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ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH AND BIOMARKERS

TGFBI Expression in Cancer Stromal Cells is Associated with Poor Prognosis and Hematogenous Recurrence in Esophageal Squamous Cell Carcinoma

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ABSTRACT

Background. Esophageal squamous cell carcinoma (ESCC) is an important cause of cancer-related death worldwide. To improve prognoses in patients with ESCC, we evaluated the potential of transforming growth factor-beta-induced protein (*TGFBI*), which is overexpressed in ESCC, as a therapeutic candidate.

Methods. We examined the clinical significance of *TBFBI* in 102 ESCC samples using real-time RT-PCR. Immunohistochemical studies were conducted to examine the localization of TGFBI. Knockdown of *TGFBI* in cocultured fibroblasts was performed to determine the roles of *TGFBI* in migration and invasion.

Results. The level of *TGFBI* in ESCC tissues was higher than that in normal tissues. The high *TGFBI* expression group ($n = 16$) had higher *TGFBI* expression and more frequent hematogenous recurrence than the low-expression group ($n = 86$). High *TGFBI* expression was an independent prognostic factor in patients with ESCC. TGFBI was mainly localized in stromal cells of ESCC. Moreover, suppression of *TGFBI* in fibroblasts inhibited the migration and invasion capacity of TE8 ESCC cells.

Conclusions. High *TGFBI* expression in ESCC tissues could be a powerful biomarker of poor prognosis and hematogenous recurrence. *TGFBI* in stromal cells might be a promising molecular target for ESCC treatment.

Esophageal cancer is a common cancer worldwide, and is associated with a very poor prognosis.[1,2] In particular, esophageal squamous cell carcinoma (ESCC) is the most prevalent type of esophageal cancer, particularly in Asia. Clinical indicators that predict progression and prognosis in ESCC are essential for improving patient survival. In a previous study, we found that expression of transforming growth factor-beta-induced protein (*TGFBI*) was higher in ESCC than in normal tissues, suggesting that *TGFBI* may be a potential prognostic marker for ESCC.[3]

TGFBI is a secreted 683-amino acid extracellular matrix (ECM) protein with four evolutionarily conserved fasciclin-1 domains and a C-terminal Arg-Gly-Asp motif.[4] TGFBI is induced by transforming growth factor-beta (TGF-β) in various human cell types.[5,6] Moreover, TGFBI plays an important role in a wide range of cellular conditions, including tumorigenesis, corneal dystrophy, and diabetes.[7–10]

In tumor cells isolated from various types of cancers, *TGFBI* functions as a tumor suppressor, and hypermethylation of *TGFBI* has been observed in tumor cells.[11–15] Moreover, TGFBI expression in the ECM has been shown to induce better responses to paclitaxel via microtubule stabilization in ovarian cancer cells.[16] Additionally, in the ECM, TGFBI has been shown to facilitate cancer metastasis via promoting extravasation of colon cancer cells.[17] In renal clear cell carcinoma, TGFBI expression is a promising prognostic marker.[18] Therefore, TGFBI has different functions in cancer progression, acting as an oncogenic protein or tumor suppressor, depending on the cell context.

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The purpose of this study was to clarify the function and clinical significance of *TGFBI* in ESCC. To this end, we used real-time RT-PCR to evaluate the relationships between *TGFBI* expression and clinicopathological factors in clinical ESCC samples. Moreover, we examined whether in vitro siRNA-mediated *TGFBI* suppression in KMST6 fibroblasts influenced the migration and invasion capacity in cocultured human TE8 ESCC cells.

MATERIALS AND METHODS

Patients and Tissues

Ninety men and 12 women diagnosed with ESCC were included in the study. Cancerous and corresponding normal esophageal tissues were obtained from the patients who had undergone curative surgery at the Department of General Surgical Science, Gunma University, between 1997 and 2009 (Table 1). Tissue samples were immediately frozen in liquid nitrogen and stored at −80 °C until RNA isolation. These samples were used after obtaining written informed consent in accordance with institutional guidelines and the Declaration of Helsinki.

Pretreatment clinical tumor stage was classified using the seventh edition of the International Union Against Cancer (UICC) TNM classification. The mean postoperative follow-up period for the 102 patients was 37.3 (range 0.7–126.4) months. None of the patients had received irradiation or chemotherapy before surgery, and none had presented with hematogenic metastases at the time of surgery. Postoperative recurrence was diagnosed by diagnostic imaging [computed tomography (CT), fludeoxyglucose-positron emission tomography/CT, endoscopy], pathological diagnosis, and/or clinical progress.

RNA Isolation and Quantitative RT-PCR

Total RNA was extracted using a miRNeasy mini kit (Qiagen, Venlo, Netherlands). RNA was quantified using a Nanodrop 1000 (Thermo Scientific, Wilmington, DE, USA). Each cDNA was synthesized from 10 ng of total RNA using an Omniscript RT kit (Qiagen) according to the manufacturer's protocol. For *TGFBI* and *TGFB1* mRNA evaluation, quantitative real-time RT-PCR was performed from 10 ng total RNA from each of 108 ESCC patients by using the GoTaq® 1-Step RT-qPCR System (Promega, Madison, WI) according to the manufacturer's protocols. The mRNA levels of these target genes were then quantified using a LightCycler 480 instrument (Roche Applied Science) with specific TGFBI primers (forward, 5′-GTGT GTGCTGTGCAGAAGGT-3′ and reverse, 5′-TTGAGAG TGGTAGGGCTGCT-3′) and TGFB1 primers (forward, 5′-CAGCAACAATTCCTGGCGATA-3′ and reverse, 5′-A AGGCGAAAGCCCTCAATTT-3′). The expression levels were normalized to those of β-actin, amplified using specific primers (forward, 5′-CTCCTCCTGAGCGCAAGTA CTC-3′ and reverse, 5′-TCCTGCTTGCTGATCCACATC-3′).

TABLE 1 *TGFBI* expression and clinicopathological factors in 102 ESCC patients

Factors	TGFBI/β-actin		
	Low expression $n = 86$	High expression $n = 16$	P value
Age (year)	64.6 + 7.9	63.4 + 5.7	0.59
Gender			
Male	75	15	0.69
Female	11	1	
T factor			
T1, 2	30	6	1
T3, 4	56	10	
N factor			
Absent	30	4	0.57
Present	56	12	
M factor			
Absent	69	14	0.73
Present	17	2	
Lymphatic invasion			
Absent	8	1	1
Present	78	15	
Venous invasion			
Absent	16	5	0.31
Present	70	11	
Stage			
I	12	2	0.83
II	27	6	
III	28	6	
IV	19	2	
TGF-β1 expression			
Low	49	2	0.0019*
High	37	14	
Recurrence			
Absent	59	8	0.16
Present	27	8	
Recurrence of lymph node metastasis (f)			
Absent	71	11	0.3
Present	15	5	
Recurrence of hematogenous metastasis (f)			
Absent	75	10	0.025*
Present	11	6	

* $P < 0.05$, f site of first recurrence

Immunohistochemistry

Four-micron sections were cut from paraffin blocks of ESCC samples. Each section was mounted on a silane-coated glass slide, deparaffinized, and soaked for 30 min at room temperature in 0.3 % H_2O_2/methanol to block endogenous peroxidases. The sections were then heated in boiled water and Immunosaver (Nishin EM; Tokyo, Japan) at 98 °C for 45 min. Nonspecific binding sites were blocked by incubation with Protein Block Serum-Free (DAKO, CA, USA) for 30 min. An anti-TGFBI specific antibody (Proteintech, Chicago, IL, USA) was applied at a dilution of 1:100 for 24 h at 4 °C. The primary antibody was visualized using the Histofine Simple Stain MAX-PO (Multi) Kit (Nichirei, Tokyo, Japan) according to the instruction manual. The chromogen 3,3′-diaminobenzidine tetrahydrochloride was applied as a 0.02 % solution containing 0.005 % H_2O_2 in 50 mM ammonium acetate-citrate acid buffer. The sections were lightly counterstained with Mayer's hematoxylin and mounted. Negative controls were established by omitting the primary antibody, and no detectable staining was evident.

Cell Lines

The cell lines Het1A, TE1, TE8, TE15, KYSE70, and KMST6 were obtained from the American Type Culture Collection (ATCC), the Cell Resource Center of Biochemical Research, Institute of Development, Aging and Cancer, Tohoku University, and JCRB cell bank. These cell lines were maintained in Roswell Park Memorial Institute (RPMI-1640) medium (Wako Pure Chemical Industries) containing 10 % fetal bovine serum (FBS) and antibiotics (100 U/mL penicillin and 100 µg/mL streptomycin) and were cultured in a humidified 5 % CO_2 incubator at 37 °C.

RNA Interference of TGFBI

For TGFBI silencing, SMARTpool siRNAs consisting of four pools of short-interfering RNA (siRNA) were purchased from Dharmacon (CO, USA). Lipofectamine RNAi MAX (Invitrogen, CA, USA) and *TGFBI*-specific siRNA were incubated in 6-well microtiter plates. After incubation, KMST-6 cells were seeded in the plates at 2.0×10^5 cells/well in a volume of 2 mL and incubated in a humidified atmosphere (37 °C and 5 % CO_2). Scrambled siRNA was used as a negative control. The cells were collected after 72 h for subsequent experiments.

Western Blot Analysis

Total protein was extracted from Het1A, TE1, TE8, TE15, KYSE70, and KMST6 cells using PROPREP protein extraction solution (Intron Biotechnology, Inc.). Total protein (10 µg) was electrophoresed through Nu-PAGE 4–12 % Bis–Tris gels (Invitrogen) and then electrotransferred to PVDF membranes using an iBlot Gel Transfer Device. The membrane was blocked with 5 % skim milk, and anti-TGFBI polyclonal antibodies (1:1,000) were used for TGFBI protein detection (Proteintech). Anti-β-actin mouse monoclonal antibodies (clone AC-74; Sigma) diluted 1:1,000 served as a control. Bands were detected using ECL Prime Western Blotting Detection Reagents, and band intensities were calculated using an Image Quant LAS 4000.

Wound Healing Assay

TE8 (2.5×10^6) and KMST-6 (1×10^6) cells were plated using a coculture model. TE8 cells were seeded in 24-well plates, and KMST6 cells transfected with *TGFBI* siRNA were seeded in the upper chamber. After the growing TE8 cell layers had reached confluence, a wound was made by scratching a straight line using a pipette tip. The cells were then washed twice and incubated with 10 % FBS containing RPMI. We subsequently evaluated the closure or filling in of the wound at 24 h after wounding using bright-field microscopy at 40× magnification. All experiments were performed in quadruplicate.

Matrigel Invasion Assay

Invasion of TE8 cells was analyzed using Matrigel-coated invasion chambers (BD Biosciences, Japan). KMST6 cells were seeded in 24-well plates in RPMI containing 10 % FBS, and TE8 cells were seeded in serum free media in the Matrigel upper chamber. After incubation for 24 h, chambers were removed, washed with phosphate-buffered saline, and cleaned using cotton swab. The cells were then fixed in methanol and stained with Diff-Quik stain (Sysmex, Japan). The membranes were cut and observed under 40× magnification using bright-field microscopy.

Statistical Analysis

Statistically significant differences were analyzed with Student's *t* test for continuous variables and the Chi square test for categorical variables. Survival curves were generated according to the Kaplan–Meier method. The differences between overall survival curves were examined using the log-rank test. Univariate and multivariate survival analyses were performed using Cox's proportional hazards model. Analysis of variance (ANOVA) was used to assess the statistical significance of in vitro assays. A probability value of less than 0.05 was considered significant. All statistical analyses were performed using JMP5.0 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Expression of TGFBI in Clinical ESCC Samples

TGFBI expression was examined by quantitative RT-PCR in 102 curative resected ESCC tissues and corresponding normal tissues. The expression of TGFBI in tumor tissues was significantly higher than that of normal tissues ($P = 0.0014$; Fig. 1a).

To investigate protein localization of TGFBI in ESCC tissues, immunohistochemical analysis was performed on 41 available clinical ESCC samples. Expression of TGFBI was localized to the cytoplasm in ESCC (Fig. 2a). In five cases (12.2 %, 5/41), expression of TGFBI in marginal regions of primary ESCC was stronger than in the central regions of ESCC and normal tissues (Fig. 2a). However, most cases (87.8 %, 36/41) did not show TGFBI expression in squamous epithelial cells, including ESCC cells,

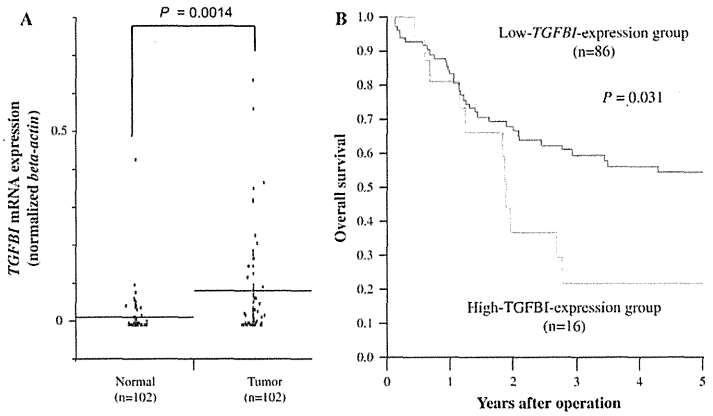

FIG. 1 Clinical significance of TGFBI mRNA expression in clinical ESCC samples. **a** *TGFBI* mRNA expression in tumor and normal tissues from ESCC patients by real-time RT-PCR ($n = 102$). *Horizontal lines* indicate means ($P = 0.014$). **b** Kaplan–Meier overall survival curves of ESCC patients according to the level of *TGFBI* mRNA. For the high *TGFBI* expression group ($n = 16$), *TGFBI* expression in the tumor was 0.15 or higher. For the low *TGFBI* expression group ($n = 86$), *TGFBI* expression in the tumor was less than 0.15 ($P = 0.031$)

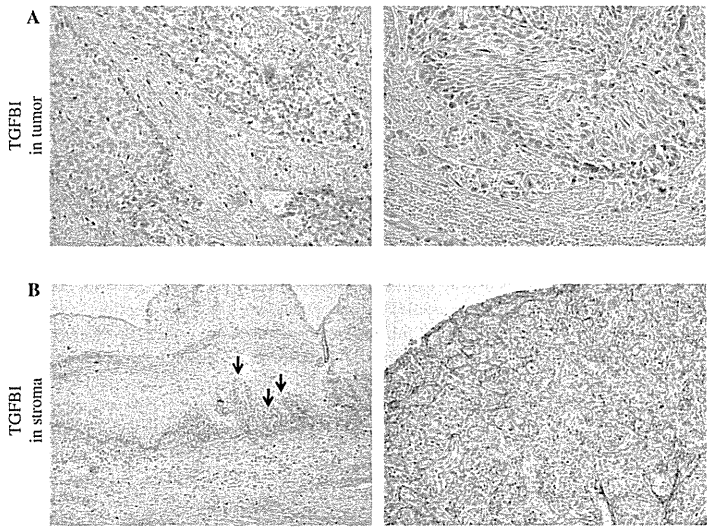

FIG. 2 Representative immunohistochemical staining of TGFBI in ESCC samples. **a** TGFBI protein expression was stronger in the marginal region of ESCC than in the center region (original magnification: *left panel*, 100×; *right panel*, 200×). **b** TGFBI protein expression was strong in the stroma and ECM of ESCC, and intratumoral neovascularity was observed (original magnification; 100×). *Black arrows* indicate intratumoral neovascularity

and TGFBI was mainly expressed in stromal cells and the ECM (Fig. 2b). Therefore, we examined the correlation with *TGFBI* mRNA expression and TGFBI protein expression in cancer cells and stromal cells. We found that *TGFBI* mRNA expression in ESCC samples was not significantly associated with TGFBI protein expression in cancer cells of ESCC tissues ($P = 0.45$). However, *TGFBI* mRNA expression in ESCC samples was significantly higher in ESCC samples with positive expression of TGFBI protein in stromal cells of ESCC tissues ($P = 0.038$; Supplementary Fig. 1). On the other hand, TGFBI expression in stromal cells and the ECM was higher in stromal tissues of noncancerous squamous epithelium and ESCC with intratumoral vascularity than in stromal tissues without intra-tumoral vascularity (Fig. 2b left panel; Supplementary Fig. 2).

Clinical Significance of TGFBI Expression in Patients with ESCC

Clinicopathological factors differed significantly in the high TGFBI expression group ($n = 16$). There was more recurrence of hematogenous metastasis ($P = 0.025$) than in the low *TGFBI* expression group ($n = 86$; Table 1). *TGF-β1* expression was positively correlated with *TGFBI* expression in this clinical ESCC sample set ($P = 0.0019$; Table 1). With regard to overall survival (Fig. 1b), patients in the high *TGFBI* expression group ($n = 16$) had a significantly poorer prognoses than those in the low *TGFBI* expression group ($n = 86$; $P = 0.031$).

Univariate analysis showed that T factor ($P < 0.001$), N factor ($P = 0.0085$), and *TGFBI* expression ($P = 0.048$) were significantly correlated with overall survival (Table 2). The multivariate regression analysis revealed that inclusion in the *TGFBI* high-expression group [relative risk (RR), 1.47; 95 % confidence interval (CI), 1.03–2.05; $P = 0.037$] was an independent predictor, of overall survival (Table 2).

Expression of TGFBI in Squamous Cell Lines and KMST6 Fibroblasts

Next, we evaluated TGFBI expression levels in Het1A, TE1, TE8, TE15, KYSE70, and KMST6 cells by Western blotting (Fig. 3a). TGFBI expression was detected in only KMST6 cells. Therefore, we used KMST6 cells to analyze whether *TGFBI* suppression in fibroblast cells influenced the migration and invasion capacities of human TE8 ESCC cells during coculture.

TGFBI Knockdown in KMST6 Cells Suppressed the Migration and Invasion Abilities of Cocultured TE8 Cells

To determine whether TGFBI expression in KMST6 cells regulated cell migration and invasion abilities in cocultured TE8 cells, we performed wound healing and invasion assays. TGFBI knockdown in KMST6 cells was validated by western blotting (Fig. 3a). We found that the migration and invasion abilities of TE8 cells were suppressed by TGFBI-dependent regulation of cocultured fibroblasts (Fig. 3b and c).

DISCUSSION

In this study, we clarified that the expression level of *TGFBI* in primary ESCC was higher than that in corresponding normal tissues, which was consistent with the results of a previous expression microarray study. We also showed that the high expression level of *TGFBI* was an independent prognostic factor in ESCC. Moreover, *TGFBI* knockdown in fibroblasts suppressed migration and invasion capacity in cocultured TE8 cells in vitro.

In this study, *TGFBI* mRNA expression in ESCC samples was associated with hematogenous recurrence and poor prognosis. To elucidate which cells were responsible for the observed *TGFBI* mRNA expression, we examined the

TABLE 2 Results of univariate and multivariate analyses of clinicopathological factors affecting overall survival rates following surgery

Clinicopathological variable	Univariate analysis			Multivariate analysis		
	RR	95 % CI	P value	RR	95 % CI	*P* value
TGFBI mRNA expression (low/high)	1.44	1.0–1.99	0.048	1.47	1.03–2.05	0.037
Age (<65/>65) (year)	1.14	0.85–1.52	0.39	–	–	–
Gender (male/female)	0.95	0.56–1.44	0.82	–	–	–
T factor (T1,T2/T3,T4)	5.18	2.15–15.35	<0.001	2.29	1.2–4.74	0.012
N factor (absent/present)	2.35	1.23–4.85	0.0085	2.31	1.18–4.94	0.013
M factor (absent/present)	1.97	0.98–3.69	0.057	–	–	–

RR relative risk, *CI* confidence interval

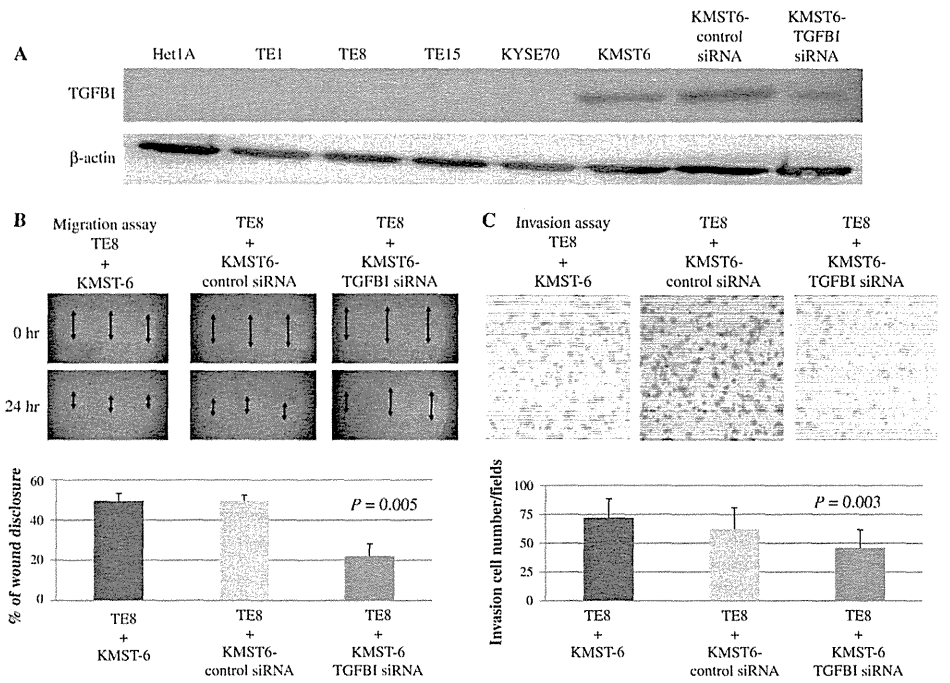

FIG. 3 TGFBI suppression in KMST6 fibroblasts reduced migration and invasion abilities in cocultured TE8 cells. **a** Expression of TGFBI protein was detected in Het1A, TE1, TE8, TE15, KYSE70, and KMST6 cells by western blotting. TGFBI expression was suppressed in KMST6 cells transfected with TGFBI siRNA. β-actin was used as the loading control. **b**, **c** Migration assay and invasion assay. The migration and invasion abilities of TE8 cells were suppressed by cocultured KMST6 cells transfected with TGFBI siRNA compared with that of control siRNA and parent KMST6 cells. The data represent the mean ± SD ($P = 0.005$ and $P = 0.003$ vs. control siRNA and parental KMST6 cells, respectively)

relationship between *TGFBI* mRNA expression and localization of TGFBI in clinical ESCC samples. Our data suggested that TGFB1 mRNA expression was derived from stromal cells of ESCC tissues (Supplementary Fig. 1). Expression of the ECM-secreted protein TGFBI has been shown to be induced by TGF-β, and the expression of this protein in cancer cells can be upregulated in response to several treatments, including common chemotherapeutic agents, UV irradiation, heat shock, desferrioxamine, hydrogen peroxide, and gamma irradiation.[19,20] Moreover, cellular stress, including reactive oxygen species (ROS), induces the expression and secretion of TGF-β1 and TGF-β2, and abundant ROS in cancer cells and cancer-associated fibroblasts promote tumor initiation, progression, and metastasis.[21] Therefore, the expression and localization of *TGFBI* in cancer cells and stromal cells may be regulated by cellular stress-induced TGF-β signaling in ESCC tissues.[22]

Importantly, our data suggested that TGFBI may be a promising prognostic marker and new candidate for targeted therapy in ESCC. TGFBI has been shown to have dual functions as a tumor suppressor and tumor promoter.[23] Interestingly, hypermethylation of the TGFBI promoter is induced by mutant hepatitis B virus, conferring noncancerous NIH3T3 cells with tumorigenic properties.[24] Moreover, TGFBI administration to model mice induces antitumor and anti-angiogenic effects in the subcutaneous tumor grafts.[25] On the other hand, suppression of melanoma cell-secreted TGFBI proteins has been shown to reduce metastatic potential and prolong the survival time of mice bearing tumors derived from human melanoma cells; therefore, ECM-localized TGFBI may be required for metastatic outgrowth.[26] Moreover, high expression of cytoplasmic TGFBI in clear cell renal cell carcinoma is associated with cancer progression and poor prognosis.[18]

Thus, TGFBI expression in cancer may be a powerful prognostic marker and a new therapeutic target in several tumor types, despite some data demonstrating that TGFBI acts as a tumor suppressor.

In this study, we found that most (90 %) ESCC samples and all ESCC cell lines did not express TGFBI. Moreover, *TGFBI* mRNA was mainly derived from stromal cells and the ECM of ESCC tissues and was associated with hematogenous recurrence in ESCC. Hematogenous metastasis is required to promote the metastatic cascade, including angiogenesis and extravasation; however, it is unclear whether the ECM-secreted TGFBI facilitates or suppresses angiogenesis.[25,27,28] In our study, we found that TGFBI protein was expressed in stromal tissues of noncancerous squamous epithelium and ESCC with intratumoral vascularity. Additionally, TGFBI knockdown in fibroblasts reduced migration and invasive abilities in cocultured TE8 cells. From these observations, at least in ESCC, we expect that ECM-localized TGFBI may be a promising target for therapeutic intervention against ESCC-inducing stromal cells and for regulating the recurrence of distant metastases thorough inhibition of the anti-angiogenic effects and migration and invasion abilities of ESCC cells.

CONCLUSIONS

The expression of *TGFBI* in cancer tissues correlated with poor prognosis and recurrence by hematogenous metastasis in ESCC patients. In addition, the invasion and migration abilities in ESCC cells were regulated through TGFBI in fibroblasts in vitro. Therefore, TGFBI expression could be a useful predictor for poor prognosis and recurrence in ESCC patients. Moreover, with respect to developing new molecular cancer therapies, TGFBI expression in cancer stromal cells may be a promising candidate to regulate recurrence of distant metastasis in ESCC.

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ANNUAL REPORT

Thoracic and cardiovascular surgery in Japan during 2012

Annual report by The Japanese Association for Thoracic Surgery

Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery · Munetaka Masuda · Hiroyuki Kuwano · Meinoshin Okumura · Jun Amano · Hirokuni Arai · Shunsuke Endo · Yuichiro Doki · Junjiro Kobayashi · Noboru Motomura · Hiroshi Nishida · Yoshikatsu Saiki · Fumihiro Tanaka · Kazuo Tanemoto · Yasushi Toh · Hiroyasu Yokomise

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The Japanese Association for Thoracic Surgery has conducted annual surveys of thoracic surgery throughout Japan since 1987 to determine the statistics regarding the number of procedures according to operative category. Here, we have summarized the results from our annual survey of thoracic surgery performed during 2012.

The incidence of hospital mortality was added to the survey to determine the nationwide status, which has contributed to the Japanese surgeons to understand the present status of thoracic surgery in Japan and to make progress to improve operative results by comparing their work with those of others. The Association was able to gain a better understanding of the present problems as well as future prospects, which has been reflected to its activity including education of its members. Thirty-day mortality (so-called "operative mortality) is defined as death within 30 days of operation regardless of the patient's geographic location and even though the patient had been discharged from the hospital.

Hospital mortality is defined as death within any time interval after an operation if the patient had not been discharged from the hospital. Hospital-to-hospital transfer is not considered discharge: transfer to a nursing home or a rehabilitation unit is considered hospital discharge unless the patient subsequently dies of complications of the operation. The definitions of the Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity of the Society of Thoracic Surgeons and

Annual report by The Japanese Association for Thoracic Surgery: Committee for Scientific Affair

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Table 1 Questionnaires sent out and received back by the end of December 2013

	Sent out	Returned	Response rate (%)
(A) Cardiovascular surgery	601	583	97.0
(B) General thoracic surgery	802	777	96.9
(C) Esophageal surgery	582	555	95.4

Table 2 Categories subclassified according to the number of operations performed

Number of operations performed	Category	
	Cardiovascular surgery	General thoracic surgery
0	39	41
1–24	46	92
25–49	99	92
50–99	163	193
100–149	86	134
150–199	60	107
≧200	90	118
Total	583	777

Number of operations performed	Esophageal surgery
0	86
1–4	99
5–9	81
10–19	105
20–29	48
30–39	35
40–49	30
≧50	71
Total	555

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the American Association for Thoracic Surgery (Edmunds et al. Ann Thorac Surg 1996;62:932–5; J Thorac Cardiovasc Surg 1996;112:708–11).

Thoracic surgery was classified into three categories—cardiovascular, general thoracic, and esophageal surgery—and the patient data were examined and analyzed for each group. Access to the computerized data is offered to all members of this Association. We honor and value all member's continued kind support and contributions (Tables 1, 2).

Abstract of the survey

We sent out survey questionnaire forms to the departments of each category in all 1,986 institutions (601 cardiovascular, 802 general thoracic and 582 esophageal) nationwide in early April 2013. The response rates in each category by the end of December 2013 were 97.0, 96.8, and 95.2 %, respectively. This high response rate has been keep throughout recent survey, and more than 95 % response rate in all fields in 2012 survey has to be congratulated.

2012 Final report

(A) Cardiovascular surgery

First, we are very pleased with the high response rate to our survey of cardiovascular surgery (97.0 %), which definitely enhances the quality of this annual report. We very much appreciate the enormous effort put into completing the survey at each participating institution.

Figure 1 shows the development of cardiovascular surgery in Japan over the last 26 years. Aneurysm surgery includes only operations for thoracic and thoracoabdominal aortic aneurysm. Pacemaker implantation includes only transthoracic implantation and transvenous implantation is excluded. The number of pacemaker and assist device implantation operations is not included in the total number of surgical operations. A total of 63,800 cardiovascular operations were performed at 583 institutions during 2012 alone and included 28 heart transplantations, which were restarted in 1999.

The number of operations for congenital heart disease (9,558 cases) decreased slightly (3.1 %) compared with that of 2011 (9,859 cases), while there was 3.9 % increase when compared with the data of 10 years ago (9,202 cases in 2002). The number of operations for adult cardiac disease (20,913 cases in valvular heart disease, 16,752 cases in ischemic heart disease, 14,944 cases in thoracic aortic aneurysm and 1,663 cases for other procedures) increased compared with those of 2011 in all categories (9.1, 7.5, 5.8 and 5.1 %, respectively). During the last 10 years, the

numbers of operations for adult heart disease increased constantly except for that of ischemic heart disease (81.0 % increase in valvular heart disease, 26.6 % decrease in ischemic heart disease, 112.4 % increase in thoracic aortic aneurysm, and 40.7 % increase in other procedures compared those of 2002). The concomitant coronary artery bypass grafting procedure (CABG) is not included in ischemic heart disease but included in other categories such as valvular heart disease in our study, then, the number of CABG still remained over 20,000 cases per year (21,569 cases) in 2012, which is 89.4 % of that in 2002 (24,135 cases).

Data for individual categories are summarized in tables through 1 to 7.

In 2012, 7,171 open-heart operations for congenital heart disease were performed with overall hospital mortality of 2.3 %. The number of operations for congenital heart disease was quite steady throughout these 10 years (maximum 7,386 cases in 2006), while overall hospital mortality decreased gradually from that of 3.6 % in 2002. In detail, the most common disease was atrial septal defect (1,331 cases), however, its number deceased to 71.7 % of that in 2002, which might be due to the recent development of catheter closure of atrial septal defect in Japan. Hospital mortality for complex congenital heart disease improved dramatically in the last 10 years such as interrupted aortic arch with ventricular septal defect (13.9 % in 2002 to 3.6 % in 2012), complete atrio-septal defect (4.2 to 3.2 %), Tetralogy of Fallot (3.8 to 1.1 %), transposition of the great arteries with and without ventricular septal defect (14.0 to 3.2 % and 7.4 to 2.6 %, respectively), single ventricle and tricuspid atresia (9.2 to 5.5 % and 3.9 to 0 %, respectively), and hypoplastic left heart syndrome (37.9 to 10.2 %). Right heart bypass surgery is now commonly performed (375 bidirectional Glenn procedures and 438 Fontan type procedures including total cavopulmonary connection) with acceptable hospital mortality (2.1 % in each procedure). Norwood type I procedure was performed in 130 cases with relatively low hospital mortality rate of 15.4 %.

As previously mentioned, the number of operations for valvular heart disease increased by 81 % in the last 10 years, and the hospital mortality associated with primary single valve replacement was 3.0 and 4.5 % for the aortic and the mitral position, while that for primary mitral valve repair was 1.3 %. However, hospital mortality rate for redo valve surgery was still high and was 9.3 and 6.7 % for aortic and mitral procedure, respectively. Finally, overall hospital mortality did not show any improvement during the last 10 years (3.1 % in 2002 and 3.2 % in 2012), which might be partially due to the recent progression of age of the patients. Repair of the valve became popular procedure (484 cases in the aortic, 6,002 cases in the mitral, and 4,947 case in the tricuspid), and mitral valve repair constituted 28.7 % of all valvular heart disease operation and 57.6 % of all mitral valve procedure (10,425 procedures), which are similar to those of the last 4 years and increased compared with those of 2002 (19.5 and 34.9 %, respectively). Aortic and mitral valve replacement with bioprosthesis were performed in 8,926 cases and 3,002 cases, respectively, with the number consistently increasing. The ratio of prostheses changed dramatically during the last 10 years, and the usage of bioprosthesis is 74.3 % at the aortic position (37.3 % in 2002) and 61.0 % at the mitral position (24.2 % in 2002). CABG as a concomitant procedure increased gradually to 23.9 % of operations for all valvular heart disease (12.1 % in 2002).

Isolated CABG was performed in 15,462 cases which were only 71.5 % of that of 10 years ago (2002), however, there was an increase of 8.5 % compared with that in 2011. Among these 15,462 cases, off-pump CABG was intended in 9,499 cases (61.4 %) with a success rate of 97.9 %, so final success rate of off-pump CABG was 60.2 %. The percentage of intended off-pump CABG was 55.2 % in 2003, and was increased to 60.3 % in 2004, then was kept over 60 % until now. Conversion rate from off-pump CABG to on-pump CABG of 2.1 % was just same as that in 2011. In 15,462 isolated CABG patients, 96.5 % of them received at least one arterial graft, while, all arterial graft CABG was performed in only 23.5 % of them.

The operative and hospital mortality rates associated with primary elective CABG procedures in 13,004 cases were 0.6 and 1.1 %, respectively. Similar data analysis of CABG including primary/redo and elective/emergency data was begun in 2003, and the operative and hospital mortality rates associated with primary elective CABG procedures in 2003 were 1.0 and 1.5 %, respectively, so operative results of primary CABG have been improved. However, hospital mortality of primary emergency CABG in 2,224 cases was 7.4 %, which was still high in spite of slight improvement compared with 9.7 % of hospital mortality rate in 2003. In comparison with data in 2003, the results of conversion improved both conversion rate (3.1 to 2.1 %) and hospital mortality (8.5 to 5.1 %).

A total of 1,274 patients underwent surgery for complications of myocardial infarction, including 413 operations for a left ventricular aneurysm or ventricular septal perforation or cardiac rupture and 296 operations for ischemic mitral regurgitation.

Operations for arrhythmia were performed mainly as a concomitant procedure in 3,992 cases with satisfactory mortality (1.8 % hospital mortality) including 3,771 MAZE procedures. MAZE procedure has become quite popular procedure when compared with that in 2002 (1,141 cases).

Operations for thoracic aortic dissection were performed in 6,266 cases. For 4,186 Stanford type A acute aortic

dissections, hospital mortality was 10.6 %, which was similar to that in 2011 (11.1 %) and better than that in 2002 (15.5 %). Operations for a non-dissected thoracic aneurysm were carried out in 8,678 cases, with overall hospital mortality of 5.4 %, which was better than that in 2011 (6.7 %). The hospital mortality associated with unruptured aneurysm was 4.0 %, and that of ruptured aneurysm was 22.2 %, which remains markedly high.

The number of stent graft procedures remarkably increased recently. A total of 835 patients with aortic dissection underwent stent graft placement: thoracic endovascular aortic repair (TEVAR) in 723 cases, open stent grafting in 109 cases, and unspecified in 3 cases. The number of TEVAR for type B chronic aortic dissections increased from 359 cases in 2011 to 492 cases in 2012. The hospital mortality rates associated with TEVAR for type B aortic dissection were 7.3 % in acute cases and 2.6 % for chronic cases, respectively.

A total of 3,236 patients with non-dissected aortic aneurysm underwent stent graft placement with 18.8 % increase compared with that in 2011 (2,725 cases); TEVAR in 3,006 cases (23.6 % increase compared with that in 2011), open stent grafting in 226 cases (20.8 % decrease compared with that in 2011), and unspecified in 4 cases. The hospital mortality rates for TEVAR were 2.5 and 16.1 % for non-ruptured and ruptured aneurysm, respectively.

In summary, the total cardiovascular operations increased during 2012 by 3,516 cases, with steadily improving results in almost all categories compared with those in 2011.

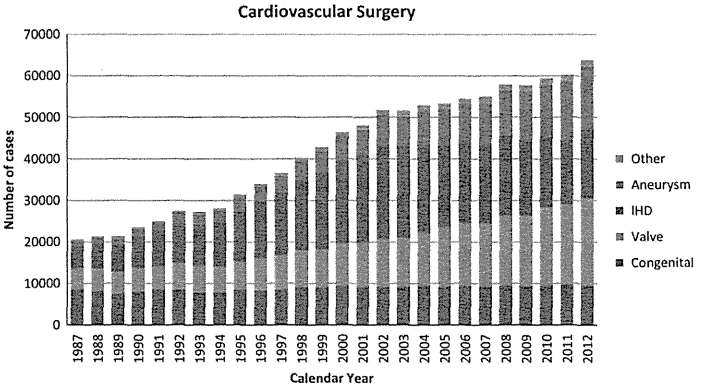

Fig. 1 Cardiovascular surgery. *IHD* ischemic heart disease

Table 1 Congenital (total; 9,558)
(1) CPB (+) (total; 7,171)

		Neonate				Infant				1–17 years				≧18 years				Total			
		Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality
			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge	
1	PDA	15	0	0	0	2	0	0	0	4	0	0	0	24	1 (4.2)	0	1 (4.2)	45	1 (2.2)	0	1 (2.2)
2	Coarctation (simple)	7	0	0	0	13	0	0	0	17	0	0	0	7	0	0	0	44	0	0	0
3	+VSD	32	2 (6.3)	0	2 (6.3)	34	0	0	0	8	0	0	0	2	0	0	0	76	2 (2.6)	0	2 (2.6)
4	+DORV	2	0	0	1 (50.0)	3	0	0	0	2	0	0	0	0	0	0	0	7	0	0	1 (14.3)
5	+AVSD	5	0	0	0	4	0	0	0	1	0	0	0	0	0	0	0	10	0	0	0
6	+TGA	3	1 (33.3)	0	1 (33.3)	3	0	0	0	1	0	0	0	0	0	0	0	7	1 (14.3)	0	1 (14.3)
7	+SV	9	2 (22.2)	0	2 (22.2)	7	0	0	0	4	0	0	0	0	0	0	0	20	2 (10.0)	0	2 (10.0)
8	+Others	2	0	0	0	5	0	0	0	4	0	0	0	1	0	0	0	12	0	0	0
9	Interrupt. of Ao (simple)	1	0	0	0	2	1 (50.0)	0	1 (50.0)	2	0	0	0	1	0	0	0	6	1 (16.7)	0	1 (16.7)
10	+VSD	25	2 (8.0)	0	2 (8.0)	16	0	0	0	4	0	0	0	10	0	0	0	55	2 (3.6)	0	2 (3.6)
11	+DORV	3	1 (33)	0	1 (33.3)	4	0	0	0	2	0	0	0	0	0	0	0	9	1 (11.1)	0	1 (11.1)
12	+Truncus	2	1 (50.0)	0	1 (50.0)	2	0	0	0	0	0	0	0	0	0	0	0	4	1 (25.0)	0	1 (25.0)
13	+TGA	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0
14	+Others	4	0	0	0	10	1 (10.0)	0	1 (10.0)	2	0	0	0	1	0	0	0	17	1 (5.9)	0	1 (5.9)
15	Vascular ring	0	0	0	0	4	0	0	0	3	0	0	0	0	0	0	0	7	0	0	0
16	PS	1	0	0	0	15	0	0	0	14	0	0	0	4	0	0	1 (25.0)	34	0	0	1 (2.9)
17	PAIVS or critical PS	12	0	0	0	50	1 (2.0)	0	1 (2.0)	55	0	0	0	2	0	0	1 (50.0)	119	1 (0.8)	0	2 (1.7)
18	TAPVR	126	9 (7.1)	0	15 (11.9)	49	1 (2)	2 (4.08)	2 (4.1)	8	0	0	0	0	0	0	0	183	10 (5)	2 (1.1)	17 (9)
19	PAPVR ± ASD	0	0	0	0	4	0	0	0	52	0	0	0	29	0	0	0	85	0	0	0
20	ASD	11	1 (9.1)	0	1 (9.1)	54	0	0	0	693	0	0	0	573	2 (0.3)	1 (0.2)	2 (0.3)	1,331	3 (0.2)	1 (0.08)	3 (0.2)
21	Cor triatriatum	1	0	0	0	13	2 (15.4)	0	2 (15.4)	3	0	0	0	4	0	0	0	21	2 (9.5)	0	2 (9.5)
22	AVSD (partial)	1	1 (100.0)	0	1 (100.0)	19	1 (5.3)	0	1 (5.3)	40	0	0	0	13	0	0	0	73	2 (2.7)	0	2 (2.7)
23	AVSD (complete)	4	0	0	1 (25.0)	108	5 (4.6)	0	5 (4.6)	69	0	0	0	4	0	0	0	185	5 (2.7)	0	6 (3.2)
24	+TOF or DORV	0	0	0	0	6	1 (16.7)	0	2 (33.3)	21	0	0	0	3	0	0	0	30	1 (3.3)	0	2 (6.7)
25	+Others	1	0	0	0	10	1 (10.0)	0	1 (10.0)	8	0	0	0	1	0	0	0	20	1 (5.0)	0	1 (5.0)
26	VSD (subarterial)	3	0	0	0	128	0	0	0	197	0	0	0	29	0	0	0	357	0	0	0
27	VSD (perimemb./ muscular)	10	0	0	0	770	0	1 (0.13)	0	390	0	0	0	90	0	0	0	1,260	0	1 (0.1)	0
28	VSD + PS	0	0	0	0	39	0	0	0	33	0	0	0	7	0	0	0	79	0	0	0
29	DCRV ± VSD	2	0	0	0	16	0	0	0	39	0	0	0	19	0	0	0	76	0	0	0
30	Aneurysm of sinus valsalva	0	0	0	0	6	0	0	0	1	0	0	0	24	0	0	0	31	0	0	0
31	TOF	15	1 (6.7)	0	1 (6.7)	168	0	0	0	231	2 (0.9)	0	2 (0.9)	22	0	0	2 (9.1)	436	3 (0.7)	0	5 (1.1)
32	PA + VSD	4	0	0	0	78	1 (1.3)	0	1 (1.3)	125	3 (2.4)	0	5 (4.0)	9	0	0	0	216	4 (1.9)	0	6 (2.8)
33	DORV	17	1 (5.9)	0	1 (5.9)	91	1 (1.1)	0	3 (3.3)	112	2 (1.8)	0	2 (1.8)	3	1 (33.3)	0	1 (33.3)	223	5 (2.2)	0	7 (3.1)
34	TGA (simple)	101	2 (2.0)	0	3 (3.0)	12	0	0	0	0	0	0	0	4	0	0	0	117	2 (1.7)	0	3 (2.6)

Table 1 continued

		Neonate				Infant				1–17 years				≧18 years				Total			
		Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality
			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge	
35	+VSD	44	1 (2.3)	0	1 (2.3)	17	1 (5.9)	0	1 (5.9)	2	0	0	0	0	0	0	0	63	2 (3.2)	0	2 (3.2)
36	VSD + PS	4	0	0	0	8	0	0	0	26	0	0	0	2	0	0	0	40	0	0	0
37	Corrected TGA	2	0	0	0	11	0	0	0	42	1 (2.4)	0	1 (2.4)	13	0	0	0	68	1 (1.5)	0	1 (1.5)
38	Truncus arteriosus	4	0	0	0	26	2 (7.7)	0	3 (11.5)	12	0	0	0	1	0	0	0	43	2 (4.7)	0	3 (7.0)
39	SV	27	5 (18.5)	0	8 (29.6)	219	7 (3.2)	0	11 (5.0)	282	4 (1.4)	0	9 (3.2)	21	2 (9.5)	0	2 (9.5)	549	18 (3.3)	0	30 (5.5)
40	TA	2	0	0	0	30	0	0	0	53	0	0	0	5	0	0	0	90	0	0	0
41	HLHS	45	10 (22.2)	0	10 (22.2)	130	11 (8.5)	1 (0.77)	15 (11.5)	71	0	0	0	0	0	0	0	246	21 (8.5)	1 (11.7)	25 (10.2)
42	Aortic valve lesion	7	3 (42.9)	0	3 (42.9)	16	0	0	0	75	3 (4.0)	0	3 (4.0)	19	1 (5.3)	0	1 (5.3)	117	7 (6.0)	0	7 (6.0)
43	Mitral valve lesion	2	1 (50.0)	0	1 (50.0)	56	0	0	2 (3.6)	75	1 (1.3)	0	1 (1.3)	14	0	0	0	147	2 (1.4)	0	4 (2.7)
44	Ebstein	10	1 (10.0)	0	1 (10.0)	17	1 (5.9)	0	1 (5.9)	31	0	0	0	12	0	0	0	70	2 (2.9)	0	2 (2.9)
45	Coronary disease	0	0	0	0	11	0	0	0	16	0	0	0	13	0	0	0	40	0	0	0
46	Others	11	0	0	1 (9.1)	27	3 (11.1)	0	3 (11.1)	34	2 (5.9)	0	2 (5.9)	14	0	0	0	86	5 (5.8)	0	6 (7.0)
47	Redo VSD	0	0	0	0	6	0	0	0	10	0	0	0	7	0	0	0	23	0	0	0
48	PS release	0	0	0	0	8	0	0	0	42	0	0	0	23	0	0	0	73	0	0	0
49	RV-PA conduit replace	0	0	0	0	3	0	0	0	68	1 (1.5)	0	1(1.5)	17	0	0	1 (5.9)	88	1 (1.1)	0	2 (2.3)
50	Others	1	0	0	0	62	6 (9.7)	0	7 (11.3)	121	2 (1.7)	0	4 (3.3)	46	1 (2.2)	0	1 (2.2)	230	9 (3.9)	0	12 (5.2)
Total		580	45 (7.8)	0	58 (10.0)	2,393	47 (2.0)	4 (0.17)	63 (2.6)	3,105	21 (0.7)	0	30 (1.0)	1,093	8 (0.7)	1 (0.1)	13 (1.2)	7,171	121 (1.7)	5 (0.1)	164 (2.3)

Values in parenthesis represent mortality %

CPB cardiopulmonary bypass, *PDA* patient ductus arteriosus, *VSD* ventricular septal defect, *DORV* double outlet right ventricle, *AVSD* atrioventricular septal defect, *TGA* transposition of great arteries, *SV* single ventricle, *Interupt. of Ao.*, interrupted aortic arch, *PS* pulmonary stenosis, *PA-IVS* pulmonary atresia with intact ventricular septum, *TAPVR* total anomalous pulmonary venous return, *PAPVR* partial anomalous pulmonary venous return, *ASD* atrial septal defect, *TOF* tetralogy of Fallot, *DCRV* double-chambered right ventricle, *TA* tricuspid atresia, *HLHS* hypoplastic left heart syndrome, *RV-PA* right ventricle–pulmonary artery

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Table 1 continued
(2) CPB (−) (total; 2,387)

		Neonate				Infant				1–17 years				≧18 years				Total			
		Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality
			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge	
1	PDA	358	2 (0.6)	0	3 (0.8)	225	0	0	2 (0.9)	46	0	0	0	1	0	0	0	630	2 (0.3)	0	5 (0.8)
2	Coarctation (simple)	21	0	0	0	14	0	0	0	4	0	0	0	1	0	0	0	40	0	0	0
3	+VSD	38	1 (2.6)	1 (2.6)	1 (2.6)	26	1 (3.8)	0	1 (3.8)	0	0	0	0	0	0	0	0	64	2 (3.1)	1 (1.6)	2 (3.1)
4	+DORV	5	0	0	1 (20.0)	2	0	0	0	0	0	0	0	0	0	0	0	7	0	0	1 (14.3)
5	+AVSD	5	1 (20.0)	0	1 (20.0)	0	0	0	0	0	0	0	0	0	0	0	0	5	1 (20.0)	0	1
6	+TGA	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0
7	+SV	5	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	7	0	0	0
8	+Others	4	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	6	0	0	0
9	Interrupt. of Ao (simple)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
10	+VSD	21	0	0	1 (4.8)	5	0	0	0	2	0	0	0	0	0	0	0	28	0	0	1 (3.6)
11	+DORV	4	1 (25)	0	2 (50)	0	0	0	0	0	0	0	0	0	0	0	0	4	1 (25)	0	2 (50)
12	+Truncus	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0
13	+TGA	2	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0
14	+Others	7	0	0	1 (14.3)	0	0	0	0	0	0	0	0	0	0	0	0	7	0	0	1 (14.3)
15	Vascular ring	1	0	0	0	12	1 (8.3)	0	1 (8.3)	9	0	0	0	0	0	0	0	22	1 (4.5)	0	1 (4.5)
16	PS	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
17	PAIVS or critical PS	30	3 (10.0)	0	3 (10.0)	26	0	0	0	3	0	0	0	2	0	0	0	61	3 (4.9)	0	3 (4.9)
18	TAPVR	1	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0
19	PAPVR ± ASD	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
20	ASD	0	0	0	0	0	0	0	0	12	0	0	0	15	0	0	0	27	0	0	0
21	Cor triatriatum	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	AVSD (partial)	2	0	0	0	4	0	0	0	1	0	0	0	0	0	0	0	7	0	0	0
23	AVSD (complete)	32	0	0	0	68	0	0	1 (1.5)	4	0	0	0	0	0	0	0	104	0	0	1 (1.0)
24	+TOF or DORV	3	0	0	0	13	1 (7.7)	0	1 (7.7)	6	0	0	0	0	0	0	0	22	1 (4.5)	0	1 (4.5)
25	+Others	3	1 (33.3)	0	1 (33.3)	4	0	0	0	2	0	0	0	0	0	0	0	9	1 (11.1)	0	1 (11.1)
26	VSD (subarterial)	2	0	0	0	11	0	0	0	2	0	0	0	2	0	0	0	17	0	0	0
27	VSD (perimemb./muscular)	38	0	0	0	117	1 (0.9)	0	3 (2.6)	5	0	0	0	1	0	0	0	161	1 (0.6)	0	3 (1.9)
28	VSD + PS	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
29	DCRV ± VSD	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	Aneurysm of sinus valsalva	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	2	0	0	0
31	TOF	24	0	0	0	100	2 (2.0)	0	2 (2.0)	13	0	0	0	4	0	0	0	141	2 (1.4)	0	2 (1.4)
32	PA + VSD	26	0	0	0	83	0	0	0	15	0	0	0	1	0	0	0	125	0	0	0
33	DORV	27	0	0	0	55	1 (1.8)	0	2 (3.6)	14	0	0	0	2	0	0	0	98	1 (1.0)	0	2 (2.0)
34	TGA (simple)	7	0	0	0	1	0	0	0	1	0	0	0	1	0	0	0	10	0	0	0

Table 1 continued

		Neonate				Infant				1–17 years				≧18 years				Total			
		Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality
			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge	
35	+VSD	7	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	10	0	0	0
36	VSD + PS	9	1 (11.1)	0	1 (11.1)	5	0	0	0	2	0	0	0	0	0	0	0	16	1 (6.3)	0	1 (6.3)
37	Corrected TGA	8	0	0	0	18	1 (5.6)	0	1 (5.6)	4	0	0	0	0	0	0	0	30	1 (3.3)	0	1 (3.3)
38	Truncus arteriosus	20	0	0	1 (5.0)	1	0	0	0	5	0	0	0	0	0	0	0	26	0	0	1 (3.8)
39	SV	72	2 (2.8)	0	3 (4.2)	57	1 (1.8)	0	3 (5.3)	21	1 (4.8)	0	1	3	1 (33.3)	0	1 (33.3)	153	5 (3.3)	0	8 (5.2)
40	TA	18	0	0	0	20	0	0	0	12	0	0	0	1	0	0	0	51	0	0	0
41	HLHS	81	2 (2.5)	0	3 (3.7)	19	0	0	0	3	0	0	0	0	0	0	0	103	2 (1.9)	0	3 (2.9)
42	Aortic valve lesion	4	0	0	0	2	0	0	0	4	0	0	0	2	0	0	0	12	0	0	0
43	Mitral valve lesion	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
44	Ebstein	6	1 (16.7)	0	2 (33.3)	4	0	0	0	1	0	0	0	3	0	0	0	14	1 (7.1)	0	2 (14.3)
45	Coronary disease	1	1 (100.0)	0	1 (100.0)	0	0	0	0	2	0	0	0	1	0	0	0	4	1 (25.0)	0	1 (25.0)
46	Others	24	1 (4.2)	0	1 (4.2)	65	1 (1.5)	0	1 (1.5)	75	1 (1.3)	0	1	23	0	0	0	187	3 (1.6)	0	3 (1.6)
47	Redo VSD	0	0	0	0	3	0	0	0	36	0	0	0	1	0	0	0	40	0	0	0
48	PS release	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0	0	0
49	RV-PA conduit replace	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	Others	18	0	0	1 (5.6)	36	0	0	0	45	0	0	0	16	1 (6.3)	0	1 (6.3)	115	1 (0.9)	0	2 (1.7)
Total		946	17 (1.8)	1 (0.1)	27 (2.9)	1,008	10 (1.0)	0	18 (1.8)	351	2 (0.6)	0	2	82	2 (2.4)	0	2 (2.4)	2,387	31 (1.3)	1 (0.04)	49 (2.1)

Values in parenthesis represent mortality %

CPB cardiopulmonary bypass, *PDA* patient ductus arteriosus, *VSD* ventricular septal defect, *DORV* double outlet right ventricle, *AVSD* atrioventricular septal defect, *TGA* transposition of great arteries, *SV* single ventricle, *Interupt. of Ao.* interrupted aortic arch, *PS* pulmonary stenosis, *PA-IVS* pulmonary atresia with intact ventricular septum, *TAPVR* total anomalous pulmonary venous return, *PAPVR* partial anomalous pulmonary venous return, *ASD* atrial septal defect, *TOF* tetralogy of Fallot, *DCRV* double-chambered right ventricle, *TA* tricuspid atresia, *HLHS* hypoplastic left heart syndrome, *RV-PA* right ventricle–pulmonary artery

Table 1 continued
(3) Main procedure

		Neonate				Infant				1–17 years				≧18 years				Total			
		Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality
			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge	
1	SP shunt	170	5 (2.9)	0	9 (5.3)	425	9 (2.1)	0	12 (2.8)	58	1 (1.7)	0	1 (1.7)	1	0	0	0	654	15 (2.3)	0	22 (3.4)
2	PAB	359	6 (1.7)	0	10 (2.8)	250	3 (1.2)	0	5 (2.0)	15	0	0	0	2	0	0	0	626	9 (1.4)	0	15 (2.4)
3	Bidirectional Glenn or hemi-Fontan ± α	0	0	0	0	265	6 (2.3)	0	6 (2.3)	106	0	0	2 (1.9)	4	0	0	0	375	6 (1.6)	0	8 (2.1)
4	Damus–Kaye–Stansel operation	4	1 (25.0)	0	2	45	2	0	2	21	0	0	0	0	0	0	0	70	3 (4.3)	0	4 (5.7)
5	PA reconstruction/repair (including redo)	9	0	0	0	99	1 (1.0)	0	2 (2.0)	108	0	0	1 (0.9)	18	0	0	1 (5.6)	234	1 (0.4)	0	4 (1.7)
6	RVOT reconstruction/ repair	16	2 (12.5)	0	2 (12.5)	107	0	0	1 (0.9)	231	2 (0.9)	0	2 (0.9)	17	0	0	0	371	4 (1.1)	0	5 (1.3)
7	Rastelli procedure	3	1 (33.3)	0	1 (33.3)	44	2 (4.5)	0	2 (4.5)	108	2 (1.9)	0	3 (2.8)	10	0	0	0	165	5 (3.0)	0	6 (3.6)
8	Arterial switch procedure	154	5 (3.2)	0	8 (5.2)	23	1 (4.3)	0	1 (4.3)	6	0	0	0	0	0	0	0	183	6 (3.3)	0	9 (4.9)
9	Atrial switch procedure	4	0	0	0	0	0	0	0	2	0	0	0	1	0	0	0	7	0	0	0
10	Double switch procedure	0	0	0	0	0	0	0	0	11	0	0	0	0	0	0	0	11	0	0	0
11	Repair of anomalous origin of CA	1	0	0	0	6	0	0	0	14	0	0	0	7	0	0	0	28	0	0	0
12	Closure of coronary AV fistula	0	0	0	0	1	0	0	0	5	0	0	1 (20.0)	24	0	0	0	30	0	0	1 (3.3)
13	Fontan/TCPC	1	0	0	0	3	0	0	0	408	4 (1.0)	0	6 (1.5)	26	2 (7.7)	0	3 (11.5)	438	6 (1.4)	0	9 (2.1)
14	Norwood procedure	42	8 (19.0)	1 (2.4)	7 (16.7)	78	7 (9.0)	0	11 (14.1)	10	1 (10.0)	0	2 (20.0)	0	0	0	0	130	16 (12.3)	1 (8.1)	20 (15.4)
15	Ventricular septation	0	0	0	0	7	2 (28.6)	0	2 (28.6)	4	0	0	0	1	0	0	0	12	2 (16.7)	0	2 (16.7)
16	Left side AV valve repair (including redo)	0	0	0	0	66	1 (1.5)	0	1 (1.5)	63	1 (1.6)	0	1 (1.6)	11	1 (9.1)	0	1 (9.1)	140	3 (2.1)	0	3 (2.1)
17	Left side AV valve replace (including redo)	1	1 (100)	0	1 (100)	15	1 (6.7)	0	1 (6.7)	41	2 (4.9)	0	2 (4.9)	20	0	0	0	77	4 (5.2)	0	4 (5.2)
18	Right side AV valve repair (including redo)	2	0	0	0	13	0	0	0	34	0	0	0	30	0	0	0	79	0	0	0
19	Right side AV valve replace (including redo)	0	0	0	0	1	0	0	0	6	0	0	0	8	0	0	0	15	0	0	0
20	Common AV valve repair (including redo)	2	1 (50.0)	0	1 (50.0)	34	5 (14.7)	0	5 (14.7)	19	1 (5.3)	0	1 (5.3)	1	0	0	0	56	7 (12.5)	0	7 (12.5)
21	Common AV valve replace (including redo)	2	1 (50.0)	0	1 (50.0)	6	1 (16.7)	0	1 (16.7)	8	0	0	1 (12.5)	3	0	0	0	19	2 (10.5)	0	3 (15.8)
22	Repair of supra-aortic stenosis	1	0	0	0	6	1 (16.7)	0	1 (16.7)	9	1 (11.1)	0	1 (11.1)	0	0	0	0	16	2 (12.5)	0	2 (12.5)
23	Repair of subaortic stenosis (including redo)	1	1 (100.0)	0	1 (100.0)	7	0	0	1 (14)	36	0	0	0	4	0	0	0	48	1 (2.1)	0	2 (4.2)
24	Aortic valve plasty ± VSD closure	3	0	0	0	12	0	0	1 (8.3)	24	0	0	0	4	0	0	0	43	0	0	1 (2.3)

Table 1 continued

		Neonate				Infant				1–17 years				≧18 years				Total			
		Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality
			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge	
25	Aortic valve replacement	0	0	0	0	2	0	0	0	22	0	0	0	23	0	0	0	47	0	0	0
26	AVR with annular enlargement	1	0	0	0	3	0	0	0	13	0	0	0	6	1 (16.7)	0	1 (16.7)	23	1 (4.3)	0	1 (4.3)
27	Aortic root replace (except Ross)	0	0	0	0	0	0	0	0	6	0	0	0	5	0	0	0	11	0	0	0
28	Ross procedure	0	0	0	0	3	0	0	0	10	0	0	0	1	0	0	0	14	0	0	0
Total		776	32 (4.1)	1 (0.1)	43 (5.5)	1,521	42 (2.8)	0	55 (3.6)	1,398	15 (1.1)	0	24 (1.7)	227	4 (1.8)	0	6 (2.6)	3,922	93 (2.4)	1 (0.03)	128 (3.3)

Values in parenthesis represent mortality %

SP systemic pulmonary, *PAB* pulmonary artery banding, *PA* pulmonary artery, *RVOT* right ventricular outflow tract, *CA* coronary artery, *AV fistula* arteriovenous fistula, *TCPC* total cavopulmonary connection, *AV valve* atrioventricular valve, *VSD* ventricular septal defect, *AVR* aortic valve replacement

Table 2 Acquired (total, (1) + (2) + (4) + (5) + (6) + (7) + isolated ope. for arrhythmia in (3); 39,177
(1) Valvular heart disease (total; 20,913)

	Valve	Cases	Operation					30-day mortality				Hospital mortality		Redo			
			Mechanical	Bioprosthesis	Ross procedure	Repair	With CABG	Hospital		After discharge				30-day mortality			Hospital mortality
								Replace	Repair	Replace	Repair	Replace	Repair	Cases	Hospital	After discharge	
Isolated	A	9,688	2,219	7,074	3	392	2,316	189 (2.0)	6 (1.5)	9 (0.1)	0	275 (3.0)	6 (1.5)	365	20 (5.5)	0	34 (9.3)
	M	4,617	721	847	0	3,049	773	45 (2.9)	23 (0.8)	1 (0.1)	2 (0.1)	71 (4.5)	41 (1.3)	356	14 (3.9)	0	24 (6.7)
	T	312	9	92		211	42	5 (5.0)	2 (0.9)	0	0	8 (7.9)	5 (2.4)	66	2 (3.0)	0	6 (9.1)
	P	18	0	15		3	1	0	0	0	0	0	0	10	0	0	0
A + M	A	1,380	444	882	0	54	215	65	(4.7)	0		96	(7.0)	100			
	M		303	383	0	694									8 (8.0)	0	11 (11.0)
A + T	A	400	110	281	1	8	45	15	(3.8)	0		29	(7.3)	55			
	T		3	23	0	374									2 (3.6)	0	5 (9.1)
M + T	M	3,388	634	925		1,829	294	65	(1.9)	0		91	(2.7)	274			
	T		6	50		3,332									14 (5.1)	0	26 (9.5)
A + M + T	A	1,040	321	689	0	30	117	37	(3.6)	0		51	(4.9)	76			
	M		262	348	0	430									4 (5.3)	0	5 (6.6)
	T		0	9	1	1,030											
Others		70	18	38	0	16	5	3	(4.3)	0		3	(4.3)	7	1 (14.3)	0	1 (14.3)
Total		20,913	5,050	11,656	5	11,452	3,808	455	(2.2)	12		676	(3.2)	1,309	65 (5.0)	0	112 (8.6)

Number of redo cases is included in total case number of 18,713

Values in parenthesis represent mortality %

CABG coronary artery bypass grafting, *A* aortic valve, *M* mitral valve, *T* tricuspid valve, *P* pulmonary valve

Table 2 continued

(2) Ischemic heart disease (total, (A) + (B) + (C); 16,752)

(A) Isolated CABG (total; (a) + (b); 15,462)

(a-1) On-pump arrest CABG (total; 3,749)

	Primary, elective				Primary, emergency				Redo, elective				Redo, emergency				Arterial graft only	Artery graft+SVG	SVG only	Others
	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality				
		Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge					
1VD	79	0	0	1 (1.3)	20	2 (10.0)	0	2 (10.0)	2	0	0	0	0	0	0	0	66	6	29	0
2VD	454	4 (0.9)	0	5 (1.1)	44	2 (4.5)	0	2 (4.5)	10	1 (10.0)	0	1 (10.0)	4	2 (50.0)	0	2 (50.0)	111	367	34	0
3VD	1,648	13 (0.8)	0	17 (1.0)	203	12 (5.9)	0	14 (6.9)	12	0	0	0	0	0	0	0	132	1,691	40	0
LMT	1,003	16 (1.6)	0	20 (2.0)	255	13 (5.1)	0	17 (6.7)	14	2 (14.3)	0	2 (14.3)	1	1 (100.0)	0	1 (100.0)	146	1,080	47	0
Uncertain						0														
Total	3,184	33 (1.0)	0	43 (1.4)	522	29 (5.6)		35 (6.7)	38	3 (7.9)		3 (7.9)	5	3 (60.0)		3 (60.0)	455	3,144	150	0
Kawasaki	10	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	7	4	0	0
Hemodialysis	193	7 (3.6)	0	8 (4.1)	40	9 (22.5)	0	10 (25.0)	4	0	0	0	2	0	0	0	13	217	9	0

Values in parenthesis represent mortality %

LMT includes LMT alone or LMT with other branch diseases. *CABG* coronary artery bypass grafting, *1VD* one-vessel disease, *2VD* two-vessel disease, *3VD* three-vessel disease, *LMT* left main trunk, *SVG* saphenous vein graft

(a-2) On-pump beating CABG (total; 2,214)

	Primary, elective				Primary, emergency				Redo, elective				Redo, emergency				Arterial graft only	Artery graft ± SVG	SVG only	Others
	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality				
		Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge					
1VD	23	0	0	1 (4.3)	14	0	0	1 (7.1)	4	0	0	0	4	1 (25.0)	0	2 (50.0)	22	5	18	0
2VD	235	2 (0.9)	0	6 (2.6)	65	7 (10.8)	0	7 (10.8)	11	1 (9.1)	0	1 (9.1)	3	0	0	0	65	223	25	1
3VD	805	8 (1.0)	1 (0.1)	16 (2.0)	211	20 (9.5)	0	28 (13.3)	12	0	0	1 (8.3)	1	0	0	0	107	889	33	0
LMT	550	4 (0.7)	0	9 (1.6)	264	27 (10.2)	1 (0.4)	36 (13.6)	10	0	0	0	2	0	0	0	139	639	48	0
Total	1,613	14 (0.9)		32 (2.0)	554	54 (9.7)		72 (13.0)	37	1 (2.7)		2 (5.4)	10	1 (10.0)		2 (20.0)	333	1,756	124	1
Kawasaki	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0
Hemodialysis	158	2 (1.3)	0	8 (5.1)	46	5 (10.9)	0	5 (10.9)	3	0	0	1 (33.3)	3	0	0	0	18	176	16	0

Values in parenthesis represent mortality %

LMT includes LMT alone or LMT with other branch diseases. *CABG* coronary artery bypass grafting, *1VD* one-vessel disease, *2VD* two-vessel disease, *3VD* three-vessel disease, *LMT* left main trunk, *SVG* saphenous vein graft

(b) Off-pump CABG (total; 9,499)

(The present section also includes cases of planned off-pump CABG in which, during surgery, the change is made to an on-pump CABG or on-pump beating-heart procedure)

	Primary, elective				Primary, emergency				Redo, elective				Redo, emergency				Arterial graft only	Artery graft+SVG	SVG only	Others
	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality	Cases	30-day mortality		Hospital mortality				
		Hospital	After discharge			Hospital	After discharge			Hospital	After discharge			Hospital	After discharge					
1VD	582	1 (0.2)	0	6 (1.0)	67	2 (3.0)	0	3 (4.5)	40	0	1	0	8	0	0	0	590	48	59	0
2VD	1,484	6 (0.4)	0	12 (0.8)	135	3 (2.2)	0	5 (3.7)	18	2 (11.1)	0	2 (11.1)	5	0	0	0	630	961	41	0
3VD	3,645	11 (0.3)	1 (0.03)	31 (0.9)	390	14 (3.6)	0	21 (5.4)	22	0	0	0	3	1 (33.3)	0	1 (33.3)	772	3,221	61	2
LMT	2,496	14 (0.6)	0	24 (1.0)	574	23 (4.0)	0	31 (5.4)	24	0	0	0	6	1 (16.7)	0	1 (16.7)	855	2,161	75	0
Total	8,207	32 (0.4)	1 (0.01)	73 (0.9)	1,166	42 (3.6)		60 (5.1)	104	2 (1.9)		2 (1.9)	22	2 (9.1)		2 (9.1)	2,847	6,391	236	2
Kawasaki	6	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	7	1	0	0
Hemodialysis	659	7 (1.1)	0	15 (2.3)	94	10 (10.6)	0	17 (18.1)	10	0	0	0	0	0	0	0	163	581	19	0

Values in parenthesis represent mortality %

LMT includes LMT alone or LMT with other branch diseases. *CABG* coronary artery bypass grafting, *1VD* one-vessel disease, *2VD* two-vessel disease, *3VD* three-vessel disease, *LMT* left main trunk, *SVG* saphenous vein graft