Table 1 ICD-10 codes utilized for identification of septic cases

Condition	Code
Salmonella septicaemia	A02.1
Septicaemic plague	A20.7
Anthrax septicaemia	A22.7
Erysipelothrix septicaemia	A26.7
Listerial septicaemia	A32.7
Streptococcal septicaemia	A40
Other septicaemia	A41
Actinomycotic septicaemia	A42.7
Disseminated herpesviral disease	B00.7
Candidal septicaemia	B37.7
Disseminated coccidioidomycosis	B38.7
Disseminated histoplasmosis capsulati	B39.3
Disseminated blastomycosis	B40.7
Disseminated paracoccidioidomycosis	B41.7
Disseminated sporotrichosis	B42.7
Disseminated aspergillosis	B44.7
Disseminated cryptococcosis	B45.7
Disseminated mucormycosis	B46.4
Puerperal sepsis	O85

ICD-10, International Classification of Diseases, 10th version.

Table 2 Hospital and patient backgrounds

Hospital background	
Number of hospitals	45
Number of patients	579
Number of beds in hospital	404.8 ± 230.2
Patient background	
Age	71.1 ± 13.2
Gender (male %)	57.3
Hospital admission course (Emergency %)	86.2
Charlson comorbidity index	Frequency (%)
0	45.6
1	23.7
2	19.3
3	6.0
4	2.6
5	2.4
≥6	0.3
Length of ICU stay (days)	7.7 ± 7.1
Length of hospital stay (days)	35.8 ± 27.4
Expected mortality (%)	22.8 ± 17.8
28-day mortality (%)	37

used in the study: (1) primary diagnosis of sepsis (Table 1); (2) secondary diagnosis of DIC [code D65 in the International Classification of Diseases, 10th version (ICD-10)]; (3) age ≥ 20 years old; and (4) entry into the ICU and hospital discharge from January 1, 2007 to December 31, 2008.

We excluded patients who were not treated with anticoagulation agents and those who died on the day on which anticoagulant therapy was initiated. Cases that required dialysis were also excluded, since anticoagulant agents such as protease inhibitors and unfractionated heparin are also administered in renal replacement therapy.

Practice patterns in DIC anticoagulant therapy

Anticoagulation therapy was defined as the use of a protease inhibitor (gabexate mesylate or nafamostat mesylate), antithrombin, unfractionated heparin, or low molecular weight heparin/danaparoid. Low molecular weight heparin and danaparoid sodium were included in one category because danaparoid sodium has stronger anti-Xa activity than unfractionated heparin. In this study, the therapeutic dose of unfractionated heparin for treatment of DIC was defined as at least 10,000 U/day. Use of a low dose of unfractionated heparin was excluded due to the difficulty of distinguishing usage of this dose between arterial monitoring and DIC therapy.

Statistical analysis

All statistical analyses were performed using SPSS software for Windows (Dr. SPSS-II, SPSS Japan Inc.). For calculation of the 28-day mortality, the onset of DIC was defined as the day on which anticoagulant therapy was started, since the true onset time could not be established from the administrative data. The association between anticoagulants and 28-day mortality was examined using a Cox proportional hazards regression model adjusted for the critical care outcome prediction equation (COPE) score [4], Charlson comorbidity index [5] and patient age. A P value below 0.05 was considered as significant. The COPE model is a risk-adjustment tool for use in ICUs that is constructed from 5 variables (age, unplanned admission, mechanical ventilation, hospital category, and admission diagnosis). This model provides the only prognostic severity score that can be obtained from administrative data alone, without use of physiological data. Previous work has shown that hospital mortality in critical care patients can be predicted using the COPE model [receiver operating characteristics area under the curve (ROC AUC) = 0.83–0.84] [4]. The Charlson comorbidity index, on which a higher score indicates greater severity, is a useful tool for measurement of the comorbid status or case mix in health care databases and has been adapted for use with ICD-10 data [6].

Results

Background

Data were examined for 37,456 patients who were treated in 45 ICUs. Among these patients, 724 (1.9%) cases of sepsis-induced DIC were identified, but 145 (20%) fulfilled the exclusion criteria, leaving 579 (80%) that were included in our analysis. The patient and hospital backgrounds are shown in Table 2. The mean age of the patients was approximately 71 years old and the expected mortality in the COPE model was 22.8%. More than half of the patients had a Charlson comorbidity index of 0 or 1. The mean length of ICU stay was 7.7 days and the mean length of hospital stay was 35.8 days.

DIC anticoagulation therapy

The frequencies of use of anticoagulation therapies are displayed in Table 3. A protease inhibitor was used in 413 of the 579 cases (71.3 %), and antithrombin, unfractionated heparin, and low molecular weight heparin/danaparoid were used in 313 (54.1%), 385 (66.5%) and 201 (34.7%) cases, respectively. These interventions were combined in various ways in many cases.

Cox proportional hazards regression model

The 28-day mortality was 37%. After adjustment for the COPE score, Charlson comorbidity index and patient age, unfractionated heparin had a significant adverse effect on the 28-day mortality [hazard ratio (HR) =1.41, P=0.02]. In contrast, protease inhibitors, antithrombin and low molecular weight heparin/danaparoid showed a tendency to reduce the 28-day mortality, but this effect was not significant (Table 4).

Table 3 Use of anticoagulant agents in cases of DIC

Anticoagulant agent (alone or in combination)	Number of cases (%)
Protease inhibitor	413 (71.3)
Antithrombin	313 (54.1)
Unfractionated heparin	385 (66.5)
Low molecular weight heparin/danaparoid	201 (34.7)

n=579 (45 ICUs).

Table 4 Relationship between anticoagulant agents and adjusted 28-day mortality (Cox proportional hazards regression model)

Anticoagulant agent	HR	95% CI	P value
Unfractionated heparin	1.41	1.06–1.87	0.02 *
Protease inhibitor	0.86	0.63–1.16	0.32
Antithrombin	0.90	0.67–1.20	0.46
Low molecular weight heparin/danaparoid	0.88	0.59–1.31	0.53

*: $P < 0.05$.
CI, confidence interval; HR, hazard ratio.

Discussion

Wada [3] suggested guidelines for DIC treatment in 2007 to facilitate evidence-based practice of anticoagulation therapy. In these guidelines, antithrombin was recommended over protease inhibitors and low molecular weight heparin/danaparoid, but our results suggest that protease inhibitors are used more frequently than antithrombin in current practice. We also found that low molecular weight heparin/danaparoid is used less commonly than other anticoagulant agents. Thus, there is a discrepancy between the guidelines and current practice, which may be due to the historical development of DIC anticoagulant agents in Japan and the absence of a high level of evidence in support of anticoagulant therapy for DIC [7]. Protease inhibitors were developed in the 1980s in Japan and unfractionated heparin has traditionally been used as an anticoagulant. In contrast, use of low molecular weight heparin/danaparoid has been relatively uncommon.

Evidence for use of unfractionated heparin for DIC has not been obtained, but this agent has traditionally been administered as a conventional indication [3]. We found that administration of unfractionated heparin is less frequent than that of protease inhibitors, and more frequent than that of antithrombin in Japan. Furthermore, unfractionated heparin had a significant adverse effect on mortality, consistent with the lower level of evidence in the guidelines. This unfavorable result with unfractionated heparin may be caused by complications of hemorrhage or use in cases with severe bleeding. However, the presence of thrombosis often requires use of unfractionated heparin based on risks and benefits, and therefore use of this agent is likely to continue in DIC cases. Previous trials of anticoagulants for DIC have often used unfractionated heparin as a control [8),9)]. An appropriate control group for a clinical study should be based on standard or usual practice, but this concept is difficult to define [10]. Our results suggest that future trials should consider using protease inhibitors or antithrombin as the control, since most physicians in multiple centers in Japan prefer these therapies for DIC. These findings are also consistent with the guidelines.

There is little evidence that shows that anticoagulation agents significantly reduce mortality [2),11)~14)]. Our analysis revealed a small trend for reduction of the 28-day mortality with use of these agents, but the effect

was not significant, as also found in previous studies. A large-scale trial in cases with severe sepsis supported a slight, but not significant, benefit of low-dose heparin for reducing 28-day mortality, but underscored the importance of heparin withdrawal in cases that involved DIC and abnormal coagulation [14]. In this study, we were unable to assess the effect of low-dose heparin since this treatment was excluded from our analysis.

The difference between the expected mortality and the 28-day mortality may have been due to the longer period of 28 days used in our study, in contrast to the period of hospitalization used in other studies. Expected mortality in the COPE model obtained from ICU data in Australia and New Zealand was defined as hospital mortality, but acute care hospitals in Japan traditionally include acute care, sub-acute care, and nursing-home care. Therefore, the length of the hospital stay in Japan is generally reported to be longer than that in other developed nations [15]. However, the length of hospital stay for patients with septic DIC may be less than 28 days in other countries, and this might account for the difference between the expected and actual 28-day mortality in our study.

There are several limitations in the present study. First, most importantly, the administrative data did not include physiological data, the International Society on Thrombosis and Haemostasis (ISTH) DIC score, the Japanese Association for Acute Medicine (JAAM) DIC score, the DIC score developed by the Ad Hoc Group of the Japanese Ministry of Health and Welfare (JMHW), or a severity score for intensive care based on APACHE II or SAPS II. These scores reflect the severity of DIC, are used to predict patient outcomes [16)~18)], and can lead to early diagnosis and improved treatment when applied appropriately in clinical management of DIC [19]. This lack of information on DIC scores is the main disadvantage of using administrative data. However, evaluation of the severity of critical care patients using the COPE model eliminated this concern, and we also adjusted for comorbidity using the Charlson comorbidity index. Second, while we had detailed data for anticoagulant use, we were unable to assess the protocol in each ICU. Therefore, we were unable to evaluate the association between mortality and each practice pattern, despite the large apparent variation in practice. Finally, the study was not performed as a randomized controlled study or a prospective study, suggesting that the results might provide a lower level of evidence. However, it was offset by the advantage of data collection from a large population with reduced effort and time.

Conclusion

In summary, current treatment for sepsis-induced DIC in Japan commonly includes use of protease inhibitors. A tendency for improvement of outcome was found with use of protease inhibitors, antithrombin, and low molecular weight heparin/danaparoid, whereas unfractionated heparin had a significant adverse effect on 28-day mortality.

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Conflict of Interest and Declarations

All authors declare no conflicts of interest. The design, data collection and analysis, and writing of the manuscript were performed by all four authors. The corresponding author takes full responsibility for the validity of the data.

References

1) Kruger D. Acute systemic disseminated intravascular coagulation: managing a complex medical condition. JAAPA 2006;19:28-32.
2) Wiedermann CJ. Clinical review: molecular mechanisms underlying the role of antithrombin in sepsis. Crit Care 2006;10:209-17.
3) Wada H. Study on guidelines for the treatment of DIC. Rinsho Ketsueki 2007;48:377-85.
4) Duke GJ, Santamaria J, Shann F, et al. Critical care outcome prediction equation (COPE) for adult intensive care. Crit Care Resusc 2008;10:41.
5) Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
6) Sundararajan V, Henderson T, Perry C, et al. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57:1288-94.
7) Wada H, Asakura H, Okamoto K, et al; Japanese Society of Thrombosis Hemostasis/DIC subcommittee. Expert consensus for the treatment of disseminated intravascular coagulation in Japan. Thromb Res 2010;125:6-11.
8) Aramoto H, Saito H, Shigematsu H, et al. Synthetic protease inhibitors in the treatment of disseminated intravascular coagulation. Nippon Rinsho 1993;51:93-8.
9) Sakuragawa N, Hasegawa H, Maki M, et al. Clinical evaluation of low-molecular-weight heparin (FR-860) on disseminated intravascular coagulation (DIC)--a multicenter co-operative double-blind trial in comparison with heparin. Thromb Res 1993;72:475-500.
10) Brower RG, Matthay M, Schoenfeld D. Meta-analysis of acute lung injury and acute respiratory distress syndrome trials. Am J Respir Crit Care Med 2002;166:1515-7.
11) Sakuragawa N, Hasegawa H, Maki M, et al. Clinical evaluation of low molecular weight heparin (FR-860) on disseminated intravascular coagulation (DIC)–a multicenter cooperative double-blind trial in comparison with heparin–. Rinsho Iyaku 1992;8:423-53.
12) Warren BL, Eid A, Singer P, et al; KyberSept Trial Study Group. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA 2001;286:1869-78.

13) Nishiyama T, Matsukawa T, Hanaoka K. Is protease inhibitor a choice for the treatment of pre- or mild disseminated intravascular coagulation? Crit Care Med 2000;28:1419-22.
14) Levi M. Disseminated intravascular coagulation. Crit Care Med 2007;35:2191-5.
15) Ikegami N, Campbell JC. Medical care in Japan. N Engl J Med 1995;333:1295-9.
16) Gando S, Saitoh D, Ogura H, et al. Natural history of disseminated intravascular coagulation diagnosed based on the newly established diagnostic criteria for critically ill cases: Results of a multicenter, prospective survey. Crit Care Med 2008;36:145-50.
17) Bakhtiari K, Meijers JCM, de Jonge E, et al. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. Crit Care Med 2004;32:2416-21.
18) Angstwurm MW, Dempfle CE, Spannagl M. New disseminated intravascular coagulation score: A useful tool to predict mortality in comparison with Acute Physiology and Chronic Health Evaluation II and Logistic Organ Dysfunction scores. Crit Care Med 2006;34:314-20.
19) Gando S, Iba T, Eguchi Y, et al. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill cases: Comparing current criteria. Crit Care Med 2006;34:625-31.

Verification Bias in Assessment of the Utility of MRI in the Diagnosis of Cruciate Ligament Tears

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OBJECTIVE. The purpose of this study was to investigate the extent to which verification bias affects the sensitivity and specificity of MRI in the diagnosis of cruciate ligament tears.

MATERIALS AND METHODS. Consecutively registered outpatients who underwent MRI evaluation of the knee were included in the study. The sensitivity and specificity of MRI were calculated for patients whose diagnosis was verified with arthroscopy. For patients who did not undergo arthroscopy, the effect of verification bias was estimated with global sensitivity analysis, a technique of graphic representation of whether a particular combination of sensitivity and specificity estimates is compatible with the observed data.

RESULTS. Among the 356 patients included in the study, 82 patients (23%) had the MRI findings verified at arthroscopy. The sensitivity and specificity of MRI among patients who underwent arthroscopy were 38% and 90%. For patients whose disease status was not verified with arthroscopy, the influence of verification bias was estimated with global sensitivity analysis. The sensitivity of MRI ranged from 3% to 73%, and the specificity from 63% to 98%. The region comprising all possible combinations of sensitivity and specificity had a butterfly shape. The sensitivity and specificity pair estimated from cases verified with arthroscopy was included in this region.

CONCLUSION. Verification bias did not greatly affect assessment of the diagnostic utility of MRI in the evaluation of cruciate ligament tears. The high specificity previously reported for MRI can be considered valid, but the sensitivity may not be as reliable.

MRI has been widely used for screening and is highly regarded as an excellent, cost-effective diagnostic tool that is both noninvasive and accurate [1, 2]. Both the sensitivity and specificity of MRI in the diagnosis of cruciate ligament tears have been reported to be greater than 80%. Concern has been raised, however, about the methods used in studies of the diagnostic accuracy of MRI, including the effect of verification bias [3–7]. Verification bias (also known as workup bias, posttest referral bias, and selection bias) occurs when not all patients are equally likely to have the diagnosis confirmed with a reference standard [4, 6]. In the evaluation of a diagnostic test against a definitive reference standard test, which can be invasive and expensive, not all patients who have negative results of the diagnostic test undergo confirmatory testing with the reference standard. Therefore, patients with verified disease status may not be representative of the population in which the diagnostic test is used. If few cases of negative test results are verified with the reference standard, few false-negative findings will be revealed, leading to overestimation of accuracy.

In the diagnosis of cruciate ligament tear, arthroscopy is currently regarded as the reference standard because of its high reported accuracy, and MRI has been evaluated in reference to arthroscopic results [8–11]. However, because of its invasive nature and the risk of serious complications, not all study participants undergo arthroscopy [12]. Rather, arthroscopy usually is performed for patients with abnormal MRI findings. If patients with arthroscopic verification are more likely to have a cruciate ligament tear than are patients without arthroscopic verification, the difference can lead to verification bias, and the sensitivity and specificity of MRI may be overestimated. In an earlier study [3], we found that verification bias can greatly affect assessment of the diagnostic utility of MRI in the diagnosis of meniscal tear. To our knowledge, however, no study has been conduct-

Keywords: arthroscopy, cruciate ligament tear, diagnosis, MRI, verification bias

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ed to investigate the extent to which verification bias affects the diagnostic performance of MRI in the evaluation of cruciate ligament tear. Because both the cruciate ligament and the meniscus are soft-tissue structures in the knee, verification bias may have considerable influence on the diagnostic accuracy of MRI of cruciate ligament tear. The purpose of this study was to use global sensitivity analysis to investigate the extent to which verification bias affects the diagnostic utility of MRI in the evaluation of cruciate ligament tear. This method, proposed by Kosinski and Barnhart [7], is a robust method of estimating the influence of verification bias [3, 13].

Materials and Methods

Subjects

The study was conducted in an outpatient clinic at a single institution. Included in the study were consecutively registered patients who reported knee pain and visited the hospital for MRI evaluation of the cruciate ligament from April 2006 through July 2008. The patients underwent MRI before arthroscopy. The study plan was announced in a poster in the hospital ward to offer the opportunity to refuse participation. Many of the study patients continued to visit the hospital for follow-up, and none had refused participation as of this writing. This study was performed at the same institution as a study of meniscal tear [3]. The exclusion criteria were previous knee surgery, more than 240 days between MRI and arthroscopy, and poor resolution of MR images. A retrospective chart review was performed to collect information on patient characteristics and clinical findings. Approval for this study was granted by the institutional review board at our institution.

Diagnosis

The same protocol was used for all MRI examinations in this study. All images were obtained with a 1.5-T MRI unit (Excelart with Pianissimo, Toshiba Medical Systems), extremity coil (quadrature coil), and the fast spin-echo method. Sagittal T2-weighted images, sagittal T1-weighted images, sagittal STIR images, sagittal T2*-weighted images, coronal STIR images, coronal T2*-weighted images, and axial T2-weighted images were obtained, each with a scanning time of 2–3 minutes. The parameters for the sagittal T2-weighted images were TR/TE, 3,628/94; field of view, 20 × 20 cm; slice thickness, 3.5 mm; interslice gap, 1.0 mm; matrix size, 224 × 288; flip angle, 90°, 160°; bandwidth, 244 Hz/pixel; echo-train length, 13. The Parameters for the sagittal T1-weighted images were 495/15; field of view, 20 cm × 20 cm; slice thickness, 3.5 mm; interslice gap 1.0 mm; matrix size, 176 × 272; flip angle 90°, 180°; bandwidth, 163 Hz/pixel; echo-train length, 0. Sagittal STIR images were obtained with the following parameters: 5,635/80; inversion time, 130 milliseconds; field of view, 20 × 20 cm; slice thickness 3.5 mm; interslice gap, 1.0 mm; matrix size, 224 × 304; flip angle 90°, 160°; bandwidth, 326 Hz/pixel, echo-train length, 15. The parameters for the sagittal T2*-weighted images were 535/15; field of view, 20 × 20 cm; slice thickness, 3.5 mm; interslice gap, 1.0 mm; matrix size, 160 × 304; flip angle, 25°; bandwidth, 61 Hz/pixel; echo-train length, 0. The parameters for the coronal STIR images were: 5,635/80; inversion time, 130 milliseconds; field of view, 20 × 20 cm; slice thickness, 3.0 mm; interslice gap, 1.0 mm; matrix size, 224 × 272; flip angle, 90°, 160°; bandwidth, 326 Hz/pixel; echo-train length, 15. The parameters for the coronal T2*-weighted images were 535/15; field of view, 20 × 20 cm; slice thickness, 3.0 mm; interslice gap, 1.0 mm; matrix size, 160 × 304; flip angle, 25°; bandwidth, 61 Hz/pixel; echo-train length, 0. The parameters for the axial T2-weighted images were 3,628/94; field of view, 18 × 20 cm; slice thickness, 4.0 mm; interslice gap, 2.0 mm; matrix size, 224 × 400; flip angle, 90°, 160°; bandwidth, 244 Hz/pixel; echo-train length, 13.

One of two radiologists with more than 10 years of experience interpreted all images. Each image was evaluated by either of two radiologists at the hospital. The image review findings were the initial clinical interpretations before arthroscopy. Cruciate ligaments were categorized into two subgroups depending on severity. Partial tear of the cruciate ligament was diagnosed if abnormal signal intensity was found in the ligament or when otherwise intact fibers appeared wavy on sagittal or coronal fast spin-echo images. Complete tear of the cruciate ligament was diagnosed if disruption of all fibers was found or if the ligament was not discernible at all on MR images.

The reference standard used in this study was arthroscopy because of its previously reported accuracy of greater than 95% [8–11]. One orthopedic surgeon with more than 15 years of experience performed arthroscopy in this study.

Analysis

The outcome measure was cruciate ligament tear, classified as anterior or posterior. We compared the results of MRI with those of arthroscopy. For the patients who underwent arthroscopy, we calculated the sensitivity and specificity of MRI. To assess the influence of verification bias, global sensitivity analysis was performed for patients who did not undergo arthroscopy [3, 7]. We simulated the complete range of possible prevalence (0–100%) of cruciate ligament tear for the MRI-positive and MRI-negative subgroups of patients who did not undergo arthroscopy then calculated and graphically plotted the sensitivity and specificity (Appendix 1). This method allowed us to depict all possible combinations of sensitivity and specificity.

We compared sensitivity and specificity in several subgroups of patients. These subgroups were based on the following factors known to influence the diagnostic accuracy of MRI: age (< 45 years, ≥ 45 years), sex (male, female), interval between MRI and arthroscopy (less than the lower quartile of this study population, lower quartile or greater), bundle tear (anterior, posterior), severity of tear (partial, complete). We performed chi-square tests to compare the positivity rate between subgroups of patients. Stata software (version 10, StataCorp) was used for statistical analysis.

Results

A flow diagram of the study is shown in Figure 1. Of the initial 361 patients, five were excluded from the final analysis because they had undergone knee surgery (three patients), had poor-resolution MR images (one patient), and had more than 240 days between MRI and arthroscopy (one patient). The general characteristics of the 356 patients included in the study (183 male patients, 174 female patients; mean age, 51 years) are shown in Table 1.

Forty-six patients had an abnormal (i.e., positive) test result, and 310 patients had a normal (i.e., negative) test result (Table 2). Only 82 patients (23%) underwent arthroscopy. Among the patients with tears verified

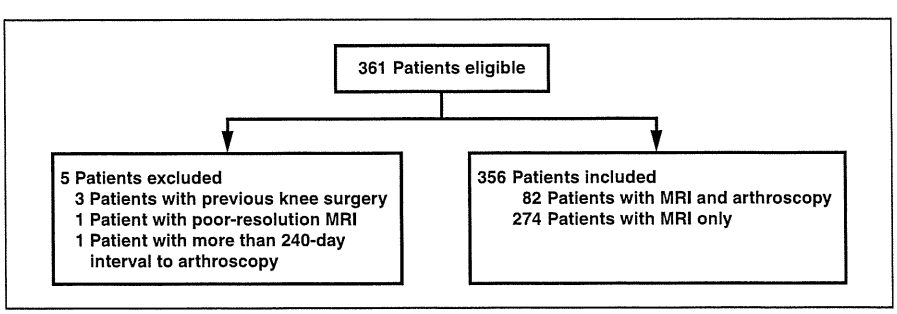

Fig. 1—Study flow diagram.

TABLE 1: Characteristics of Patients Included in Study (n = 356)

Characteristic	Value
Age (y)	
Mean	51
SD	20
Range	7–93
Sex	
Male	182
Female	174
Location of cruciate ligament tear	
Anterior	37
Posterior	9
Severity of cruciate ligament tear	
Partial	33
Complete	13

Note—Except for age, values are number of patients.

TABLE 2: Frequency of Test Results

MRI Result	Verified Cruciate Ligament Tear		Not Verified	Total
	Present	Absent		
Positive	8	6	27	41
Negative	13	55	247	315
Total	21	61	274	356

Note—Values are number of patients.

with arthroscopy, the sensitivity was 38% and the specificity 90%. The graph of the area comprising all possible combinations of sensitivity and specificity based on global sensitivity analysis is shown in Figure 2. This region included the estimated point of sensitivity and specificity (point estimate) calculated from the subgroup of patients with verified disease status (base case). Sensitivity (3–73%) varied to a greater extent than specificity (63–98%).

The subgroup for the second analysis consisted of 82 patients who underwent both MRI and arthroscopy. The characteristics of the 82 patients (48 male patients, 34 female patients; mean age, 52 years) are shown in Table 3. In all cases, the interval between MRI and arthroscopy was less than 6 months. Twenty-four cruciate ligament tears were verified with arthroscopy. Stratified comparisons were made by use of the chi-square test (Table 4). Statistically significant differences in sensitivity were observed for anterior and posterior tear location (35% vs 75%, $p = 0.02$) and in specificity were observed for partial and complete tear severity (90% vs 99%, $p = 0.02$).

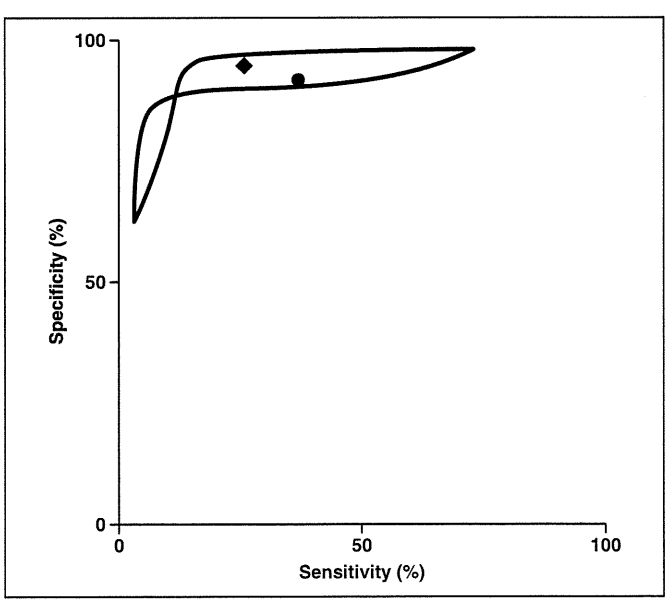

Fig. 2—Plot shows all possible combinations of sensitivity and specificity. Enclosed areas represent all possible combinations of values of sensitivity and specificity estimated with global sensitivity analysis. Circle indicates point estimate of sensitivity and specificity based only on data verified with arthroscopy (base case). Diamond indicates point estimate of sensitivity and specificity based on missing at random assumption.

Discussion

We used global sensitivity analysis to investigate the effect of verification bias on the sensitivity and specificity of MRI in the diagnosis of cruciate ligament tear. Previous studies of the diagnostic utility of MRI in the evaluation of cruciate ligament tear have shown high accuracy, but these studies predominantly included patients whose disease status was confirmed with arthroscopy [14–16]. Several studies have been conducted in attempts to correct for this verification bias, but none of the methods used in those studies successfully eliminate the bias [2, 17]. A simple way to correct for verification bias is to include in the study only patients who undergo both MRI and arthroscopy; the assumption is that patients whose condition is not verified with arthroscopy are as likely as patients whose condition is verified to have a cruciate ligament tear [4, 5]. Alternatively, the condition of patients with negative MRI results can be verified with a different, often less thorough method, such as follow-up imaging or evaluation for physical signs [18]. However, use of such methods cannot exclude the bias completely and can lead to inaccurate conclusions about the diagnostic utility of MRI. Physical signs and the medical history are clinically important but are not sensitive enough to exclude cruciate ligament tear [19].

Global sensitivity analysis is the most robust approach to assessment of the effect of verification bias [3, 7]. This method of analysis simulates the behavior of sensitivity and specificity in that the disease prevalence among patients whose condition is not verified with arthroscopy takes all possible values. Therefore, global sensitivity analysis can be used to determine graphically whether a particular pair of sensitivity and specificity estimates are compatible with observed data. In our study, the region of possible sensitivity and specificity pairs represented a butterfly

TABLE 3: Characteristics of Patients Undergoing Both MRI and Arthroscopy (n = 82)

Characteristic	Value
Age (y)	
Mean	52
SD	18
Range	13–79
Sex (no. of patients)	
Male	48
Female	34
Interval to arthroscopic reference test (d)	
Mean	41
SD	38
Range	1–167
Location of cruciate ligament tear (no. of tears)	
Anterior	20
Posterior	4
Severity of cruciate ligament tear (no. of tears)	
Partial	14
Complete	10

TABLE 4: Results of Stratified Comparisons of Sensitivity and Specificity in Five Subgroups of Patients Undergoing Both MRI and Arthroscopy

Characteristic	Sensitivity (%)	p[a]	Specificity (%)	p[a]
Age (y)		0.40		0.16
< 45	79		81	
≥ 45	87		93	
Sex (no. of patients)		0.07		0.47
Male	92		89	
Female	76		92	
Interval to reference test (d)		0.37		0.64
< 16	77		93	
≤ 16	87		89	
Location of cruciate ligament tear (no. of tears)		0.02		0.14
Anterior	35		90	
Posterior	75		99	
Severity of cruciate ligament tear (no. of tears)		0.48		0.02
Partial	23		90	
Complete	38		99	

[a]Chi-square test.

shape, as depicted in Figure 2. A point estimate within the region of possible sensitivity and specificity pairs indicates that verification bias does not exist or has a small influence. This was the case in our study, suggesting that the base case point estimate is compatible with observed data and thus that verification bias has little effect. Previous studies have shown sensitivity and specificity of more than 80% in the MRI diagnosis of cruciate ligament tear [1, 20, 21]. Although no correction was made for verification bias, indexes from these studies also may be consistent with our data.

One easy method to correct for verification bias is to calculate bias-corrected point estimates based on the missing at random assumption that within each subgroup of patients with positive or negative MRI findings, disease status is independent of whether a patient undergoes arthroscopy [3, 7, 22] (Appendix 2). The sensitivity and specificity of the missing at random estimate were 28% and 94%. This point estimate was within the presumed region and was compatible with the observed data. Compared with this missing at random point estimate, the sensitivity of the base case was lower and the specificity was higher, suggesting that sensitivity was underestimated and specificity was overestimated. Nevertheless, the differences in sensitivity and specificity in the base case point estimate and missing at random point estimate were small, thus verification bias had little effect on the diagnostic utility of MRI in the diagnosis of cruciate ligament tear. Bias correction is a complex field, and various methods have been attempted. The missing at random assumption is certainly not perfect, but the compatibility with the observed data in our study support missing at random as a valid method of estimating actual sensitivity and specificity.

One of the major findings in our study was that the specificity was greater than 85% for most of the presumed range determined with global sensitivity analysis. The presumed range widens as the condition of fewer patients is verified and is particularly wide when more patients have an unverified condition than have a verified condition. In our global sensitivity analysis, specificity varied much less than sensitivity. The high specificity and its narrow presumed range are consistent with the high specificity reported in previous studies.

The sensitivity of MRI in this study was remarkably low compared with values reported in previous studies by other investigators. This low sensitivity may have had a number of explanations. The first is the long interval between MRI and arthroscopy. The sensitivity of MRI for cruciate ligament tear decreases as the interval increases. In our study, more patients had a longer interval between MRI and arthroscopy than had a shorter interval, possibly resulting in lower sensitivity. This finding also may be associated with subsequent spontaneous healing. The second explanation is the possibility of spontaneous healing found in a previous study [23–27]. Spontaneous healing converts a positive arthroscopic result into a negative result. Furthermore, we predict that MRI of a

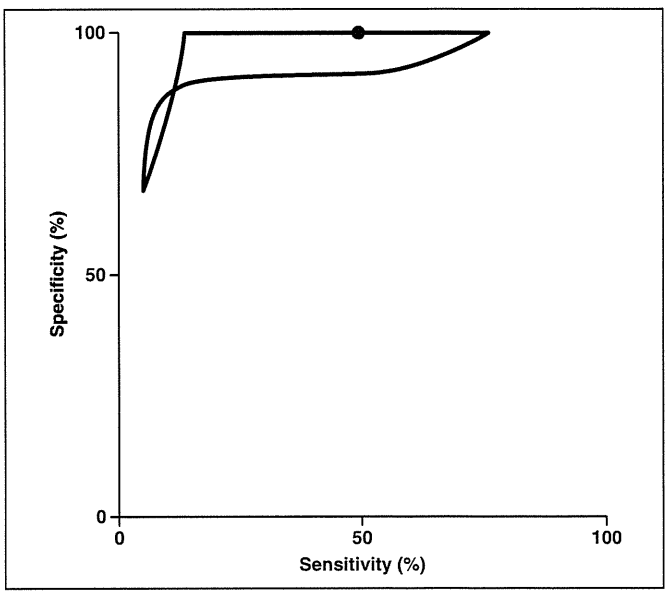

Fig. 3—Plot shows all possible combinations of sensitivity and specificity in first hypothetical case. Enclosed areas represent all possible combinations of values of sensitivity and specificity estimated with global sensitivity analysis. Circle indicates point estimate of sensitivity (52%) and specificity (100%).

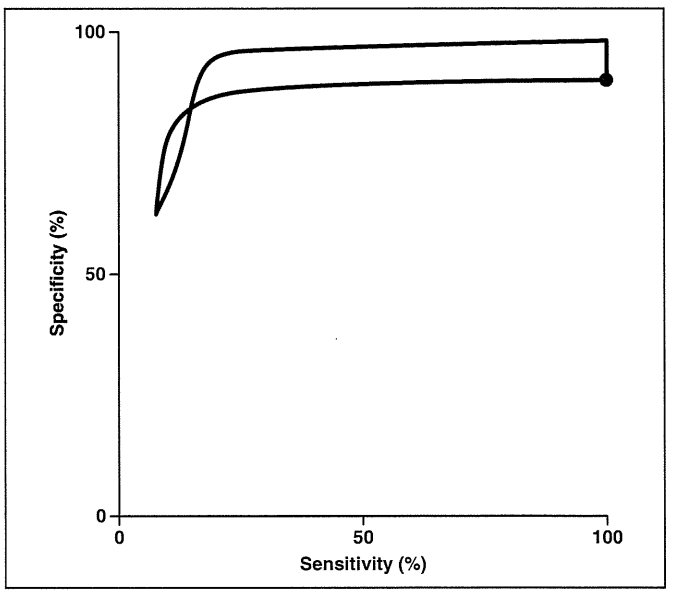

Fig. 4—Plot shows all possible combinations of sensitivity and specificity in second hypothetical case. Enclosed areas represent all possible combinations of values of sensitivity and specificity estimated with global sensitivity analysis. Circle indicates point estimate of sensitivity (100%) and specificity (100%).

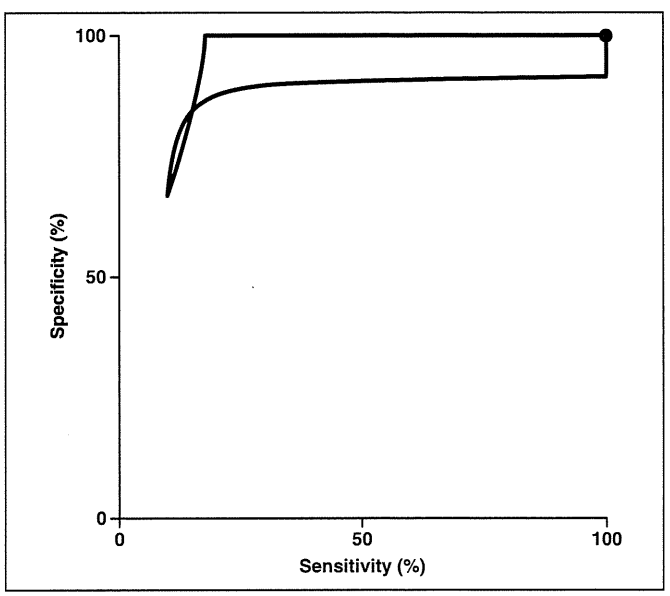

Fig. 5—Plot shows all possible combinations of sensitivity and specificity in third hypothetical case. Enclosed areas represent all possible combinations of values of sensitivity and specificity estimated with global sensitivity analysis. Circle indicates point estimate of sensitivity (100%) and specificity (100%).

patient with spontaneous healing will be associated with a positive arthroscopic result. As such, more cases of spontaneous healing lead to lower sensitivity.

The third explanation for the low sensitivity in this study relates to differences in the patient population that undergoes arthroscopy, which might be associated with the health care system in Japan. In many countries, patients who undergo arthroscopy are stringently selected and referred to a specialized institution by general physicians or primary care physicians. In Japan, specialized tests such as arthroscopy are provided by the same institution as the initial evaluation without stringent selection, and many patients with false-negative findings undergo arthroscopy, resulting in lower sensitivity. We therefore applied global sensitivity analysis to three hypothetical high-sensitivity cases to determine whether lower sensitivity affected the results. In the first high-sensitivity case it was assumed that all patients with false-positive results (six patients) had true-positive results. The sensitivity and specificity in that case were 52% and 100% (Fig. 3). In the second case it was assumed that all patients with false-negative results (13 patients) had true-positive results. The sensitivity and specificity in this case were 100% and 90% (Fig. 4). In the third case it was assumed that all patients with false-positive results and all patients with false-negative results had true-positive results. The sensitivity and specificity in that case were 100% and 100% (Fig. 5). In all cases, the global sensitivity analysis region included the point estimate of sensitivity and specificity. Consequently, these results indicate the robustness of the study, regardless of sensitivity.

In a study in which we used global sensitivity analysis to assess the influence of verification bias on the MRI diagnosis of meniscal tear [3], the presumed region also represented a butterfly shape. The point estimate in our previous study, however, was not included in the presumed region. We concluded that the point estimate was not compatible with observed data and that there was marked verification bias. The main difference between the current study and our previous study is the extent rather than the presence or absence of verification bias. In both studies, the sensitivity and specificity in the base case and the missing at random point estimates differed, but to different degrees. Therefore, the diagnostic utility of MRI can

be affected by verification bias, although the extent of the effect can vary depending on the condition being diagnosed.

In the diagnosis of cruciate ligament tears, verification bias has a small effect on the diagnostic utility of MRI. Given the high specificity reported in previous studies and in this study, MRI is reliable in its specificity in the diagnosis of cruciate ligament tear. Our findings, however, suggest that the sensitivity of MRI may not be as reliable as the specificity. As such, in interpreting MRI findings in the diagnosis of cruciate ligament tear, clinicians should consider possible factors that affect the sensitivity of MRI, such as the interval between MRI and arthroscopy.

References

1. Jackson JL, O'Malley PG, Kroenke K. Evaluation of acute knee pain in primary care. *Ann Intern Med* 2003; 139:575–588
2. Oei EH, Nikken JJ, Verstijnen AC, Ginai AZ, Myriam Hunink MG. MR imaging of the menisci and cruciate ligaments: a systematic review. *Radiology* 2003; 226:837–848
3. Nishikawa H, Imanaka Y, Sekimoto M, Hayashida K, Ikai H. Influence of verification bias on the assessment of MRI in the diagnosis of meniscal tear. *AJR* 2009; 193:1596–1602
4. Begg CB. Biases in the assessment of diagnostic tests. *Stat Med* 1987; 6:411–423
5. Begg CB, Greenes RA. Assessment of diagnostic tests when disease verification is subject to selection bias. *Biometrics* 1983; 39:207–215
6. Revesz G, Kundel HL, Bonitatibus M. The effect of verification on the assessment of imaging techniques 1983. *Invest Radiol* 1990; 25:461–464
7. Kosinski AS, Barnhart HX. A global sensitivity analysis of performance of a medical diagnostic test when verification bias is present. *Stat Med* 2003; 22:2711–2721
8. Vaz CE, Camargo OP, Santana PJ, Valezi AC. Accuracy of magnetic resonance in identifying traumatic intraarticular knee lesions. *Clinics (Sao Paulo)* 2005; 60:445–450
9. DeHaven KE, Collins HR. Diagnosis of internal derangements of the knee: the role of arthroscopy. *J Bone Joint Surg Am* 1975; 57:802–810
10. Fischer SP, Fox JM, Del Pizzo W, Friedman MJ, Snyder SJ, Ferkel RD. Accuracy of diagnoses from magnetic resonance imaging of the knee: a multicenter analysis of one thousand and fourteen patients. *J Bone Joint Surg Am* 1991; 73:2–10
11. Halbrecht JL, Jackson DW. Office arthroscopy: a diagnostic alternative. *Arthroscopy* 1992; 8:320–326
12. Reigstad O, Grimsgaard C. Complications in knee arthroscopy. *Knee Surg Sports Traumatol Arthrosc* 2006; 14:473–477
13. Danias PG, Parker JA. Novel Internet-based tool for correcting apparent sensitivity and specificity of diagnostic tests to adjust for referral (verification) bias. *RadioGraphics* 2002; 22:e4
14. Lee JK, Yao L, Phelps CT, Wirth CR, Czajka J, Lozman J. Anterior cruciate ligament tears: MR imaging compared with arthroscopy and clinical tests. *Radiology* 1988; 166:861–864
15. Moore SL. Imaging the anterior cruciate ligament. *Orthop Clin North Am* 2002; 33:663–674
16. Mellado JM, Calmet J, Olona M, Giné J, Sauri A. Magnetic resonance imaging of anterior cruciate ligament tears: reevaluation of quantitative parameters and imaging findings including a simplified method for measuring the anterior cruciate ligament angle. *Knee Surg Sports Traumatol Arthrosc* 2004; 12:217–224
17. Vincken PW, ter Braak BP, van Erkell AR, et al. Effectiveness of MR imaging in selection of patients for arthroscopy of the knee. *Radiology* 2002; 223:739–746
18. Knottnerus JA. The effects of disease verification and referral on the relationship between symptoms and diseases. *Med Decis Making* 1987; 7:139–148
19. Solomon DH, Simel DL, Bates DW, Katz JN, Schaffer JL. The rational clinical examination: does this patient have a torn meniscus or ligament of the knee? Value of the physical examination. *JAMA* 2001; 286:1610–1620
20. Spindler KP, Wright RW. Clinical practice: anterior cruciate ligament tear. *N Engl J Med* 2008; 359:2135–2142
21. Sandberg R, Balkfors B, Nilsson B, Westlin N. Operative versus non-operative treatment of recent injuries to the ligaments of the knee: a prospective randomized study. *J Bone Joint Surg Am* 1987; 69:1120–1126
22. Cecil MP, Kosinski AS, Jones MT, et al. The importance of work-up (verification) bias correction in assessing the accuracy of SPECT thallium-201 testing for the diagnosis of coronary artery disease. *J Clin Epidemiol* 1996; 49:735–742
23. Fujimoto E, Sumen Y, Ochi M, Ikuta Y. Spontaneous healing of acute anterior cruciate ligament (ACL) injuries: conservative treatment using an extension block soft brace without anterior stabilization. *Arch Orthop Trauma Surg* 2002; 122: 212–216
24. Kurosaka M, Yoshiya S, Mizuno T, Mizuno K. Spontaneous healing of a tear of the anterior cruciate ligament: a report of two cases. *J Bone Joint Surg Am* 1998; 80:1200–1203
25. Buss DD, Min R, Skyhar M, Galinat B, Warren RF, Wickiewicz TL. Nonoperative treatment of acute anterior cruciate ligament injuries in a selected group of patients. *Am J Sports Med* 1995; 23:160–165
26. Ihara H, Miwa M, Deya K, Torisu K. MRI of anterior cruciate ligament healing. *J Comput Assist Tomogr* 1996; 20:317–321
27. Boks SS, Vroegindeweij D, Koes BW, Hunink MG, Bierma-Zeinstra SM. Follow-up of posttraumatic ligamentous and meniscal knee lesions detected at MR imaging: systematic review. *Radiology* 2006; 238:863–871

(Appendixes start on next page)

APPENDIX 1: Global Sensitivity Analysis

Global sensitivity analysis is a method for graphically determining whether a particular pair of sensitivity and specificity estimates is compatible with the observed data, including cases unverified with the reference standard. The complete range of possible prevalence (0–100%) of cruciate ligament tears for the MRI-positive and the MRI-negative subgroups of cases unverified with arthroscopy is simulated. Sensitivity and specificity then are computed and graphically plotted to depict all possible sensitivity and specificity pairs, including those for unverified cases. The frequency of test results is shown in Table 5. Estimates of sensitivity (*Se*) and specificity (*Sp*) are calculated with the following equations:

TABLE 5: Variables for Calculation of Frequency of Test Results

MRI Result	Verified Cruciate Ligament Tear		Not Verified	Total
	Present	Absent		
Positive	$a+E\times e$	$b+(1-E)\times e$	e	$n1$
Negative	$c+F\times f$	$d+(1-F)\times F$	f	$n2$
Total				N

Note—E = frequency of cruciate ligament tear in patients with positive MRI results without arthroscopy test; F = frequency of cruciate ligament tear in patients with negative MRI results without arthroscopy; a = number of patients with positive MRI and positive arthroscopic results; b = number of patients with positive MRI and negative arthroscopic results; c = number of patients with negative MRI and positive arthroscopic results; d = number of patients with negative MRI and negative arthroscopic results; e = number of patients with positive MRI results who did not undergo arthroscopy; f = number of patients with negative MRI results who did not undergo arthroscopy; $n1$ = number of patients with positive MRI results; $n2$ = number of patients with negative MRI results; N = number of all included patients.

$$Se\,(E,F)=\frac{a+E\times e}{a+E\times e+c+F\times f}\times 100 \qquad Sp\,(E,F)=\frac{d+(1-F)\times f}{b+(1-E)\times e+d+(1-F)\times f}\times 100$$

E and F are independent of each other and can be any value from 0 to 1. All possible combinations of values are assigned to E and F, and Se and Sp for each combination of E and F can be calculated as in Table 6 with Microsoft Excel software. Pairs of calculated Se and Sp then are graphically plotted.

TABLE 6: Calculation of Sensitivity and Specificity

Row	A	B	C	D	E	F	G	H
1		Arthroscopy performed	Arthroscopy not performed	Not verified		a=8		
2	MRI result positive	8	6	27		b=6		
3	MRI result negative	13	55	247		c=13		
4				274		d=55		
5						e=27		
6		Arthroscopic result positive	Arthroscopic result negative	Not verified	Total	f=247		
7	MRI result positive	$a+E^*e$	$b+(1-E)^*e$	e	$n1$	$n1$=41		
8	MRI result negative	$c+F^*f$	$d+(1-F)^*f$	f	$n2$	$n2$=315		
9					N	n=356		
10								
11	E(%)	F(%)	$a+E^*e$	$b+(1-E)^*e$	$c+F^*f$	$d+(1-F)^*f$	Se(%)	Sp(%)
12	0	0	8.00	33.00	13	302	38.09524	90.14925
13	1	0	8.27	32.73	13	302	38.88105	90.22197
14	2	0	8.54	32.46	13	302	39.64717	90.2948
15	3	0	8.81	32.19	13	302	40.39431	90.39775
16	4	0	9.08	31.92	13	302	41.12319	90.44082
17	5	0	9.35	31.65	13	302	41.83445	90.51401
18	6	0	9.62	31.38	13	302	42.52874	90.58732
19	7	0	9.89	31.11	13	302	43.20664	90.66074
20	8	0	10.16	30.84	13	302	43.86874	90.73429
21	9	0	10.43	30.57	13	302	44.51558	90.80795
22	10	0	10.7	30.3	13	302	45.14768	90.88173
23	11	0	10.97	30.03	13	302	45.76554	90.95564
24	12	0	11.24	29.76	13	302	46.36964	91.02966
25	13	0	11.51	29.49	13	302	46.96042	91.1038
26	14	0	11.78	29.22	13	302	47.53834	91.17807
27	15	0	12.05	28.95	13	302	48.10379	91.25246
28	16	0	12.32	28.68	13	302	48.65719	91.32696

APPENDIX 2: Missing at Random Point Estimates

If only patients with verified disease status are considered in the assessment of a diagnostic test, sensitivity estimates can be calculated as $a / (a + c)$ and specificity estimates as $d / (b + d)$. In practice, however, this assumption is unlikely to be true, and the estimates often are subject to verification bias. According to the missing at random assumption, selection of patients with a verified condition is independent of the unobserved variable, and the verification bias–corrected sensitivity and specificity estimates can be calculated by assigning $a / (a + b)$ to E and $c / (c + d)$ to F. Sensitivity and specificity point estimates corrected for verification bias are expressed as follows:

$$Se\ (MAR) = \frac{n1 \times a / (a + b)}{n1 \times a / (a + b) + n2 \times c / (c + d)} \times 100$$

$$Sp\ (MAR) = \frac{n2 \times d / (c + d)}{n1 \times b / (a + b) + n2 \times d / (c + d)} \times 100$$

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Impact of Intensive Care Unit Physician on Care Processes of Patients with Severe Sepsis in Teaching Hospitals

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Abstract

Objective: The purpose of the study was to investigate associations among intensive care unit (ICU) staffing and care processes in patients with severe sepsis.

Design: An observational multicenter cross-sectional study performed from October 2007 to March 2008.

Setting: Forty-nine teaching hospitals in Japan.

Participants: Patients (n=576) with severe sepsis identified using ICD-10 codes from administrative data.

Main outcome measures: Care processes including mechanical ventilation, dialysis, enteral feeding, parentetal nutrition, and antibiotic empirical therapy which were available in administrative data.

Results: ICUs were classified as high- or low-intensity based on policies regarding the responsibilities of intensivists. There were no differences in baseline patient characteristics between the ICU groups. In the high-intensity group, ICU stay for survivors was about two days shorter and hospital stay was significantly shorter by three days. Majority of patients had high rates of enteral feeding; however, the high-intensity group had significantly earlier initiation of enteral feeding and a significantly shorter duration of mechanical ventilation. A shorter duration of mechanical ventilation was significantly associated with the ICU structure.

Conclusions: The results showed an association between ICU physician and processes of intensive care, and high-intensity ICU was aggressive in mechanical ventilation in patients with severe sepsis.

Keywords: Intensive care unit; Sepsis; Structure; Care process; Multicenter study

Introduction

Patients in the intensive care unit (ICU) require complex care relating to a broad range of acute illnesses and pre-existing conditions. The innate complexity of the ICU makes organizational structuring of care an attractive quality measure and a target for performance improvement strategies. In other words, organizational features relating to medical and nursing leadership, communication and collaboration among providers, and approaches to problem-solving may capture the quality of ICU care more comprehensively than do practices related to specific processes of care.

Many authors have shown wide variations in mortality in ICU, which may have developed studies on the associations between ICU organizations and outcomes. There is many patterns in ICU organization, [3,42] and it seemed that differences in ICU organization associated with patient outcomes. For instance, ICU staffings focused on the role of intensivists in critical care units.

The relationship between the role of intensivists and outcomes has been examined since the 1980s. A number of studies have shown that staffing the ICU with intensivists has a beneficial impact on outcomes. [2-16] A recent multicenter retrospective study using a large database of critically ill patients, however, showed that hospital mortality was higher for patients managed by ICU physicians. [17] Intensivists may improve clinical outcomes, but these paradoxical results may be due to differences in patient characteristics and methodology among these studies.

Although indicators such as morbidity and mortality have been used as performance measures of intensive care, it is usually difficult to assess performance of ICUs by simply using of crude mortality, since clinical conditions of patients (i.e., as patient characteristics, diseases, and severity of illness) are quite different between them. Therefore, risk adjustment mortality has been used in ICU outcome study. Clear findings regarding associations between ICU staffings and outcomes, however, have not been gained yet, and it has been desirable to assess ICU structure and care processes to achieve further opinion about ICU performance. [14,11,13] Kahn et al. [26] demonstrated that evidence based approach was associated with the role of intensivists in the ICU. Intensivists may have important role for processes affecting to patient outcomes. We hypothesize that staffing ICUs with critical care physicians (intensivists) have significant association with care processes in intensive care units. In this study, we investigated the effect of ICU physicians on care processes, which were available in administrative data, in patients with severe sepsis. In this study, we used large administrative database of Japan, which is called "Diagnosis procedure combination (DPC)" data introduced in Japanese medical payment system since 2002 [43].

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Materials and Methods

Setting

All data were extracted from the Quality Indicator / Improvement Project (QIP). The QIP collects Japan's administrative healthcare data (Diagnosis Procedure Combination data; DPC data) from hospitals and analyzes numerical indices of the healthcare process, patient outcomes, and management efficiency and provides feedback to participating establishments. Administrative data were comprised of clinical information and healthcare claim data. Clinical information included patient demographics, primary and secondary diagnoses, comorbidities at the time of and after admission, operative data, severity of illnesses, as well as any special treatments (i.e., radiation therapy, artificial respiration, chemotherapy). In contrast, healthcare claim data itemized the type, quantity, and fees for all tests, medications, procedures, use of intensive or specialized care, and nursing services.

At the time of the study, one hundred and eight medical institutions voluntarily participated. Among these institutions, we selected 70 teaching hospitals with ICU, which accounted for approximately 10 % of all teaching hospitals in Japan. In November 2008, we sent questionnaires to the directors of these 70 hospitals, with a request for information on ICU management to be provided by the physician responsible for intensive care.

Organizational model

For consistency with previous studies, [2] if the ICU physicians had primary responsibility or mandatory critical care consultation (the intensivist is the patient's primary attending physician or the intensivist is not the patient's primary attending physician, but every patient admitted to the ICU receives a critical care consultation), the ICU was defined as a high-intensity ICU. In contrast, if the ICU physicians had elective critical care consultation or no critical care physician (the intensivist is involved in the care of the patient only when the attending physician requests a consultation or intensivists were unavailable), the ICU was defined as a low-intensity ICU. An intensivist was defined as a physician with a primary appointment in the ICU.

Patient characteristics

All patients who were treated for severe sepsis in ICUs in the studied hospitals between October 1, 2007, and March 31, 2008 were included in the study. Severe sepsis was defined based on the sepsis-related ICD-10 code and coding for single or multiple organ failure (Table 1). Organ failure was based on Martin's study, [18] and ICD9-clinical modification (CM) codes were converted to ICD-10 codes. We excluded ICUs with less than 5 patients of severe sepsis. Patients younger than 20 years of age and those hospitalized for more than 60 days were also excluded from the analysis, since patients with extremely long hospitalization might involve social problems such as the lack of an available nursing home.

Patient characteristics were identified from administrative data. The administrative data included clinical information such as patient demographics, diagnoses, comorbidities at the time of and after admission, operative data, and treatment (radiation therapy, mechanical ventilation, chemotherapy). Age, gender, and reasons for ICU entry were recorded for all patients. To evaluate severity, the expected mortality was calculated using the Critical care Outcome Prediction Equation (COPE). [19] The COPE model uses information from standard administrative data and is a robust, risk-adjusted hospital mortality prediction tool. And we showed that the COPE model had good performance for ICU patients in Japan [20].

Care processes evaluation

Measures for process of care were selected among quality indicators for intensive care that are associated with outcomes and available in administrative data. [21-24] for patients under mechanical ventilation, non-invasive positive pressure ventilation was excluded. Dialysis included continuous renal replacement therapy, intermittent renal replacement therapy, plasma absorption, and plasma exchange, but excluded peritoneal dialysis since this is rarely used for ICU patients. We also examined the initiation of antibiotic empirical therapy (defined as use of a carbapenem, a 3rd or 4th generation cephalosporin, or a combination of a β-lactam and an aminoglycoside [25]) during the ICU stay. Therefore, processes were evaluated based on the initiation of

Condition	Code	Organ failure	Code
Salmonella septicemia	A02.1	Respiratory	
Septicemic plague	A20.7	Acute respiratory failure	J96.0
Anthrax septicemia	A22.7	Adult respiratory distress syndrome	J80
Erysipelothrix septicemia	A26.7	Respiratory arrest	R09.2
Listerial septicemia	A32.7	Ventilator management	a
Streptococcal septicemia	A40	Cardiovascular	
Other septicemia	A41	Orthostatic hypotension	I95.1
Actinomycotic septicemia	A42.7	Cardiogenic shock	R57.0
Disseminated herpesviral disease	B00.7	Hypovolemic shock	R57.1
Candidal septicemia	B37.7	Septic shock	A41.9
Disseminated coccidioidomycosis	B38.7	Idiopathic hypotension	I95.0
Disseminated histoplasmosis capsulati	B39.3	Renal	
Disseminated blastomycosis	B40.7	Acute renal failure	N17
Disseminated paracoccidioidomycosis	B41.7	Acute nephritic syndrome	N00
Disseminated sporotrichosis	B42.7	Hemodialysis	a
Disseminated aspergillosis	B44.7	Hepatic	
Disseminated cryptococcosis	B45.7	Hepatic failure, not elsewhere classified	K72
Disseminated mucormycosis	B46.4	Hematologic	
Puerperal sepsis	O85	Disseminated intravascular coagulation	D65
		Purpura and other haemorrhagic conditions	D69
		Metabolic	
		Acidosis	E87.2
		Neurologic	
		Delirium, not induced by alcohol and other psychoactive substances	F05
		Anoxic brain damage, not elsewhere classified	G93.1
		Encephalopathy, unspecified	G93.4
		Coma, unspecified	R40.2

[a]Specific code for a universal fee schedule in Japan

Table 1: ICD-10 codes used for identification of septic patients and acute organ dysfunction.

	High-intensity group (n=234)	Low-intensity group (n=342)	P-value
Number of hospitals	19	30	
Number of patients	234	342	
Hospital background			
Number of beds in hospital	637.8±333.4	467.2±153.2	0.15
Number of ICU beds	12.7±9.9	5.8±4.6	0.01*
Number of intensivists per bed	0.4±0.3	0.3±0.4	0.62
Number of nurses per bed per day	1.8±0.9	1.7±1.1	0.72
Patient background			
Age	71.6±12.7	71.4±13.8	0.86
Gender (male %)	60.2	58.7	0.74
(female %)	79.8	41.3	
Admission course (%)			
Scheduled	12.3	12.9	0.85
Emergency	87.7	87.1	
Reason for ICU entry (%)			
Internal medical disease	57.4	44.6	
Post-emergency surgery	21.8	31.3	0.11
Post-scheduled surgery	20.8	24.1	
Processes of care			
Initiation of antibiotic empirical therapy during ICU stay (%)	86.3	85.4	0.89
(Carbapenem) (%)	52.1	52.6	0.51
(3rd or 4th generation cephalosporin) (%)	24.8	26.1	0.59
(Combination of a β-lactam and an aminoglycoside) (%)	9.4	6.7	0.48
Enteral feeding (%)	90.2	88.6	0.45
Timing of initiation of enteral feeding (days)	6.0±8.4	9.0±10.1	<0.01**
(Gastrointestinall diseases)	7.8±6.9 (n=68)	9.8±7.6 (n=129)	0.32
(Other diseases)	5.4±5.4 (n=166)	7.9±7.8 (n=213)	0.04*
Parenteral nutrition (%)	71.7	74.2	0.45
Timing of initiation of parenteral nutrition (days)	2.9±5.0	2.6±3.8	0.54
Mechanical ventilation (%)	67.2	65.6	0.69
Duration of mechanical ventilation (days)	7.5±7.3	11.5±10	<0.01**
Dialysis (%)	6.6	8.9	0.35
Times of dialysis	4.6±4.2	4.4±6.3	0.85
Outcomes			
Duration of hospital stay for survivors (days)	29.5±14.2 (n=111)	33.1±14.9 (n=162)	0.04*
Duration of hospital stay for non-survivors (days)	20.5±16.4 (n=123)	22.2±15.5 (n=180)	0.36
ICU duration of stay for survivors (days)	8.8±5.6 (n=172)	10.5±9.7 (n=267)	0.15
ICU duration of stay for non-survivors (days)	6.5±7.4 (n=62)	7.6±9.5 (n=75)	0.52
Expected mortality (%)	21.7±19.8	20.6±18.7	0.54
ICU mortality (%)	26.5	21.9	0.21
28-day mortality (%)	39.2	44.4	0.53
Hospital mortality (%)	47.4	45.9	0.73

[a]Continuous variable: mean ± SD; Categorical variable: percentage; *: $p < 0.05$, **: $p < 0.01$

Table 2: Hospital and patient backgrounds, processes and outcomes in ICU organizational structures[a].

empirical therapy, frequency and timing of enteral feeding, frequency and timing of parenteral nutrition, use of mechanical ventilation, duration of mechanical ventilation (days), dialysis, and times of dialysis. Monitoring of medical care on an hourly basis is not possible using administrative data, but data based on a calendar day were available. Thus, initiation of enteral feeding and parenteral nutrition therapy were defined with a baseline of the day of ICU entry. The duration of ICU stay and ICU mortality were determined as outcomes.

Statistical analysis

Continuous variables are presented as means ± standard deviations, and categorical variables as percentages. Analyses were performed using a Student t-test or one way analysis of variance for continuous variables and a χ-square test for categorical variables, with $P<0.05$ regarded as significant. To evaluate differences in process of intensive care between high- and low-intensity groups, Cox proportional hazards analysis or multiple logistic regression analysis were performed. Cox proportional hazards analysis used for continuous variables as independent variables. Multiple logistic regression analysis used for nominal variables. All analyses were performed using SPSS 11.0J (SPSS Inc., Chicago, IL). The Institutional Review Board of the Faculty of Medicine at the Graduate School of Medicine of Kyoto University approved the study.

Results

Fifty-two hospitals (74.3%) with ICUs responded to the questionnaire. Between October 1, 2007, and March 31, 2008, a total of 665,442 patients were discharged from these 52 hospitals, and among these patients, 609 (0.1%) patients with severe sepsis were identified. An initial analysis of 665,442 patients discharged from these 52 hospitals identified 609 (0.1%) patients of severe sepsis in ICU patients. Three of the 52 hospitals (5.8%) and 33 of the 609 patients (5.4%) met the exclusion criteria, leaving 576 (94.6%) patients in 49 hospitals for analysis. 52 hospitals in this analysis were general hospitals and had more than 300 beds.

Characteristics of organizations and patients

In 19 of the 49 hospitals (38.8%), the ICU physicians had primary responsibility or mandatory critical care consultation. In another 30 hospitals (61.2%), the ICU physicians had elective critical care consultation. All ICUs in the study had intensivists on staff.

The patients included 234 patients in 19 ICUs in the high-intensity group, and 342 patients in 30 ICUs in the low-intensity group. Patients were identified with an ICD-10 code: the most frequent code was A41 (other septicemia, 94.1 %), followed by A40 (streptococcal septicemia, 3.0%), and B37.7 (candidal septicemia, 2.3%). There were no significant differences in the hospital backgrounds except for the number of ICU beds (Table 2). The mean age of patients (about 71 years old), the percentage of male patients (approximately 60%), and the reasons for ICU entry did not differ significantly between the ICU groups. However, internal medical disease was significantly more frequent in the high-intensity group (57.4% vs. 44.6%).

Variable	Adjusted Relative Risk Measure (95 % CI) Hazards Ratio or Odds Ratio	95 % CI	P-value
Duration of mechanical ventilation[a]	1.36	1.01-1.81	0.04*
Initiation of enteral feeding on ICU day 0[b]	0.87	0.54-1.41	0.57
Initiation of enteral feeding by ICU day 1[b]	0.96	0.58-1.60	0.87
Initiation of enteral feeding by ICU day 2[b]	1.17	0.68-2.02	0.58
Initiation of enteral feeding by ICU day 3[b]	1.15	0.64-2.04	0.65
Duration of hospital stay for survivors[a]	1.14	0.91-1.43	0.27

[a]Hazards Ratio
[b]Odds Ratio
*: $p < 0.05$, **: $p < 0.01$
CI: Confidence Interval
A Hards Ratio > 1 indicates a shorter duration of mechanical ventilation or shorter duration of hospital stay for survivors in high-intensity ICU.
The Odds Ratio indicates the incidence of enteral feeding for the low-intensity ICU versus high-intensity ICU

Table 3: Results of Cox proportional hazards analysis and multiple logistic analysis.

Care process evaluation in different icu physician staffing models

Associations between ICU groups and processes of care are shown in (Table 2). The initiation of antibiotic empirical therapy during the ICU stay (86.3% vs. 85.4%) and the frequency of use of each antibiotic therapy did not differ significantly between the high- and low-intensity groups. Most patients received enteral feeding and the frequency did not differ significantly between the two groups (90.2% vs. 88.6%, p=0.45). However, initiation of enteral feeding occurred significantly earlier in the high-intensity group (6.0 vs. 9.0 days, $p < 0.01$). Initiation of enteral feeding in patients with gastrointestinal diseases did not differ significantly between the two groups (7.8 vs. 9.8 days, p=0.32), but significantly earlier initiation of feeding in patients of non-gastrointestinal diseases occurred in the high-intensity group (5.4 vs. 7.9 days, p=0.04). The frequency (71.7% vs. 74.2%, p=0.45) and initiation time (2.9 vs. 2.6 days, p=0.54) of parenteral nutrition did not differ significantly between the two groups.

The frequency of mechanical ventilation in the high- and low-intensity groups did not differ significantly (67.2 vs. 65.6%, p=0.69), but the duration of mechanical ventilation was significantly shorter in the high-intensity group (7.5 vs. 11.5 days, $p<0.01$). The rate and times of dialysis did not differ significantly between the two groups. The mean duration of ICU stay was shorter by approximately 2 days for surviving patients in the high-intensity group (8.8 vs. 10.5 days, p=0.15; Table 2), whereas non-survivors had a similar ICU stay in the high- and low-intensity groups (6.5 vs. 7.6 days; p=0.52). The mean duration of hospital stay was significantly shorter for survivors in the high-intensity group (29.5 vs. 33.1 days, p=0.04), but did not differ significantly for non-survivors (20.5 vs. 22.2 days; p=0.36). There were no significant differences in ICU (26.5% vs. 21.9%, p=0.21), 28-day (39.2% vs. 44.4%, p=0.53), and hospital (47.4% vs. 45.9%, p=0.73) mortality between the high- and low-intensity groups.

Cox proportional hazards analysis or multiple logistic regression analysis

Cox proportional hazards analysis was used to examine the impact between both ICU groups on duration of mechanical ventilation, and on duration of ICU stay for survivors after adjusted for variables of severity of illness (expected mortality calculated from COPE model), age, sex, and the number of ICU beds. In duration of mechanical ventilation, patients were censored for death (n = 113) or long-term ventilator facility (n = 8). The high-intensity group was associated with a shorter duration of mechanical ventilation after adjusted to covariates (Hazards Ratio [HR] 1.36; 95 % CI 1.01 to 1.81; Table 3), but this study showed that duration of hospital stay for survivors had no significant impact on ICU structure (HR 1.14; 95 % CI 0.91 to 1.43; Table 3).

Multiple logistic regression analysis was used for the examination of the impact of ICU structure on initiation of enteral feeding after controlling for the variables by similar approach. The dependent variable in multiple logistic regression analysis was defined as initiation of enteral feeding on ICU day 0, day 1, day 2, and day 3, respectively, because the definition of timing of enteral feeding was controversial, which should be initiated as early as possible. ICU day 0 was defined as the day of entry into ICU. ICU structure was not related to the initiation of enteral feeding by ICU day 3 (Table 3).

Discussion

A systematic review of physician staffing patterns and outcomes in critically ill patients showed that high-intensity ICU physician staffing reduces hospital and ICU mortalities and the durations of hospital and ICU stays compared with low-intensity ICU physician staffing. [2] In comparisons of the duration of ICU stay between staffing models, Pronovost et al. [3] and Rosenfeld et al.[5] found a shortened ICU stay in high-intensity models, whereas Dimick et al. [6] found no significant difference in ICU stay between high- and low-intensity models. Mortality from acute lung injury is lower in a closed-model ICU than in an open-model ICU, [7] and lower mortality has been reported in trauma patients in an intensive model compared to an open ICU. [8] Improved outcomes after a structural change from an open to closed ICU model have also been found, indicating that the staffing model has an important relationship with the outcome. Contrary to reports showing improvement of outcomes by ICU staffing, Levy et al. [17] recently suggested that patients managed by intensivists for the entire ICU stay had a higher risk of death compared to management by non-critical care physicians. Mortality and duration of stay had high impact of ICU studies. However, the effects of ICU staffing for outcomes, such as mortality and duration of stay, were controversial. In this study, there were no significant differences in outcomes in high- and low-intensity groups, except for duration of hospital stay for survivors.

In trend to discussing mortality and duration of stay as outcome indicators on ICU structural studies, Kahn et al. [26] examined some processes in different staffing models, and demonstrated that evidence based approach (e.g. the sedation interruption) was more likely to be taken in high-intensity ICUs, compared to low-intensity ICUs. The sedation interruption contributed to progressive weaning from mechanical ventilation and shorter duration of mechanical ventilation. [27] Singer et al. [28] examined duration of mechanical ventilation (care process) as main outcome on ICU staffing model, showed that a high-intensity ICU was associated with approximately 40 hours lower duration of mechanical ventilation, and that duration of mechanical ventilation was useful indicator for ICU structural study. In this study, we evaluated processes of ICU quality indicators to assess the impact of ICU organization. Addition to mechanical ventilation, indicators

related to renal, nutritional, and antibiotic management were also selected as process measures, since these are important indicators at intensive care unit [21-24] and nutrition and anti-infective support in ICUs are essential for critically ill patients. [29,30] Our study also showed that high intensity ICU model was associated with 4 days shorter duration of mechanical ventilation, which supported the findings in previous studies on ICU staffing models, although mortality was not associated with ICU structure in this study. The difference in duration of mechanical ventilation in previous study may cause by the difference in patient settings whether various diseases or only septic patients in the study object.

The association between the timing of initiation of enteral feeding and outcomes in patients with sepsis has been widely investigated. Several meta-analyses and systematic reviews [31-33] have indicated that early initiation of enteral feeding may reduce the incidence of infectious complications and shorten the duration of stay, but Ibrahim et al. [34] and Eyer et al. [35] found no significant effect of early enteral feeding on the incidence of infectious complications or duration of stay. Such mixed results on the effectiveness of nutritional therapy may be due to differences among study subjects and in the definition of early enteral feeding among studies. In this study, we showed earlier initiation of enteral feeding in high-intensity ICU, but the effect of ICU structure on enteral feeding was limited.

To assess antibiotic therapy, we investigated the initiation of antibiotic empirical therapy during the ICU stay. Based on a literature review of antimicrobial therapy for severe sepsis and septic shock using an evidence-based approach, Bochud et al. [25] found that a carbapenem, a 3rd or 4th generation cephalosporin, or a combination of a β-lactam and an aminoglycoside provided equally effective antibiotic empirical therapy. Therefore, we used these therapies as one variable in our study. Rapid initiation of appropriate antimicrobial therapy is a key to improving outcomes and reducing mortality in patients with sepsis and other infectious diseases. [25] In addition, daily reassessment of antibiotic use and discontinuation of antimicrobial therapy for non-infectious diseases are recommended in the 2008 Surviving Sepsis Campaign guidelines, and implementing these protocols may improve outcomes in patients with hospital-acquired pneumonia in critical care. [36]We could not evaluate these recommendations due to the limitations of our data.

In our study, duration of hospital stay was extremely longer than those reported by previous studies. There a specific reason for such long hospitalizations in Japan. Acute care hospitals in Japan have traditionally also provided sub-acute care and sometimes long-term care. [37] Recently shorter duration of hospital stay in the acute care hospitals has been promoted for pressure from Japanese Government. The duration of stay in Japan, however, has been much longer than in most Western nations, and a longer hospital stay may increase hospital mortality. Our results showed higher hospital mortality (45%) and longer hospital stays (20-30 days) in patients with severe sepsis, compared to 18-30% and 12-17 days reported in other countries. [18,38,39] Differences in the function of acute care, in which sub-acute care and nursing home care may or may not be included, in Japan and Western countries may account for these differences. However, ICU mortality (24.2%) and the duration of ICU stay (8.4 days) in our study were similar to the values of 10-35% and 7 days found by Vincent et al. [40] The ICU and hospital stays for survivors were both shorter by 2-3 days in the high-intensity group. This may suggest that the hospital stay is affected by differences in processes, especially duration of mechanical ventilation, in the ICU. Although Singer et al. [28] showed that the high-intensity ICU was associated with a reduced hospital mortality, it was difficult to evaluate the affect of ICU organization to hospital mortality in previous studies with regard to functional differences between Japan and other countries. As concerns ICU mortality, further examination should be performed using generalized severity coring system.

Our study has several limitations. First, risk adjustment and calculation of expected mortality of ICU patients are usually performed using the Acute Physiology and Chronic Health Evaluation (APACHE) versions I-IV, the Mortality Prediction Model (MPM) versions I-II, or the Simplified Acute Physiology Score (SAPS) versions I-III. However, administrative data in Japan does not include these scores. Thus, we evaluated illness severity using the COPE model, which require only administrative data. Second, we do not know the accuracy of the coding for sepsis, since the standard of coding and range of severity may differ among institutions. However, studies of septic patients using administrative data are accepted widely. [18,41] Therefore, we evaluated septic patients regardless of a coding bias among hospitals. In addition, the actual number of septic patients in our settings may be higher than 576 patients, because we selected patients for which both sepsis-related codes as the primary diagnosis and acute organ dysfunction were recorded. We believed that our inclusion criteria were small coding bias compared to the criteria including sepsis-related codes as the primary diagnosis and co-morbidities. In addition, university hospitals were not included in the QIP, which may have led to inclusion of only a small number of severe septic patients. Third, there may be a selection bias of ICU entry and intervention therapy. However, we believe that the effects of these biases were small since the ICUs in our study met the standards of the Ministry of Health, Labor, and Welfare. These standards specify ICU entry criteria and the processes we evaluated are widely performed in critical care settings. Finally, the study included only a small number of the acute-care hospitals in Japan, and the majority of hospitals in the study were large and/or educational hospitals. Therefore, further investigation is needed in smaller and/or non-educational hospitals and in a greater number of hospitals.

The current study is significant as the evaluation of care processes, which were available in administrative data, in ICU organization. The results showed a clear association between ICU organization and care processes. High-intensity ICU is associated with improved quality of care on mechanical ventilation.

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References

1. Zimmerman JE, Shortell SM, Rousseau DM, Duffy J, Gillies RR, et al. (1993) Improving intensive care: observations based on organizational case studies in nine intensive care units: a prospective, multicenter study. Crit Care Med 21: 1443-1451.
2. Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, et al. (2002) Physician staffing patterns and clinical outcomes in critically ill patients. JAMA 288: 2151-2162.
3. Pronovost PJ, Jenckes MW, Dorman T, Garrett E, Breslow MJ, et al. (1999) Organizational characteristics of intensive care units related to outcomes of abdominal aortic surgery. JAMA 281: 1310-1317.
4. Dimick JB, Pronovost PJ, Heitmiller RF, Lipsett PA (2001) Intensive care unit physician staffing is associated with decreased length of stay, hospital cost, and complications after esophageal resection. Crit Care Med 29: 753-758.
5. Rosenfeld BA, Dorman T, Breslow MJ, Pronovost P, Jenckes M, et al. (2000) Intensive care unit telemedicine: alternate paradigm for providing continuous intensivist care. Crit Care Med 28: 3925-3931.

6. Dimick JB, Pronovost PJ, Lipsett PA (2002) The effect of ICU physician staffing and hospital volume on outcomes after hepatic resection. Journal of Intensive 17: 41-47.
7. Treggiari MM, Martin DP, Yanez ND, Caldwell E, Hudson LD, et al. (2007) Effect of intensive care unit organizational model and structure on outcomes in patients with acute lung injury. Am J Respir Crit Care Med 176: 685-690.
8. Nathens AB, Rivara FP, MacKenzie EJ, Maier RV, Wang J, et al. (2006) The impact of an intensivist-model ICU on trauma-related mortality. Ann Surg 244: 545-554.
9. Flaatten H (2005) Effects of a major structural change to the intensive care unit on the quality and outcome after intensive care. Qual Saf Health Care 14: 270-272.
10. Vincent JL (2000) Need for intensivists in intensive-care units. Lancet 356: 695-696.
11. Brown JJ, Sullivan G. (1989) Effect on ICU mortality of a full-time critical care specialist. Chest 96: 127-129.
12. Baldock G, Foley P, Brett S (2001) The impact of organizational change on outcome in an intensive care unit in the United Kingdom. Intensive Care Med 27: 865-872.
13. Reynolds HN, Haupt MT, Thill-Baharozian MC, Carlson RW (1988) Impact of critical care physician staffing on patients with septic shock in a university hospital medical intensive care unit. JAMA 260: 3446-3450.
14. Li TC, Phillips MC, Shaw L, Natanson C, Goldman L (1984) On-site physician staffing in a community hospital intensive care unit. Impact on test and procedure use and on patient outcome. JAMA 252: 2023-2027.
15. Manthous CA, Amoateng-Adjepong Y, al-Kharrat T, Jacob B, Alnuaimat HM, et al. (1997) Effects of a medical intensivist on patient care in a community teaching hospital. Mayo Clin Proc 72: 391-399.
16. Blunt MC, Burchett KR. (2000) Out-of-hours consultant cover and case-mix-adjusted mortality in intensive care. Lancet 356: 735-736.
17. Levy MM, Rapoport J, Lemeshow S, Chalfin DB, Phillips G, et al. (2008) Association between critical care physician management and patient mortality in the intensive care unit. Ann Intern Med 148: 801-809.
18. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348: 1546-1554.
19. Duke GJ, Santamaria J, Shann F, Stow P, Pilcher D, et al. (2008) Critical care outcome prediction equation (COPE) for adult intensive care. Crit Care Resusc 10: 35-41.
20. Umegaki T, Sekimoto M, Hayashida K, Imanaka Y (2010) An outcome prediction model for adult intensive care. Crit Care and Resusc 12: 96-103.
21. de Vos M, Graafmans W, Keesman E, Westert G, van der Voort PH (2007) Quality measurement at intensive care units: which indicators should we use? J Crit Care 22: 267-274.
22. Cahill NE, Dhaliwal R, Day AG, Jiang X, Heyland DK. (2010) Nutrition therapy in the critical care setting: What is "best achievable" practice? An international multicenter observational study. Crit Care Med 38: 395-401.
23. Gibney RT, Bagshaw SM, Kutsogiannis DJ, Johnston C (2008) When should renal replacement therapy for acute kidney injury be initiated and discontinued? Blood Purif 26: 473-484.
24. Hsu CL, Chang CH, Wong KN, Chen KY, Yu CJ, et al. (2009) Management of severe community-acquired septic meningitis in adults: from emergency department to intensive care unit. J Formos Med Assoc 108: 112-118.
25. Bochud PY, Glauser MP, Calandra T (2001) Antibiotics in sepsis. Intensive Care Med 27: S33-48.
26. Kahn JM, Brake H, Steinberg KP (2007) Intensivist physician staffing and the care process of care in academic medical centres. Qual Saf Health Care 16: 329-333.
27. Kress JP, Pohlman AS, O'Connor MF, Hall JB (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 342: 1471-1477.
28. Singer JP, Kohlwes J, BentS, Zimmerman L, Eisner MD (2010) The impact of a "Low-Intensity" versus "High-Intensity" medical intensive care unit on patient outcomes in critically ill veterans. J Intensive Care Med 25: 233-239.
29. Boumendil A, Somme D, Garrouste-Orgeas M, Guidet B (2007) Should elderly patients be admitted to the intensive care unit? Intensive Care Med 33: 1252-1262.
30. Aarts MA, Brun-Buisson C, Cook DJ, Kumar A, Opal S, et al. (2007) Antibiotic management of suspected nosocomial ICU-acquired infection: does prolonged empirical therapy improve outcome? Intensive Care Med 33: 1369-1378.
31. Lewis SJ, Egger M, Sylvester PA, Thomas S (2001) Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ 323: 773-776.
32. Marik PE, Zaloga GP (2001) Early enteral feeding in acutely ill patients: a systematic review. Crit Care Med 29: 2264-2270.
33. Zaloga GP (1999) Early enteral feeding nutritional support improves outcome: hypothesis or fact? Crit Care Med 27: 259-261.
34. Ibrahim EH, Mehringer L, Prentice D, Sherman G, Schaiff R, et al. (2002) Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. J Parenter Enteral Nutr 26: 174-181.
35. Eyer SD, Micon LT, Konstantinides FN, Edlund DA, Rooney KA, et al. (1993) Early enteral feeding does not attenuate metabolic response after blunt trauma. J Trauma 34: 639-643.
36. Lancaster JW, Lawrence KR, Fong JJ, Doron SI, Garpestad E, et al. (2008) Impact of an institution-specific hospital-acquired pneumonia protocol on the appropriateness of antibiotic therapy and patient outcomes. Pharmacotherapy 28: 852-862.
37. Ikegami N, Campbell JC (1995) Medical care in Japan. N Engl J Med 333: 1295-1299.
38. Lever A, Mackenzie L (2007) Sepsis: definition, epidemiology, and diagnosis. BMJ 335: 879-883.
39. Jacobson S, Johansson G, Winso O (2004) Primary sepsis in a university hospital in northern Sweden: A retrospective study. Acta Anaesthesiol Scand 48: 960-967.
40. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, et al. (2006) Sepsis in European intensive care units: Results of the SOAP study. Crit Care Med 34: 344-353.
41. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, et al. (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29: 1303-1310.
42. Groeger JS, Strosberg MA, Halpern NA, Raphaely RC, Kaye WE, et al. (1992) Descriptive analysis of critical care units in the United States. Crit Care Med 20: 846-863.
43. Takezawa J (2008) Performance measurement and reimbursement for ICU. J Jpn Soc Intensive Care Med 15: 171-178.

手術室運用の効率性指標の検討と多施設間比較

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要　旨：【背景】手術室の効率性を検討する際に，多施設間比較に基づく評価や各施設の資源や機能を考慮した評価が必要とされている。【目的】手術室の運用度を評価するための指標の候補を検討し，その候補指標の関連要因を，重回帰分析を用いて明らかにする。さらに，重回帰モデルに基づく各施設の資源や機能を考慮した予測値を用いて，手術室運用の効率性指標を提案する。【方法】2006年4月から2008年3月までの133の急性期病院のDPCデータおよび施設調査表を用いた。133病院のデータをランダムに開発用サンプルと検証用サンプルの2群に分け，開発用サンプルを用いて，ステップワイズ法により重回帰分析を行い，予測値を算出した。続いて，検証用サンプルでモデルの安定性を検証した。さらに，算出した予測値を用いて，実測値と予測値の比（以下，OE比とする）と実測値と予測値の差（以下，OE差とする）を施設ごとに示した。【結果】1ヵ月1手術室あたりの手術件数，手術手技報酬と施設の資源や機能との関連がみられた。重回帰分析では，1ヵ月1手術室あたりの手術件数は1手術室あたりの外科系医師数および平均在院日数により，手術手技報酬は1手術室あたりの外科系医師数および病床数により，そのばらつきが説明された。【結論】1ヵ月1手術室あたりの手術件数，手術手技報酬を用いた多施設間比較を行った。また，各施設の資源や機能を考慮した予測値を用いたOE比とOE差を手術室運用の効率性指標として提案する。

キーワード：手術室の効率性，多施設間比較，評価指標

背　景

昨今，医療機関では，効率的かつ安定した経営維持のために必要となる診療報酬を確保するため，経営陣や医師，看護師，医療技術職をはじめとする職員が各々の立場で，医療機関の効率的な運用を実現するための取り組みに努めている[1]。また，医療機関を効率よく運用するためのシステムとして，例えばTQM (Total Quality Management) やBSC (Balanced Score Card) といったツールを活用した経営・目標管理システムを導入し，医療機関組織全体および医療機関における各部門の運用度を把握し，評価し，改善する取り組みを行っている[2, 3]。そのなかで，近年とりわけ着目されている部門として手術室があげられる。それは，これまでの研究では，各医療機関で確保する診療報酬の合計と手術件数には，高い相関関係があることが報告されていることがあげられる[4]。また，手術室で得られる主な診療行為である手術の診療報酬が，出来高払い制であり，手術実施に対して，直接その対価として診療報酬を確保することができること[5]やQIP (Quality Indicator / Improvement Project) に提出された2009年4月～2009年9月の153病院のDPCデータにおいて，全診療報酬に占める手術・麻酔の診療報酬の割合は28.1%であり，全診療報酬に占める手術に関連する診療報酬が高いことから，手術室は，他の部門よりいっそう効率的な運用が重要となる。さらに，定期的に利用状況を把握し，スケジューリングの見直しを行うことも重要となる[6, 7]。以上のことから，医療機関では，より効率的な手術室の運用が求められており[8-11]，手術室で実施される件数や手術手技報酬といった手術室の運用度を把握し，それを評価し，改善する仕組みが必要とされている[8]。

しかしながら，今日，手術室の運用度を評価するための指標や方法が標準化されていないのが現状である。各々の医療機関では，手術室の実績として，手術件数や手術手技報酬，手術の時間などを時系列の変化を見た評価にとどまっている医療機関が少なくない。また，医療機関における診療実績を多くの施設とベンチマークを行い，その結果に基づき評価することは重視されているが[12]，手術室においては未成熟である。

表1　1ヵ月手術室あたりの手術件数の関連要因

	β	P	VIF
1手術室あたりの外科系医師数	0.488	0.002	1.174
平均在院日数	−0.348	0.020	1.174
			$R^2 = 0.489$

表2　1ヵ月手術室あたりの手術手技報酬の関連要因

	β	P	VIF
1手術室あたりの外科系医師数	0.413	0.014	1.220
病床数	0.350	0.034	1.220
			$R^2 = 0.415$

そのため，一般的に手術室の評価は，他の医療機関の手術件数の実績と比較し，その比較に基づく評価にとどまっており，医療機関によって，手術室におけるスタッフ数，手術室数，病床数など資源や機能に差異があるにも関わらず，それらを考慮した評価がなされていない。これらを回避するためには，各々の施設の資源や機能を考慮したうえで，手術室の運用度を評価し，その評価結果に基づき，手術室の運用度の効率性を高め，より効果的な手術室の運用を実施することが求められている[13]。

目　的

本研究の目的は，急性期医療を担う医療機関で用いられている客観データであるDPCデータを用いて，医療機関の経営陣ならびに手術室スタッフが活用しうる手術室の運用度を評価するための指標の候補を検討し，その候補指標の関連要因を，重回帰分析を用いて明らかにする。さらに，重回帰モデルに基づく各施設の資源や機能を考慮した予測値を用いて，手術室運用の効率性指標を提案することである。

方　法

本研究は，DPC（Diagnosis Procedure Combination）データおよび参加医療機関の施設調査表（病床数，職員数，平均在院日数，手術室数等）を用いた。本研究では，QIP（医療の質指標改善プロジェクト：http://med-econ.umin.ac.jp/QIP/）に提出された2006年4月から2008年3月までの133の急性期病院のDPCデータE，Fファイルおよび施設調査表を使用した。はじめに，各施設の1手術室あたりの医師数や看護師数，そして平均在院日数，病床数などの施設の資限や機能に関する指標ならびに，これまでの研究や医療機関経営の現場で用いられている指標として[2, 5, 7-11]，件数や報酬を示す1ヵ月1手術室あたりの手術件数ならびに手術手技報酬の記述統計を算出した。なお，手術室で実施されている手術の同定は，1病院の過去3年間の手術室における手術実績ならびに各診療科専門医の意見に基づき同定した。統計解析には，Dr. SPSS II for Windowsを用いた。施設の資源や機能と1ヵ月1手術室あたりの手術件数ならびに手術手技報酬の関連性をみるために，単変量解析を行いPearsonの相関係数を算出した。さらに，重回帰分析を用いて，手術室の実績の関連要因を明らかにし，各施設の機能を考慮した各施設の手術室における平均的な運用度である予測値を算出するため，重回帰モデルを作成した。133病院のデータをランダムに2群に分け，一方を開発用サンプルとし，もう一方を検証用サンプルとした[15, 16]。はじめに，開発用サンプルを用いて，目的変数を1ヵ月1手術室あたりの手術件数とし，説明変数に単変量解析で有意（$P < 0.05$）であった施設の資源や機能に関する指標を投入し，ステップワイズ法を用いて重回帰分析を行い，1ヵ月1手術室あたりの手術件数の関連要因を同定するとともに，重回帰モデルを作成し，予測値を算出した。また，目的変数を1ヵ月1手術室あたりの手術手技報酬とした場合についても同様に行った。その後，検証用サンプルを用いてモデルの妥当性を検証した。さらに，重回帰モデルを用いて，1ヵ月1手術室あたりの手術件数ならびに手術手技報酬の予測値を用いて，実測値（Observed Value）と予測値（Expected Value）の比であるOE比と実測値と予測値の差であるOE差を用いて多設間比較を行った。

結　果

各施設の資源や機能を示す指標全てにおいて大きなばらつきがみられた。また，1ヵ月1手術室あたりの手術件数の平均は46件で範囲は10～107件，1ヵ月1手術室あたりの手術手技報酬の平均は7,403千円で範囲は1,147～18,919千円であった。2つの指標において，大きなばらつきがみられた。つづいて，Pearsonの相関係数を算出した結果，1つの手術室で行う手術件数は，施設の資源や機能に強い関連を示しており，人的資源を表す1手術室あたりの外科系医師数で正の相関がみられ，診療プロセスを示す平均在院日数については，負の相関がみられた。また，1つの手術室あたりで確保できる手術手技に対する報酬も同様に施設資源や機能に強く関連している。さらに，目

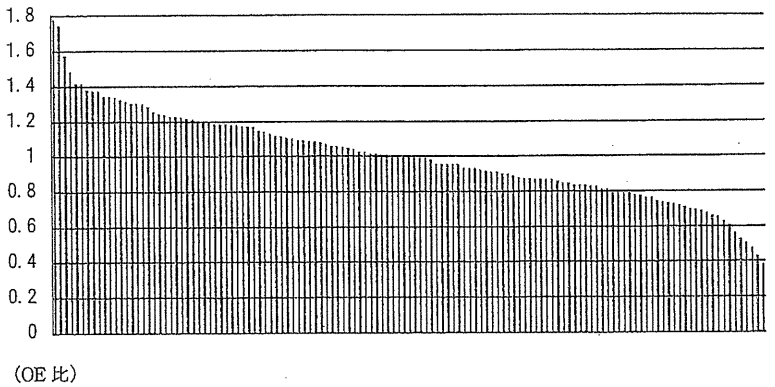

図1　1ヵ月1手術室あたりの手術件数のOE比（＝実測値／予測値）

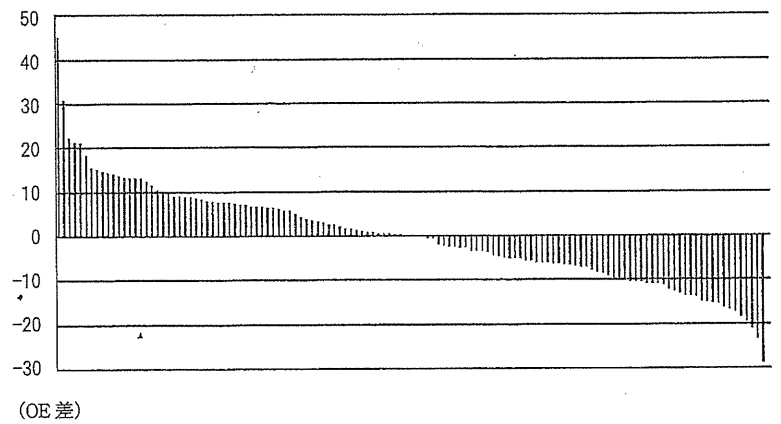

図2　1ヵ月1手術室あたりの手術件数のOE差（＝実測値－予測値）

的変数を1ヵ月1手術室あたりの手術件数とし，説明変数に単変量解析で有意（$P < 0.05$）であった施設の資源や機能に関する指標を投入し，ステップワイズ法を用いて重回帰分析を行った。結果は，表1の通りである。表1の通り，説明変数として選択されたのは，1手術室あたりの外科系医師数ならびに平均在院日数であった。同様に，目的変数を1ヵ月1手術室あたりの手術手技報酬とし重回帰分析を行った結果は，表2の通りである。

表2の通り，説明変数として選択されたのは，1手術室あたりの1手術室あたりの外科系医師数ならびに病床数であった。その後，作成した重回帰モデルの安定性を検証するため，検証用サンプルにおいて，R^2を算出した結果，1ヵ月1手術室あたりの手術件数のR^2は0.508，手術手技報酬のR^2は0.500であり，重回帰モデルのR^2と比較すると近い値となった。

その後，1ヵ月1手術室あたりの手術件数を上記の重回帰モデルに投入し，予測値（Expected Value）と実測値（Observed Value）の比（OE比）と予測値と実測値の差（OE差）を算出し，その結果を図1，図2に示した。同様に，1ヵ月1手術室あたりの手術手技報酬についても算出した。OE比は，1より高いものは，実測値が予測値を上回り，1より低いものは実測値が予測値を下回ることを示す。OE差は，0より高いものは，実測値が予測値を上回り，0より低いものは，実測値が予測値を下回ることを示す。

考　察

本研究では，1ヵ月1手術室あたりの手術件数，手術手技報酬を用いたが，これらの指標は，互いに強い相関がみられた。これより，件数を多く実施している施設ほど手術手技報酬も多く確保できていることがわかる。また，1ヵ月1手術室あたりの手術件数，手術手技報酬は，施設の機能や資源に影響することが示された。重回帰分析の結果より，1手術室あたりの外科系医師数が多いほど，また平均在院日数が短いほど件数が多く，予測値は高い値を示すことが明らかとなった。そこで，経営管理の仕組みの中で目標管理があげられ目標管理において重要な点として，具体的な数値目標を示し改善につなげることとされている

が[2, 17, 18]，本研究で提案する方法として，図1，図2では，1ヵ月1手術室あたりの手術件数のそれぞれOE比，OE差を示しており，OE比を用いることにより，各医療機関が自院の1ヵ月1手術室あたりの手術件数が予測値と比較して，手術件数がどの程度多いのか，もしくはどの程度少ないのかを比で把握することでき，数値化された手術件数の目標値として活用することが可能となる。さらに，OE差を用いることにより，1ヵ月1手術室あたりの手術件数が予測値と比較して，何件多いのか，もしくは何件少ないのかを実数で把握することができる。同様に，1ヵ月1手術室あたりの手術手技報酬は，手術手技報酬が予測値と比較して，どの程度高いのか低いのかを比で把握することや何円高いか何円低いかを実数でも把握が可能である。

本研究では，重回帰モデルを用いて予測値を算出し，実測値と予測値の比であるOE比と実測値と予測値の差であるOE差を算出した。予測値との差には，R^2で説明される部分とその他の病院に関連する要因，そして，誤差が含まれているが，本研究では，その誤差の幅について検証されていないため今後検証する余地がある。しかしながら，本研究では，検証用サンプルを用いて，重回帰モデルの安定性の検証を行い，大きな相違はみられなかった。

本研究の新規性は，第一に，先行研究では手術室の指標を用いた研究では，アンケート調査に基づくものが一般的で，客観データを用いる研究が極めて稀であったため，多施設の手術件数や手術手技報酬を統一の定義で数値化がされていなかった。しかし，本研究では，本邦の多数の急性期病院で用いられている客観データであるDPCデータを用いることにより，統一の定義での指標の算出を可能とし，手術件数，手術手技報酬の多施設間での比較を可能とした。以前より，多施設間ベンチマーキングには，自組織の強み弱みを把握することができること，多くの位置を知ることができること，ベスト・プラクティスを参考にできるなどといった利点があり，目標管理や業務改善の方法として有効であるとされ[13, 19]，本研究もその可能性を秘めている。第二に，これまでの医療経営の領域で用いられていた手術室の運用度を測定する方法としては，時系列の変化に基づく実績の評価や他の施設の資源や機能を考慮しないままの手術の件数のみで評価を行い目標管理がなされていたが，本研究では，特に現場の努力で直ちに変更できないような施設の資源や機能との関連要因を，重回帰分析を用いて明らかにした後，予測値を算出することにより，OE比やOE差を用いた件数，報酬の視点から目標値を設定することが可能となった。

近年，手術室の運用の効率化と目標管理の必要性がいっそう高まりつつあるため[8]，本研究で考案した手術室運用の効率性指標は，急性期医療を担う医療機関経営に求められているものであると言えよう。考案した指標は，全国共通の標準データセットであるDPCデータを用いているため，他のDPCを導入している医療機関においても適応することが可能であり，今後，さらに多数の医療機関においての分析も期待できる。

結　論

本研究では，1ヵ月1手術室あたりの手術件数，手術手技報酬を統一の定義で多施設間比較可能な形で算出することができた。また，これらの指標と1手術室あたりの外科系医師数ならびに病床数や平均在院日数といった施設の資源や機能に強い関連がみられた。これらの関連の強い変数群を反映した予測値を算出し，1ヵ月1手術室あたりの手術件数，手術手技報酬の実測値と予測値の比（OE比）ならびに差（OE差）を手術室運用の効率性指標として提案する。

参考文献

1) Wang BB, Wan TT, Falk JA, Goodwin D：Management strategies and financial performance in rural and urban hospital. Journal of Medical System 2001；25 (4)：241-255.
2) 医療の質・安全と財務向上による持続的組織成長のための人材養成．平成19年度経済産業省医療経営人材育成事業報告書．京都大学大学院医学研究科医療経済学分野 2008：2-7.
3) 今中雄一：顧客満足からトータル・クオリティ・マネジメントへ．岩崎　榮，編：医を測る医療サービスの品質管理とは何か．東京，厚生科学研究所 1998：82-90.
4) 堀田哲夫，ほか：国立大学病院の現状からみた手術部看護師の適正数．手術医学 2009；30：9-19.
5) 冨岡俊也，真野俊樹，山田芳嗣，ほか：大規模急性期病院の効率的運営に関する医療経済的検討．日本医療・病院管理学会誌 2008；45-2：55-62.
6) 日本手術医学会：手術医療の実践ガイドライン．日本手術医学会誌 2009；29：1-9.
7) Stepaniak PS：Modeling procedure and surgical time for current procedural terminology-anesthesia-surgeon combinations and evaluation in terms of