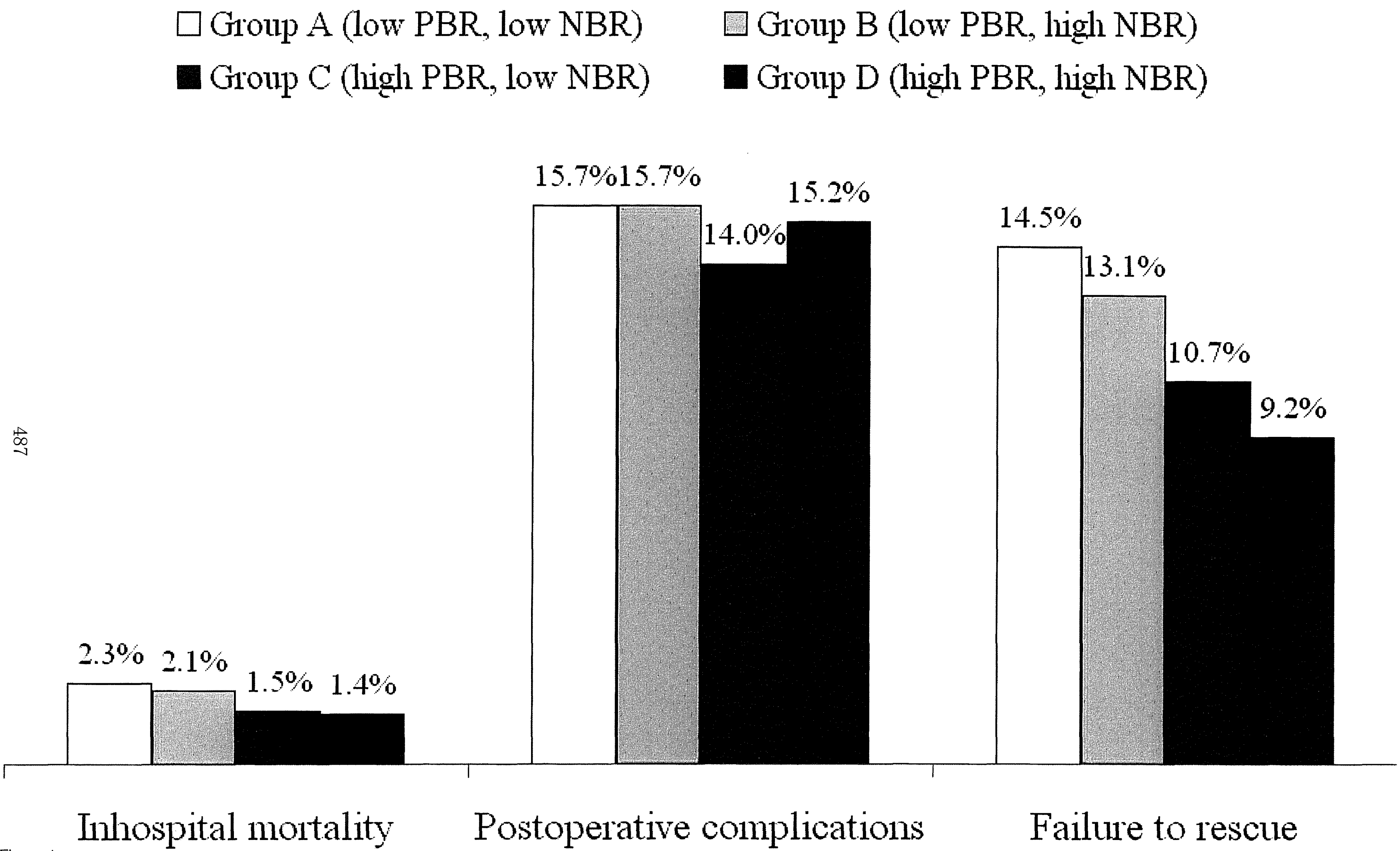

Group A (low PBR, low NBR)
Group B (low PBR, high NBR)
Group C (high PBR, low NBR)
Group D (high PBR, high NBR)
2.3%
2.1%
1.5%
1.4%
15.7%
15.7%
14.0%
15.2%
14.5%
13.1%
10.7%
9.2%
Inhospital mortality
Postoperative complications
Failure to rescue

Figure 1

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ORIGINAL ARTICLE

Risk-adjusted and case-matched comparative study between antegrade and retrograde cerebral perfusion during aortic arch surgery: based on the Japan Adult Cardiovascular Surgery Database

The Japan Cardiovascular Surgery Database Organization

Akihiko Usui, MD, PhD · Hiroaki Miyata, PhD
Yuichi Ueda, MD · Noboru Motomura, MD, PhD
Shinichi Takamoto, MD

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Abstract
Purpose. Antegrade cerebral perfusion (ACP) and retrograde cerebral perfusion (RCP) are two major types of brain protection for aortic arch surgery. A large-scale clinical study of RCP and ACP is important to clarify the respective characteristics for major adverse events. We conducted a comparative study to evaluate up-to-date clinical outcomes in Japan based on the Japan Adult Cardiovascular Surgery Database (JACVSD).
Methods. The subjects were confined to cases undergone electively with ACP or RCP for nondissection aneurysms in the ascending aorta and aortic arch between 2005 and 2008 from 13 467 aortic surgeries. There were 2209 ACP cases and 583 RCP cases. A risk-adjusted comparison based on 30-day mortality, operative mortality, and major morbidity was assessed by a multivariable logistic regression analysis. A conditional logistic regression analysis was also conducted in 499 propensity matched-pairs with ACP and RCP.
Results. A risk-adjusted analysis showed no significant differences between the ACP and RCP groups regarding 30-day mortality (3.5% vs. 2.6%), operative mortality (5.3% vs. 4.1%), or stroke (6.8% vs. 3.1%). Propensity-matched pairs also revealed no significant differences between ACP and RCP regarding 30-day mortality (3.4% vs. 2.4%), operative mortality (3.8% vs. 3.4%), or stroke rate (5.0% vs. 3.0%); however, RCP resulted in a significantly higher rate of transient neurological dysfunction (3.0% vs. 5.8%) and need for dialysis (1.6% vs. 4.2%).
Conclusion. Both RCP and ACP provide comparable clinical outcomes regarding both the mortality and stroke rates. RCP resulted in a higher incidence only in patients demonstrating transient neurological dysfunction and the need for dialysis.

Key words Brain protection · Aortic surgery · Stroke · Mortality · Database

A. Usui (✉) · H. Miyata · Y. Ueda · N. Motomura · S. Takamoto
Department of Cardiac Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai, Showa-ku, Nagoya, Aichi 466-8550, Japan
Tel. +81-52-744-2376; Fax +81-52-744-2383
e-mail: ausui@med.nagoya-u.ac.jp

Introduction

The optimal type of brain protection remains controversial for aortic arch surgery. There are two major brain protection methods that are generally utilized. One is antegrade cerebral perfusion (ACP), which maintains cerebral circulation by a low-flow volume of cold blood perfusion via two or three arch branches with separate cannulas under moderate or deep hypothermia. The other is retrograde cerebral perfusion (RCP), which is an alternate method of brain protection during deep hypothermic circulation arrest by perfusing a small volume of blood flow via the superior vena cava retrogradely.[1,2] Both ACP and RCP have advantages and drawbacks; therefore, surgeons should select the most appropriate modality according to the respective characteristics of these methods.

There have so far been a few prospective randomized clinical trials and numerous retrospective clinical studies to compare ACP and RCP.[3–5] They indicated either no obvious differences between the methods or a slight superiority of ACP; however, these data have not been updated, and their evidence level remains weak. Large-scale randomized prospective clinical studies are a reliable method to clarify the superiority of each type of brain protection, but a comparative clinical study utilizing a large database is also important to achieve a higher evidence level and to obtain up-to-date clinical outcomes. We used the Japan Adult Cardiovascular Surgery Database (JACVSD), which currently contains the clinical data from nearly half of all hospitals at Japanese institutions performing cardiovascular surgery. It is similar to The Society of Thoracic Surgeons National Adults Cardiac Database, and we thus conducted a large-scale comparative clinical study based on recent cases.[6] Although there were certain limitations in interpreting and evaluating results, the present study is considered to be the first clinical comparison of RCP and ACP using a large-volume database. This attempt should provide updated clinical outcomes, certain helpful information regarding the recent selection criteria of brain protection for aortic arch surgery, and thereby improve the quality control in the treatment of such cases.

Methods

Study population

The JACVSD started in 2000 to estimate the surgical outcomes after cardiovascular procedures in many centers throughout Japan. The database currently captures clinical information from nearly half of the hospitals of all Japanese units performing cardiovascular surgery. The data collection form has a total of 255 variables (definitions are available online at http://www.jacvsd.umin.jp), and they are almost identical to those in the STS National Database (definitions are available online at http://sts.org). JACVSD developed a software program for a web-based data collection system, and through this system the data manager of each participating hospital was responsible for forwarding their data electronically to the central office. Although participation in the JACVSD is voluntary, the completion of such data is normally given high priority. The accuracy of the submitted data was maintained by a data audit, which was achieved by random, monthly visits by administrative office members to a participating hospital when the data were checked against clinical records. The validity of JACVSD data has been further confirmed by an independent comparison of the volume of cardiac surgery at a particular hospital entered in the JACVSD versus that reported to the Japanese Association for Thoracic Surgery Registry.[7]

We examined 13 467 thoracic aortic surgery procedures between January 1, 2005 and December 31, 2008. Clinical outcomes of thoracic aortic surgery are affected by various factors, especially aneurysm type, range of replacement, and emergency status. We therefore excluded patients with a ruptured aneurysm, Stanford A/B dissection, surgical status of urgent/emergent/salvage, and range of replacement descending/thoracoabdominal/abdominal. We also excluded procedures performed at low-volume centers, defined as those in which the average annual thoracic aortic surgery volume was fewer than five procedures. The subjects analyzed in the present study were confined to those with nondissection aneurysms of the ascending aorta and aortic arch who underwent aortic arch surgery electively via a median sternotomy in large-volume centers. The subjects comprised 4642 cases; and another 3075 patients were treated while under brain protection. There were 2209 patients with ACP, 583 with RCP, 266 with hypothermic circulatory arrest (HCA), and 17 who were subjected to other methods.

The JACVSD has no exclusion criteria regarding patient selection. All adult patients, including those in emergency situations, are therefore considered to be candidates for JACVSD. In addition, any JACVSD records that had been obtained without the patients' informed consent were excluded from this analysis. Records with missing (or out of range) age, sex, or 30-day status were also excluded. With the exception of the body surface area, all missing or out-of-range values were imputed using the sex-specific median value; these cases comprised only 3.1% of all cases. After this data cleaning, the population for this risk model analyses resulted in 2792 instances of thoracic aortic surgery (2209 ACP, 583 RCP) from 143 participating sites throughout Japan (Fig. 1).

Endpoints

The primary outcomes measured from the JACVSD were the 30-day mortality rate and the operative mortality rate. The 30-day mortality included death within 30 days of operation even though the patient was discharged from the hospital within 30 days of operation. Operative mortality meant that any patient who died within the index hospitalization, regardless of the length of hospital stay, and including any patient who died after being

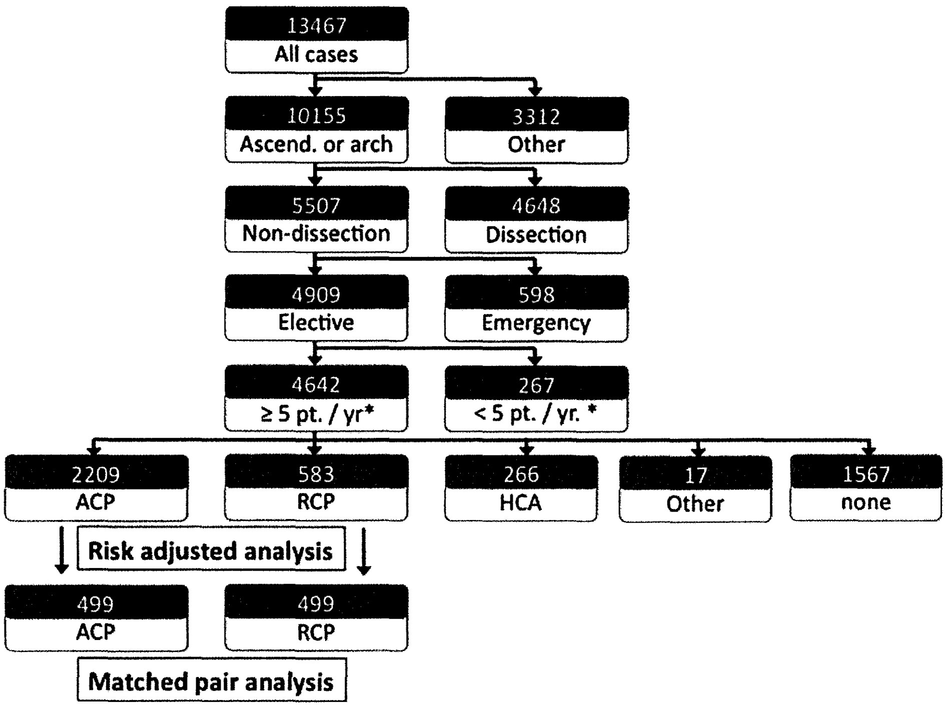

Fig. 1 Patient selection. *Ascend.*, ascending; *ACP*, antegrade cerebral perfusion; *RCP*, retrograde cerebral perfusion; *HCA*, hypothermic circulatory arrest. *Average annual thoracic aortic surgery volume

discharged from hospital up to 30 days from the date of the operation. Hospital-to-hospital transfer was not considered discharge.[8]

In a previous study,[9] major morbidity was defined as the following five postoperative in-hospital complications: stroke that was a new neurological dysfunction and continuing for >72 h; reoperation for any reason; need for mechanical ventilation for more than 24 h after surgery; renal failure requiring dialysis; a deep sternal wound infection. In this study we also use transient neurological dysfunction, continuous coma over 24 h, and paraparesis/paraplegia as neurological complications of thoracic aortic surgery. Transient neurological dysfunction included any neurological dysfunction that recovered completely within 72 h, including transient ischemic attack, reversible ischemic neurological deficit, or delirium, regardless of the radiological findings.

Statistical analysis

We compared the baseline demographics for patients who underwent RCP surgery with those who had ACP surgery. Differences between the two types of brain protection were determined using the χ^2 test for categorical variables and the *t*-test for continuous variables. The trends in RCP surgery over time were determined using logistic regression analysis, whereby the independent variable was the type of brain protection and the dependent variable was the month of surgery.

The unadjusted effects of RCP at 30 days and the operative mortality and five major postoperative morbidities were assessed using logistic regression analysis. For risk-adjusted comparisons, a multivariable logistic regression model was used to determine the effect of RCP. The preoperative risk factors described in Table 1 (hospital thoracic aortic surgery volume, time trends, and range of replacement), which were shown as predictors for mortality and morbidity in JACVSD thoracic aorta risk models,[6] were listed as dependent variables, and mortality or morbidity was established as an independent variable according to a logistic regression analysis.

The second method of adjustment involved matching patients with similar probability of undergoing RCP surgery. Because the patients were not randomly assigned to receive RCP, we used propensity score matching to adjust for differences in baseline characteristics.[10] We performed a one-to-one matched analysis without replacement on the basis of the estimated propensity score, calculated from 37 variables mainly collected from the preoperative and operative factors of each patient (Table 1). The log odds of the probability that a patient received a RCP (the "logit") was modeled as a function of the confounders that we identified and included in our data set. Using the estimated logits, we first randomly selected a patient in the group undergoing RCP and then matched that patient with a patient in the group receiving ACP with the closest estimated logit value. Patients

Table 1 Variables for propensity matching analysis

Variable	*P*	Odds ratio	95% CI	
			Low	High
Time trend	0.1042	0.9328	0.8577	1.0145
Age	0.0107	0.9037	0.8362	0.9767
Sex	0.8772	1.0249	0.7506	1.3993
Smoking	0.0410	0.7867	0.6250	0.9903
Diabetes	0.0578	1.3900	0.9891	1.9533
Renal failure	0.1832	0.7178	0.4406	1.1696
Dialysis	0.3066	0.6123	0.2391	1.5681
Hyperlipidemia	0.7550	1.0372	0.8247	1.3044
Hypertension	0.0677	0.7945	0.6207	1.0169
Cerebrovascular accident	0.1824	0.3422	0.0707	1.6552
Endocarditis	0.2709	2.0373	0.5739	7.2324
COPD (moderate, severe)	0.0249	1.7574	1.0737	2.8765
extracardiac disease, peripheral	0.0127	1.4980	1.0900	2.0588
Neurological dysfunction	0.4434	0.7743	0.4025	1.4893
Marfan syndrome	0.0443	0.3841	0.1511	0.9759
Aortic stenting	0.2459	0.3593	0.0638	2.0246
Myocardial infarction	0.1315	1.5167	0.8827	2.6059
Congestive heart failure	0.2019	1.3272	0.8593	2.0499
Unstable angina	0.9949	1.0038	0.3107	3.2431
Shock	0.9996	0.0000	0.0000	–
Cardiopulmonary resuscitation	0.9991	0.0000	0.0000	–
Arrhythmia	0.6028	0.9049	0.6212	1.3184
NYHA class IV	0.4337	0.4814	0.0772	3.0016
Preoperative inotropic agents	0.0073	3.9837	1.4512	10.9356
Triple-vessel disease	0.0339	1.6946	1.0409	2.7588
Left main disease	0.2663	0.6874	0.3549	1.3312
LV function (poor)	0.9619	0.9740	0.3308	2.8681
Aortic valve stenosis	0.0003	1.8764	1.3362	2.6352
Tricuspid valve insufficiency	0.6819	0.5749	0.0407	8.1145
Reoperation	0.2803	1.2422	0.8379	1.8414
CABG surgery	0.2321	1.1993	0.8902	1.6159
Valve surgery	0.0110	1.5117	1.0992	2.0790
BMI >30 kg/m^2	0.2352	0.6733	0.3504	1.2937
BSA >1.5	0.8635	1.0069	0.9310	1.0890
Range of replacement				
Root	0.4516	1.1542	0.7945	1.6766
Ascending	0.6171	1.0643	0.8336	1.3590
Arch	0.0000	0.2100	0.1627	0.2710

CI, confidence interval: COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; LV, left ventricular; CABG, coronary bypass graft; BMI, body mass index; BSA, body surface area

Table 2 Baseline patient characteristics

Variable	Antegrade cerebral perfusion		Retrograde cerebral perfusion		*P*
	No.	%	No.	%	
Patients	2209		583		
Sex (male)	1642	74	393	67	0.001
Smoking	1229	56	254	44	0.000
BMI >30 kg/m^2	78	4	14	2	0.193
Diabetes	317	14	84	14	1.000
Renal failure	187	8	30	5	0.009
Dialysis	43	2	8	1	0.392
Cerebrovascular accident	342	15	64	11	0.007
COPD (moderate, severe)	100	5	25	4	0.824
Extracardiac disease, peripheral	285	13	67	11	0.364
Neurological dysfunction	76	3	13	2	0.147
Myocardial infarction	75	3	26	4	0.261
Congestive heart failure	83	4	60	10	0.000
Arrhythmia	175	8	59	10	0.093
NYHA class IV	9	0	2	0	1.000
Preoperative inotropic agents	11	0	11	2	0.002
Left main disease	71	3	17	3	0.791
LV function (bad)	14	1	7	1	0.176
Reoperation	146	7	49	8	0.143
CABG surgery	404	18	109	19	0.857
Range of replacement					
root	140	6	99	17	0.000
Ascending	854	39	358	61	0.000
Arch	1843	83	237	41	0.000
Age (years), mean (SD)	70.4 (9.9)		66.9 (11.4)		0.000
BSA, mean (SD)	1.63 (0.18)		1.62 (0.18)		0.100

in the group undergoing RCP who had an estimated logit within 0.6 SD of the selected patients in the group receiving ACP were eligible for matching. We selected 0.6 SD because this value has been shown to eliminate approximately 90% of the bias in observed confounders[11] (C-statistic of the propensity model is 0.778 ± 0.011). Differences in clinical variables were tested using the χ^2 test for categorical variables and the *t*-test for continuous variables. A conditional logistic regression analysis was used to determine the overall effect of RCP surgery in these matched-pairs groups.

We also examined the effect of RCP on prespecified high-risk subgroups, including elderly patients (≥65 and <65 years old), range of replacement (ascending, arch), and operating time including the cross-clamp time and perfusion time.

Results

Patient characteristics

There were 2209 patients who underwent ACP and 583 patients who had RCP. Patient characteristics of the two groups are shown in Table 2. The RCP group showed a

Table 3 Risk-adjusted analysis

Parameter	Antegrade cerebral perfusion		Retrograde cerebral perfusion		Odds ratio (95% CI)	*P*
Patients	No. 2209	%	No. 583	%		
30-day mortality	77	3.5	15	2.6	0.63 (0.25–1.58)	0.324
Operative mortality	118	5.3	24	4.1	0.74 (0.37–1.49)	0.401
Morbidity						
Stroke	151	6.8	18	3.1	0.61 (0.29–1.28)	0.189
Transient	100	4.5	29	5.0	1.45 (0.91–2.32)	0.123
Continuous coma ≥24 h	62	2.8	7	1.2	0.99 (0.99–1.00)	0.563
Paraparesis/paraplegia	58	2.6	16	2.7	0.96 (0.41–2.28)	0.934
Prolonged ventilation	404	18.3	83	14.2	1.00 (0.67–1.50)	0.996
Reoperation for any reason	204	9.2	45	7.7	0.98 (0.59–1.65)	0.948
Renal failure dialysis required	74	3.3	26	4.5	2.51 (1.04–6.03)	0.040
Deep sternal infection	45	2.0	16	2.7	1.12 (0.39–3.24)	0.837
ICU stay ≥8 days	323	14.6	68	11.7	1.03 (0.99–1.09)	0.838

ICU, intensive care unit

significant lower male ratio, smoking rate, renal failure rate, and cerebrovascular accident rate compared to the ACP group. On the other hand, the RCP group was younger and showed a higher rate of congestive heart failure and the use of preoperative inotropic agents than did the ACP group. Replacement in the RCP group occurred at a higher frequency in the aortic root and ascending aorta than in ACP group and at a lower frequency in the aortic arch.

Risk-adjusted analysis

The 30-day and operative mortality rates were 3.5% and 5.3%, respectively, for ACP patients and 2.6% and 4.1%, respectively, for RCP patients; no significant differences were observed between the groups according to a risk-adjusted analysis. The stroke rate was 6.8% in the ACP group and 3.1% in the RCP group. The RCP group had a rather lower stroke rate, but the difference was not significant. The rates of prolonged ventilation, reoperation, deep sternal infection, and paraparesis/paraplegia also showed no significant differences between the groups. Only the rate of renal failure that required dialysis was higher in the RCP group (4.5%) than in the ACP group (3.3%) with significance ($P = 0.04$). (Table 3).

Propensity-matched pairs

Based on the above results, we evaluated 499 ACP patients and 499 RCP patients using case-matching with the propensity score. There were no significant differences in the various preoperative factors even regarding the range of replacement (Table 4). There were no significant differences between the two groups regarding

Table 4 Patient characteristics by propensity-matched pairs

Variable	Antegrade cerebral perfusion		Retrograde cerebral perfusion		*P*
Patients	No. 499	%	No. 499	%	
Sex (male)	333	67	334	67	1.000
Smoking	228	46	219	44	0.611
BMI >30 kg/m^2	11	2	13	3	0.837
Diabetes	73	15	68	14	0.716
Renal failure	24	5	27	5	0.774
Dialysis	6	1	7	1	1.000
Cerebrovascular accident	57	11	57	11	1.000
COPD (moderate, severe)	25	5	22	4	0.765
Extracardiac disease peripheral	70	14	62	12	0.513
Neurological dysfunction	12	2	13	3	1.000
Myocardial infarction	23	5	22	4	1.000
Congestive heart failure	45	9	41	8	0.735
Arrhythmia	51	10	48	10	0.832
NYHA class IV	0	0	1	0	1.000
Preoperative inotropic agents	7	1	4	1	0.547
Left main disease	11	2	15	3	0.522
LV function (bad)	4	1	5	1	1.000
Reoperation	41	8	38	8	0.815
CABG surgery	89	18	89	18	1.000
Range of replacement					
Root	75	15	73	15	0.929
Ascending	285	57	286	57	1.000
Arch	235	47	235	47	1.000
Age (years), mean (SD)	67.8 (12.2)		67.5 (11.3)		0.723
BSA, mean (SD)	1.61 (0.19)		1.62 (0.18)		0.383

Table 5 Outcomes of propensity-matched analysis

Variable	Antegrade cerebral perfusion		Retrograde cerebral perfusion		Odds ratio (95%CI)	*P*
Patients	No. 499	%	No. 499	%		
30-Day mortality	17	3.4	12	2.4	0.75 (0.35–1.59)	0.454
Operative mortality	19	3.8	17	3.4	0.96 (0.48–1.87)	0.894
Morbidity						
Stroke	25	5.0	15	3.0	0.62 (0.32–1.21)	0.164
Transient	15	3.0	29	5.8	2.11 (1.11–4.02)	0.022
Continuous coma ≥24 h	9	1.8	5	1.0	0.74 (0.24–2.27)	0.598
Paraparesis/paraplegia	14	2.8	15	3.0	1.09 (0.52–2.30)	0.811
Prolonged ventilation	83	16.6	69	13.8	0.89 (0.62–1.27)	0.541
Reoperation for any reason	50	10.0	35	7.0	0.69 (0.39–1.23)	0.219
Renal failure dialysis required	8	1.6	21	4.2	2.87 (1.25–6.60)	0.013
Deep sternal infection	8	1.6	10	2.0	1.23 (0.48–3.15)	0.569
ICU stay ≥8 days	52	10.4	56	11.2	1.13 (0.75–1.69)	0.551

30-day mortality (ACP 3.4% vs. RCP 2.4%) and operative mortality (ACP 3.8% vs. RCP 3.4%). The rate of neurological complications was interesting. The RCP group showed a somewhat lower stroke rate but without a significant difference (ACP 5.0% vs. RCP 3.0%); however, a significantly higher rate of transient neurological dysfunction was observed (ACP 3.0% vs. RCP 5.8%). The presence of continuous coma and paraparesis/paraplegia showed no significant differences between the groups. The rate of renal failure requiring dialysis was also significantly higher in the RCP group than in the ACP group (ACP 1.6% vs. RCP 4.2%).

Other types of morbidity included prolonged ventilation, reoperation, and deep sternal infection, but no significant differences were observed between the groups. The rate of a long ICU stay (>8 days) was also similar for the two groups (Table 5).

Discussion

Generally, the most utilized major brain protection methods are ACP and RCP. Each method has advantages and disadvantages. RCP requires no additional cannulas or clamps on the aortic arch branches, which might cause arterial damage or embolic stroke, and no additional extracorporeal circuits such as those used in ACP. However, RCP has the drawback of a limited safe duration. Ueda and coworkers reported RCP to be a useful adjunct for aortic arch surgery with up 80 min of HCA, although prolonged RCP is a risk factor for mortality and morbidity.[12] Generally, RCP should not exceed 60 min when flow is insufficient because it is nonphysiological perfusion.[13] The RCP duration has been reported to be associated with the incidence of stroke, as well as with transient neurological dysfunction.[14] There is some correlation between the severity of transient neurological dysfunction and the duration of RCP.[3]

On the other hand, ACP provides reliable cerebral circulation, but it requires additional cannulas on the arch branches, which increases the chance of embolic stroke, and additional pump circuits, which clutter the operative field. ACP can provide better and more uniform brain protection than can RCP for a long period of time. Di Eusanio and colleagues demonstrated that ACP of >90 min is not associated with an increased risk of mortality or a negative neurological outcome.[15] Therefore, the most important advantage of ACP is the fact that it has no time restrictions, even for complicated aortic arch reconstruction. However, ACP is associated with an increasing risk of embolic stroke.[16] Cannulation or clamping of the arch branches increases the chance of embolism of arteriosclerotic debris or air. An uneven distribution of the intracranial blood flow is associated with selective cannulation , which may cause local brain damage.

There have been a few randomized comparative studies and many retrospective ones between RCP and ACP.[17] Okita and colleagues evaluated 60 consecutive total arch replacements allocated randomly to RCP or ACP and concluded that both RCP and ACP resulted in acceptable levels of mortality and morbidity, but the prevalence of transient brain dysfunction was significantly higher in RCP.[3] Hagl and associates retrospectively analyzed the outcomes in 717 survivors of ascending and aortic arch surgery and determined that the method of brain protection did not influence the outcome of stroke; however, ACP did result in a significant reduction in the incidence of transient neurological dysfunction.[4] Barnard and coworkers searched 408 papers on RCP and ACP and showed ACP to be superior as an adjunct to HCA when compared to RCP or HCA alone, but their clinical evidence was weak.[5]

The surgical outcomes after aortic surgery are strongly affected by an emergency state including aortic rupture or acute aortic dissection. The range of aneurysms, including those of the aortic root, ascending, aortic arch, descending, or thoracoabdominal aorta, is also a strong predictor for mortality and morbidity. The 2006 annual survey of thoracic and cardiovascular surgery in Japan revealed the 30-day mortality to be 10.9% for acute and 4.4% for chronic Stanford type A dissection, and it was 4.5% for unruptured nondissection aneurysm and 19.4% for the ruptured type.[7] The 30-day mortality was also different depending on the replaced site. It was 2.6% in the ascending aorta, 4.5% in the ascending and arch, 11.0% in the arch and descending aorta, 4.5% in the descending aorta, and 9.0% in the thoracoabdominal aorta, respectively, in unruptured nondissection aneurysms. Therefore, we excluded dissection, rupture, and urgent/emergent/salvage status. The range of replacement was also limited to within the ascending aorta and aortic arch, excluding the descending/thoracoabdominal/abdominal aorta. The surgical outcomes may be affected by the clinical experience of the surgeons, and so we excluded any procedures performed at low-volume centers where the annual thoracic aortic surgery volumes were fewer than five procedures.

The results of this study were simple. No significant differences were detected between the groups regarding mortality, including 30-day mortality and operative mortality. No postoperative in-hospital complications showed any significant differences, except for transient neurological dysfunction and renal failure. It is interesting to note that RCP was associated with either an identical or somewhat lower stroke rate but a significantly higher rate of transient neurological dysfunction in comparison to ACP. These results are consistent with those of previous reports in regard to the fact that RCP results in an increased incidence of transient neurological dysfunction. Transient neurological dysfunction may be caused by brain ischemia during RCP. RCP is a nonphysiological type of perfusion that provides only a limited protective effect for the brain. Therefore, prolonged RCP may cause neurological dysfunction. A significant difference was observed only in the propensity-matched analysis, which synchronized each factor but showed no significant differences in the risk-adjusted analysis by using logistic regression analysis.

As a result, all surgeons know of the disadvantages and limitations of RCP. They should therefore carefully select the patients based on the appropriate indications and thus should use RCP only on a case-by-case basis.

It was also an interesting finding that RCP is more often (than ACP) associated with renal failure that requires dialysis, whereas RCP had a lower rate of preoperative renal failure. The incidence of postoperative renal failure is thought to be related to the length of lower body ischemia. ACP may supply a limited blood flow even for the lower body via collateral circulation, whereas RCP cannot provide any blood flow to the lower body. It is a new and important finding that RCP may increase the risk of postoperative renal failure.

Circulatory arrest is another brain protection modality for aortic arch surgery. There were 266 patients with deep hypothermic circulatory arrest in this study. The 30-day and operative mortality rates for these patients were 3.0% and 4.9%, respectively. The postoperative complication rate of stroke, transient neurological dysfunction, continuous coma, paraparesis/paraplegia, and renal failure requiring dialysis were 6.0%, 2.6%, 2.6%, 3.0%, and 3.8%, respectively. No significant differences were observed between RCP and hypothermic circulatory arrest using the χ^2 test (Table 3). This comparison was not a risk-adjusted analysis; however, hypothermic circulatory arrest was also found to provide comparable clinical outcomes, including mortality and neurological dysfunction.

Limitations

There were several limitations in the present study in regard to data interpretation. It was a retrospective clinical study based on a large-scale database, and it provides weaker clinical evidence than does a randomized prospective study. The selection criteria for type of brain protection varies at each institution depending on institutional strategies or each surgeon's preference. Surgical strategy for aortic arch surgery also tends to differ at each institution.

The duration of RCP or ACP was not evaluated because these factors were not described in the JACVSD database. It is a major limitation of this study but cannot be addressed. Although there were no significant effects of RCP on operative mortality regarding the cross-clamp time [odds ratio (OR): <120 min, 1.71, $P = 0.361$; ≥120 min, 0.71, $P = 0.44$), perfusion time (OR: <200 min, 0.73, $P = 0.652$; ≥200 min, 1.138, $P = 0.745$); or operating time (OR: <400 min, 0.732, $P = 0.621$; ≥400 min, 1.335, $P = 0.487$), there may be a tendency for RCP to be used less frequently than ACP for complex arch reconstruction. However, it is most important that the brain protection method be selected on a case-by-case basis in consideration of aortic anatomy, aortic disease, or co-morbidities.

Conclusion

The present study is the first clinical study based on a large-scale database. The findings indicated that both RCP and ACP provide excellent and comparable clinical outcomes, including mortality and stroke rates. RCP resulted only in a higher incidence of transient neurological dysfunction and renal failure that required dialysis. As ACP and RCP have their own advantages and drawbacks, surgeons should select the most appropriate modality according to the respective characteristics of the methods and of the patients.

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