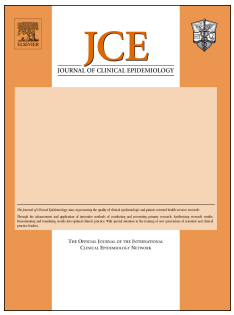

New outcome-specific comorbidity scores excelled in predicting in-hospital mortality and healthcare charges in administrative databases

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TITLE PAGE

Title

New outcome-specific comorbidity scores excelled in predicting in-hospital mortality and healthcare charges in administrative databases

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Abstract

Objective: To determine the most reliable comorbidity measure, we adapted and validated outcome-specific comorbidity scores to predict mortality and hospital charges using the comorbidities composing the Charlson and Elixhauser measures, and the combination of these two used in developing Gagne's combined comorbidity scores (CC, EC, and GC, respectively).

Study Design and Setting: We divided cases of patients discharged in 2016–17 from the Diagnosis Procedure Combination database (n=2,671,749) into two: one to derive weights for the scores, and the other for validation. We further validated them in subgroups, such as that with a selected diagnosis.

Results: The c-statistics of the models predicting in-hospital mortality using new mortality scores using the CC, EC, and GC were 0.780, 0.795, and 0.794, respectively. Among them, that using the EC showed the best calibration. To predict hospital charges and length of hospital stay (LOS), the models using variables indicating the GC performed the best. The performances of the mortality and expenditure scores were considerably different in predicting each outcome.

Conclusion: The new score using the EC performed the best in predicting in-hospital mortality for most situations. For hospital charges and LOS, the binary variables of the GC showed the best results. The outcome-specific comorbidity scores should be considered for different outcomes.

Keywords: Comorbidity, Charlson, Elixhauser, In-hospital mortality, Hospital charges, Length of hospital stay.

Running title: New outcome-specific comorbidity scores

Word count (excluding subheadings): 200 words

1. Introduction

The Charlson comorbidity index (CCI) and Elixhauser comorbidity measures are the two most frequently used methods to measure comorbidity burdens in studies using administrative databases [1]. The CCI was developed as a method of classifying comorbid conditions that might affect the risk of short-term mortality for patients enrolled in longitudinal studies [2]. The Elixhauser comorbidity measures comprise 30 conditions used as binary variables in regression models to predict in-hospital mortality, hospital charges, and length of hospital stay (LOS) in administrative databases [3]. Although incorporating 30 variables indicating comorbidities in a model can allow the adjustment of comorbidity burdens more precisely than can a summarized score, a comorbidity score is beneficial in a certain situation, such as studies with small sample sizes, and has shown its validity as a substitute for a set of variables [4]. Summarized scores using the conditions making up the Elixhauser comorbidity measure have also been developed by researchers, such as van Walraven et al [5-7]. Using the comorbid conditions of the Charlson and Elixhauser measures, Gagne et al. introduced the combined comorbidity score and reported that it performed better in predicting mortality than the Charlson and Elixhauser/van Walraven indices [8].

For studies of Japanese populations, the CCI has been used almost exclusively without thorough validation. Although the Elixhauser measures and the Gagne's combined score have been reported to outperform the CCI [1,8-10], only a study has compared the Charlson and Elixhauser comorbidity measures for a Japanese population [11].

Moreover, most comorbidity scores were developed using models having mortality as an outcome variable. Two recently developed morbidity scores—one for mortality and the other for expenditures—showed that these outcome-specific scores performed better at predicting their respective outcomes [12]. Charlson et al. also adapted the CCI to predict the resource utilization of patients with chronic diseases [13].

Thus, this study aimed to determine the most reliable method for measuring comorbidity burdens in database studies of various outcomes. To this end, first, we derived weights for

outcome-specific comorbidity scores to predict in-hospital mortality and hospital charges based on the comorbid conditions composing the Charlson and Elixhauser comorbidity measures, and the combination of these 2 sets of conditions used by Gagne et al. to develop combined comorbidity scores using a large Japanese inpatient database. Second, we validated and compared preexisting measures and our new scores in predicting in-hospital mortality, hospital charges, and LOS on various populations: patients with/without surgery, aged ≥ 75 years, and 7 diagnosis-based subgroups. We also compared the performance between comorbidity indices, which were the sum of each weight for comorbid conditions, and the sets of comorbidity variables used in each comorbidity measure.

2. Methods

2.1. Data source

We used Diagnosis Procedure Combination (DPC) data from the Quality Indicator/Improvement Project (QIP) database. The QIP database contains DPC data from acute care hospitals voluntarily participating in the project. The cumulative number of participating hospitals was over 500, which were located all over Japan and included both public and private hospitals with various size: the number of general beds, which are hospital beds that are not psychiatric, infectious diseases, and tuberculosis beds according to Japanese classification of hospital beds, ranged from 30 to 1,151 in 2016. The DPC/per-diem payment system (PDPS) is a Japanese prospective payment system applied to acute care hospitals. There were 1,667 hospitals adopting the DPC/PDPS in 2016, which accounted for 56% (495,227/891,398) of all general beds of Japanese hospitals in 2016 [14]. The DPC data consist of claims and discharge summaries, including International Classification of Diseases, Tenth Revision (ICD-10) codes classifying the main diagnosis, cause of admission, the most and second-most medical-resource-intensive diagnoses, up to 10 comorbidities, and 10 complications. The DPC data also contain codes of all services provided during each hospitalization as well as PDPS information. Using this information, we calculated fee-for-service charges as “hospital charges” in this study, not the actual claimed charges of PDPS, to measure the actual amount of consumed medical resources. The calculation

of the hospital charges, which include both hospital and physician fees, was based on the fee schedule of Japan National Health Insurance; the fee schedule is uniform nationally.

2.2. Study population

We included nonmaternal cases of inpatients aged ≥ 18 years and discharged between April 1, 2016, and March 31, 2018 (fiscal years 2016–17). We excluded hospitalization for special purposes, such as repeated chemotherapy, clinical trials, and 1 day of LOS. We then randomly selected 70% of the cases for adaptation; the remaining 30% were used for validation.

For further validation, we created subgroups of patients with/without surgery, aged ≥ 75 years, and with 7 selected diagnoses causing the admission. The 7 diagnosis-based subgroups included diagnoses with higher prevalence, mortality, and/or longer LOS in our study population: lung cancer, acute myeloid leukemia, diabetes mellitus with complications, schizophrenia, acute myocardial infarction, cerebral infarction, and pneumonia.

2.3. Derivation of weights for mortality scores

We fitted multilevel models that were generalized linear mixed models (GLMMs) with logit link functions incorporating hospital codes as random-effects. The fixed-effects of the model included sex, age strata (18–19, 5-year intervals from 20 to 99, and 100–), and dichotomous variables indicating disease conditions that composing the Charlson and Elixhauser comorbidity measures, and the combined comorbidities used to develop Gagne's combined comorbidity score (hereinafter referred to as CC, EC, and GC, respectively). The dependent variables were the dichotomous variables indicating in-hospital deaths.

The number of comorbid conditions modeled by Gagne et al. to derive the weights for their combined comorbidity score was 33, which were coded according to Romano's adaptation of the Charlson index [8]. In our study, we used a coding algorithm for ICD-10 codes, which is based on Deyo's adaptation of the Charlson index [15]. As the definitions of "hemiplegia or paraplegia" in CC

and “paralysis” in EC were the same according to this algorithm, the number of GC was reduced to 32 in our study.

The weights were assigned by dividing each regression coefficient by 0.3 and rounding it to the nearest integer [16]. Thus, 1 point corresponds to a 35% increase in the probability of in-hospital death. We adopted the median values of 1,000 bootstrapped resamples as regression coefficients for weights, because some conditions, such as AIDS/HIV and drug abuse, have an extremely low prevalence in the Japanese population; the regression coefficients thus might differ considerably among samples.

2.4. Derivation of weights for expenditure scores

Several models have been suggested to model skewed healthcare-related data [17-20]. In this study, we adopted a generalized linear model (GLM) with a gamma distribution having a logarithmic link function, which has proven to be one of the most reliable models for healthcare costs [20]. The dependent variable for the model was hospital charges, and the independent variables were the same as those in the models for predicting in-hospital mortality. Since the regression coefficient values of expenditure models were smaller than those of mortality models, the weights were calculated by multiplying each regression coefficient by 10 and rounding to the nearest integer [21].

2.5. Validation of scores

Comorbidity scores were calculated by summing up the derived weights of comorbid conditions that each individual had. We validated (1) 3 newly adapted scores for mortality calculated using the weights derived from the models incorporating the CC, EC, and GC, (2) 3 new scores for expenditure, (3) 3 preexisting scores, which were the CCI, Elixhauser/van Walraven index, and Gagne’s combined comorbidity score, and (4) 3 sets of binary variables indicating the CC, EC, and GC by fitting GLMMs with logit link functions incorporating hospital codes as random-effects. We calculated c-statistics of fitted models as measures to compare their performance.

Similarly, we validated (1) 3 new mortality scores, (2) 3 new expenditure scores, (3) 3 preexisting scores, and (4) 3 sets of variables by fitting GLMs with gamma distributions having logarithmic link functions to predict hospital charges and LOS. We then calculated the explained variances of each model, which were 1 − (deviance of each model / deviance of the null model, which had only an intercept with no independent variables) [12,13].

2.6. Calibration of scores

We calibrated scores by plotting the mean predicted and observed values of the cases with the same scores in the main validation population [22]. A score accounting for less than 0.5% of the population was merged with adjacent score(s).

2.7. Sensitivity analyses

First, we validated our new scores in population during the fiscal year 2014–15, since the maximum number of codable comorbidities of the DPC data changed from 4 to 10 in fiscal year 2016.

Second, in our study population, the proportion of in-hospital mortality was higher for men than for women in all age groups, but the mean hospital charges for men and women crossed at a certain age; hospital charges of men who were below the age were higher, but those of men who were older than that age were lower than those of women (Figure S1 in the supplementary material). For this reason, we added the interaction terms of sex and age strata in the validation models with expenditure scores.

Third, we derived weights for expenditure using linear regression models whose dependent variables were log-transformed hospital charges. This type of model was also one of the most popular models for predicting healthcare costs [3,13,17-20].

Finally, similar to the DRG (Diagnosis Related Group) screening in the Elixhauser comorbidity measures [3], we created sets of indicator variables that ignored the comorbidity category containing the ICD-10 code for the diagnosis causing each hospitalization. For example, if a patient had lung cancer, of which ICD-10 codes was C34.x, in the “cause of admission” field of DPC data, we coded

dummy variables of “any malignancy” in CC or “solid tumor without metastasis” in EC as 0 regardless of having codes for lung cancer in “comorbidity” fields of DPC data. Comorbidity scores were also derived using these sets of “screened” comorbidity variables. We then validated these screened scores and variables in the main validation population and the diagnosis-specific subgroups.

SAS® software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all analyses; PROC GLIMMIX and PROC GENMOD were used to fit GLMMs and GLMs, respectively.

2.8. Ethical considerations

This study was conducted in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labour and Welfare, Japan. The Ethics Committee, Graduate School of Medicine, Kyoto University approved the study (approval number: R0135).

3. Results

3.1. Study population

Table 1 shows the characteristics of the study populations. The number of cases was 2,671,749. Table S1 in the supplementary material shows the number of cases by age strata and cases having each comorbid condition. The most frequent comorbid condition was hypertension (n = 792,422; 29.7%).

3.2. Derivation of weights and calculation of scores

Table 2 presents the regression coefficients, odds ratios, their 95% confidence intervals (CIs), and assigned weight of each comorbid condition. Metastatic cancer was assigned the highest weight for mortality, but that for expenditure was among the lowest. Conversely, the weights for congestive heart failure, paralysis, and AIDS/HIV were high for expenditure but low for mortality. The distributions of the scores for all study populations including subgroups are presented in Table S2 in the supplementary material.

3.3. Validation of scores for in-hospital mortality

Table 3 presents the c-statistics of the models incorporating the scores and binary variables indicating comorbid conditions. The c-statistics of the models using our new mortality scores (0.780–0.794) were almost the same as those of the models using binary variables of corresponding comorbidities (0.781–0.795). The highest c-statistic was obtained from the models incorporating the new mortality score based on the EC (0.795, CI: 0.793–0.797), and sets of variables indicating the EC and the GC (0.795, CI: 0.793–0.798 for both). The new mortality score using the GC also performed well (0.794, CI: 0.792–0.796). These 4 measures outperformed the preexisting scores as well as the new score and the sets of variables indicating the CC (0.781, CI: 0.779–0.783), even after taking the CIs into consideration. The new expenditure scores could not capture comorbidity burdens on mortality; the c-statistics of the models using these scores were not different from the models without comorbidity scores.

3.4. Validation of scores for expenditure

Table 3 presents the explained variances of the validating models for predicting hospital charges and LOS. Unlike the mortality scores, the explained variances of the models incorporating new expenditure scores were considerably lower than those incorporating the variables of corresponding comorbidities for predicting hospital charges, whereas the differences in explained variances were minimal for predicting LOS. Among the scores, the new expenditure scores based on the GC outperformed the preexisting scores and other new scores including the new mortality scores (explained variances: 0.072 vs 0.020–0.069). The models using the set of comorbidity variables showed the same results; those using the GC showed the best results (explained variance: 0.074, CI: 0.072–0.076). Although the expenditure scores were derived from the models having hospital charges as outcome variables, they showed considerably better performance for predicting LOS than scores for mortality; the expenditure scores based on the EC and the GC outperformed other scores including the new

mortality scores (explained variances: 0.088 vs 0.062–0.080).

3.5. Calibration of scores

Figure 1 shows the results of the calibration of preexisting and new scores (Tables S3 and S4 in supplementary material present the corresponding value of each mark in Figure 1). All newly adapted scores indicated better calibration than their predecessors. For mortality, the newly adapted scores using the EC and the GC were calibrated better than those using the CC. The spreads of prediction by the models incorporating the new scores based on the CC, EC, and GC were not considerably different (0.02–0.76, 0.01–0.74, 0.01–0.72, respectively). These prediction values are different from those in Figure 1 because the marks in Figure 1 are the aggregation of scores for extreme values. Although the slopes of the regression lines for the calibration plots of the newly adapted expenditure scores were less than 1 (0.55–0.59), these new scores showed better calibration than the preexisting scores. Among 3 new expenditure scores, the scores based on the EC had the widest spread of prediction (the actual spread, not that in Figure 1; 678,680–6,541,290 Japanese Yen, JPY) and the slope nearest to 1.

3.6. Subgroup analyses

Table S1 in the supplementary material presents the characteristics of the subgroups. Among the subgroups with mixed diagnoses, the "without surgery" group showed the highest proportion of in-hospital death (7.7%), the "with surgery" group showed the highest hospital charges (median: 728,340 JPY), and the "≥ 75 years old" group showed the longest LOS (median: 13 days). For the diagnosis-specific subgroups, the proportion of in-hospital death varied from 1.2% (schizophrenia) to 25.9% (acute myeloid leukemia). The median hospital charges were the highest in the acute myeloid leukemia group (1,985,570 JPY), and the LOS of the schizophrenia group was the longest (median: 45 days).

Table S2 in the supplementary material presents the distributions of comorbidity scores. Both preexisting and new mortality scores of the "without surgery" group were the highest among subgroups

235 of mixed diagnoses, whereas for the new expenditure scores, those of the "≥ 75 years old" group were
236 the highest. Among the diagnosis-specific subgroups, the pneumonia group showed the highest
237 mortality scores, and the acute myocardial infarction group showed the highest expenditure scores.

238 Among the scores for mortality, the new scores based on the EC showed the highest c-statistics,
239 except for the acute myocardial infarction group; for this subgroup, the model using the new score based
240 on the GC showed the highest c-statistic (Table 4). When used as variables, the models incorporating the
241 variables of the EC and the GC outperformed those of the CC (Table 4).

242 The new expenditure scores based on the GC performed relatively well among the scores for
243 predicting hospital charges and LOS of the subgroup with mixed diagnoses in terms of the explained
244 variance (Table 4). However, performance for the diagnosis-specific subgroups was not satisfactory; the
245 explained variances of the models using the new scores and those incorporating the variables of
246 comorbidities were considerably different. The models having the variables of the GC showed the
247 highest explained variances for most subgroups (Table 4).

248

249 *3.7. Sensitivity analyses*

250 The number of coded comorbid conditions for the population during the fiscal year 2014–15
251 were smaller than that of the main study population; the mean numbers were 2.3 (median: 2) for the
252 2014–15 populations, and 2.8 (median: 3) for the 2016–17 population (Table S1 in the supplementary
253 material). Consequently, the comorbidity scores were lower in the 2014–15 populations (Table S2 in the
254 supplementary material). Although the c-statistics and explained variances were marginally lower than
255 those of the main study population, the new mortality score based on the EC and the expenditure score
256 based on the GC outperformed the others (Table 4). However, the performance of the models using the
257 new score in predicting hospital charges and LOS was considerably lower than that of the models
258 incorporating the variables based on the GC.

259 The influence of the interaction terms for sex and age strata was marginal; the explained
260 variances of the models having the interaction terms were slightly higher in models for predicting LOS,

but they were slightly lower in models for predicting hospital charges (see Table S5 in the supplementary material).

Table S6 in the supplementary material presents the new expenditure scores derived from the linear regression models with log-transformed hospital charges as outcome variables. Table S7 in the supplementary material presents the calculated scores using these weights. The explained variances of the models using these new scores show mixed results. For predicting hospital charges, the explained variances of the models using these scores were almost the same as those of the main analysis. However, for predicting LOS, the models with the new sets of scores performed better than those with the scores of the main analyses (Table S8 in the supplementary material).

Among the diagnoses for subgroups, pneumonia was not included in any set of comorbidities, so the screening made no change. For the main validation population and most diagnosis-specific subgroups, the c-statistics and explained variances were lowered by the screening (Table S9 in the supplementary material).

4. Discussion

In this study, we adapted and validated comorbidity scores to predict in-hospital mortality and hospital charges based on the CC, EC, and GC. In predicting mortality, new scores using the weights derived from the model incorporating the EC and GC showed better discrimination than those incorporating the CC and the preexisting scores. Not only the scores based on EC and GC, but also the models using the sets of comorbidity variables used in EC and GC also outperformed those with the set of comorbidity variables used in CC in terms of c-statistics. Incorporating the results for the subgroups, our results suggest that our new mortality score based on the EC yields the best summarized comorbidity score for predicting mortality.

In predicting hospital charges and LOS, no score was predominant. Although the scores performed worse than the variables, our subgroup analyses showed the expenditure score based on the GC performed better in the subgroup with mixed diagnoses than those with specific diagnoses. This

suggests that the best strategy to measure comorbidity burdens for models with skewed healthcare data would be to use 32 binary variables indicating the GC; our new expenditure score based on the GC might be used for the general population, but not for a diagnosis-specific population.

Constantinou et al. proved that each outcome-specific comorbidity score should be used to predict mortality and expenditure [12]. Our results were in line with theirs; the mortality scores could not measure comorbidity burdens thoroughly in predicting hospital charges, and the expenditure scores could not measure them in predicting mortality. Also, our results suggested the expenditure-based scores using the EC and GC could be a better choice for the models predicting LOS as well as hospital charges than any other comorbidity scores for predicting mortality. It indicated that LOS, similar to hospital charges, was related more with resource consumption than mortality risks. Moreover, differences of explained variances between the models using expenditure scores and those using comorbidity variables for predicting LOS were greater than the differences for hospital charges. It implies that the use of outcome-specific comorbidity score is important because the expenditure scores were not sufficiently effective even though hospital charges and LOS were closely related.

Our results showed that the performance of comorbidity scores and variables varied by diagnosis-specific subgroups. The performance was thought to be related with the impacts of comorbidities on each disease and each outcome. For example, the impact of comorbidities on mortality of diabetes might be greater than that of pneumonia. Similarly, the impact on hospital charges of acute myeloid leukemia might be greater than that of lung cancer. Not only the impact of comorbidities as a whole, but that of each comorbidity on each outcome varied. For example, because the impact of metastatic cancer on hospital charge of patients with lung cancer was greater than that of patients with other diseases, the explained variance of the model using original Gagne's score was higher than our new expenditure score based on Gagne's comorbidity conditions. This might be due to the difference in weights for metastatic cancer of these two scores, which were 5 for original score and 1 for new score.

In calculating the weights for mortality, some comorbid conditions assigned negative weights. In previous studies, hypertension was one such condition, which was considered a coding bias; seriously

ill patients may have more severe comorbid conditions than hypertension, so having hypertension as a coded comorbidity might mean the patient is relatively healthy [3,5,8,11]. For our study populations, peptic ulcers and obesity, as well as hypertension, were assigned negative weights for mortality.

The performance of model for hospital charges and LOS incorporating the interaction terms of age and sex did not change consistently. Although the interaction terms showed statistically significant effects on outcomes, the regression coefficients of them were minimized since the men had more comorbidities than women in most of the age strata. However, the impact of the interaction might be larger for other study populations. To predict hospital charges and LOS, it should be investigated whether the relationship between these outcomes and age differs between females and males.

This study has some limitations. First, we used the DPC database, an administrative database, for the study; the number of diagnoses for comorbid conditions was limited. A previous study reported that the limited number of diagnoses in the Japanese data underestimated the prevalence of comorbidities [23]. The maximum number of diagnoses of comorbidities increased in 2016 from 4 to 10, but our results showed that the mean number only increased by 0.5. Second, we validated new scores using only the DPC data; external validity should therefore be evaluated for different populations. Third, we validated new scores as continuous variables. Categorizing them or using restricted cubic spline regression [24] might improve performance.

Despite these limitations, this study is the first to adapt and validate various comorbidity measures including new and preexisting measures including the Charlson, Elixhauser, and Gagne's measures for a Japanese population using a large inpatient database. Our results imply that our new outcome-specific scores and the sets of variables based on the EC and GC should be considered for future studies to measure comorbidity burdens.

5. Conclusion

In predicting in-hospital mortality, the newly adapted mortality score based on the Elixhauser Comorbidities outperformed others in most situations and showed the broadest range of prediction. In

predicting hospital charges and LOS, the model incorporating the set of binary variables indicating the Combined Comorbidities showed the best results. Although no scores were predominant for these outcomes, the newly adapted expenditure score using the Combined Comorbidities showed the best results among scores for predicting hospital charges and LOS of the general population. The outcome-specific comorbidity scores should be considered for the different outcomes of mortality and expenditure.

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TABLE 1. Characteristics of the study populations

	All		Adaptation		Validation	
Number of cases (number of hospitals)	2,671,749	(324)	1,870,225	(324)	801,524	(324)
Male	1,421,042	(53.2%)	995,252	(53.2%)	425,790	(53.1%)
Age (years)	69.7	± 16.5	69.7	± 16.5	69.7	± 16.6
	73	(62, 82)	73	(62, 82)	73	(62, 82)
Length of hospital stay (day)	17.6	± 27.9	17.5	± 27.9	17.6	± 27.8
	10	(5, 20)	10	(5, 20)	10	(5, 20)
Costs data missing	49,364	(1.8%)	34,652	(1.9%)	14,712	(1.8%)
Hospital charges (Japanese Yen)	938,559	± 1,207,600	937,502	± 1,183,765	941,344	± 1,261,529
	579,690	(293,550, 1,151,440)	579,240	(293,380, 1,151,090)	581,045	(294,270, 1,152,765)
Surgery during the admission	1,385,927	(51.9%)	969,617	(51.8%)	416,305	(51.9%)
Emergency admission	1,480,170	(55.4%)	1,036,598	(55.4%)	443,572	(55.3%)
In-hospital mortality	133,518	(5.0%)	93,330	(5.0%)	40,188	(5.0%)
Comorbidities						
Number of coded conditions	2.8	± 2.2	2.8	± 2.2	2.8	± 2.2
	3	(1, 4)	3	(1, 4)	3	(1, 4)
Charlson comorbidity index	1.1	± 1.7	1.1	± 1.7	1.1	± 1.7
	1	(0, 2)	1	(0, 2)	1	(0, 2)
Elixhauser/van Walraven index	3.0	± 4.8	3.0	± 4.8	3.0	± 4.8
	0	(0, 5)	0	(0, 5)	0	(0, 5)
Gagne's combined comorbidity score	0.7	± 1.5	0.7	± 1.5	0.7	± 1.5
	0	(0, 1)	0	(0, 1)	0	(0, 1)

Values are presented as mean ± standard deviation and median (1st quartile, 3rd quartile) for continuous variables, and *n* (%) for categorical variables.

TABLE 2. Regression coefficients, odds ratios, and derived weights for each comorbid condition

Charlson comorbidities

Comorbid condition	Charlson comorbidity index	Mortality				Expenditure		
		Regression coefficient*	Odds ratio (95% CI)		New weight for mortality	Regression coefficient† (95% CI)		New weight for expenditure
Myocardial infarction	1	0.1162	1.12	(1.07, 1.18)	0	0.1647	(0.1517, 0.1775)	2
Congestive heart failure	1	0.4236	1.53	(1.50, 1.56)	1	0.3503	(0.3439, 0.3569)	4
Peripheral vascular disease	1	0.0544	1.06	(1.00, 1.11)	0	0.2613	(0.2476, 0.2748)	3
Cerebrovascular disease	1	0.1660	1.18	(1.15, 1.21)	1	0.2070	(0.2001, 0.2129)	2
Dementia	1	0.2195	1.25	(1.22, 1.28)	1	0.0878	(0.0813, 0.0936)	1
Chronic pulmonary disease	1	0.1370	1.15	(1.11, 1.17)	0	0.0272	(0.0197, 0.0341)	0
Rheumatic disease	1	0.2179	1.24	(1.17, 1.33)	1	0.1514	(0.1379, 0.1658)	2
Peptic ulcer disease	1	-0.4189	0.66	(0.64, 0.68)	-1	0.1370	(0.1282, 0.1448)	1
Mild liver disease	1	0.2769	1.32	(1.26, 1.37)	1	0.0399	(0.0309, 0.0486)	0
Diabetes without chronic complication	1	-0.0969	0.91	(0.89, 0.93)	0	0.1666	(0.1619, 0.1718)	2
Diabetes with chronic complication	2	-0.0964	0.91	(0.88, 0.94)	0	0.0904	(0.0806, 0.0991)	1
Hemiplegia or paraplegia	2	0.1868	1.21	(1.12, 1.30)	0	0.5228	(0.5040, 0.5417)	5
Renal disease	2	0.5281	1.70	(1.66, 1.74)	2	0.2129	(0.2047, 0.2214)	2
Any malignancy, including lymphoma and leukemia, except for malignant neoplasm of skin	2	0.2999	1.35	(1.32, 1.38)	1	0.0409	(0.0342, 0.0477)	0
Moderate or severe liver disease	3	1.5549	4.73	(4.43, 5.00)	5	-0.0620	(-0.0868, -0.0349)	-1
Metastatic solid tumor	6	2.3602	10.59	(10.36, 10.80)	8	0.1096	(0.1009, 0.1178)	1
AIDS/HIV	6	0.2760	1.32	(0.69, 2.48)	0	0.5304	(0.3173, 0.7389)	5

(continues)

TABLE 2. (continued)
Elixhauser comorbidities

Comorbid condition	Elixhauser/van Walraven index	Mortality				Expenditure		
		Regression coefficient*	Odds ratio (95% CI)		New weight for mortality	Regression coefficient† (95% CI)		New weight for expenditure
Congestive heart failure	7	0.4519	1.57	(1.54, 1.61)	2	0.2891	(0.2825, 0.2957)	3
Cardiac arrhythmias	5	0.1373	1.15	(1.12, 1.17)	0	0.1972	(0.1908, 0.2028)	2
Valvular disease	-1	0.0591	1.06	(1.02, 1.11)	0	0.3459	(0.3343, 0.3580)	3
Pulmonary circulation disorders	4	0.5717	1.77	(1.60, 1.96)	2	0.2372	(0.2089, 0.2646)	2
Peripheral vascular disorders	2	0.1159	1.12	(1.06, 1.18)	0	0.2329	(0.2187, 0.2457)	2
Hypertension	0	-0.5672	0.57	(0.55, 0.57)	-2	0.1743	(0.1707, 0.1780)	2
Paralysis	7	0.2666	1.31	(1.21, 1.40)	1	0.4949	(0.4764, 0.5135)	5
Other neurological disorders	6	0.4851	1.62	(1.57, 1.67)	2	0.3403	(0.3301, 0.3515)	3
Chronic pulmonary disease	3	0.1384	1.15	(1.11, 1.17)	0	0.0200	(0.0125, 0.0266)	0
Diabetes, uncomplicated	0	-0.0248	0.98	(0.95, 0.99)	0	0.1507	(0.1455, 0.1559)	2
Diabetes, complicated	0	-0.0105	0.99	(0.96, 1.02)	0	0.1214	(0.1123, 0.1296)	1
Hypothyroidism	0	-0.0196	0.98	(0.92, 1.05)	0	0.0384	(0.0247, 0.0540)	0
Renal failure	5	0.5549	1.74	(1.70, 1.79)	2	0.1893	(0.1814, 0.1975)	2
Liver disease	11	0.5223	1.69	(1.64, 1.75)	2	0.0255	(0.0168, 0.0342)	0
Peptic ulcer disease excluding bleeding	0	-0.5229	0.59	(0.57, 0.61)	-2	0.1063	(0.0982, 0.1146)	1
AIDS/HIV	0	0.1233	1.13	(0.60, 2.16)	0	0.4917	(0.2752, 0.6994)	5
Lymphoma	9	0.7825	2.19	(1.96, 2.41)	3	0.2289	(0.1946, 0.2636)	2
Metastatic cancer	12	2.4394	11.47	(11.18, 11.73)	8	0.1465	(0.1380, 0.1544)	1
Solid tumor without metastasis	4	0.5990	1.82	(1.78, 1.86)	2	0.0403	(0.0329, 0.0475)	0
Rheumatoid arthritis/collagen vascular diseases	0	0.2157	1.24	(1.18, 1.32)	1	0.1397	(0.1270, 0.1526)	1
Coagulopathy	3	1.4840	4.41	(4.20, 4.74)	5	0.7726	(0.7418, 0.8046)	8
Obesity	-4	-0.3060	0.74	(0.50, 0.87)	-1	0.2889	(0.2576, 0.3241)	3
Weight loss	6	1.2065	3.34	(3.06, 3.63)	4	0.2403	(0.2060, 0.2755)	2
Fluid and electrolyte disorders	5	0.5366	1.71	(1.66, 1.76)	2	-0.0859	(-0.0936, -0.0786)	-1
Blood loss anemia	-2	0.3045	1.36	(1.24, 1.48)	1	0.1658	(0.1426, 0.1894)	2
Deficiency anemia	-2	-0.1014	0.90	(0.86, 0.95)	0	0.1899	(0.1806, 0.1988)	2
Alcohol abuse	0	0.1754	1.19	(1.12, 1.30)	1	-0.0447	(-0.0628, -0.0260)	0
Drug abuse	-7	0.3044	1.36	(0.67, 2.18)	1	0.0677	(-0.0536, 0.1996)	1
Psychoses	0	0.2358	1.27	(1.20, 1.33)	1	0.1768	(0.1606, 0.1940)	2
Depression	-3	-0.1438	0.87	(0.81, 0.93)	0	0.0887	(0.0750, 0.1008)	1

(continues)

TABLE 2. (continued)
Gagne's combined comorbidities

Comorbid condition	Gagne's combined comorbidity score	Mortality				Expenditure		
		Regression coefficient*	Odds ratio (95% CI)		New weight for mortality	Regression coefficient† (95% CI)		New weight for expenditure
Myocardial infarction‡	0	0.1889	1.21	(1.16, 1.27)	1	0.1252	(0.1123, 0.1379)	1
Cerebrovascular disease‡	0	0.1901	1.21	(1.18, 1.24)	1	0.1671	(0.1604, 0.1726)	2
Dementia‡	2	0.1800	1.20	(1.17, 1.22)	1	0.0764	(0.0698, 0.0826)	1
Peptic ulcer disease‡	0	-0.3743	0.69	(0.67, 0.71)	-1	0.1219	(0.1134, 0.1295)	1
Any malignancy, including lymphoma and leukemia, except for malignant neoplasm of skin‡	1	0.2952	1.34	(1.31, 1.37)	1	0.0506	(0.0441, 0.0573)	1
Congestive heart failure§	2	0.4389	1.55	(1.52, 1.59)	1	0.2878	(0.2813, 0.2945)	3
Cardiac arrhythmias§	0	0.1303	1.14	(1.11, 1.17)	0	0.1924	(0.1859, 0.1981)	2
Valvular disease§	0	0.0621	1.06	(1.02, 1.11)	0	0.3456	(0.3341, 0.3579)	3
Pulmonary circulation disorders§	2	0.5787	1.78	(1.61, 1.98)	2	0.2404	(0.2117, 0.2681)	2
Peripheral vascular disorders§	1	0.1040	1.11	(1.05, 1.16)	0	0.2258	(0.2119, 0.2390)	2
Hypertension§	-1	-0.5803	0.56	(0.55, 0.57)	-2	0.1623	(0.1587, 0.1660)	2
Paralysis ‖	0	0.2218	1.25	(1.16, 1.34)	1	0.4703	(0.4516, 0.4887)	5
Other neurological disorders§	0	0.4425	1.56	(1.50, 1.60)	1	0.3186	(0.3084, 0.3298)	3
Chronic pulmonary disease ‖	1	0.1474	1.16	(1.12, 1.18)	0	0.0208	(0.0134, 0.0274)	0
Diabetes, uncomplicated§	0	-0.0273	0.97	(0.95, 0.99)	0	0.1466	(0.1415, 0.1518)	1
Diabetes, complicated§	1	-0.0197	0.98	(0.95, 1.01)	0	0.1133	(0.1045, 0.1217)	1
Hypothyroidism§	0	-0.0161	0.98	(0.92, 1.05)	0	0.0375	(0.0235, 0.0529)	0
Renal failure§	2	0.5513	1.74	(1.70, 1.79)	2	0.1880	(0.1801, 0.1963)	2
Liver disease§	1	0.5493	1.73	(1.68, 1.79)	2	0.0298	(0.0212, 0.0386)	0
AIDS/HIV ‖	-1	0.1228	1.13	(0.58, 2.16)	0	0.4952	(0.2796, 0.7025)	5
Metastatic cancer ‖	5	2.3359	10.34	(10.10, 10.58)	8	0.1428	(0.1344, 0.1510)	1
Rheumatoid arthritis/collagen vascular diseases§	0	0.2164	1.24	(1.18, 1.32)	1	0.1432	(0.1305, 0.1562)	1
Coagulopathy§	1	1.4912	4.44	(4.23, 4.76)	5	0.7750	(0.7440, 0.8063)	8
Obesity§	0	-0.2932	0.75	(0.50, 0.88)	-1	0.2939	(0.2625, 0.3289)	3
Weight loss§	2	1.2062	3.34	(3.06, 3.63)	4	0.2328	(0.1987, 0.2661)	2
Fluid and electrolyte disorders§	1	0.5327	1.70	(1.66, 1.75)	2	-0.0914	(-0.0989, -0.0841)	-1
Blood loss anemia§	0	0.3214	1.38	(1.26, 1.50)	1	0.1628	(0.1396, 0.1863)	2
Deficiency anemia§	1	-0.0884	0.92	(0.87, 0.96)	0	0.1911	(0.1817, 0.2000)	2
Alcohol abuse§	1	0.1692	1.18	(1.11, 1.30)	1	-0.0448	(-0.0626, -0.0261)	0
Drug abuse§	0	0.3041	1.36	(0.66, 2.23)	1	0.0703	(-0.0496, 0.2011)	1
Psychoses§	1	0.2084	1.23	(1.16, 1.29)	1	0.1686	(0.1527, 0.1864)	2
Depression§	0	-0.1486	0.86	(0.81, 0.93)	0	0.0852	(0.0714, 0.0973)	1

Abbreviation: CI, confidence interval.
Regression coefficients are the median of 1,000 bootstrapped resamples.
Confidence intervals are the 2.5 and 97.5 percentiles of 1,000 bootstrapped resamples.
*Derived from generalized linear mixed models with in-hospital mortality as dependent variables and hospital codes as random-effects.
†Derived from generalized linear models with gamma distributions having log link functions; dependent variables of the models are hospital charges.
‡Charlson/Deyo' s definition is used.
§Elixhauser's definition is used.
‖Charlson/Deyo's and Elixhauser's definitions are the same.

TABLE 3. C-statistics and explained variances of the validation models with preexisting comorbidity scores, new scores, and variables indicating comorbid conditions for predicting in-hospital mortality, hospital charges, and length of hospital stay

	C-statistic (95% CI)		Explained variance* (95% CI)			
	In-hospital mortality		Hospital charges		Length of hospital stay	
Sex and age strata only	0.704	(0.701 to 0.706)	0.019	(0.018 to 0.020)	0.054	(0.052 to 0.055)
plus comorbidity score for mortality						
Charlson comorbidity index	0.772	(0.770 to 0.775)	0.030	(0.029 to 0.031)	0.075	(0.073 to 0.076)
Elixhauser/van Walraven index	0.769	(0.767 to 0.771)	0.033	(0.031 to 0.034)	0.071	(0.069 to 0.072)
Gagne's combined comorbidity score	0.783	(0.781 to 0.786)	0.026	(0.025 to 0.027)	0.069	(0.068 to 0.071)
New mortality score based on Charlson's	0.780	(0.778 to 0.782)	0.022	(0.021 to 0.023)	0.064	(0.063 to 0.066)
New mortality score based on Elixhauser's	0.795	(0.793 to 0.797)	0.020	(0.019 to 0.021)	0.062	(0.061 to 0.064)
New mortality score based on Gagne's	0.794	(0.792 to 0.796)	0.020	(0.019 to 0.021)	0.064	(0.062 to 0.065)
plus comorbidity score for expenditure						
New expenditure score based on Charlson's	0.705	(0.703 to 0.708)	0.049	(0.047 to 0.050)	0.074	(0.072 to 0.076)
New expenditure score based on Elixhauser's	0.704	(0.701 to 0.706)	0.069	(0.067 to 0.071)	0.080	(0.079 to 0.082)
New expenditure score based on Gagne's	0.704	(0.701 to 0.707)	0.072	(0.070 to 0.074)	0.088	(0.086 to 0.089)
plus comorbidities as indicator variables						
Charlson’s	0.781	(0.779 to 0.783)	0.049	(0.048 to 0.051)	0.087	(0.085 to 0.089)
Elixhauser’s	0.795	(0.793 to 0.798)	0.070	(0.068 to 0.072)	0.098	(0.096 to 0.100)
Gagne’s	0.795	(0.793 to 0.798)	0.074	(0.072 to 0.076)	0.107	(0.105 to 0.109)

Abbreviation: CI, confidence interval.
Values are presented as the mean (2.5th to 97.5th quartile) of 1,000 bootstrapped resamples.
*Explained variance = 1 − (deviance of each model / deviance of the null model, which has only an intercept with no independent variables).
“Charlson’s” and “Elixhauser’s” refer to the comorbid conditions composing Charlson and Elixhauser comorbidity measures, respectively.
“Gagne’s” refers to the comorbid conditions incorporated to derive weights for the Gagne’s combined comorbidity score.

TABLE 4. C-statistics and explained variances of the validation models with preexisting comorbidity scores, new scores, and the variables indicating comorbid conditions

C-statistics of the model predicting in-hospital mortality

			C-statistic								
				Plus comorbidity scores						Plus comorbidity variables	
	N	In-hospital mortality	Sex and age strata only	Charlson comorbidity index	Elixhauser/ van Walraven index	Gagne's combined comorbidity score	New mortality score based on Charlson's	New mortality score based on Elixhauser's	New mortality score based on Gagne's	Charlson's	Elixhauser's	Gagne's
Validation population	801,524	5.0%	0.704	0.772	0.769	0.783	0.780	**0.795**	0.794	0.781	**0.795**	**0.795**
Fiscal years of 2014–2015	3,353,159	5.0%	0.697	0.768	0.766	0.779	0.775	**0.790**	0.789	0.776	**0.791**	0.790
Subgroups												
With surgery	1,385,922	2.5%	0.699	0.778	0.783	0.792	0.776	**0.796**	0.795	0.784	0.807	**0.810**
Without surgery	1,285,827	7.7%	0.688	0.743	0.736	0.753	0.757	**0.771**	0.769	0.759	**0.774**	0.773
≥ 75 years old	1,221,649	7.5%	0.645	0.698	0.700	0.713	0.707	**0.728**	0.727	0.709	0.729	**0.729**
Lung cancer	34,563	21.5%	0.764	0.789	0.787	0.796	0.795	**0.801**	0.801	0.798	**0.807**	**0.807**
Acute myeloid leukemia	2,952	25.9%	0.751	0.751	0.752	0.756	0.752	**0.763**	0.762	0.758	**0.776**	**0.776**
Diabetes mellitus with complications	21,286	1.6%	0.853	0.864	0.865	0.876	0.864	**0.882**	0.881	0.878	**0.890**	**0.890**
Schizophrenia	1,984	1.2%	0.801	0.798	0.800	0.807	0.801	**0.822**	0.818	0.838	0.862	**0.864**
Acute myocardial infarction	20,942	7.2%	0.731	0.734	0.748	0.767	0.746	0.796	**0.803**	0.763	0.826	**0.827**
Cerebral infarction	76,689	5.1%	0.724	0.747	0.759	0.768	0.757	**0.774**	0.770	0.765	0.788	**0.790**
Pneumonia	94,052	9.7%	0.682	0.694	0.696	0.706	0.705	**0.722**	0.718	0.714	**0.730**	**0.730**

(continues)

TABLE 4. (Continued)
Explained variance* of the model predicting hospital costs

			Explained variance									
				Plus comorbidity scores						Plus comorbidity variables		
	N	Mean hospital charges (Japanese Yen)	Sex and age strata only	Charlson comorbidity index	Elixhauser/ van Walraven index	Gagne's combined comorbidity score	New expenditure score based on Charlson's	New expenditure score based on Elixhauser's	New expenditure score based on Gagne's	Charlson's	Elixhauser's	Gagne's
Validation population	786,812	579,240	0.019	0.030	0.033	0.026	0.049	0.069	**0.072**	0.049	0.070	**0.074**
Fiscal years of 2014–2015	3,302,413	559,630	0.019	0.030	0.032	0.026	0.045	**0.067**	**0.067**	0.050	0.075	**0.079**
Subgroups												
With surgery	1,362,638	728,340	0.019	0.052	0.058	0.041	0.080	0.114	**0.124**	0.086	0.125	**0.133**
Without surgery	1,259,747	476,450	0.045	0.051	0.052	0.049	0.057	0.064	**0.066**	0.062	0.072	**0.075**
≥ 75 years old	1,208,096	648,730	0.001	0.009	0.011	0.007	0.021	**0.036**	**0.036**	0.024	0.039	**0.042**
Lung cancer	27,395	935,635	0.011	0.017	0.016	**0.019**	0.011	0.011	0.012	0.026	0.030	**0.031**
Acute myeloid leukemia	2,946	1,985,570	0.138	0.138	0.138	0.138	0.138	**0.140**	0.139	0.152	0.156	**0.157**
Diabetes mellitus with complications	20,684	524,420	0.021	**0.067**	0.028	0.064	0.054	0.031	0.027	0.108	0.120	**0.123**
Schizophrenia	1,978	1,034,055	0.034	0.035	**0.038**	0.035	0.035	**0.038**	0.037	0.047	**0.056**	0.054
Acute myocardial infarction	20,763	1,837,700	0.016	0.028	0.036	**0.041**	0.039	0.034	0.033	0.051	0.074	**0.084**
Cerebral infarction	75,853	976,300	0.008	0.016	0.019	0.017	0.019	0.015	**0.021**	0.026	0.028	**0.039**
Pneumonia	92,739	522,240	0.046	0.053	0.056	**0.061**	0.058	0.058	0.060	0.065	0.079	**0.084**

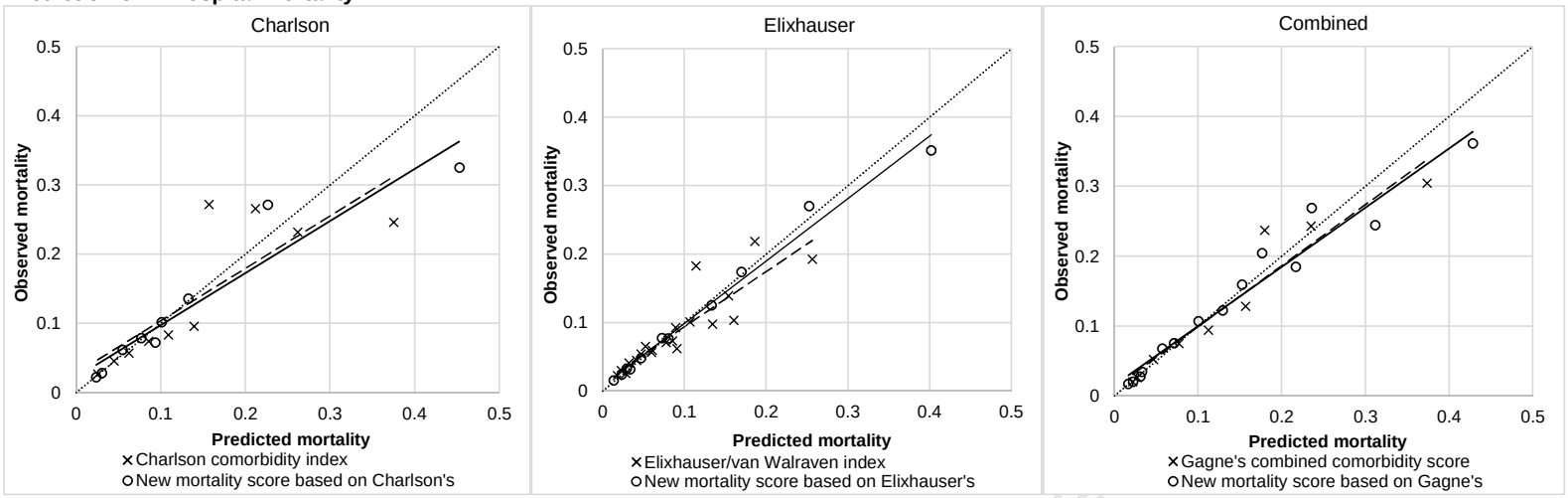
(continues)

TABLE 4. (Continued)
Explained variance* of the model predicting length of hospital stay

			Explained variance									
				Plus comorbidity scores						Plus comorbidity variables		
	N	Mean length of hospital stay (day)	Sex and age strata only	Charlson comorbidity index	Elixhauser/ van Walraven index	Gagne's combined comorbidity score	New expenditure score based on Charlson's	New expenditure score based on Elixhauser's	New expenditure score based on Gagne's	Charlson's	Elixhauser's	Gagne's
Validation population	801,524	10	0.054	0.075	0.071	0.069	0.074	0.080	**0.088**	0.087	0.098	**0.107**
Fiscal years of 2014–2015	3,353,159	10	0.045	0.066	0.062	0.059	0.060	0.065	**0.068**	0.077	0.089	**0.097**
Subgroups												
With surgery	1,385,922	8	0.050	0.093	0.083	0.082	0.084	0.096	**0.108**	0.109	0.131	**0.146**
Without surgery	1,285,827	12	0.056	0.060	0.060	0.059	0.064	0.066	**0.069**	0.070	0.076	**0.080**
≥ 75 years old	1,221,649	13	0.012	0.027	0.024	0.025	0.026	0.027	**0.030**	0.038	0.040	**0.051**
Lung cancer	34,563	14	0.007	0.041	0.036	**0.043**	0.021	0.013	0.015	0.046	0.050	**0.053**
Acute myeloid leukemia	2,952	31	0.064	**0.067**	0.065	0.064	0.066	0.065	0.065	0.081	0.085	**0.087**
Diabetes mellitus with complications	21,286	15	0.038	**0.070**	0.042	**0.070**	0.058	0.043	0.043	0.097	0.100	**0.106**
Schizophrenia	1,984	45	0.038	0.039	0.044	0.042	0.039	**0.048**	0.046	0.049	**0.070**	0.069
Acute myocardial infarction	20,942	14	0.046	0.079	0.086	**0.096**	0.085	0.072	0.077	0.097	0.118	**0.126**
Cerebral infarction	76,689	19	0.017	0.021	0.022	**0.024**	0.021	0.019	0.020	0.025	0.032	**0.034**
Pneumonia	94,052	13	0.064	0.070	0.070	**0.075**	0.072	0.069	0.072	0.080	0.088	**0.096**

The values in bold indicate the best values of c-statistics and explained variances among the models using scores and among the models using the variables indicating comorbid conditions.
*Explained variance = 1 − (deviance of each model / deviance of the null model, which has only an intercept with no independent variables).
"Charlson's" and "Elixhauser's" refer to the comorbid conditions composing the Charlson and Elixhauser comorbidity measures, respectively.
"Gagne's" refers to the comorbid conditions incorporated to derive weights for the Gagne's combined comorbidity score.

Prediction of in-hospital mortality



Prediction of hospital charges

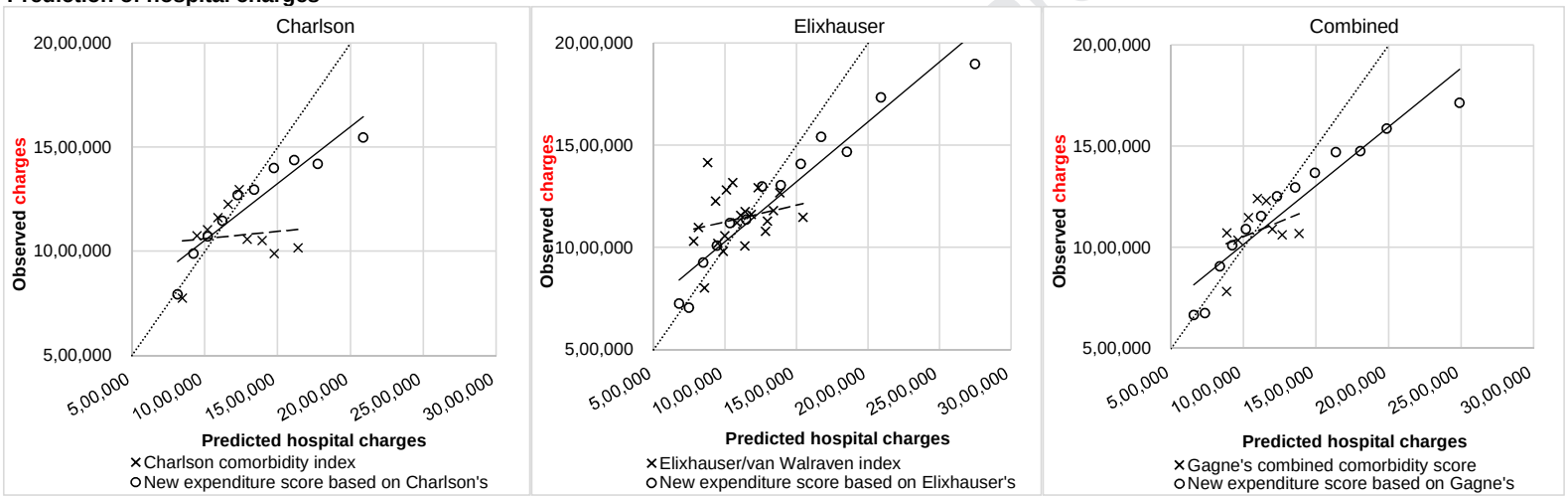


FIGURE 1. Calibration of models with preexisting comorbidity scores and new scores for predicting in-hospital mortality and hospital charges in Japanese Yen for the validation population.

Each mark represents a certain score value, where the value of the x-axis and the y-axis is the mean of the predicted and observed values for patients with the corresponding score, respectively.

Solid lines are the regression lines for the marks of new scores, and broken lines are the regression lines for the marks of preexisting scores. Dotted lines have slopes of 1, which means perfect calibration; a regression line with a slope more similar to that of the dotted line is considered better calibrated.

“Charlson’s” and “Elixhauser’s” refer to the comorbid conditions composing Charlson and Elixhauser comorbidity measures, respectively.

“Gagne’s” refers to the comorbid conditions incorporated to derive weights for the Gagne’s combined comorbidity score.

What is new?

Key findings

- The comorbidity scores using the new weights derived from a Japanese inpatient database outperformed previous measures.
- The comorbidity scores developed for predicting mortality could not adjust comorbidity burdens thoroughly in models for predicting hospital charges and length of hospital stay.

What this adds to what is known?

- The weights composing comorbidity scores were not acceptable universally; for different study populations and outcomes, researchers should consider updating them or adopting the newer weights available.

What is the implication and what should change now?

- Researchers should consider using the newer comorbidity measures with better predictability for future studies.
- For studies to predict healthcare charges and LOS, researchers should consider using the comorbidity scores that were developed for predicting such outcomes, or the binary variables indicating comorbidities.

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