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ORIGINAL ARTICLE
Cardiovascular Surgery

Coronary Artery Bypass Grafting in Hemodialysis-Dependent Patients

– Analysis of Japan Adult Cardiovascular Surgery Database –

Takashi Yamauchi, MD, PhD; Hiroaki Miyata, PhD; Taichi Sakaguchi, MD, PhD; Shigeru Miyagawa, MD, PhD; Yasushi Yoshikawa, MD; Koji Takeda, MD, PhD; Noboru Motomura, MD, PhD; Hiroyuki Tsukihara, MD, PhD; Yoshiki Sawa, MD, PhD

Background: Perioperative risk during coronary artery bypass grafting (CABG) is reportedly high in patients with chronic renal disease. We aimed to determine postoperative mortality and morbidity and identify the perioperative risk factors of mortality during CABG in hemodialysis (HD)-dependent patients.

Methods and Results: From the Japan Adult Cardiovascular Surgery Database, we compared 1,300 HD-dependent chronic renal failure patients with 18,387 non-HD patients who all underwent isolated CABG between January 2005 and December 2008. The operative mortality and mortality, including major morbidity, was 4.8% vs. 1.4% and 23.1% vs. 13.7% in the HD and non-HD groups, respectively. Preoperative predictors of operative mortality included age, chronic obstructive pulmonary disease, peripheral arterial disease, congestive heart failure, arrhythmia, preoperative inotropic agent requirement, New York Heart Association class IV, urgent or emergency operation, poor left ventricular function, aortic valve regurgitation (>2), and mitral valve regurgitation (>3). Postoperative predictors of operative mortality included stroke, infection, prolonged ventilation, pneumonia, heart block, and gastrointestinal complications.

Conclusions: Compared with non-HD patients, CABG in HD patients was associated with high mortality and morbidity rates. An appropriate surgical strategy and careful perioperative assessment and management for prevention of respiratory and gastrointestinal complications might contribute to improved clinical outcomes after CABG in these patients. (*Circ J* 2012; **76:** 1115–1120)

Key Words: Coronary artery bypass grafting; Hemodialysis; Risk factor

Coronary artery disease (CAD) frequently occurs in patients with chronic renal failure (CRF) and is a major cause of mortality and morbidity in these patients.[1] CRF patients with CAD often need myocardial revascularization, and of the revascularization techniques, coronary artery bypass grafting (CABG) has been reported as having satisfactory survival rates in patients with kidney disease.[2,3] CABG has also been shown to yield better overall and angina-free survival than does percutaneous coronary intervention (PCI).[4–6] However, the operative mortality and morbidity are reportedly high compared with those of non-hemodialysis (HD) patients in both the short- and long-term. The hospital death rate after isolated CABG in HD-dependent patients was reported to be approximately 10%, which was higher than that for PCI.[7,8]

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Therefore, an appropriate surgical strategy and perioperative medical treatment based on the identification of perioperative risk factors would lead to an improvement in the clinical outcomes of these surgical procedures. For the past few decades, various studies have reported the clinical outcome of cardiac surgery in CRF patients, but almost all have been from single centers or consist of less than 200 patients.[1] Moreover, we found few previous large-scale studies that focused on isolated CABG and included multivariate analysis of perioperative risk factors of operative mortality.[8]

Therefore, in the present study we examined 19,687 isolated CABG patients, including 1,300 HD-dependent patients,

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Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, Suita (T.Y., T.S., S.M., Y.Y., K.T., Y.S.); Department of Cardiac Surgery, Faculty of Medicine (N.M., H.T.), Department of Healthcare Quality Assessment (H.M.), Graduate School of Medicine, University of Tokyo, Tokyo, Japan
Mailing address: Yoshiki Sawa, MD, PhD, Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita 565-0871, Japan. E-mail: sawa@surg1.med.osaka-u.ac.jp
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Table 1. Baseline Characteristics of Patients Undergoing CABG

	Non-HD (n=18,387)	HD (n=1,300)	P value
Age, years			
≤60	17.9	28.3	<0.0001
61–65	13.8	19.0	
66–70	18.6	19.3	
71–75	22.0	17.9	
76–80	18.7	11.6	
≥81	9.0	3.8	
Mean age, years	68.7±9.4	65.4±9.2	<0.0001
BSA	1.64±0.39	1.59±0.16	0.001
Male (%)	77.3	78.7	0.246
History of smoking (%)	53.0	46.2	<0.0001
Current smoking (%)	20.0	16.7	0.004
DM (%)	48.0	65.7	<0.0001
DM requiring medication (%)	40.7	56.9	<0.0001
Serum creatinine (mg/dl)	1.01±1.1	8.61±25.2	<0.0001
Hyperlipidemia (%)	57.0	36.5	<0.0001
Hypertension (%)	73.3	83.1	<0.0001
History of cerebrovascular event (%)	13.5	17.7	<0.0001
Recent (<2 weeks) cerebrovascular event (%)	0.6	0.8	0.295
History of infective endocarditis (%)	0.1	0.2	0.342
Chronic lung disease (moderate, severe) (%)	1.5	1.4	0.650
Extracardiac arterial disease (%)	15.4	27.0	<0.0001
Peripheral arterial disease (%)	14.3	25.4	<0.0001
Thoracic aortic disease (%)	2.1	2.2	0.699
Mental disorder (%)	3.1	4.5	0.006
History of coronary intervention (%)	25.1	28.1	0.015
Previous MI (%)	34.7	31.1	0.008
Congestive heart failure (2 weeks) (%)	13.7	22.8	<0.0001
Angina (%)	88.2	89.9	0.056
Unstable (%)	28.8	34.7	<0.0001
Cardiogenic shock (%)	4.3	6.6	0.0001
Arrhythmia (%)	7.4	9.7	0.003
Inotropic agents requirement (%)	3.5	4.9	0.010
Reoperation (%)	2.2	2.3	0.875
Urgent operation (%)	11.8	13.7	0.044
Emergency operation (%)	6.9	8.7	0.017
BMI mean	24.0±29.7	22.7±14.0	0.003
>26 (%)	21.5	12.0	<0.0001
>30 (%)	3.7	2.2	0.004
NYHA class			
NA (%)	14.1	10.1	<0.0001
I (%)	26.3	23.1	0.011
II (%)	36.2	35.2	0.465
III (%)	14.1	17.8	0.0003
III or IV (%)	23.0	30.8	<0.0001
No. of diseased vessels (%)			
1	4.4	4.9	0.381
2	24.8	23.9	0.465
3	69.4	70.2	0.531
Ejection fraction (%)			
>60	48.9	34.1	<0.0001
30–60	44.4	55.4	<0.0001
<30	6.2	9.8	<0.0001
AS (%)	1.7	6.5	<0.0001
MS (%)	0.3	1.2	<0.0001
AVR (>2) (%)	5.6	5.7	0.845
MVR2 (>2) (%)	11.5	20.7	<0.0001
TVR2 (>2) (%)	5.4	8.7	<0.0001
AVR3 (>3) (%)	0.6	0.7	0.768
MVR3 (>3) (%)	1.4	4.4	<0.0001
TVR3 (>3) (%)	0.6	1.3	0.002

(Table 1 continued the next column.)

CABG, coronary artery bypass grafting; HD, hemodialysis; BSA, body surface area; DM, diabetes mellitus; MI, myocardial infarction; BMI, body mass index; NYHA, New York Heart Association; AS, aortic stenosis; MS, mitral stenosis; AVR, aortic valve regurgitation; MVR, mitral valve regurgitation; TVR; tricuspid valve regurgitation.

from between 2005 and 2008 in the Japan Adult Cardiovascular Surgery Database (JACVSD) to determine the contemporary clinical outcome of isolated CABG and to determine the risks for perioperative death following CABG in patients with HD-dependent CRF. We then discuss the appropriate surgical strategy for and the perioperative medical management of such patients.

Methods

Study Population

The JACVSD was initiated in 2000 to estimate surgical outcomes after cardiovascular procedures in many centers throughout Japan. The JACVSD adult cardiovascular division currently captures clinical information from nearly half of all Japanese hospitals performing cardiovascular surgery. The data collection form has a total of 255 variables (definitions are available online at http://www.jacvsd.umin.jp), and these are almost identical to those in the Society of Thoracic Surgeons (STS) National Database (definitions are available online at http://sts.org). The JACVSD has developed software for a web-based data collection system through which the data manager of each participating hospital electronically submits the data to the central office. Although participation in the JACVSD is voluntary, data completeness is a high priority. Accuracy of submitted data is maintained by data audit achieved by monthly visits by administrative office members to the participating hospital to check data against clinical records. Validity of data is further confirmed by an independent comparison of the volume of cardiac surgery at a particular hospital entered in the JACVSD with that reported to the Japanese Association for Thoracic Surgery annual survey.[9]

We examined cases of isolated CABG between January 1, 2005 and December 31, 2008. JACVSD records that had been obtained without the patient's informed consent were excluded from this analysis. Records with missing or out of range age, sex, or 30-day status (see Endpoints section below) were also excluded. After data cleaning, the population for this risk model analysis consisted of 1,300 HD-dependent patients and 18,387 non-HD-dependent patients who underwent cardiovascular procedures at 167 participating sites throughout Japan.

Endpoints

The primary outcome measure of the JACVSD was 30-day operative mortality, which was defined exactly the same as the 30-day operative mortality in the STS National Database. The 30-day operative mortality included any patient who died during the index hospitalization, regardless of the length of hospital stay, and any patient who died after being discharged from hospital within 30 days of the operation. Operative mortality also included any patients who died after 31 days during the hospital stay in addition to patients included in the 30-day mortality. Using a definition from previous studies,[10,11] major morbidity was defined as any of the following 5 postoperative in-hospital complications: stroke, reoperation for any reason, need for mechanical ventilation for more than 24 h after surgery, renal failure, or deep sternal wound infection.

Statistical Analysis

We examined differences between 2 groups (isolated CABG with and without HD) using bivariate tests: Fisher's exact test and the chi-square test for categorical covariates, and the unpaired t-test or Wilcoxon rank sum test for continuous covariates. To develop risk models of isolated CABG with HD, we conducted multivariate stepwise logistic regression analysis for each outcome. Stability of the model was checked every time a variable was eliminated. When all statistically non-significant variables ($P<0.10$) had been eliminated from the model, "goodness-of-fit" was evaluated and the area under the receiver-operating characteristic curve was used to assess how well the model could discriminate between patients who lived from those who had died. To investigate the relationship between postoperative complications and operative death in HD patients, we conducted multivariate stepwise logistic regression analysis for operative mortality. Complications such as cardiac arrest and multisystem failure were excluded from this analysis because they are highly associated with operative death.

Results

Patient Demographics

Baseline characteristics of the study population are summarized in **Table 1**. Patients in the HD group were significantly younger (65.4±9.2 vs. 68.7±9.4 years) and had less body surface area (1.59 vs. 1.64 m^2) than the non-HD patients. As expected, the HD-dependent patients had a significantly greater degree of baseline comorbidity than did non-HD patients. Patients in the HD group were more likely to have a history of diabetes (56.9% vs. 40.7%), hypertension (83.1% vs. 73.3%), and peripheral vascular disease (27.0% vs. 15.4%). A higher rate of current congestive heart failure (22.8% vs. 13.7%) with a lower ejection fraction and lower New York Heart Association (NYHA) status was observed in the HD group. As for valvular disease, aortic stenosis (6.5% vs. 1.7%), mitral valve regurgitation (MVR) (>2) (20.7% vs. 11.5 %), and tricuspid valve regurgitation (>2) (8.7% vs. 5.4%) were more common in HD patients. In both the HD and non-HD groups, off-pump surgery was performed approximately twice as often as on-pump surgery, and the off-pump ratio did not differ between groups. Transfusion was required more often in the HD group. Bilateral internal mammary artery usage in the HD group was less frequent than in the non-HD group (22.8% vs. 31.4%) (**Table 2**).

Postoperative Outcomes

In-hospital outcomes are summarized in **Table 3**. The 30-day mortality was 4.8% vs. 1.4% and the operative mortality was 7.8% vs. 2.1% in the HD and non-HD groups, respectively. Both the 30-day and operative mortalities in HD patients were approximately 3-fold more frequent than in non-HD patients. Operative mortality with a major complication was more frequent in the HD group (23.1% vs. 13.7%).

Multivariate Predictors of In-Hospital Death

Multivariate predictors of operative mortality are summarized in **Table 4**. Predictors of operative mortality included

Table 2. Intraoperative Characteristics

	Non-HD CABG (n=18,387)	HD CABG (n=1,300)	P value
On-pump surgery (%)	37.3	35.6	0.230
Transfusion (%)	52.5	87.8	<0.0001
Bilateral IMA usage (%)	31.4	22.8	<0.0001
Single IMA usage (%)	61.7	68.7	<0.0001

IMA, internal mammary artery. Other abbreviations see in Table 1.

Table 3. Mortality and Morbidity

	Non-HD CABG (n=18,387)	HD CABG (n=1,300)	P value
30-day mortality (%)	1.4	4.8	<0.0001
Operative mortality (%)	2.1	7.8	<0.0001
Operative mortality+major complication (%)	13.7	23.1	<0.0001
Reoperation (any reason)	5.4	6.6	0.067
Infection			
Deep sternum	1.8	2.6	0.026
Thoracotomy	0.5	1.1	0.007
Leg	1.9	4.5	<0.0001
Urinary	0.8	0.6	0.402
Septicemia	1.0	2.7	<0.0001
Prolonged ventilation	6.6	9.4	<0.0001
Pneumonia	2.4	4.4	<0.0001
Pulmonary embolism	0.2	0.2	0.989
Stroke	1.5	1.6	0.636
TIA	1.3	2.4	0.001
Coma	0.6	1.1	0.017
Paraparesis	0.3	0.4	0.871
Atrial fibrillation	13.2	14.9	0.076
Heart block requiring pacemaker	0.5	0.8	0.159
Cardiac arrest	1.0	2.8	<0.0001
Reoperation for bleeding	1.8	3.0	0.003
Anticoagulant complication	0.3	0.5	0.084
Tamponade requiring drainage	1.0	1.4	0.132
Gastrointestinal complication	1.6	3.9	<0.0001
Multisystem failure	0.9	2.6	<0.0001
Dissection aorta	0.1	0	0.378
Dissection iliac	0.02	0.1	0.138
Limb ischemia	0.2	0.7	0.001
Re-admission	1.9	2.5	0.193
ICU stay >8 days	5.7	11.2	<0.0001

TIA, transient ischemic attack; ICU, intensive care unit. Other abbreviations see in Table 1.

Table 4. Multivariate Preoperative Predictors of Operative Mortality of CABG for HD Patients

Characteristic	RR (95%CI)	P value
Age	1.38 (1.184–1.604)	<0.0001
Chronic pulmonary disease (moderate severe)	5.52 (1.786–17.033)	0.003
Extracardiac arterial disease	1.86 (1.15–3.01)	0.011
Congestive heart failure	1.77 (1.06–2.957)	0.029
Arrhythmia	1.84 (1.02–3.325)	0.043
Preoperative inotropic agent	2.46 (1.204–5.024)	0.014
NYHA class IV	1.99 (1.1–3.599)	0.023
Urgent operation	2.02 (1.085–3.752)	0.027
Emergency operation	2.27 (1.177–4.372)	0.014
Ejection fraction <30%	2.06 (1.125–3.787)	0.019
AVR ≥2	3.98 (1.987–7.979)	<0.0001
MVR ≥3	2.32 (1.094–4.913)	0.028

RR, relative risk; CI, confidence interval. Other abbreviations see in Table 1.

Table 5. Multivariate Postoperative Predictors of Operative Mortality of CABG for HD Patients

	OR	CI	P value
Stroke	9.85	3.1–30.8	<0.0001
Infection	6.72	2.6–17.7	<0.0001
Prolonged ventilation	3.82	2.1–7.0	<0.0001
Pneumonia	13.15	6.3–27.4	<0.0001
Gastrointestinal complication	5.43	2.3–12.7	<0.0001
Heart block	12.46	2.4–64	0.003

OR, odds ratio. Other abbreviations see in Tables 1,4.

age (odds ratio [OR]=1.38, P<0.0001), chronic obstructive pulmonary disease (COPD) (OR=5.52, P=0.003), peripheral arterial disease (OR=1.86, P=0.011), congestive heart failure (OR=1.77, P=0.029), arrhythmia (OR=1.84, P=0.043), preoperative inotropic agent requirement (OR=2.46, P=0.014), NYHA class IV (OR=1.99, P=0.023), urgent operation (OR= 2.02, P=0.027), emergency operation (OR=2.27, P=0.014), ejection fraction <30% (OR=2.06, P=0.019), aortic valve regurgitation (AVR) (>2) (OR=3.98, P<0.0001), and MVR (>3) (OR=2.32, P=0.028).

Relationship Between Operative Mortality and Postoperative Complications

Results are summarized in **Table 5**. Among the complications observed relatively often (incidence >3%), prolonged ventilation (OR=3.82), pneumonia (OR=13.15), infection (OR=6.72), and gastrointestinal complications (OR=5.43) were significant factors in operative mortality.

Discussion

We investigated the clinical outcomes and risk factors of operative mortality and morbidity in patients with (n=1,300) and without (n=18,387) HD who underwent isolated CABG. The study data was extracted from the JACVSD, and is one of the largest comparative series of post-CABG outcomes in such patients.[8,12]

The operative mortality of HD patients after isolated CABG in this study was 7.8%, which was similar to previous studies that reported an operative mortality of approximately 10%.[8,12] As previously reported, HD patients have more preoperative comorbidities. Compared with other reports, the rates of emergency operation, male sex, shock state, and off-pump CABG tended to be high in this study, and those of congestive heart failure and chronic lung disease tended to be low. Age, hypertension, NYHA status, and prevalence of valvular disease were comparable. The postoperative morbidity rate of the HD group was higher than that in the non-HD group. Major postoperative morbidity (stroke, prolonged ventilation, deep sternal infection, renal failure and reoperation for any reason) were also comparable with those in the reports from the STS database, which included 7,152 dialysis patients.[8] Besides the major complications, the prevalence of leg infection, pneumonia, transient ischemic attack, cardiac arrest, gastrointestinal complications, multisystem failure, and limb ischemia in HD patients was significantly higher than in non-HD patients.

A series of studies have reported early and late outcomes of CABG with and without valve operations in CRF patients.[13–16] In those studies, several risk factors were reported for mortality after cardiac surgery in HD-dependent patients. Many reports have found a low ejection fraction to be an independent risk factor,[17–20] which was consistent with the findings of the present study. However, we found no previous large-scale studies that focused on isolated CABG and included a multivariate analysis of risk factors for hospital mortality. As a large-scale report that focused on isolated CABG, Cooper et al demonstrated that the glomerular filtration rate was a powerful predictor of operative morbidity after isolated CABG in 7,152 HD patients.[8] Charytan et al analyzed 77,323 non-HD and 635 HD patients who underwent CABG that included valve surgery. They demonstrated that HD-dependence, congestive heart failure, valvular heart disease, valve surgery, female sex, age, pathological weight loss, chronic lung disease, neurological disorders, admission for myocardial infarction, and liver disease were adjusted risks for perioperative mortality.[12]

Regarding valvular disease, we also demonstrated that AVR (>2) and MVR (>3) were independent risk factors for operative mortality after isolated CABG. The question then arose regarding whether valve operation should be performed simultaneously with CABG when moderate AVR or MVR was complicated. Horst et al reported that the risk for perioperative death associated with CABG combined with valve operation was approximately 10-fold that for isolated CABG.[1] Charytan et al also demonstrated concomitant valve surgery as a perioperative risk factor.[12] the surgical management of moderate, chronic ischemic MVR combined with CABG is still controversial.[21,22] Combined mitral valve surgery has been reported to be significantly associated with a lower residual grade of MVR compared with CABG alone. On the other hand, it has been reported that CABG alone was able to reduce the MVR grade in 40% of patients.[23] From the postoperative NYHA status perspective, the effect of mitral valve surgery is also controversial.[23,24] As for late mortality, a meta-analysis of 2,479 ischemic MVR patients showed that mitral valve surgery did not have advantages for late mortality compared with CABG alone.[24] As for aortic valve disease, most surgeons would not perform concomitant aortic valve surgery in HD patients with AVR=2. However, concomitant aortic valve surgery might be taken into consideration in some cases complicated by AVR >3. In the present study, the cohort of AVR >3 was very small (non-HD group: <100 patients, HD group: <10 patients.) Therefore, it was very difficult to investigate whether AVR >3 is a risk factor or not for postoperative mortality in our multivariate analysis.

In summary, concomitant surgery should be performed with consideration of the "risks and benefits" of additional valve surgery, and further study is necessary.

Relatively few large-series reports have documented the detailed incidence of postoperative morbidity after isolated CABG in HD-dependent patients.[8,12] Compared with non-HD patients, the incidence of major postoperative complications was high in HD-dependent patients in the present study, as previously reported. Postoperative complications could be considered to be closely associated with higher mortality. The higher incidence of these complications in HD-dependent patients might partly explain their poor clinical outcomes. To improve the clinical outcome of isolated CABG in HD, it seems important to prevent these complications. The complications that occurred at a relatively high incidence (>3%) in the present study were infection, prolonged ventilation, pneumonia, atrial fibrillation, reoperation for bleeding, and gastrointestinal complications. Among these, infection, prolonged ventilation, pneumonia, and gastrointestinal complications were significant independent risk factors for operative mortality.

Several studies have reported that higher mortality rates are associated with infection in HD-dependent patients undergoing cardiac surgery. Takami et al reported that following cardiac surgery in their 245 HD patients, almost half of the cases of hospital death were related to infection.[25] Akman et al demonstrated that infection was an independent postoperative risk factor for mortality after CABG in HD-dependent patients, and suggested the importance of early diagnosis of infection for both early recovery and shorter hospitalization in the postoperative period.[7]

Mangi et al reported that the incidence of gastrointestinal complications requiring surgical repair after cardiac and vascular surgery was 0.53% (46/8,709).[26] Of these, mesenteric ischemia comprised 67% and two-thirds of these patients died. To prevent gastrointestinal complications, especially mesenteric ischemia, preoperative abdominal screening, bowel preparations, and postoperative volume control might be important in isolated CABG for HD-dependent patients.

To prevent postoperative pulmonary complications, preoperative risk stratification and a risk-reduction strategy seem important. As for postoperative respiratory complications, COPD, the prevalence of which is higher by 10–12% among cardiovascular surgical candidates compared with aged-matched populations, might be one of the most important risk factors.[27] Several advances in surgery and anesthetic care have been shown to be particularly beneficial for COPD patients. Compared with standard operations, minimally invasive procedures produce less tissue damage and, in turn, attenuated neurohumoral and inflammatory responses.[27] Off-pump bypass is considered to be a minimally invasive surgery in coronary artery operations. Patients with FEV_1 (1 s to forced vital capacity) less than the lower limit of normal have better outcomes after off-pump bypass compared with those post-CABG.[28]

Conclusions

Compared with non-HD patients, CABG in HD patients was associated with high mortality and morbidity rates in the present study. An appropriate surgical strategy and careful perioperative assessment and management for prevention of respiratory and gastrointestinal complications might contribute to improvements in clinical outcomes after CABG in HD-dependent patients.

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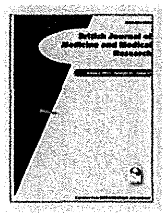

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Steady-State Levels of Troponin and Brain Natriuretic Peptide for Prediction of Long-Term Outcome after Acute Heart Failure with or without Stage 3 to 4 Chronic Kidney Disease

Yutaka Endo[1*], Shun Kohsaka[1], Toshiyuki Nagai[1], Kimi Koide[1], Masashi Takahashi[1], Yuji Nagatomo[1], Kazuki Oshima[1], Hiroaki Miyata[2], Keiichi Fukuda[1] and Tsutomu Yoshikawa[3]

[1]Division of Cardiology, Keio University School of Medicine, Tokyo, Japan
[2]Department of Healthcare Quality Assessment, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
[3]Director, Division of Cardiology, Sakakibara Heart Institute, Tokyo, Japan.

Authors' contributions

This work was carried out in collaboration between all authors. YE collected the clinical data, designed the study, performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript, and managed the literature searches. SK designed the study, wrote the protocol, managed the literature searches and supervised the literature. TN, KK, MT and YN managed the literature searches. KO collected the clinical data. HM managed the literature searches and performed the statistical analysis. KF managed the literature searches and supervised the literature. TY designed the study, managed the literature searches and supervised the literature. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aim: To determine whether assessment of a combination of steady-state discharge levels of biomarkers improves risk stratification after acute decompensate HF.
Study Design: Retrospective cohort study.
Place and Duration of Study: Keio University Hospital, between January 2006 and September 2011.
We analyzed 244 patients with acute HF due to ischemic or dilated cardiomyopathy who

**Corresponding author: Email: yuendou-kei@umin.ac.jp;*

were enrolled in a prospective, single institution-based registry between January 2006 and September 2011. Patients were stratified by discharge values of BNP and/or TnT. The primary endpoint was a composite of HF readmission or death during the 2-year period after discharge.
Results: The population was predominantly male (69.3%), and the mean age was 66.6±15.3 years. Patients with higher BNP levels or detectable TnT had a worse prognosis (BNP45.0% vs. 18.8%, p<0.001; TnT 43.8% vs. 25.1%, p=0.002, respectively). The primary event rate was additively worse among patients with both increased BNP levels and detectable TnT compared to those with increased levels of BNP or detectable TnT alone (log-rank p<0.001). A similar trend was observed in the subgroup of patients with CKD stage III–V (n=172).
Conclusion: Assessment of both BNP and TnT values may have a significant predictive value for HF prognosis, even among patients with CKD, a condition affecting biomarker levels.

Keywords: Biomarkers; heart failure; chronic kidney disease.

1. INTRODUCTION

Heart failure (HF) is a disorder that has major clinical and public health impacts worldwide (Young, 2004). In Japan, the number of HF admissions reached 582,000 in 2008 and HF consumes a significant proportion of the funds allocated for cardiovascular care, which totaled $713 billion in 2009 (Report from Japanese Health and Welfare, 2009). HF is estimated to affect over 5 million people in the US, and it is the most common Medicare diagnosis-related group. Furthermore, as the population ages, HF prevalence increases; currently, the HF incidence approaches 10 per 1000 among those older than 65 years, and the estimated cost of HF treatment in the United States was $37 billion in 2009 (Lloyd-Jones et al., 2009).

Several major advances in the management of HF have been achieved in the past decade, and some data suggest that these new advances are beginning to impact the prognosis of HF in the community (Polanczyk et al., 2000). One such advance is the reorganization of high-risk patients stratified by biomarkers. In particular, biomarkers representing a patient's fluid status (e.g., brain natriuretic peptide [BNP]) or degree of myocardial injury (e.g., highly sensitive troponins [TnT]) are valuable tools for predicting the long-term prognosis of HF (Peacock et al., 2008; Braunwald, 2008; Brugger-Andersen et al., 2008; Felker et al., 2000).

However, the impact of the combination of BNP and TnT values has not been thoroughly investigated, particularly among patients with chronic kidney disease (CKD). Kidney disease affects HF through various mechanisms, including those described by the low-flow-state hypothesis, intraabdominal and central venous pressure elevation, sympathetic overactivity, rennin-angiotensin-aldosterone system overactivity, and oxidative injury. HF affects biomarker levels, but its impact on the long-term outcome is unclear. Data on biomarker levels are also particularly sparse in the Japanese population where a non-ischemic etiology is the dominant characteristic of HF. Therefore, we sought to investigate whether evaluation of a combination of biomarkers could improve risk stratification of patients with acute decompensated HF, particularly those with CKD.

2. MATERIALS AND METHODS

2.1 Study Subjects

Between January 2006 and September 2011, we prospectively registered 244 consecutive patients who were admitted to Keio University Hospital for the treatment of decompensate HF defined according to the Framingham criteria. To avoid the influence of acute coronary events and renal dysfunction, patients with clinical or electrocardiographic evidence of acute coronary syndrome in the previous 3 months, those with coronary revascularization in the previous 3 months, those with renal failure (serum creatinine concentration, ≥2.5 mg/dl), and those undergoing hemodialysis were excluded (Srisawasdi et al., 2010). Patients with terminal cancer, infections and inflammatory diseases were also excluded. The primary endpoint was a composite of all-cause mortality plus HF requiring hospitalization. The mean length of follow-up was 730 days (interquartile range 397 to 730). Informed consent was obtained from each patient upon enrollment.

Dilated cardiomyopathy is characterized by dilatation and impaired contraction of 1 or both ventricles and an EF of <45% without the presence of obstructive coronary disease. Ischemic cardiomyopathy was defined by a-number-of-diseased-vessels classification which is the presence of obstruction (more than 75%) in one or more coronary (Felker et al., 2002). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and the study was approved by the institution's human research committee.

2.2 Measurement of Cardiac Biomarkers

Plasma TnT and BNP levels were measured before discharge. Commercially available assay kits were used for the measurement of TnT (4th generation high sensitivity assay,Roche Diagnostics, Tokyo, Japan) and BNP (Shionogi, Tokyo, Japan). The lower limit of detection for TnT was 0.01 ng/mL, and BNP was subclassified by level according to receiver operating characteristic (ROC) analysis (Cut-off value; 239.5 pg/mL). Serum creatinine and hemoglobin levels were determined by standard laboratory methods. Glomerular filtration rate (GFR) was estimated using the equation from the Modification of Diet in Renal Disease Study: eGFR (mL•min-1•1.73 m-2) = 0.741 × 175 × Age-0.203 × SCr-1.154 (× 0.724 for females). CKD was defined as an eGFR of <60 mL/min at the time of discharge. Diabetes mellitus was defined according to the criteria of the American Diabetes Association. Before discharge, experienced technicians who had no knowledge of the biochemical data performed two-dimensional echocardiography in a standard manner using a Hewlett Packard 5500. Clinical data were obtained by interviewing patients and from hospital medical records. Physicians were blinded to the data on biochemical markers and treatment was selected based on the patient's symptoms and physical findings.

2.3 Statistical Analysis

Categorical variables were expressed as numbers (percentages) and continuous variables were expressed as the mean ± standard deviation. An unpaired t-test and chi-square test were used for between-group comparisons of continuous and categorical variables, respectively. If the data were skewed, the nonparametric Mann-Whitney test was used to compare continuous variables. ROC analysis was performed to determine the cut-off values for the conversion of continuous variables into categorical variables when analyzing BNP. Overall survival and survival without hospitalization for HF were analyzed by the Kaplan-

Meier method, and the curves were compared by the log-rank test. We also performed an analysis based on the presence/absence of CKD.

Univariate and multivariate Cox regression analyses were performed to determine the associations between TnT and other variables. For each covariate, categorical variables were allowed to enter in a stepwise forward multivariate Cox model with the use of a probability value ≤0.10 for inclusion or ≤0.05 for deletion. The multivariate model included categorical variables that were statistically significant according to univariate analysis as well as clinically important. A P value of <0.05 was considered significant. Statistical analyses were performed with SPSS version 16.0 software (SPSS Inc., Chicago, Illinois).

3. RESULTS AND DISCUSSION

3.1 Study Population

At baseline, the mean age of all patients was 66.6±15.3 years; 69.3% were men. About half of the patients had non-ischemic cardiomyopathy (47.5%). TnT was detectable (≥0.01 ng) in 73(29.9%) patients at discharge, with interquartile range 0.00 to 0.02. The median level of BNP was 206 pg/mL (interquartile range 108 to 490) at discharge. Notably, our population included a large group of patients with CKD (68.0%). Threshold for BNP was determined via ROC curve analysis (239.5 pg/mL). TnT threshold for detectable vs non detectable was 0.01 ng/mL.

The patients were subsequently divided into 3 groups based on biomarker levels at discharge: patients with both lower BNP levels and undetectable TnT (group 0, n=107); those with either higher BNP levels or detectable TnT (group 1, n=84); and those with both higher BNP level and detectable TnT (group 2, n=53). Patients with elevated biomarker levels also had a greater likelihood of diabetes mellitus (p=0.007), factors suggestive of impaired renal function (such as eGFR, p<0.001), elevated blood urea nitrogen (p<0.001), and a higher rate of CKD (p<0.001) and anemia (p<0.001) at discharge (Table 1).

3.2 Outcomes

During the 2-year follow-up period, 75(30.7%) events were recorded (28 deaths and 66 readmissions). Kaplan-Meier event curves comparing the prognosis of patients with higher vs. lower BNP levels, and patients with detectable vs. undetectable TnT levels are shown in Fig. 1A. During the follow-up period, primary event rates were higher among patients with elevated BNP levels (log-rank test; p<0.001) or detectable TnT (p=0.007) compared with those with lower BNP levels or undetectable TnT. When the patients were stratified into 3 groups based on biomarker values, the primary event rate was additively worse among patients with both increased BNP values and detectable TnT levels (Fig. 1B; log-rank p<0.001).For the individual comparison, there were statistically significant differences in the outcome of both biomarker positive groups (double and single positive group) compared to control group (p<0.001). There were no statistically significant difference in the outcome of double-positive (TNT[+]/BNP[+]) when compared to single-positive group (TNT[+] or BNP[+]; p=0.318). Similar trend was seen when the outcome of death and heart failure were assessed individually.

Table 1. Baseline characteristics of the patients by the BNP and TnT values

		All (=244)	Group 0(=107)	Group 1(=84)	Group 2(=53)	P value
Patients characteristics						
Age		66.6±15.3	61.1±14.9	69.7±15.0	72.9±12.8	<0.001
Male (%)		69.3	70.1	66.7	71.7	0.799
Etiology (%)	DCM	47.5	58.9	36.9	41.5	0.018
	ICM	27.0	18.7	32.1	35.8	
	others	25.4	22.4	31.0	22.6	
DM (%)		30.5	24.3	27.4	48.1	0.007
AF/Af (%)		34.0	29.0	41.7	32.1	0.174
smoke (%)		36.1	42.7	34.4	25.0	0.153
BMI		23.3±5.6	24.3±4.7	22.2±6.3	22.3±6.1	0.030
HTN (%)		44.6	44.0	43.8	47.2	0.914
On admission						
NYHA ▯ 2 (%)		77.2	70.2	82.1	83.0	0.079
eGFR		50.8±20.2	58.4±17.1	48.8±20.9	38.6±18.1	<0.001
CKD (%)		68.0	52.3	76.2	86.8	<0.001
Hb		12.9±2.4	13.6±2.2	12.7±2.4	11.7±2.3	<0.001
sBP		130.0±29.2	131.4±28.3	128.8±30.5	129.1±29.2	0.808
HR		89.1±24.9	90.6±27.8	86.8±23.6	89.6±20.2	0.602
Na		139.5±4.2	140.5±3.1	138.9±5.0	138.6±4.3	0.007
K		4.4±0.5	4.3±0.4	4.4±0.5	4.5±0.7	0.126
BUN		23.0±10.8	19.3±7.2	23.7±12.3	29.2±11.2	<0.001
On discharge						
NYHA =>2 (%)		2.1	0	2.4	5.8	0.055
LAD		45.1±10.2	45.3±10.3	43.8±9.3	46.6±11.7	0.324
LVDd		56.8±14.9	58.4±15.5	54.7±14.8	56.6±13.3	0.233
LVEF		35.8±13.5	35.9±13.2	35.9±14.1	35.6±13.5	0.991
eGFR		50.3±20.0	57.6±18.2	47.4±20.3	40.1±17.5	<0.001
CKD (%)		70.5	56.1	78.6	86.8	<0.001
Hb		13.0±2.4	13.9±2.2	12.8±2.5	11.8±2.2	<0.001
sBP		108.0±17.4	107.6±17.2	109.3±19.0	109.8±15.0	0.688
HR		73.3±15.4	72.3±13.6	74.8±17.4	72.8±16.0	0.560
Na		138.3±3.7	138.6±2.9	138.5±4.1	137.4±4.4	0.110
K		4.5±0.5	4.5±0.4	4.4±0.4	4.6±0.5	0.036
BUN		25.5±12.8	21.1±9.6	25.1±10.8	35.1±16.2	<0.001
Medication						
BB (%)		78.7	82.1	75.9	76.0	0.516
AceiARB (%)		74.9	82.2	72.3	64.2	0.030
Diuretics (%)		77.9	78.5	72.6	84.9	0.236
Warfarin (%)		37.3	38.3	34.5	39.6	0.800
Aspirin (%)		34.2	30.8	40.5	30.8	0.320
Biomarker						
BNP		350.3±439.5	122.8±94.2	385.7±267.5	753.6±704.2	<0.001
TnT		0.03±0.14	0	0.015±0.039	0.13±0.28	<0.001

3.3 Outcomes of the CKD Subgroup

The presence of CKD had a significant negative impact on patient survival; overall, CKD patients had significantly more primary events than did non-CKD patients (log-rank test; p=0.004). A separate analysis was performed to demonstrate the impact of biomarkers in CKD patients (Fig. 2A) in comparison to non-CKD patients (Fig. 2B). Similar to our main results, primary events were more frequent among patients with higher BNP levels (log-rank test; p=0.007) or detectable TnT levels (p=0.082) compared with their counterparts. Event rates were also additively worse as the number of elevated biomarkers increased (Fig. 2B; log-rank p=0.012).

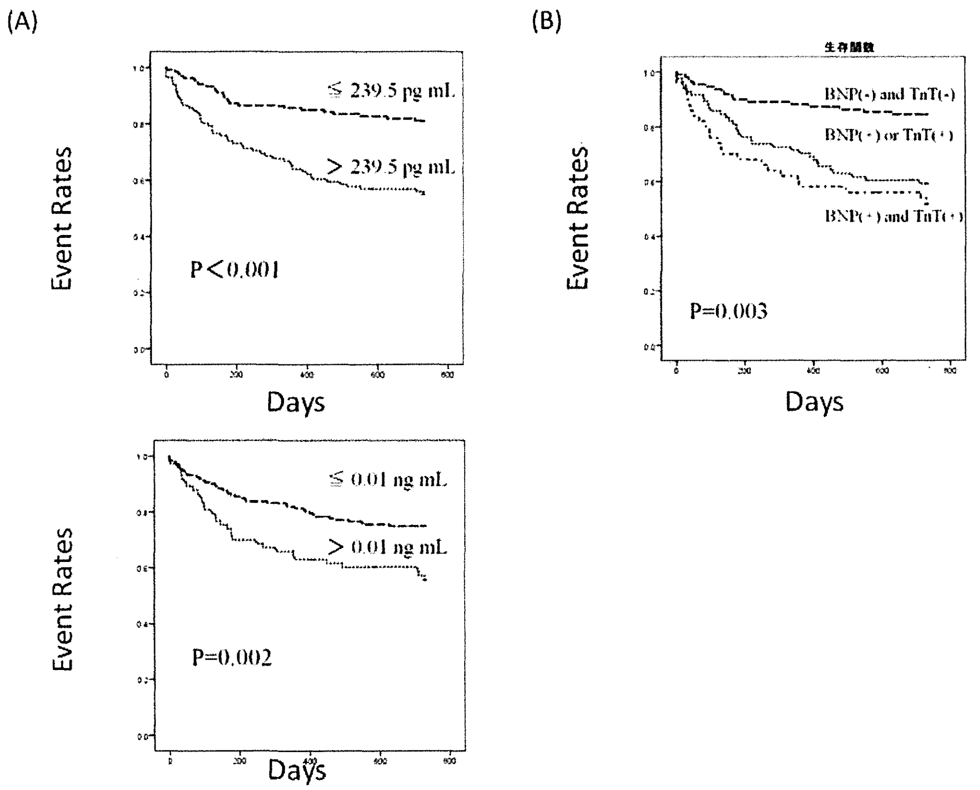

Fig. 1. The long-term prognosis by the stratification of BNP and TnT in all patients. (A) The long-term prognosis of the HF patients stratified by the combination of BNP and TnT level.(B)

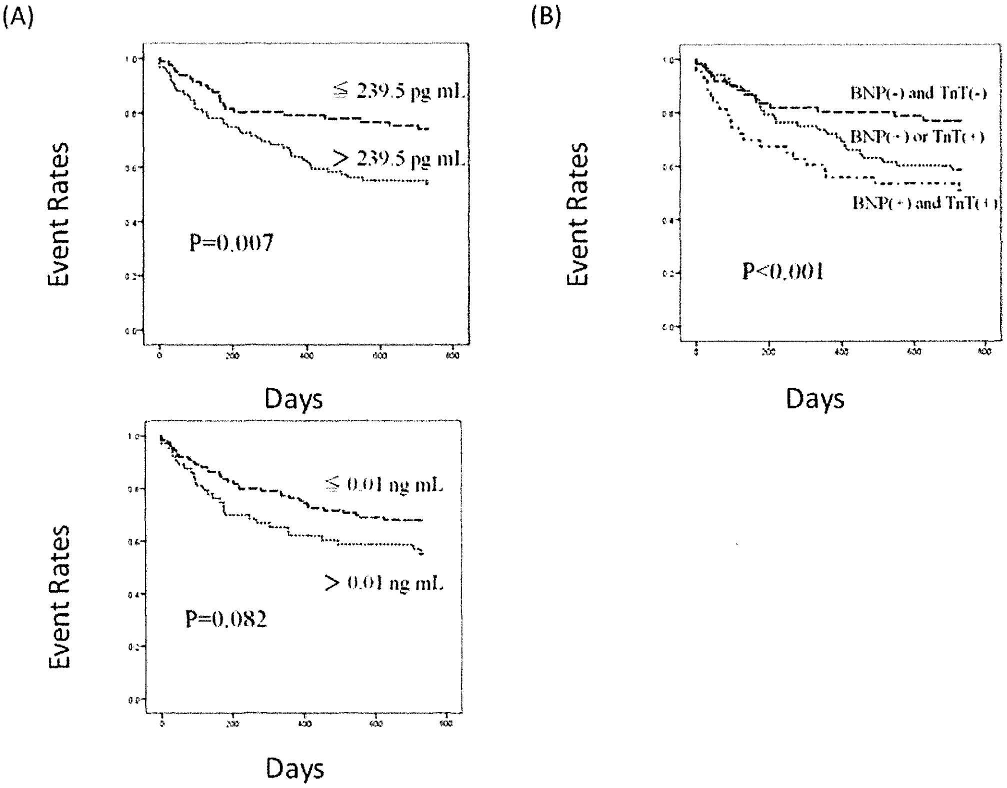

Fig. 2. The long-term prognosis by the stratification of BNP and TnT in subgroup of patients withCKD. (A) The long-term prognosis of the HF patients with CKD stratified by the combination of BNP and TnT level. (B)

3.4 Univariate and Multivariate Cox Hazard Models

The results of the univariate and multivariate models are shown in Table 2. Significant predictors of events were age (HR 1.02; 95% CI, 1.01–1.04; p=0.005), BNP levels (HR, 2.86; 95% CI, 1.77–4.63; p<0.001), TnT levels (HR, 2.01; 95% CI, 1.27–3.16; p=0.003), and the combination of BNP/TnT levels (HR, 1.94; 95% CI, 1.46–2.59; p<0.001). When adjusted for known predictors, the combination of BNP/TnT levels was associated with the combined outcome of HF readmission and all-cause mortality (HR, 1.02; 95% CI, 1.00–1.05; p=0.046 and HR=1.544; 95% CI, 1.11–2.15; p=0.010, respectively). A similar trend was observed in the analysis of HF patients with CKD (Table 2).

Table 2. Result of multivariable analysis. Predictors of composite outcome in all patients and in subgroup of patients with CKD

All	**HR**	**95%CI**	**95%CI**	**P value**
Age	1.003	0.982	1.023	0.806
Left atrial diameter	1.024	1.000	1.049	0.046
CKD	1.507	0.748	3.034	0.251
Hemoglobin	0.957	0.848	1.079	0.473
BUN	1.007	0.986	1.029	0.504
Use of ACE inhibitors or ARB	0.680	0.398	1.163	0.159
Positive BNP or TnT values on discharge	1.544	1.110	2.146	0.010
CKD				
	HR	**95%CI**	**95%CI**	**P value**
Left atrial diameter	1.025	0.998	1.053	0.071
Left ventricular diastolic dimension	1.025	1.000	1.051	0.048
BUN	1.014	0.992	1.036	0.224
Use of ACE inhibitors or ARB	0.595	0.324	1.023	0.063
Positive BNP or TnT values on discharge	1.435	1.020	2.020	0.008

3.5 Discussion

The present study revealed that discharge levels of both BNP and TnT were associated with the composite of HF readmission and all-cause mortality in patients with acute decompensate HF. In addition, the combination of elevated BNP and TnT levels further stratified the risk and had an additive effect on the patients' long-term prognosis. Measuring the combination of these biomarkers on discharge appeared to be a useful method for stratification of HF patients, including those with CKD.

Ample evidence has demonstrated the value of natriuretic peptides for predicting adverse outcomes, and the prognostic potential of BNP values was examined in the multicenter Rapid Emergency Department Heart Failure Outpatients Trail (REDHOT), which showed that BNP values were very strong predictors of 90-day outcomes (Maisel et al., 2004). The many mechanisms of BNP release in acute HF, including myocyte stretch and cardiac remodeling, show why these markers are so profoundly prognostic in HF patients.

Serum biomarkers of cardiac stress and malfunction as well as myocyte injury have grown in clinical importance for predicting the prognosis of HF patients. TnT is produced from cardiac myocytes as a consequence of myocardial ischemia. The level of TnT has a significant negative predictive value among HF patients with CKD (Koide et al., 2010). Furthermore, patients with preserved kidney condition may very well be able to tolerate ongoing myocardial injury, whereas patients with CKD are strongly affected by troponin leakage (Kociol et al., 2010).

The assessment of a combination of these conventional biomarkers could potentially improve the risk stratification of acute decompensated HF patients; moreover, kits for such assessments are both inexpensive and widely available. In previous studies, Ishii et al. reported that the combination of cardiac TnT and BNP levels on admission might be highly effective for the risk stratification of patients with chronic HF (Ishii et al., 2002), but little information is available on the association of this combination of biomarkers after acute decompensation of HF (Nishio et al., 2007; Taniguchi et al., 2006). In our study, CKD had a significant impact on the long-term outcome, as has previously been reported, and we demonstrated that patients with CKD can also be efficiently stratified by levels of BNP, TnT, and the combination of these 2 biomarkers. Patients with even mild chronic renal insufficiency have significantly increased cardiovascular morbidity and mortality, and chronic renal insufficiency also affects concentrations of biomarkers (Heywood et al., 2007; Ronco et al., 2008; McAlister et al., 2004). We showed, for the first time, that the prognostic value of biomarkers and their combination is not necessarily altered by the presence of renal impairment.

Our study has several limitations. Since we performed a retrospective analysis of registry data, we cannot establish cause and effect. However, the associations are consistent with prior analyses of troponin in patients with acute decompensate HF. Plenty of factors could have affected the results of the biomarker tests. First, we used the results of various biomarker assays for which we defined cutoff points rather than core laboratory results. Second, bias may have been introduced because we were unable to analyze patients with HF in whom troponin was not assessed, and we were unable to determine why physicians obtained, or did not obtain, biomarker measurements. Third, our cohort included mainly Japanese individuals, and there is some difference between Japan and western countries in terms of HF etiology and medication (Oshima et al., 2009).We also did not have information on BNP isoform. However, most of them showed equal predictability when compared to original BNP assay (van Kimmenade et al., 2009) and we believe that the absence of BNP isoform measurements will not alter our main results. Fourth, the 4th generation cTnT assay was used in our study, which is no longer available in most parts of the world and BNP was measured with Shionogi assay which is not used outside of Japan. This BNP assay is known to provide lower values than most of the commercially available BNP assays. Thus, the study has limited generalizability, but we believe that they confirm the principle that discharge values of both markers are suitable for risk stratification. Finally, we excluded the patients undergoing haemodialysis (CKD stage 5) since effect of biomarkers was unclear in these patients. BNP is known to increase exponentially with the stage of renal disease and likely skew the main result of our analysis.

4. CONCLUSION

In conclusion, our study suggests that levels of both BNP and TnT have a significant predictive value for the prognosis of HF. Assessment of the combination of these biomarkers, which is both inexpensive and readily available, may provide additional information.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this paper.

ETHICAL APPROVAL

All authors hereby declare that all human studies have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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Variation in cancer surgical outcomes associated with physician and nurse staffing: a retrospective observational study using the Japanese Diagnosis Procedure Combination Database

Hideo Yasunaga[1*]
[*] Corresponding author
Email: yasunagah-tky@umin.ac.jp

Hideki Hashimoto[2]
Email: hidehashimoto-circ@umin.ac.jp

Hiromasa Horiguchi[1]
Email: hiromasa-tky@umin.ac.jp

Hiroaki Miyata[3]
Email: h-m@umin.ac.jp

Shinya Matsuda[4]
Email: smatsuda@med.uoeh-u.ac.jp

[1] Department of Health Management and Policy, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan

[2] Department of Health Economics and Epidemiology Research, School of Public Health, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan

[3] Department of Health Quality Assessment, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan

[4] Department of Preventive Medicine and Community Health, University of Occupational and Environmental Health, Fukuoka, Japan

Abstract

Background

Little is known about the effects of professional staffing on cancer surgical outcomes. The present study aimed to investigate the association between cancer surgical outcomes and physician/nurse staffing in relation to hospital volume.

Methods

We analyzed 131,394 patients undergoing lung lobectomy, esophagectomy, gastrectomy, colorectal surgery, hepatectomy or pancreatectomy for cancer between July and December, 2007–2008, using the Japanese Diagnosis Procedure Combination database linked to the

Survey of Medical Institutions data. Physician-to-bed ratio (PBR) and nurse-to-bed ratio (NBR) were determined for each hospital. Hospital volume was categorized into low, medium and high for each of six cancer surgeries. Failure to rescue (FTR) was defined as a proportion of inhospital deaths among those with postoperative complications. Multi-level logistic regression analysis was performed to examine the association between physician/nurse staffing and FTR, adjusting for patient characteristics and hospital volume.

Results

Overall inhospital mortality was 1.8%, postoperative complication rate was 15.2%, and FTR rate was 11.9%. After adjustment for hospital volume, FTR rate in the group with high PBR (≥19.7 physicians per 100 beds) and high NBR (≥77.0 nurses per 100 beds) was significantly lower than that in the group with low PBR (<19.7) and low NBR (<77.0) (9.2% vs. 14.5%; odds ratio, 0.76; 95% confidence interval, 0.68–0.86; $p < 0.001$).

Conclusions

Well-staffed hospitals confer a benefit for cancer surgical patients regarding reduced FTR, irrespective of hospital volume. These results suggest that consolidation of surgical centers linked with migration of medical professionals may improve the quality of cancer surgical management.

Background

Cancer is one of the major causes of death in developed nations, and it is the leading cause of death in Japan [1]. The frequency of cancer surgeries has also been increasing in Japan from 30,605 per month in 1996 to 44,010 per month in 2008 [2], presumably due to population ageing, improved access to cancer screening, and a wider use of surgery because of development of less invasive approaches for previously untreatable patients. With the rise of cancer surgical cases, better allocation of limited healthcare resources is crucial to optimize cancer surgical management and improve operative outcomes.

Numerous studies have reported an association between hospital volume and cancer surgical outcomes in the US [3-5] and Japan [6-9]. Previous studies have also suggested that professional staffing is associated with better short-term outcomes, including physician staffing [10-12] and nurse staffing [13-15]. However, little is known about the concurrent effects of professional staffing and hospital volume on surgical outcomes.

Japan is unique in that the numbers of physician/nurses per bed are extremely low compared with Western standards; there are 26.5 physicians and 117.8 nurses per 100 beds in Japan, while there are 96.1 and 268.1, respectively, in Organization for Economic Cooperation and Development countries [16]. This situation has been created by an excess in the number of hospitals and beds. Regarding nurse staffing, the Japanese government has established standard criteria for the nurse-to-bed ratio in the public health insurance system, which has given hospital administrators a financial incentive to increase the nurse-to-bed ratio. With regard to physician staffing, only the minimum standard (at least 1 physician per 16 acute care beds in Medical Service Law) is set without further incentives to raise the physician-to-bed ratio, which varies widely between hospitals. Under such an extremely low end of