dissection (LND), which is suggested to contribute to the prognosis of patients with curatively resected colon cancers without distant metastasis,[5,6] is even less clear in patients treated with palliative primary tumor resection. In this study, we aimed to determine the prognostic impact of primary tumor resection and the extent of LND in patients with mCRC in a multicenter retrospective study of Japanese referral hospitals using propensity score analysis.

METHODS

Patients

Data of patients with stage IV colorectal cancer treated from January 1997 to December 2007 ($n = 3,183$) were obtained from the prospective databases of 17 referral hospitals of the Japanese Study Group for Postoperative Follow-up of Colorectal Cancer. Patients treated with resection of both the primary and metastatic lesions ($n = 1038$), including patients with R0 resection ($n = 876$), and those with R1 or R2 resection ($n = 162$) were excluded. Thus, a total of 1,982 patients with mCRC comprised the study population. The median follow-up period of patients was 13.3 months. The study protocol was approved by local ethics committees.

Analysis of Prognostic Factors

Factors contributing to the overall survival (OS) were analyzed in a multivariate analysis. The study period was divided into the former half (from January 1997 to May 2003) and the latter half (from June 2003 to December 2007) periods. The extent of LND was defined as D3 dissection when the lymph nodes up to the origin of the feeding artery from the superior mesenteric artery (proximal colon) or those at the origin of the inferior mesenteric artery (distal colon and rectum) were dissected,[7] and the impact of D3 LND on OS was analyzed in comparison with less extensive LND (D0–2).

Statistics

A paired *t*-test was used for the comparison of continuous variables, and the Chi-square test was used for the comparison of categorical data. OS rate was estimated by the Kaplan–Meier method and compared using the log-rank test. A multivariate analysis for factors contributing to OS was performed using the Cox proportional hazards model. To mitigate the selection bias by the retrospective nature of this study, the treatment groups (primary tumor resection vs. no resection, and D3 vs. D0–2 LND) were matched using propensity scores for clinical and pathological features affecting the prognosis of the patients, and the impact of primary tumor resection and D3 LND on OS were analyzed. Covariates were chosen for their potential association with OS based on the results of the Cox proportional hazards model ($p < 0.05$), and propensity scores were calculated by fitting a logistic regression model. One-to-one pair matching was done without replacement, and propensity scores were matched with calipers less than 0.001. Data analyses were performed using the JMP statistical software package (SAS Institute Inc., Cary, NC, USA) and statistical program R (http://www.R-project.org/); p values < 0.05 were considered statistically significant.

RESULTS

Clinical and pathological features of the study population ($n = 1,982$) are shown in Table 1. The median OS was 15.6 months. The primary colorectal lesions were palliatively resected in 1,782 patients (89.9 %) and were not resected in 200 patients (10.1 %).

Prognostic Impact of Primary Tumor Resection

Multivariate analysis of prognostic factors in the whole study population was performed. A total of 1,619 events (deaths) were observed during the follow-up period. Primary tumor resection and treatment in the latter half period were significantly associated with an improved OS; age over 70 years, clinical lymph node metastasis, and metastasis to multiple organs were significantly associated with a decreased OS (Table 2). Institutions where patients were treated were also associated with OS. Primary tumor resection was preferentially performed in female patients, patients with colon cancers, and patients with a less advanced disease, i.e. without invasion to adjacent organs, without clinical lymph node metastasis, and without multiple organ metastasis (Table 3, full cohort). In the cohort matched by the propensity scores for treatment period, institution, age, sex, carcinoembryonic antigen (CEA) level, tumor location, clinical tumor depth, clinical lymph node metastasis, and number of metastatic organs, patients treated with primary tumor resection showed a significantly better OS than those without tumor resection (median OS 13.8 vs. 6.3 months; $p = 0.0001$) [Table 3]. The concordance index for this matching model was 0.738.

Prognostic Impact of D3 Lymph Node Dissection

Multivariate analysis of prognostic factors in patients treated with primary tumor resection was performed. A total of 1,462 events (deaths) were observed during the follow-up period. D3 LND and treatment in the latter half

TABLE 1 Clinical and pathological features of the study population

Period[a,b]	
Former	986 (49.8)
Latter	994 (50.2)
Age (years)[c]	64
Sex[b]	
Male	1,208 (61.0)
Female	773 (39.0)
CEA (ng/dL)[c]	633
Location[b]	
Colon	1,534 (77.4)
Rectum	448 (22.6)
Invasion to organ[b]	
−	1,453 (80.9)
+	343 (19.1)
Lymph node metastasis[b]	
−	278 (18.2)
+	1,249 (81.8)
Metastasis[b]	
Single organ	1,254 (63.3)
Multiple organs	728 (36.7)
Primary tumor resection[b]	
Yes	1,782 (89.9)
No	200 (10.1)
Median overall survival (months)	15.6

CEA carcinoembryonic antigen

[a] Former: from January 1997 to May 2003; Latter: from June 2003 to December 2007

[b] Data are expressed as *n* (%)

[c] Values are expressed as means

period were significantly associated with an improved OS; age over 70 years, histology of poorly differentiated adenocarcinoma, mucinous adenocarcinoma or signet ring cell carcinoma, pathological lymph node metastasis, lymphovascular invasions, and metastasis to multiple organs were significantly associated with a decreased OS (Table 4). Institutions where patients were treated were also associated with OS. D3 LND was performed more frequently in the latter period and in younger patients, patients with rectal cancers, patients with well or moderately differentiated adenocarcinomas, and patients without multiple organ metastasis (Table 5, full cohort). In the cohort matched by the propensity scores for the treatment period, institution, age, sex, CEA level, tumor location, histology, pathological tumor depth, pathological lymph node metastasis, lymphovascular invasion, and number of metastatic organs, patients treated with D3 LND showed a significantly better OS than those with less extensive (D0–2) LND (median OS 17.2 vs. 13.7 months; $p < 0.0001$) [Table 5]. The concordance index for this matching model was 0.633.

DISCUSSION

We analyzed the prognostic impact of primary tumor resection and D3 LND in patients with stage IV colorectal cancer treated in referral hospitals and whose metastatic lesions were not surgically resected. Primary tumor resection and D3 LND were significantly and independently associated with an improved OS in the multivariate analysis and propensity score analysis. Many reports have also suggested the positive prognostic impact of primary tumor resection in mCRC;[3,4] however, the decision to surgically resect the primary colorectal lesion when a colorectal cancer is diagnosed with unresectable metastases remains controversial, particularly for patients without symptoms related to the primary lesions, such as bowel obstruction, perforation, and hemorrhage.[1,4,8]

Recent advances in chemotherapy for colorectal cancers have enabled a rapid response and increased survival exceeding 2 years in patients with advanced or recurrent colorectal cancers.[9–11] Thus, the alternative strategy to first give chemotherapy without performing primary tumor resection can be considered in the presence of effective chemotherapy, particularly for patients with asymptomatic mCRC.[8] In this study, data regarding chemotherapy are lacking, constituting a limitation of this study; therefore, the influence of chemotherapy, which might be given prior to or following the operation, on the benefit of primary tumor resection observed in this study, is unclear. In the primary tumor resection cases, the median (range) interval between diagnosis of stage IV disease and surgery was 12 (0–2,053) days; therefore, surgery was performed immediately after diagnosis, possibly without chemotherapy, for the majority of the cases. Operation was performed after > 30 days of diagnosis in 15.6 % of primary tumor resection cases, which might have included upfront chemotherapy cases. When cases operated within or after 30 days of diagnosis were separately compared with no resection cases, primary tumor resection was independently associated with an improved OS (data not shown), suggesting that palliative primary tumor resection improves OS with or without prior chemotherapy. In the multivariate analysis, patients treated in the latter half period showed a significantly better OS than those treated in the former half period. During the 10 years of this study, an increasing number of effective chemotherapeutic agents or regimens that have improved patient survival have been reported.[9–11] Therefore, this advancement in chemotherapy may improve the prognosis of patients treated in the latter half period. As shown by the multivariate analysis and

TABLE 2 Factors associated with overall survival (whole study population)

	Median overall survival (months)	Univariate analysis		Multivariate analysis	
		HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Period[a]					
Latter/Former	19.1/13.1	0.72 (0.65–0.79)/1	<0.0001	0.74 (0.66–0.83)/1	<0.0001
Institution[b]	–	–	<0.0001	–	<0.0001
Age (years)					
70≤/70>	13.2/17.0	1.21 (1.09–1.34)/1	0.0004	1.24 (1.10–1.40)/1	0.0003
Sex					
Female/Male	14.7/16.4	1.11 (1.00–1.22)	0.0499	1.09 (0.97–1.22)/1	0.234
CEA (ng/dL)					
5≤/5>	15.2/17.6	1.24 (1.08–1.42)/1	0.0018	1.15 (0.99–1.35)/1	0.1172
Location					
Rectum/Colon	18.2/15.0	0.89 (0.79–0.99)/1	0.0441	1.00 (0.87–1.15)/1	0.4282
Invasion to organ					
+/–	13.7/16.6	1.15 (1.00–1.30)/1	0.0434	1.14 (0.98–1.32)/1	0.1799
Lymph node metastasis					
+/–	15.3/19.0	1.28 (1.11–1.48)/1	0.0005	1.22 (1.06–1.43)/1	0.0023
Metastasis					
Multiple/Single organ(s)	12.1/18.2	1.55 (1.40–1.71)/1	<0.0001	1.49 (1.32–1.67)/1	<0.0001
Primary tumor resection					
Yes/No	16.9/6.2	0.37 (0.31–0.44)/1	<0.0001	0.41 (0.33–0.53)/1	<0.0001

HR hazard ratio, *CI* confidence interval, *CEA* carcinoembryonic antigen

[a] Former: from January 1997 to May 2003; Latter: from June 2003 to December 2007

[b] 17 hospitals were included

TABLE 3 Comparison of patients treated with and without primary tumor resection

	Full cohort			Propensity score-matched cohort		
	Resection (n = 1782)	No resection (n = 200)	*p* value	Resection (n = 75)	No resection (n = 75)	*p* value
Period[a]: Latter	890 (49.9)	104 (52.5)	0.4906	38 (50.7)	36 (48.0)	0.7439
Institution[b]	–	–	<0.0001	–	–	0.9264
Age ≥70 years	579 (32.5)	71 (35.5)	0.3959	20 (26.7)	23 (30.7)	0.5879
Sex: Male	1,073 (60.2)	135 (67.5)	0.0439	59 (78.7)	53 (70.7)	0.2592
CEA ≥5 ng/dL	1,398 (81.3)	168 (88.0)	0.0259	63 (84.0)	65 (86.7)	0.6442
Location: Rectum	387 (21.8)	61 (31.3)	0.0036	20 (26.7)	21 (28)	0.8546
Invasion to organ (+)	293 (18.0)	50 (30.5)	0.0002	17 (22.7)	17 (28.0)	0.4524
Lymph node metastasis (+)	1,160 (81.3)	89 (89.0)	0.0408	66 (88.0)	65 (86.7)	0.806
Multiple organ metastasis	634 (35.6)	94 (47.0)	0.0017	36 (48.0)	37 (49.3)	0.8702
Median overall survival (months)	16.9	6.2	<0.0001	13.8	6.3	0.0001

Data are expressed as n (%) unless specified otherwise

CEA carcinoembryonic antigen

[a] Former: from January 1997 to May 2003; Latter: from June 2003 to December 2007

[b] 17 hospitals were included

propensity score analysis, primary tumor resection was associated with an improved OS when controlled for patients treated in both the former and the latter periods, which may indirectly indicate that primary tumor resection improves patient prognosis in the presence of effective chemotherapy. Metallic bowel stent is a palliative modality that has been reported to be effective in the palliation of obstructive stage IV colorectal cancer.[12] However, it has

TABLE 4 Factors associated with overall survival (primary tumor resection cases)

	Median overall survival (months)	Univariate analysis		Multivariate analysis	
		HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Period[a]					
Latter/Former	20.2/14.3	0.71 (0.64–0.79)/1	<0.0001	0.74 (0.66–0.84)/1	<0.0001
Institution[b]	–	–	<0.0001	–	<0.0001
Age (years)					
70≤/70>	14.4/18.1	1.23 (1.10–1.37)/1	0.0003	1.23 (1.08–1.39)/1	0.0015
Sex					
Female/Male	15.4/17.9	1.15 (1.03–1.27)/1	0.0113	1.07 (0.95–1.21)/1	0.2383
CEA (ng/dL)					
5≤/5>	16.4/19.3	1.24 (1.08–1.43)/1	0.0024	1.17 (0.99–1.38)/1	0.0517
Location					
Rectum/Colon	20.7/16.0	0.86 (0.76–0.97)/1	0.0124	0.90 (0.78–1.04)/1	0.1502
Histology					
Por, Muc, Sig/Wel, Mod	10.0/17.8	1.86 (1.60–2.15)/1	<0.0001	1.72 (1.45–2.03)/1	<0.0001
Invasion to organ					
+/−	13.6/17.6	1.22 (1.10–1.42)/1	0.0085	1.15 (0.97–1.36)/1	0.1074
Lymph node metastasis					
+/−	16.4/22.7	1.45 (1.26–1.68)/1	<0.0001	1.34 (1.14–1.60)/1	0.0003
Lymphatic invasion					
+/−	16.2/26.1	1.61 (1.36–1.92)/1	<0.0001	1.41 (1.13–1.78)/1	0.0022
Venous invasion					
+/−	16.3/21.3	1.28 (1.10–1.52)	0.0017	1.30 (1.07–1.60)/1	0.0092
Metastasis					
Multiple/Single organ(s)	13.1/19.2	1.57 (1.41–1.74)/1	<0.0001	1.48 (1.31–1.68)/1	<0.0001
Lymph node dissection					
D3/D0–2	20.8/13.9	0.70 (0.63–0.78)/1	<0.0001	0.66 (0.56–0.75)/1	<0.0001

HR hazard ratio, *CI* confidence interval, *CEA* carcinoembryonic antigen, *Por* poorly differentiated adenocarcinoma, *Muc* mucinous adenocarcinoma, *Sig* signet-ring cell carcinoma, *Wel* well differentiated adenocarcinoma, *Mod* moderately differentiated adenocarcinoma

[a] Former: from January 1997 to May 2003; latter: from June 2003 to December 2007

[b] 17 hospitals were included

been reported that the use of metallic stents for bowel obstruction worsened the survival of patients without metastasis, and patients were eventually treated by curative resection.[13] Therefore, the oncological significance of palliative metallic stents must be determined in prospective studies[14] comparing them with palliative primary tumor resection.

In patients treated with primary tumor resection, D3 LND was significantly associated with a better OS of patients with mCRC. D3 LND, which is also described as high tie or central vascular ligation, removes lymph nodes up to the origin of the feeding artery and is reported to improve survival of patients with curatively resected colorectal cancers without distant metastasis.[5,6,15] However, there is no report showing the oncological benefit of D3 LND in patients with colorectal cancer with unresectable distant metastasis. The benefit of curative D3 LND in colorectal cancers without distant metastasis, and possibly in those with resectable distant metastasis,[16] can be understood by its radicality of clearance of cancer, which may be present in the lymph nodes at the origin of the feeding artery; however, the positive prognostic impact of D3 LND on patients with mCRC observed in this study is interesting because removal of regional lymph nodes theoretically does not improve the survival of patients with mCRC whose metastatic lesions are apparently left unresected. Furthermore, in the multivariate analysis, D3 LND was associated with an improved OS independent of the presence of lymph node metastasis, and although data were not shown, D3 LND was also an independent prognostic factor when separately analyzed in patients without lymph node metastasis (hazard ratio 0.72; 95 % confidence interval 0.54–0.96; $p = 0.0244$). These data suggest that the dissection of non-metastatic lymph nodes might

TABLE 5 Comparison of patients treated with D3 and D0–2 lymph node dissection

	Full cohort			Propensity score-matched cohort		
	D3 (n = 690)	D0-2 (n = 941)	p value	D3 (n = 365)	D0–2 (n = 365)	p value
Period[a]: Latter	363 (52.6%)	447 (47.5)	0.0395	168 (46.0)	186 (51.0)	0.1824
Institution[b]	–	–	<0.0001	–	–	0.9914
Age ≥70 years	185 (26.8)	342 (36.3)	<0.0001	106 (29.0)	101 (27.7)	0.6814
Sex: Male	422 (61.2)	561 (59.6)	0.4896	228 (62.5)	224 (61.4)	0.7065
CEA ≥5 ng/dL	552 (82.5)	741 (82.5)	0.9977	310 (84.9)	299 (81.9)	0.2733
Location: Rectum	166 (21.8)	188 (20.0)	0.048	79 (21.6)	80 (21.9)	0.9285
Histology: Por, Muc, Sig	69 (10.1)	161 (17.3)	<0.0001	39 (10.7)	46 (12.6)	0.419
Invasion to organ (+)	95 (13.8)	132 (14.2)	0.8478	41 (11.2)	45 (12.3)	0.646
Lymph node metastasis (+)	105 (15.3)	167 (18.4)	0.1106	308 (84.4)	317 (86.8)	0.3423
Lymphatic invasion (+)	619 (86.6)	839 (89.7)	0.7403	331 (90.7)	333 (91.2)	0.7963
Venous invasion (+)	599 (87.4)	829 (88.7)	0.4547	326 (89.3)	331 (90.7)	0.5372
Multiple organ metastasis	204 (30.4)	357 (37.9)	0.0004	110 (30.1)	125 (34.3)	0.2346
Median overall survival (months)	20.8	13.9	<0.0001	17.2	13.7	<0.0001

Data are expressed as n (%) unless specified otherwise

CEA carcinoembryonic antigen, *Por* poorly differentiated adenocarcinoma, *Muc* mucinous adenocarcinoma, *Sig* signet-ring cell carcinoma

[a] Former: from January 1997 to May 2003; latter: from June 2003 to December 2007

[b] 17 hospitals were included

improve the prognosis of mCRC patients without regional lymph node metastasis. Although the mechanism of this observation is unclear, a possible mechanism may be speculated from the viewpoint of cancer immunity. It is considered that there are two aspects of cancer immunity exerted by tumor-draining lymph nodes, namely antitumor immunity and tolerance for cancer, and that the balance of cancer immunity inclines toward tolerance as the cancer advances.[17] It has been reported that Foxp3, a nuclear transcription factor, which identifies regulatory T cells, accumulates positive T cells in tumor-draining lymph nodes of patients with colorectal cancer[18] and limits the onset of CD8+T-cell responses by inducing perforin-dependent dendritic cell death.[19] Therefore, resection of regional lymph nodes, despite them not being metastatic nodes, may reset this 'cancer-friendly' immunological balance, resulting in an improvement of patient prognosis.

The most important limitation of the present study is its selection bias due to its retrospective nature. A recent meta-analysis supported the prognostic benefit of primary tumor resection in mCRC compared with chemotherapy alone.[20] Other studies have also been performed;[3,4] however, most studies are retrospective and there is no definite prospective study regarding primary tumor resection in mCRC. Patient symptoms, such as bowel obstruction, perforation, and hemorrhage, are usually indications for primary tumor resection. In this study, data regarding symptoms of the patients are lacking; however, primary tumor resection was preferentially performed in patients with less advanced disease, which is considered to have less associated symptoms. Therefore, the presence of symptoms is not a sole indication for primary tumor resection. On the other hand, there is a possibility that primary tumor resection, as well as D3 LND, were indicated for 'more favorable' patients and consequently showed a better prognosis. In fact, primary tumor resection and D3 LND were preferentially indicated for younger patients, patients without invasion to adjacent organs, and patients without lymph node or multiple organ metastasis. In this study, we employed the propensity score analysis, which mitigates selection bias in observational studies,[21] and as shown in Tables 3 and 5, the patient groups were well matched regarding the covariates examined in this study after propensity score matching. However, a direct indicator of the patient's general condition or his/her fitness for surgery, such as the American Society of Anesthesiologists (ASA) score, is lacking. From the available data, age and sex were partly correlated to the patients' condition because older patients[22] and male patients[23] were shown to have higher ASA scores and more comorbid diseases than younger patients and female patients, respectively. Furthermore, the advancement of cancer indicated by tumor depth, nodal involvement, and number of metastatic organs might also be correlated to the patients' general condition. Therefore, it is considered that control of these data by multivariate analysis and propensity score matching might partly compensate for the lack of more direct indicators of the fitness of the patients, such as ASA scores.

CONCLUSION

Although this is a retrospective study, the results of the multivariate analysis and propensity score analysis suggest that primary tumor resection with D3 LND may improve the survival of patients with mCRC; however, these findings must be confirmed in future prospective randomized studies.

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Radial coronary interventions and post-procedural complication rates in the real world: A report from a Japanese multicenter percutaneous coronary intervention registry

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Annual trend

Coronary interventions performed through transradial approach intervention (TRI) have been shown to be as effective as, and potentially safer than, transfemoral approach intervention (TFI) [1,2]. However, despite growing interest in the transradial approach, its real-world implementation and consequences have not been thoroughly investigated [3]. This is partly related to the low rate of TRI performance in the US and European countries, which has ranged from just 3% to 10% across various clinical studies and registries [4]. By comparison, radial interventions have grown exponentially in Japan in recent years owing to a high interest among local interventional cardiologists, the small size of the body habitus, and patient preference toward less invasive procedures. This has provided us with a unique opportunity to investigate TRI usage trends and the relationship between TRI and in-hospital complication rates.

We analyzed data from the JCD-KICS Registry, which is an ongoing multicenter PCI database in Tokyo, Japan. The majority of clinical variables in this registry were defined according to the National Cardiovascular Data Registry sponsored by the American College of Cardiology to conduct comparative research to determine the factors that lead to disparities in PCI management [5]. Before the launch of the JCD, information on the objectives of the present study, its social significance, and an abstract were provided for clinical trial registration with the University Hospital Medical Information Network (UMIN R000005598). The study protocol was approved by the institutional review board committee at each site. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

A total of 9423 consecutive patients (TRI, 2954; 31.3%) who underwent PCI procedures at 15 Japanese hospitals from January 2009 to December 2012 were analyzed. Patient characteristics were compared between PCIs performed in earlier years (2009–2010) and later years (2011–2012).

The percentage of patients who undergo TRI with comorbidities such as high BMI, diabetes, hypertension, or history of PCI increased from 2009–2010 to 2011–2012 (Table 1A). Notably, TRI was performed less frequently in ST-segment elevation myocardial infarction (STEMI) patients (15.4% in 2009–2010 and 9.8% in 2011–2012). The overall preference for TRI seemed to be similar between the two time intervals. Common clinical predictors associated with TRI use were male sex, non-shock status, peripheral arterial disease, no previous CABG, and non-ACS presentation (Table 1B). The figure shows the relative increase in the number of TRIs during 2009–2012 (Fig. 1). A decreasing trend in the rate of in-hospital bleeding complications was observed along with the increasing number of TRIs.

In our dataset, the increasing number of TRIs paralleled with the decreasing number of overall bleeding complications, despite only a small change in preoperative variables for patient selection between TRI and non-TRI patients during the study period. These results further support the use of TRI in the real world. One of the important future clinical implications here is the need to improve the reluctance to perform TRI in acute conditions such as STEMI. Recent studies indicate that TRI is safe and effective even in STEMI patients, and further investigation is needed in implementing its use in acute conditions [6].

Previous studies have also attributed temporal changes in antithrombotic strategies for the reduction in post-coronary intervention bleeding observed over time [4,7]. However, heparin is the only intravenous anticoagulant approved for use in the setting of a coronary intervention in

Table 1A
Characteristics of patients treated with the radial approach, comparing the pre- and post-2011 periods.

	2009–2010, n = 3396	2011–2012, n = 6027	p-Value
Clinical variables			
Age, y	67.4 ± 11	68.1 ± 10.4	0.130
Female	16.7%	16.7%	1.000
BMI	3.5%	3.6%	0.006
Current smoker	31.8%	34.8%	0.133
Hypertension	73.4%	79.0%	0.002
Dyslipidemia	68.9%	70.7%	0.336
Diabetes	37.7%	42.1%	0.033
PAD	10.8%	9.6%	0.325
Chronic kidney disease	1.2%	1.7%	0.403
History of PCI	39.3%	44.4%	0.014
History of CABG	1.6%	2.4%	0.252
Shock	0.8%	1.1%	0.541
Cardiac arrest	0.5%	0.8%	0.625
Diagnosis			
STEMI	15.4%	9.8%	<0.001
NSTEMI	7.9%	6.4%	0.155
Unstable angina	20.2%	20.8%	0.756
Stable angina	30.8%	34.7%	0.057
Angiographic variables			
Left main disease	7.7%	5.7%	0.056
Two vessel disease	41.9%	41.2%	0.734
Triple vessel disease	22.0%	19.5%	0.143

BMI, body mass index; PAD, peripheral artery disease; GFR, glomerular filtration rate; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; NSTEMI, non ST elevation myocardial infarction.

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Table 1B
Predictors of radial approach for coronary intervention in the different time intervals.

	Odds ratio (95%CI)	p-Value
2009–2010		
Female	0.705 (0.56–0.888)	0.003
Shock	0.301 (0.12–0.757)	0.011
PAD	2.593 (1.883–3.569)	<0.001
Previous history of CABG	0.235 (0.128–0.432)	<0.001
STEMI	0.551 (0.41–0.742)	<0.001
Diabetes	0.662 (0.472–0.929)	0.017
2011–2012		
Female	0.742 (0.644–0.857)	<0.001
Shock	0.427 (0.27–0.674)	<0.001
PAD	1.733 (1.401–2.143)	<0.001
History of CABG	0.311 (0.228–0.423)	<0.001
STEMI	0.218 (0.184–0.258)	<0.001
NSTEMI	0.586 (0.473–0.727)	<0.001
Hypertension	1.284 (1.123–1.468)	<0.001
Triple vessel disease	0.808 (0.703–0.928)	0.003
Previous history of PCI	1.171 (1.038–1.321)	0.01

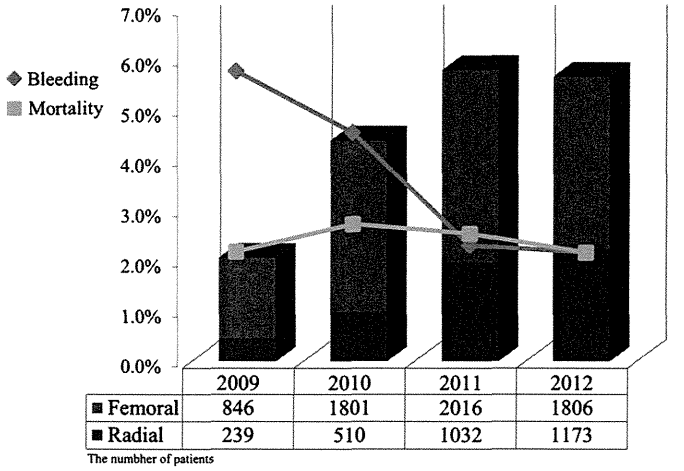

Fig. 1. TRI and TFI numbers. Blue bars represent the femoral approach; red bars represent the radial approach; the lines represent bleeding and mortality. PCI, percutaneous coronary intervention; TRI, transradial approach intervention; TFI, transfemoral approach intervention.

Japan (because of frequently observed bleeding complications with agents such as IIb–IIIa inhibitors), and no alterations in antithrombotic strategy have been implemented during our study period [8].

In conclusion, about one-third of our multicenter Japanese registry patients underwent TRI. The number of TRIs increased over the years, and increasing TRI use was associated with a decreasing trend in bleeding complications. TRI was preferred in non-complex cases and further studies are needed to implement this technique in acute PCIs.

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Results of Data Verification of the Japan Congenital Cardiovascular Database, 2008 to 2009

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Abstract

Background: Since 2008, data concerning pediatric cardiovascular surgeries performed in Japan have been collected in the Japan Congenital Cardiovascular Surgery Database (JCCVSD). We assessed the quality of the JCCVSD data through data verification activities conducted in 2010. **Methods:** During 2008 to 2009, 3345 patients with 4327 procedures at 25 hospitals were registered in the JCCVSD. Among them, six sites were selected for data verification. The completeness of case registration was assessed by comparison with original operational logs. Also, data accuracy of patient demographics, surgical outcomes, and processes were assessed with 10% of the registered cases by comparison with medical records. **Results:** Verification of case registration completeness involved 968 (28.9%) patients and 1279 (29.1%) procedures. As to completeness, we confirmed 1266 (99.0%) of the 1279 procedures. Data accuracy was verified for 129 (3.9%) patients. Accuracy of status of discharge and 30 and 90 days after surgery were very high (99.2%, 100%, and 100%, respectively). Data items with numeric information exhibited lower exact accuracy due to typing error and inconsistent use of rounding; however, the differences between the submitted and the original data were not statistically significant. **Conclusions:** High completeness and acceptable range of data accuracy were verified for the data submitted to the JCCVSD in 2008 to 2009. The high accuracy regarding follow-up outcomes was especially noteworthy. The initial success of the JCCVSD should be strengthened through further sophistication of registration protocol, continual training of data managers and auditors, and rigorous expansion of verification activities.

Keywords

congenital heart surgery, congenital heart disease, database (all types), statistics

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Introduction

Clinical registry database has been increasingly recognized as a powerful tool to promote health care quality improvement initiatives and to support decision making of various stakeholders including patients, clinical specialists and their staff, hospital administrators, and government agencies.[1-3] Recent projects to strengthen clinical databases through the linkage of the data with claim data and other existing databases[4] have sought to further extend the potential of clinical registries to enhance international collaborative research[5] and clinical trials.[6]

To achieve these purposes in a scientifically sound manner, it is imperative to assure the quality of clinical registry database.[7] However, false reports due to the underreporting of adverse events are often problematic and can seriously bias the validity of conclusions based on the clinical database of concern.[8,9] Data verification for quality assurance is highly recommended,[10-12] although the implementation of a verification regimen can often be an enormous challenge.

Data verification is often conducted by comparing the information in primary source documents in hospitals with the

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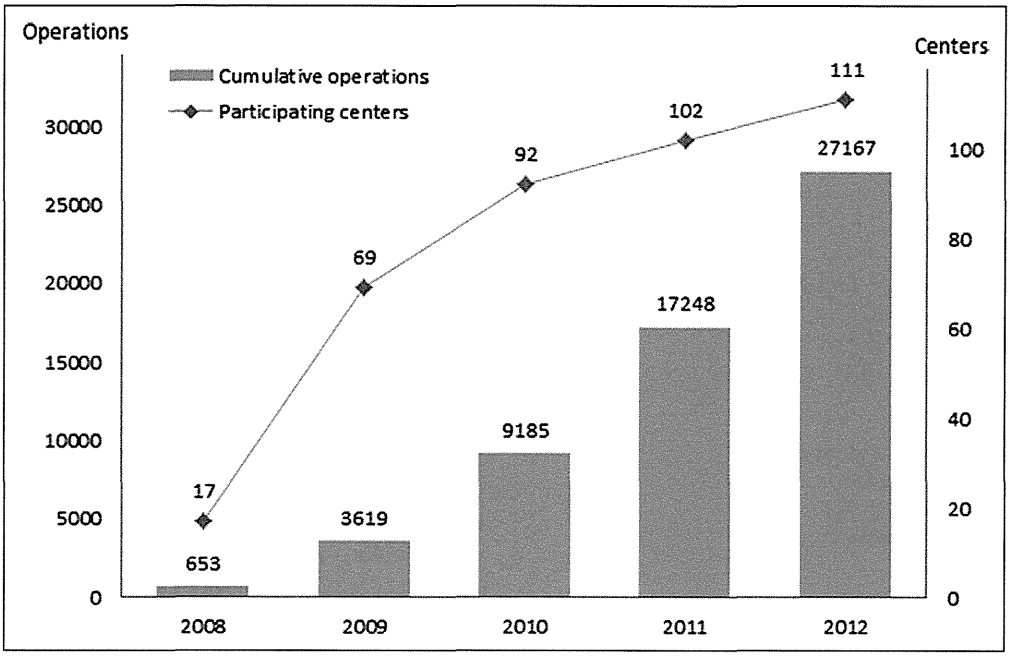

Figure 1. Total number of participating hospitals and operations in the Japan Congenital Cardiovascular Surgery Database (JCCVSD).

database information.[13] Data quality is assessed in terms of completeness of the registry (whether all eligible patients are registered)[14] and the accuracy of data entry (whether the collected data are consistent with the primary source documents).[15] Clinical databases including the Society of Thoracic Surgeons (STS) National Database, the European Congenital Heart Surgeons Association/European Association for Cardio-Thoracic Surgery Database, and National Cardiovascular Data Registry founded by the American College of Cardiology have already adopted this method.[16-19] Although data verification requires intensive resource, data verification through inspection of participating sites is one of the most effective methods to assure data quality.

There are few clinical registry systems in Japan. Among them, the Japan Congenital Cardiovascular Surgery Database (JCCVSD)[20] began the registration of pediatric cardiovascular surgeries nationwide in 2008. This is the first report on the JCCVSD data quality based on data verification activities conducted in 2010.

Materials and Methods

Data Source

The JCCVSD was established by the Japan Cardiovascular Surgery Database Organization as a part of a large project to establish a nationwide database to assess outcomes of cardiovascular surgeries with the goal of improving the quality of care. Hospitals that participated in the JCCVSD are required to register all congenital cardiovascular surgery cases. From August 2008 to December 2009, 25 hospitals submitted data of 3345 patients with 4327 procedures to the JCCVSD. Recently, participating hospitals in the JCCVSD have increased, and 25 hospitals of 2008 to 2009 are 22.5% in the participating hospitals of 2012 (Figure 1). The JCCVSD is the nationwide database that covers all congenital cardiovascular surgeries, in Japan now.

Data were collected using specialized data collection forms that contain approximately 300 variables, including demographics, preoperative risk, operative information, postoperative complication, and outcomes. These variables are almost identical to those of the STS registry; the JCCVSD and STS use the same definitions for variable items. Data are submitted through an Internet case form and are automatically checked for selected key items. Registration is closed annually, with the data fixed to allow no further entry. Each participating hospital is required to assign a data manager accountable for data traceability. Each hospital must also obtain ethical approval from its institutional review board for the entry of all patient information to the database.

Methods of Data Verification

Of the 25 participating hospitals, 6 were selected for data verification. Three of the sites were nominated by the JCCVSD steering committee, because this was the first trial for the JCCVSD. The remaining three were randomly selected with consideration given to the balance of hospital volume and types of hospital (eg, university hospital, highly specialized hospital, and public hospital). The selected hospitals registered 968 patients with 1279 procedures, which represented 28.9% and 29.1% of the total registry, respectively.

Verification was conducted between December 2010 and July 2011. For the completeness check, we compared an operation log with the data submitted to the JCCVSD. If patient

Table 1. List of Abstracted Data Elements.

ID
Gender
Blood type
Date of birth
Date of admission
Date of surgery
Date of death
Date of discharge
Readmission within 30 days after surgery (yes or no)
Status at discharge (alive or dead)
Status at 30 days after surgery (alive or dead)
Status at 90 days after surgery (alive or dead)
Height
Weight
Cardiopulmonary bypass time in minutes
Aortic cross-clamp time in minutes
Operation time in hours and minutes
Anesthesia time in hours and minutes
Intubation (yes or no)
Date and time of intubation
Date and time of extubation

identification (ID) and the date of operation matched the database record, the case was regarded as "confirmed." If not, the case was regarded as "unconfirmed," and medical records other than an operation log were referred to. Nonregistered cases or those found in an operation log without registration to the JCCSVD were systematically reviewed by the JCCVSD steering committee to decide whether they should be registered or not.

For the accuracy check, the cases were selected randomly to ensure representative of each hospital statistically. In the view of the feasibility of data verification, 10% of the cases registered for the first admission and first operation were randomly selected if the number of registered cases in a particular hospital was more than 100. Otherwise, ten cases were randomly selected to ensure a sufficient number of cases for comparison. In all, 129 cases were randomly selected, which corresponded to 10.2% of the total registry in the six hospitals or 3.9% of the total JCCVSD registration. Accuracy assessment involved 25 variables including patient demographics, intraoperative information, and outcomes as listed in Table 1. We chose these variables for verification due to several reasons. First, these variables are regarded as influential parameters to define the quality of surgery. Second, the definition of the terms must be unambiguous and standardized. Third, identification of the variables in the existing medical records is relatively easy. At each on-site visit, we referred to hospital records regarding surgery, anesthesia, intensive care unit and nurse care, and cardiopulmonary bypass as source documents and checked the consistency of variable values with those in the registered data. Continuous values were rounded off. If the data submitted to the JCCVSD were the same as those in the source documents, we judged the items as "consistent." If any value was inconsistent, we sought additional information to identify the cause of the discrepancy.

The time of the start and end of each verification procedure was recorded to assess the variability of the verification process. When data inconsistency was found, requiring additional information sources, the search was limited to within approximately 20 minutes. Since the first hospital was used as a pilot test for the verification procedures, the verification time was measured in the remaining five hospitals after the standardization of the procedure. We hypothesized that the time needed for verification should be shorter when the source of reference records was electronic rather than paper based, the number of auditors was larger, and the degree of record accuracy was higher.

A nonclinical department (Department of Healthcare Quality Assessment, Graduate School of Medicine, University of Tokyo), which was commissioned as a neutral and impartial institution by the Japan Cardiovascular Surgery Database Organization, was in charge of data verification in collaboration with the JCCVSD steering committee. Data verification was carried out by two staff members who were independent of the JCCVSD, free from any clinical practice, and who had general medical knowledge (one was a registered nurse and the other was a health information manager) after standardized audit training. The auditors had a written contract to strictly follow the confidentiality obligation for hospital information and were allowed access to the data only for verification.

Statistical Analysis

Completeness of case registrations was assessed with the following aspects: (1) proportion of confirmed cases in registered cases, (2) proportion of multiple cases in registered cases, and (3) proportion of unregistered cases in recorded cases of operating log in hospitals.

Accuracy of data entry was expressed as a proportion of consistent items among 21 items per verified case. We also calculated an item-wise proportion of data consistency between source data and the data submitted to the JCCVSD. For continuous variables, we calculated the mean and standard deviation and compared the difference between the source and the submitted data by paired t test. In some cases where we could not identify the original source in the unified method, it was considered missing and was excluded from the calculation.

The total time to verify the data for each case was compared using the medical records (paper and/or electronic), the number of auditors, and the degree of accuracy. The degree of record accuracy per case was categorized into four levels (100% [25 of 25 items], 90% to 99% [23-24 of 25 items], 80% to 90% [20-22 of 25 items], or $\leq$80% [20 of 25 items]) using nonparametric tests.

All analyses were performed with SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

Completeness of Registration

We confirmed 1266 of the 1279 cases, and the proportion of confirmed cases in registered cases was 99.0%. Nine cases

Table 2. Results of Item-Wise Accuracy of Registered Data Compared to Original Records (N = 129).

	n	Proportion of Consistent	95% CI	Range for Each Site	The Difference Between the Means of Collected Data and Data in Primary Source[a]		
					Mean[c]	SD	*P* Value[b]
ID	127	0.99	(0.98-1.01)	(0.90, 1.00)	–	–	–
Gender	127	0.99	(0.98-1.01)	(0.97, 1.00)	–	–	–
Blood type	127	0.99	(0.98-1.01)	(0.94, 1.00)	–	–	–
Date of birth	127	0.98	(0.96-1.01)	(0.90, 1.00)	0.26	2.39	.21
Date of admission	127	0.98	(0.95-1.00)	(0.90, 1.00)	0.24	2.39	.26
Date of surgery	127	0.98	(0.95-1.00)	(0.86, 1.00)	−0.04	0.26	.10
Date of death	127	1.00	–	(1.00, 1.00)	–	–	–
Date of discharge	127	0.99	(0.98-1.01)	(0.97, 1.00)	−0.12	1.50	.38
Readmission within 30 days after surgery (yes or no)	127	0.98	(0.95-1.00)	(0.80, 1.00)	–	–	–
Status at discharge (alive or dead)	127	0.99	(0.98-1.01)	(0.97, 1.00)	–	–	–
Status at 30 days after surgery (alive or dead)	124	1.00	–	(1.00, 1.00)	–	–	–
Status at 90 days after surgery (alive or dead)	120	1.00	–	(1.00, 1.00)	–	–	–
Height	124	0.87	(0.81-0.93)	(0.55, 1.00)	−0.19	1.49	.15
Weight	127	0.83	(0.77-0.90)	(0.36, 1.00)	−0.13	3.18	.64
Cardiopulmonary time in minutes	124	0.99	(0.98-1.01)	(0.97, 1.00)	−0.007	0.09	.32
Aortic cross-clamp time in minutes	124	1.00	–	(1.00, 1.00)	–	–	–
Operation time in hours and minutes	127	0.99	(0.98-1.01)	(0.93, 1.00)	−0.02	0.26	.32
Anesthesia time in hours and minutes	127	0.94	(0.89-0.98)	(0.64, 1.00)	−0.57	11	.56
Intubation (yes or no)	127	0.98	(0.96-1.01)	(0.86, 1.00)	–	–	–
Date and time of intubation	123	0.43	(0.34-0.52)	(0.12, 1.00)	−582	6526	.32
Date and time of extubation	115	0.79	(0.72-0.87)	(0.69, 1.00)	9.1	124	.41

Abbreviations: χ^2, chi-square; CI, confidence interval; SD, standard deviation.

[a] In this verification, we did not collect the data of nonregistered cases.

[b] Paired *t* test for numeric data and χ^2 test for categorical data.

[c] The measures of each numeric variable are as follows: day—date of birth, date of admission, date of surgery, date of death, and date of discharge; minute—cardiopulmonary time in minutes, aortic cross-clamp time in minutes, operation time in hours and minutes, anesthesia time in hours and minutes, date and time of intubation, and date and time of extubation; cm—height; and g—weight.

were falsely duplicated due to typing error or incomplete assignment of unique ID, and proportion of multiple cases in registered cases was 0.7% (9 of 1266). We could not confirm four cases in the operation log submitted by the hospitals. There were 13 cases that were not registered yet should have been eligible, and the proportion of unregistered cases in the recorded cases of operating log in hospitals was 1.0% (13 of [1266 + 13]).

Accuracy of Data Entry

Source documents for 2 of the 129 cases were not identified at the time of verification (one was in use by hospital staff for clinical purposes and the other was not prepared due to unknown reasons).

The following items displayed item-wise data accuracy higher than 95%: ID, gender, blood group, date of birth, date of admission, date of surgery, date of discharge, status at discharge, cardiopulmonary bypass time and aortic cross-clamp time, date of death, readmission within 30 days after surgery, and the status 30 and 90 days after surgery. Among them, status at 30 and 90 days after surgery exhibited a perfect match between registration and original records. The items with a proportion higher than 80% were height and weight, and those less than 80% were date and time of intubation and extubation. No statistically significant difference was found for postoperative hospital length of stay, age at operation, weight, height, and operation time (Table 2). Among the 129 cases, median case-wise accuracy was 91% with interquartile range of 86% to 95%.

Most of the data inconsistencies were due to typing errors. In addition, operation time, anesthetic time, and date and time of intubation and extubation were often inconsistently rounded up, out, or down by ten minutes the in registration records. The JCCVSD could not detect the date/time of height, weight, and other measurements that were repeated in a single hospitalization event, which hindered the identification of source records. Some data managers mistook the definition of date and time of intubation and incorrectly entered date and time at patient entry to the operation room.

Table 3. Time Spent for Data Verification.

	n	Mean (SD)	Median	Min – Max
All	110	7.1 (3.9)	6.0	2.0 – 20.0
Medium of source document				
Electric health record	64	7.7 (4.0)	6.0	2.0 – 20.0
Both electric health record and paper record	32	6.6 (3.7)	5.0	3.0 – 20.0
Paper record	14	5.4 (2.9)	5.0	2.0 – 11.0
Number of auditing staff to verify for each case				
One staff	71	8.0 (4.0)	6.0	3.0 – 20.0
Two staffs	39	5.5 (3.0)	5.0	2.0 – 15.0
Number and proportion of agreement items for each case				
25 items (100%)	29	6.9 (4.2)	6.0	2.0 – 20.0
23-24 items (90% < 99%)	36	5.9 (3.1)	5.0	2.0 – 15.0
20-22 items (80 < 90%)	33	8.3 (4.2)	8.0	3.0 – 20.0
<20 items (≤80%)	12	7.8 (3.5)	6.5	4.0 – 15.0

Abbreviation: SD, standard deviation.

Furthermore, in cases involving transfer to other facilities after surgery, completeness of the follow-up of survival information varied among the hospitals.

Time Spent for Data Verification

Median time for data verification per case was 6.0 minutes, ranging from 2.0 to 20.0 minutes (Table 3). Verification of paper-based records took a median of 5.0 minutes, while electronic and the combination of both types took 6.0 and 5.0 minutes, respectively ($P = .08$). Median time of verification was 6.0 minutes when one auditor conducted the verification, and 5.0 when both the auditors participated ($P < .05$). Concerning the degree of record accuracy per case, the median time in minutes was 6.0, 5.0, 8.0, and 6.5 for 100%, 90% to 99%, 80% to 90%, and ≤80%, respectively ($P < .05$).

Comment

Quality improvement initiatives need to be based on the scientific evidence generated from reliable and valid data. In this report, we demonstrated that the JCCVSD on pediatric cardiovascular surgeries achieved fairly complete registration of cases and accurate data collection of clinical information. Thus, this database could potentially be useful in improving the quality of care.

In regard to the completeness of registration, there were very few unregistered patients for the first operations in the same administration. Duplicated registration occurred mainly due to typing error and misassignment of unique patient ID. Such cases could have been avoided by fool-proof modification of data entry to display potential duplication if several essential variables (eg, ID, birth date, sex, and date of surgery) were identical. More fundamentally, however, a hospital's capacity to maintain operation logs and other clinical record documentation in an accountable and traceable fashion is essential. An interview with a data manager revealed that failed registration happened, because the site hospitals differently interpreted the registration criteria for subsequent operations during the same administration and arbitrarily decided whether such cases should be registered as independent operation or operative complication for any reason after surgery. This underscores the importance of keeping data managers informed about the criteria for clarification. As such, validation could involve interactive processes between daily practice at the site hospitals and refinements of the registration system.

As to the accuracy of data, categorical information such as demographics showed a high proportion of consistency. Continuous variables presented a lower level of accuracy due to inconsistent use of rounding up, mistyping, and other technical reasons; however, the difference between the submitted data and the source documents was relatively small. Some clinical databases have adopted "acceptable range" for the judgment of data consistency for continuous variables.[21] As such, the judgment rule of accuracy for continuous variables is a matter of debate in other databases.[19,21] Training of data managers in each site hospital was also essential for accurate data collection through enhanced compliance with the definition of data items. The display design of entry form was another influential factor in avoiding entry errors. In this regard, the JCCVSD has some important factors to maintain high-quality data, such as nomination of the data manager in charge of securing data traceability, a fool-proof entry system that does not allow missing values for essential information, and organizing a meeting of data managers twice each year for continuous training.

Another characteristic of the JCCVSD is high accuracy in follow-up outcomes, especially the 90-day mortality after surgery, compared to other congenital databases,[17] which warrants some discussion. Success of patient follow-up could be attributed to social environments specific to Japan, such as longer length of hospital stay, limited number of hospitals eligible for congenital heart surgery, and better accessibility to continuous treatment under universal coverage by public health insurance system.[22]

When the activities of data audit expand, we should take serious account of efficiency in terms of cost and time. As we evaluated the time required for data verification, paper-based source and the number of auditors were significant factors to reduce the time. However, we have not yet determined how many auditors are most efficient in what conditions. Additionally,

the time for data verification can be affected by whether hospitals have standardized formats of medical records or not. The methodology of data verification of clinical databases remains to be systematically studied, and we acknowledge the need of further surveys to establish standardized and efficient mode of data verification in comparison with examples from other recommendations.[23] Appropriate size and method of sampling for validation is another important factor to determine efficiency as well as validity of audit. In this regard, the current data verification chose six hospitals in an ad hoc manner, which should be recognized as a study limitation.

The present study demonstrates the initial success of the JCCVSD in high-quality data collection for improvement in the quality of pediatric cardiovascular surgery. However, we are still challenged by some limitations for further improvements. First, hospitals adopted a variety of record formats for operation logs that seriously hindered standardized data collection and threatened the results of our assessment of registry completeness. This should be resolved through standardization of clinical information on operation logs based on the subspecialty consensus. Second, we found that the registration of adult cases with congenital heart conditions could be problematic, given that such a case may be inconsistently registered to the adult cardiovascular surgery database rather than pediatric database. This should also be solved by consensus building among the subspecialty circle. Third, as already mentioned, half of the hospitals we surveyed were selected randomly, but the rest were selected by request from the JCCVSD committee. Thus, there might be selection bias of hospitals. Furthermore, we did not calculate sample size for statistical power, which might have led to overlooking significant inconsistency. Fourth, we should add other important variables for data verification of clinical databases. For example, diagnosis, procedure, and outcomes (eg, postoperative complications) are important information as fundamental statistics in clinical databases. Assessment of accuracy in coding these variables with systematic method of verification will be required to assure quality of clinical database.

In summary, we conducted data verification of the JCCVSD and found that data of the JCCVSD in 2008 to 2009 exhibited high completeness of registration and accuracy of data entry. The initial success in quality assurance of the JCCVSD should be strengthened through further sophistication of registration protocol, continual training of data managers and auditors, and rigorous expansion of verification activities.

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ORIGINAL ARTICLE – ADULT CARDIAC

Surgical results of reoperative tricuspid surgery: analysis from the Japan Cardiovascular Surgery Database†

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Abstract

OBJECTIVES: Tricuspid valve insufficiency (TI) following cardiovascular surgery causes right-side heart failure and hepatic failure, which affect patient prognosis. Moreover, the benefits of reoperation for severe tricuspid insufficiency remain unclear. We investigated the surgical outcomes of reoperation in TI.

METHODS: From the Japan Cardiovascular Surgery Database (JACVSD), we extracted cases who underwent surgery for TI following cardiac surgery between January 2006 and December 2011. We analysed the surgical outcomes, specifically comparing tricuspid valve replacement (TVR) and tricuspid valve plasty (TVP).

RESULTS: Of the 167 722 surgical JACVSD registered cases, reoperative TI surgery occurred in 1771 cases, with 193 TVR cases and 1578 TVP cases. The age and sex distribution was 684 males and 1087 females, with an average age of 66.5 ± 10.8 years. The overall hospital mortality was 6.8% and was significantly higher in the TVR group than in the TVP group (14.5 vs 5.8%, respectively; $P < 0.001$). Incidences of dialysis, prolonged ventilation and heart block were also significantly higher in the TVR group than in the TVP group. Logistic regression analysis revealed that the risk factors of hospital mortality were older age, preoperative renal dysfunction, preoperative New York Heart Association Class 4, left ventricular dysfunction and TVR.

CONCLUSIONS: Surgical outcomes following reoperative tricuspid surgery were unsatisfactory. Although TVR is a last resort for non-repairable tricuspid lesions, it carries a significant risk of surgical mortality. Improving the patient's preoperative status and opting for TVP over TVR is necessary to improve the results of reoperative tricuspid surgery.

Keywords: Tricuspid valve • Reoperation • Database

INTRODUCTION

Tricuspid valve insufficiency (TI) following cardiovascular surgery causes right-sided heart failure and hepatic failure, which affect the prognosis [1, 2]. Tricuspid valve repair after cardiac surgery is less commonly performed than left-sided valve repair, and there are relatively few reports with small samples [3–5]. Thus, the outcomes of surgical intervention for severe tricuspid insufficiency remain unclear. The Japan Adult Cardiovascular Surgery Database (JACVSD) is a nationwide database established in 2000. The number of participating hospitals has gradually increased, and now, most hospitals performing cardiovascular surgeries have been enrolled. The Japan System for Cardiac Operative Risk Evaluation (Japan SCORE) is a risk model developed from JACVSD [6–8]. Therefore, we used JACVSD to examine the results of surgical treatment for TI following cardiac surgery. The objective of this study is to analyse the surgical outcomes, specifically comparing tricuspid valve replacement (TVR) and tricuspid valve plasty (TVP).

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MATERIALS AND METHODS

Study population

JACVSD was established to facilitate evaluation of surgical outcomes after cardiovascular procedures in centres throughout Japan. It currently captures clinical information from most Japanese hospitals. The data collection form has a total of 255 variables that are almost identical to those of the Society of Thoracic Surgeons' (STS) National Database [(definitions are available online at Websites: Japan Adult Cardiovascular Database. http://www.jacvsd.umin.jp) (The Society of Thoracic Surgeons. http://sts.org)]. JACVSD has developed a software for web-based data collection that enables the data manager at participating hospitals to electronically submit the data to the central office. Although participation in JACVSD is voluntary, data completeness is high, and the accuracy of submitted

data is maintained by regular data auditing in which monthly visits are made to participating hospitals to check the reported data against clinical records. Data validity is further confirmed by independent comparison of the cardiac surgery volume at specific hospitals entered in JACVSD with that reported in the annual survey of the Japanese Association for Thoracic Surgery.

Comparison of tricuspid valve replacement with tricuspid valve plasty cases

We examined all patients undergoing tricuspid valve repair after primary cardiac surgery between 1 January 2006 and 31 December 2011. In particular, we compared TVR with TVP cases. JACVSD records obtained without informed patient consent were excluded. Approximately 20% of patients were asymptomatic; however, they had some evidence of deterioration of end-organ function such as that of liver or kidney. Records with missing age (or age out of range), missing sex or missing 30-day status were also excluded.

Hospital death was defined as follows: death from any cause within 30 days after surgery if the patient was discharged from hospital or death at any time if the patient was not discharged. Using the definition from a previous study, major morbidity was defined as any of the following five postoperative in-hospital complications: stroke, reoperation for any reason, mechanical ventilation beyond 24 h after surgery, renal failure or deep sternal wound infection [9, 10].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were compared using the χ^2 test or Fisher's exact test. Continuous variables were compared using Student's *t*-test. In case of non-normal distribution, the non-parametric Wilcoxon test was used. Logistic regression analysis was used to identify independent predictors of clinical outcomes. Predictors associated with a *P* value of <0.2 on univariate analysis were entered into multivariate analysis using stepwise selection. Results were expressed using hazard ratios. Preoperative patient risk factors in the JACVSD risk models were entered as independent variables. All *P* values were two sided, and $P < 0.05$ was considered statistically significant.

RESULTS

There were 167 722 surgical cases from 516 participating institutes throughout Japan registered with JACVSD. After applying the exclusion criteria, the available population for analysis was 1771 cases who underwent tricuspid insufficiency repair following primary cardiac surgery. These included 193 cases of TVR and 1578 cases of TVP.

Baseline characteristics

Comparisons of baseline characteristics between the TVR and TVP groups are presented in Table 1. There were 684 male and 1087 female patients, with an average age of 66.5 ± 10.9 years. Patients in the TVR group were significantly younger than those in the TVP group ($P = 0.002$). Furthermore, the patients undergoing TVR had a higher prevalence of hypertension and hyperlipidaemia. Among all the patients, 738 (41.7%) were New York Heart Association (NYHA) Class 3 or 4; the TVR group also had a higher incidence of NYHA Class 3 or 4 ($P < 0.001$) and preoperative congestive heart failure within 2 weeks of surgery ($P < 0.001$).

Of the total number of patients, 229 (12.9%) had cerebrovascular disease (CVD), and the prevalence of CVD in the TVP group was higher than that in the TVR group ($P = 0.013$). The prevalence rate of renal failure and infective endocarditis was 171 (9.7%) and 143 (8.1%) cases, respectively, and there was no difference between the groups. Urgent and emergency surgery was required in 61 (3.4%) and 21 patients (1.2%), respectively, and the rates were similar in both groups. The 30-day mortality and hospital mortality calculated by the Japan SCORE were 7.4 ± 9.1 and 10.3 ± 11.5%, respectively, and they were similar between the two groups.

Cardiac status and concomitant procedure

Comparison of cardiac status and concomitant procedures between the TVP and TVR groups are presented in Tables 2 and 3. The TVP group patients had a higher prevalence of aortic valve stenosis ($P = 0.008$), mitral valve stenosis and concomitant aortic valve replacement ($P < 0.001$), mitral valve replacement ($P < 0.001$) and multiple valve operations performed ($P < 0.001$). More than half of the patients in the TVR group underwent single valve operations. The patients in the TVR group also had a higher incidence of TI Grade 3 or 4 ($P < 0.001$) and tricuspid stenosis ($P < 0.001$).

Surgical results

Comparison of surgical results is presented in Table 4. Aortic clamp time was significantly longer in the TVP group (20 min). The overall intubation time was 58 ± 237 h; in the TVR group, it was 115 ± 396 h, which was significantly longer than that in the TVP group ($P < 0.001$). Intensive care unit stay was also significantly longer in the TVR group ($P < 0.001$). Actual mortality was lower than logistic mortality, except for hospital mortality in the TVR group.

Morbidities are shown in Table 5. More than 14% of all patients were ventilated for longer than 24 h, and this figure approached 20% in the TVR group. The total number of renal failure and hemodialysis cases was 181 (10.2%) and 100 (5.6%), respectively, with more cases in the TVR group ($P = 0.01$) than in the TVP group ($P = 0.044$). Heart block occurred in 7.8% of the TVR group patients. Gastrointestinal bleeding and multiorgan failure were also significantly higher in the TVR group, at *P* values of 0.008 and 0.001, respectively.

Risk factor analysis

Risk factors for operative death are displayed in Table 6. The following were determined to be risk factors for operative death: age, NYHA Class 4, renal dysfunction, active infective endocarditis, shock, inotropic agent use, aortic stenosis, left ventricular dysfunction and TVR. Preoperative status, including the use of inotropes and shock, also had a high hazard ratio. The hazard ratio for TVR was 3.188.

Table 1: Baseline characteristics

	Total (n = 1771)	TVR (n = 193)	TV repair (n = 1578)	P value
Age (years)	66.5 ± 10.9	63.4 ± 13.3	66.6 ± 10.5	0.002
Body surface area (m^2)	1.49 ± 0.17	1.49 ± 0.17	1.49 ± 0.19	0.617
Body mass index	20.9 ± 3.05	21.0 ± 3.5	20.9 ± 3.0	0.445
Male:female	684:1087	71:122	613:965	0.579
Smoking	417 (23.5%)	37 (19.2%)	380 (24.1%)	0.129
Diabetes mellitus	281 (15.9%)	26 (13.5%)	255 (16.2%)	0.335
Diabetes mellitus therapy	207 (11.7%)	22 (11.4%)	185 (11.7%)	0.895
Hyperlipidaemia	371 (17.6%)	18 (9.3%)	293 (18.6%)	*0.001
Hypertension	625 (35.3%)	50 (25.9%)	575 (36.4%)	*0.004
NYHA 3 or 4	738 (41.7%)	107 (55.4%)	631 (40.0%)	*< 0.001
Canadian Cardiovascular Society 3 or 4	77 (4.3%)	14 (7.3%)	63 (4.0%)	*0.036
Urgent	61 (3.4%)	7 (3.6%)	54 (3.4%)	0.883
Emergent	21 (1.2%)	2 (1.0%)	19 (1.2%)	0.839
Renal failure	171 (9.7%)	21 (10.9%)	150 (9.5%)	0.541
Hemodialysis	41 (2.3%)	3 (1.6%)	38 (2.4%)	0.457
Creatinin (mg/dl)	1.18 ± 5.2	1.06 ± 0.62	1.20 ± 5.5	0.497
Cerebrovascular disorder	229 (12.9%)	14 (7.3%)	215 (13.6%)	*0.013
Recent cerebrovascular disorder	12 (0.7%)	2 (1.0%)	10 (0.6%)	0.52
Infectious endocarditis	143 (8.1%)	14 (7.3%)	129 (8.2%)	0.658
Active infectious endocarditis	76 (4.3%)	5 (2.3%)	71 (4.5%)	0.217
Moderate-to-severe respiratory disorder	102 (5.8%)	14 (7.3%)	88 (5.6%)	0.345
Extracardiovascular disease	99 (5.6%)	11 (5.7%)	88 (5.6%)	0.944
Peripheral artery disease	68 (3.8%)	7 (3.6%)	61 (3.9%)	0.871
Thoracic vascular disease	48 (2.7%)	6 (3.1%)	42 (2.7%)	0.718
Neurological disorder	30 (1.7%)	2 (1.0%)	28 (1.8%)	0.453
Myocardial infarction	50 (2.8%)	5 (2.6%)	45 (2.9%)	0.836
Angina pectoris	71 (4.0%)	5 (2.6%)	66 (4.2%)	0.287
Unstable angina pectoris	11 (0.6%)	1 (0.5%)	10 (0.6%)	0.847
Congestive heart disease	795 (44.9%)	124 (64.2%)	671 (42.5%)	*<0.001
Shock	34 (1.9%)	4 (2.1%)	30 (1.9%)	0.87
Atrial fibrillation	1053 (59.5%)	106 (54.9%)	947 (60.0%)	0.174
Inotropic agents	30 (1.7%)	5 (2.6%)	25 (1.6%)	0.306
Percutaneous cardiac intervention	64 (3.6%)	6 (3.8%)	58 (3.7%)	0.69
Logistic 30-day mortality	7.4 ± 9.1%	6.7 ± 9.2%	7.5 ± 9.1%	0.257
Logistic operative mortality	10.3 ± 11.5%	10.8 ± 11.9%	10.2 ± 11.4%	0.532
Logistic 30-day mortality and morbidity	32.7 ± 14.9%	36.7 ± 15.6%	32.2 ± 14.7%	*<0.001

TV: tricuspid valve; TVR: tricuspid valve replacement.
*Means significant.

Table 2: Cardiac status

	Total (n = 1771)	TVR (n = 193)	TV repair (n = 1578)	P-value
Tricuspid stenosis	15 (0.8%)	12 (6.2%)	15 (0.2%)	*<0.001
Tricuspid valve insufficiency 3 or 4	1072 (60.5%)	149 (77.2%)	923 (58.5%)	*<0.001
Aortic stenosis	372 (21%)	25 (13.0%)	347 (21.0%)	*0.004
Mitral stenosis	719 (40.6%)	26 (13.5%)	693 (43.9%)	*<0.001
Pulmonary stenosis	4 (0.2%)	1 (0.5%)	3 (0.2%)	0.365
AV insufficiency 3 or 4	141 (8.0%)	6 (3.1%)	135 (8.6%)	*0.008
MV insufficiency 3 or 4	744 (42%)	45 (23.3%)	699 (44.3%)	*<0.001
Triple vessel disease	38 (2.1%)	1 (0.5%)	2.3 (4.8%)	*0.098
Left main trunk	31 (1.8%)	1 (0.5%)	30 (2.2%)	0.167
Left ventricle function medium or bad	818 (46.2%)	110 (57.0%)	708 (44.9%)	*0.008

AV: aortic valve; MV: mitral valve; TV: tricuspid valve; TVR: tricuspid valve replacement.
*Means significant.

DISCUSSION

Tricuspid valve regurgitation is harmful to long-term survival and can lead to biventricular heart failure. Tricuspid regurgitation, which is at least moderate, has been associated with increased mortality, regardless of the pulmonary artery systolic pressure of left ventricular ejection fraction [1]. Indeed, guidelines indicate the need for more aggressive treatment of tricuspid regurgitation [11].

Table 3: Concomitant procedures

	Total (n = 1771)	TVR (n = 193)	TV repair (n = 1578)	P-value
Aortic valve plasty	19 (1.1%)	1 (0.5%)	18 (1.1%)	0.428
Aortic valve replacement	467 (26.4%)	24 (12.4%)	443 (28.1%)	*<0.001
Mitral valve plasty	182 (10.2%)	11 (5.7%)	170 (10.8%)	*0.028
Mitral valve replacement	1268 (71.6%)	67 (34.3%)	1201 (76.1%)	*<0.001
Single valve operation	158 (8.9%)	99 (51.3%)	59 (3.7%)	*<0.001
Multivalve operation	1613 (91.1%)	94 (48.7%)	1519 (96.3%)	*<0.001
Triple valve operation	333 (18.8%)	11 (5.7%)	322 (20.4%)	*<0.001
Coronary artery bypass grafting	96 (5.4%)	4 (2.1%)	92 (5.8%)	*0.03

TV: tricuspid valve; TVR: tricuspid valve replacement.
*Means significant.

Table 4: Surgical outcomes

	Total (n = 1771)	TVR (n = 193)	TV repair (n = 1578)	P-value
Operation time (min)	432 ± 145	457 ± 176	429 ± 140	*0.031
Extracorporeal circulation time (min)	204 ± 80.2	201 ± 100	204 ± 77	0.586
Clamp time (min)	133 ± 54	110 ± 64	135 ± 53	*<0.001
Intubation time (h)	58 ± 237	115 ± 396	51 ± 208	*<0.001
ICU stay longer than 8 days	260 (14.7%)	48 (24.9%)	212 (13.4%)	*<0.001
30-day mortality (%)	69 (3.9%)	13 (6.7%)	56 (3.6%)	*0.031
Hospital mortality (%)	120 (6.8%)	28 (14.5%)	92 (5.8%)	*<0.001
30-day mortality and morbidity	405 (22.9%)	52 (26.9%)	353 (22.9%)	0.153

TV: tricuspid valve; TVR: tricuspid valve replacement; ICU: intensive care unit.
*Means significant.

Table 5: Morbidities

	Total (n = 1771)	TVR (n = 193)	TV repair (n = 1578)	P-value
Reoperation for bleeding	137 (7.7%)	15 (7.8%)	122 (7.7%)	0.984
Stroke	39 (2.2%)	2 (1.0%)	37 (2.3%)	0.242
Prolonged ventilation (over 72 h)	257 (14.5%)	38 (19.7%)	219 (13.9%)	*0.031
Pneumonia	115 (6.5%)	25 (13.0%)	90 (5.7%)	*<0.001
Renal failure	181 (10.2%)	30 (15.5%)	151 (9.6%)	*0.01
Dialysis required	100 (5.6%)	17 (8.8%)	83 (5.3%)	*0.044
Heart block	73 (4.1%)	15 (7.8%)	58 (3.7%)	*0.007
Gastrointestinal bleeding	55 (3.1%)	12 (6.2%)	43 (2.7%)	*0.008
Multiorgan failure	64 (3.6%)	15 (7.8%)	49 (3.1%)	*0.001

Prolonged ventilation: ventilation for more than 24 h; Renal failure: postoperative creatinine level twice the preoperative level; TV: tricuspid valve; TVR: tricuspid valve replacement.
*Means significant.

For recurrent cases of isolated tricuspid regurgitation, reoperation is associated with high mortality rates and is rarely recommended [3–5, 12–14]. In this study, many of the patients requiring tricuspid valve repair following cardiac surgery had severe preoperative statuses, with prior congestive heart failure, poor cardiac function, NYHA Class 3 or 4 and CVD. The patients in the TVR group had a higher prevalence of congestive heart failure, NYHA Class 3 or 4 and poor left ventricular function than those in the TVP group.

The TVP group patients had a higher prevalence of comorbid valve disease than the TVR group patients, requiring more concomitant valve procedures rather than a relatively simple, isolated tricuspid valve repair. The patients in the TVR group had higher grades of TI and stenosis requiring isolated TVR operations. Despite the complex multivalve procedures in the TVP group, extracorporeal circulation time was similar between the two groups and operation time was significantly longer in the TVR group. This

Table 6: Risk factors for operative death

Variables	Univariate *P*-value	Multivariate *P*-value	HR	95% CI
Age	<0.001	0.001	1.255	1.091–1.443
NYHA 4	<0.001	<0.001	2.739	1.569–4.782
Renal dysfunction	<0.001	0.001	2.575	1.554–4.268
Active infectious endocarditis	<0.001	0.014	2.494	1.204–5.164
Shock	<0.001	0.002	4.189	1.727–10.163
Inotropic agents	<0.001	0.007	3.519	1.403–8.824
Aortic stenosis	0.38	0.017	1.8	1.109–2.924
Left ventricle dysfunction	<0.001	0.001	2.031	1.332–3.097
Tricuspid valve replacement	<0.001	<0.001	3.188	1.93–5.266

HR: heart rate; 95% CI: 95% confident interval; NYHA: New York Heart Association.

suggests that TVR was performed after failed repair due to severe tricuspid regurgitation and stenosis, resulting in prolonged extracorporeal circulation and operative time. The poorer preoperative status of patients in the TVR group resulted in significantly worse surgical results despite similar surgical results in both groups.

TVR is the last resort for nonrepairable tricuspid pathology. The hospital mortality of TVR is unsurprisingly higher than that of TVP [1, 3, 15, 16]. There are few articles focusing on tricuspid valve reoperation or repair. Park *et al.* [3] and Jeong *et al.* [5] included small samples and reported hospital mortality rates at 0 and 2%, respectively. In an earlier nationwide study that included primary operation, Shabocky *et al.* reported an overall in-hospital mortality rate of 10.6%, with 13.6% in the TVR group and 9.5% in the TVP group [13]. We found an overall mortality rate of 6.8%, with the TVR and TVP groups at 14.5 and 5.8%, respectively. Therefore, our hospital mortality for reoperation was lower.

Various risk factors have been identified previously. Jeong *et al.* [5] reported age and low ejection fraction as risk factors for tricuspid reoperation. Jeganathan *et al.* [12] reported age, male gender, postoperative low cardiac output syndrome and stroke as risk factors for early death with neither pathology nor surgery type influencing early mortality. However, in this study, multivariate analysis revealed that, in addition to the preoperative status (i.e. age, NYHA class, renal function, infective endocarditis, shock, neck vessel stenosis and active infective endocarditis), TVR itself was a major risk factor for operative death, with a hazard ratio of 3.188. To minimize TI after cardiac surgery, it is important to improve a patient's preoperative status and avoid TVR where possible.

According to the ESC/EACTS guideline [17], isolated operation on the tricuspid valve should be considered for persistent or recurrent severe TR after left-sided valve surgery either for symptomatic or asymptomatic patients having progressive RV dilatation or dysfunction. Valve repair is preferable to valve replacement and surgery should be carried out early enough to avoid irreversible RV dysfunction and better management.

Limitations

Although this study is a relatively large-scale, multicentre study, it is retrospective in design. For patients with tricuspid valve disease, liver dysfunction resulting from right-sided heart failure is an important issue; however, data regarding liver function have only recently been included in JACVSD and have not been obtained in this study. There is a potential selection bias inherent to a database dataset. 'Because of the large number difference between the two groups, good matched pairs or propensity score matching analysis was not possible'.

Furthermore, information on the previous operation was lacking because the categorizations in the database were changed during the study period. The late outcome and quality-of-life data were also not available in the database.

CONCLUSION

In conclusion, we described reoperation for tricuspid valve repair following cardiac surgery. Many of the patients had complex comorbidities and poor cardiac function. Therefore, the operative risk was high, and the results were not entirely satisfactory. However, we were able to determine that TVR itself carries a significant risk of operative mortality. Improvement of a patient's preoperative status and choice of TVP over TVR are important factors that can improve the outcomes of reoperation for tricuspid valve repair following cardiac surgery.

Conflict of interest: none declared.

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