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ORIGINAL COMMUNICATION

Heterogeneity in costs and prognosis for acute ischemic stroke treatment by comorbidities

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Abstract

Objective Comorbidities are prevalent among stroke patients. The current study assesses the variations in cost and stroke prognosis by concurrent comorbidities in patients with acute ischemic stroke.

Methods The Charlson comorbidity index was used as the composite comorbidity level (0 none, 1 mild, 2 moderate, and ≥3 severe). Outcomes included modified Rankin Scale (mRS) at 3 months and 1-year mortality and stroke recurrence. We utilized a multivariate log-normal model for cost, a proportional Cox hazards model for outcomes, and a decision analytic model for the excess cost per unit change in outcome probability compared with the no-comorbidity group.

Results A total of 3605 consecutive patients were enrolled. At 3 months, the severe comorbidity group was 0.32 times less likely to have mRS ≤ 2, and were 4.86 times more likely to die from stroke than the no-comorbidity group. Within 1 year, the severe comorbidity group showed 10.36 and 3.38 times higher likelihoods of death from stroke and stroke recurrence than the no-comorbidity group. The incremental cost was 4376 in 3 months and 7074 USD in 1 year for the severe comorbidity group, and 985 in 3 months and 1265 USD in 1 year for the mild comorbidity group compared to the no-comorbidity group.

Conclusion The excess cost per unit increase of a short-term good prognosis was largest for the severe comorbidity group. Patients with severe comorbidities showed poor prognosis and large health expenditure. Assessing comorbidity level is crucial for better prediction of outcomes and excess cost.

Keywords Comorbidity · Excess cost · Prognosis · Ischemic stroke · Heterogeneity

Introduction

Stroke is one of the most common causes of death and disability-adjusted life years [1]. Approximately 6.7 million people died worldwide due to stroke in 2012, making it the second most fatal disease after ischemic heart disease [1]. The burden of stroke is not only due to death, but also to disability [2]. Most strokes occur in the elderly. Age constitutes a well-known prognostic factor for stroke [3, 4], and older people are more likely to have multiple comorbidities [5–7]. Various comorbidities have been reported as **r**isk and prognostic factors in patients with ischemic stroke [3, 8, 9]. Chronic comorbidities, including cancer, are also common among stroke patients [10, 11]. Patients with cancer or similar burdensome diseases are assumed to be prone to death or poor intermediate or long-term prognosis regardless of the occurrence of stroke. Therefore, assessing the composite impact of multiple morbidities on the prognosis for stroke would improve the predictability of stroke treatment and its cost.

Euna Han and Tae Hyun Kim contributed equally to this work as the first authors.

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A scientific statement released in 2016 by the American Stroke Association noted for the first time that the safety and efficacy of standard care for ischemic stroke may vary due to comorbidity [12]. However, no specific recommendation regarding the treatment guidelines for patients with comorbidities was provided due to a lack of scientific evidence [2]. The current study fills this gap in the literature by assessing variations in the cost and effectiveness of stroke prognosis by a composite comorbidity status for patients with acute ischemic stroke. We determined the excess cost per unit change in the probability of outcome for a given comorbidity level compared to a status of no-comorbidity.

Materials and methods

Data

Subjects for this study were consecutive patients with acute ischemic stroke who were registered from January 2007 to June 2013 at the Yonsei Stroke Registry, a retrospective hospital-based registry for who were diagnosed with cerebral infarction or transient ischemic attack within 7 days of the onset of symptoms [13]. During admission, the medical history, clinical manifestations, and presence of vascular risk factors were thoroughly investigated.

Variables

Clinical outcomes

Initial stroke severity was determined by National Institutes of Health Stroke Scale (NIHSS) scores and score tertiles (0–4, 5–11, and ≥ 12) to represent mild, moderate, severe stroke [14–18]. Surviving patients were followed through outpatient clinic attendance or by a structured telephonic interview at 3 months and every year after discharge. Functional outcomes were determined based on modified Rankin Scale (mRS). Major adverse cardiovascular events included stroke recurrence, myocardial infarction, and death. The date and cause of death during the study period were confirmed by matching information in the death records from the Korean National Statistical Office. The causes of death were coded according to the International Classification of Disease, 10th revision (ICD-10). Cardiovascular death included fatal stroke (I60–64) and fatal ischemic heart disease caused by myocardial infarction (I21–23, I46) [19].

Post-stroke mRS is recommended for measuring the extent of functional outcome within 90 days from stroke onset [20–22]. The short-term outcomes were measured as prognosis at 3 months from initial stroke occurrence as a series of following dummy indicators: mRS ≤ 2 for a good prognosis; mRS between 3 and 5 for a poor, but not fatal outcome; and, mRS 6 for fatal status. The long-term outcomes included 1-year mortality with and without relation to stroke and nonfatal recurrence of stroke.

Cost

The total healthcare cost for the treatment of acute ischemic stroke was calculated by adding up the following individual cost items:

1. diagnostic tests using a computed tomography scan, magnetic resonance imaging scan, cardiac evaluation, or neurosonographic evaluation;
2. blood and urine tests;
3. inpatient drug therapies relevant to ischemic stroke symptoms;
4. hospitalization for stroke events and long-term medical and rehabilitation care;
5. fees for physician services.

We focused on the variations in cost by comorbidity status from a restricted societal perspective. Therefore, both patients' out-of-pocket expenses and expenses reimbursed by the National Health Insurance Service for acute ischemic stroke were included, but indirect costs, such as loss of productivity, were not considered in this study. All costs are reported in units of US dollars (USD) at 2015, where 1 unit is approximately equal to 1000 Korean Won (KRW), deflated using the Korean price index for healthcare services [23].

Comorbidity

We compared treatment costs and outcomes for acute ischemic stroke by comorbidity level, which was measured with the Charlson comorbidity index (CCI) [24]. CCI was scored using ICD-10 codes and a chart review. Possible stroke-related complications during admission were excluded. Because previous cerebrovascular disease and hemiplegia can overlap, these two comorbidities were aggregated into one. We also aggregated mild liver disease with moderate or severe liver disease because defining the difference is difficult. We utilized four dummy indicators, representing a CCI score of 0 (none), 1 (mild), 2 (moderate), and ≥ 3 (severe).

Model

Multivariate regression model

We applied a multivariate log-normal model for cost and a proportional Cox hazards model for likelihood of outcomes. The log-adjusted cost was retransformed to the unlogged form by applying Duan's smearing estimate, assuming the

non-normal distribution and heterogeneity of the error term by the comorbidity status in the cost estimation [25]. The incremental differences in the adjusted cost and adjusted outcomes for each comorbidity level in comparison with the no-comorbidity group were obtained from the estimates, with standard errors derived from 10,000 bootstrapping.

A rich set of risk factors were adjusted for in all models including followings: (1) patients' demographic characteristics (age in years and gender); (2) dummy indicators for underlying health conditions (hypertension, diabetes mellitus, hypercholesterolemia, and current smoking); (3) a dummy indicator for any complications at the onset of stroke including herniation, intracerebral hemorrhage (either symptomatic or asymptomatic), any infection (including pneumonia, urinary tract infection, sepsis, and other), bleeding other than intracerebral hemorrhage, bed sore, pulmonary embolism, deep vein thrombosis, trauma, and myocardial infarction.

Decision analytic model

We applied a decision analytic model by setting up a 1-year static decision tree to calculate (Fig. 1) to excess cost according to a unit change in the probability of outcome for a given comorbidity level compared to no-comorbidity status. The probability nodes for each comorbidity level were established according to the NIHSS group, for each of which the probability of the end outcome was obtained from data for the current study (Table in S1 Table). The end outcomes were measured both at 3 months and 1 year. The standard errors for the excess cost to outcome ratio were bootstrapped with 10,000 replications.

Ethical approval

The institutional review board of Severance Hospital, Yonsei University Health System, approved this study and waived the patients' informed consent because of a retrospective design and the observational nature of this study (4-2015-1196).

Results

Data distributions

A total of 4105 consecutive patients with acute ischemic stroke or transient ischemic attack were registered during the study period. Excluded patients from this study were those with transient ischemic attack ($n=326$), non-Korean citizens ($n=48$), lost to follow-up ($n=96$), and missing data ($n=30$). A total of 3605 patients were finally enrolled.

Slightly less than two-thirds (73.59%) of the patients had a good prognosis with mRS ≤ 2, and 6.4% patients were deceased at 3 months (mRS = 6). The mortality rate related to stroke increased to 8.1% in 1 year from

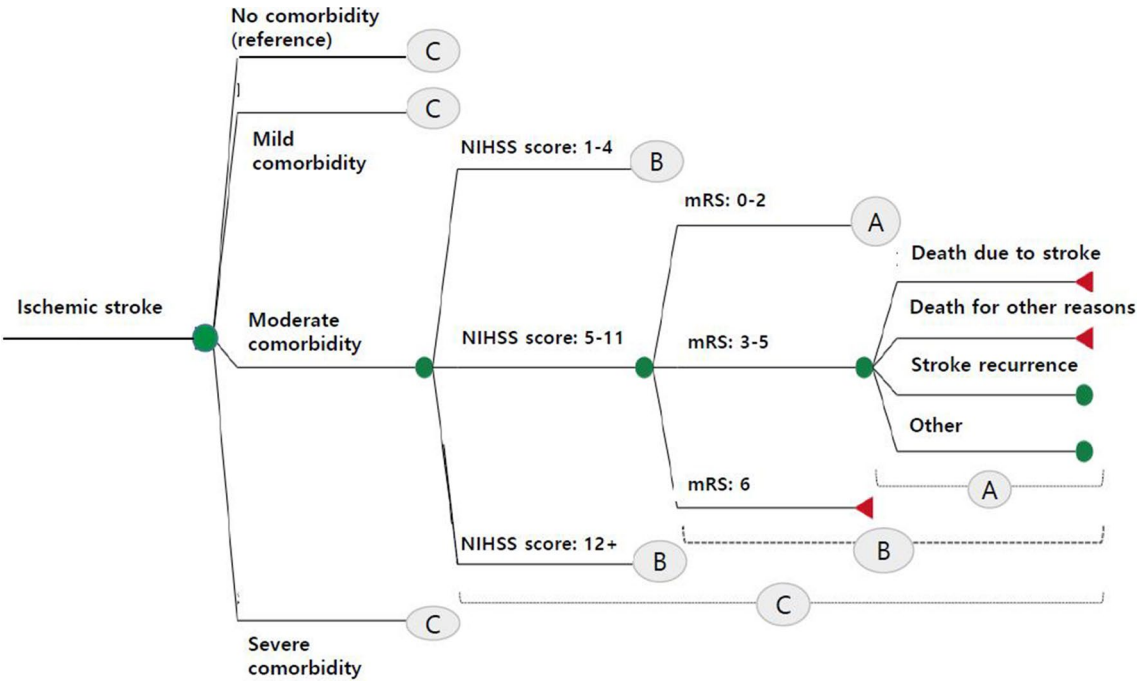

Fig. 1 Decision tree for the decision analytic model. Note: The circle and triangle represent chance node and absorbing outcome, respectively. mRS and NIHSS denote modified Rankin score and National Institutes of Health Stroke Scale, respectively

stroke onset. The nonfatal recurrence of stroke after 1 year occurred in 2.5% of study patients. The total cost during 3 months and after 1 year from admissions due to acute ischemic stroke was 17,116 USD and 18,912 USD, respectively, on average. Approximately 40% of patients had no comorbidities, and approximately 16% had CCI ≥ 3 (Table 1).

Table 1 Data distributions

$n = 3605$	n (%)
Outcomes	
Modified Rankin score (mRS) at 3 months from the stroke index	
0	870 (24.13)
1	1281 (35.53)
2	502 (13.93)
3	226 (6.27)
4	318 (8.82)
5	175 (4.85)
6	233 (6.46)
Outcomes in 3 months	
mRS ≤ 2 (good prognosis)	2653 (73.59)
mRS ≥ 3	952 (26.41)
Death related to stroke	233 (6.46)
Outcomes in 1 year	
Recurrence of stroke	79 (2.50)
Death related to stroke	285 (8.10)
Death unrelated to stroke	74 (2.05)
Cost (unit, USD)	
Total cost 3 months from the index	17,116 (18,747)
Total cost 1 year from the index	18,912 (26,547)
Main independent variable	
Charlson Comorbidity Index at baseline	
0	1466 (40.67)
1	1076 (29.85)
2	467 (12.95)
≥ 3	596 (16.53)
Covariates at baseline	
National Institute of Health Stroke Scale	5.57 (6.27)
0–4	1584 (43.94)
5–12	864 (23.97)
> 6	1157 (32.09)
Hypertension	2676 (74.23)
Hypercholesterolemia	752 (20.88)
Current smoker	851 (23.63)
Subtypes of ischemic stroke	
Large artery atherosclerosis	750 (20.79)
Lacunar infarct	327 (9.07)
Other determined etiology	88 (2.45)
Undetermined etiology because of two or more causes	663 (18.39)
Undetermined etiology because of negative or incomplete evaluation	799 (22.18)
Cardioembolism	978 (27.12)
Thrombolysis	414 (11.48)
Any complications	597 (16.56)
Age	65.90 (12.57)
Male gender	2189 (60.72)

Multivariate Cox proportional hazard model

Patients with severe comorbidities were 0.32 times less likely to have a good prognosis at 3 months from stroke onset (95% CI 0.22–0.45) compared to those without comorbidities. The likelihood of death at 3 months was 4.86 times (95% CI 3.17–7.44) for stroke patients with severe comorbidities, whereas it was 1.76 times (95% CI 1.09–2.84) for those with moderate comorbidities compared with those without comorbidities. Patients with severe comorbidity were 10.36 times (95% CI 5.09–21.07) and 3.89 times (95% CI 2.64–5.73) more likely to die due to stroke and reasons other than stroke, respectively, than those without comorbidities. Recurrent stroke that occurred within 1 year after the initial stroke was 3.38-fold higher (95% CI 1.47–7.77) than those without comorbidities (Table 2).

Multivariate log linear model

A greater total health expenditure was incurred by the higher comorbidity group, compared to the no-comorbidity group in both the short-term (3 months) and long-term (1 year) periods. Compared with patients in the no-comorbidities group, the increment of the severe comorbidity group was 4376 USD in 3 months and 7074 USD in 1 year from stroke occurrence, whereas the marginal increases were 2463 in 3 months and 3407 in 1 year for the moderate comorbidity group, and 985 in 3 months and 1265 USD in 1 year for the mild comorbidity group, respectively (Table 3).

Table 2 The effect of comorbidity on stroke outcomes: multivariate proportional hazards model

Comorbidity level by Charlson Comorbidity Index	Hazards ratio [95% confidence interval]		
	Short-term (3 months) outcomes [$n=3605$]		
	mRS = 1–2	mRS = 3–5	mRS = 6
0 (reference)	–	–	–
1	0.61*** [0.46, 0.80]	1.12 [0.77, 1.63]	1.10 [0.71, 1.70]
2	0.55** [0.39, 0.79]	1.33 [0.95, 1.87]	1.76* [1.09, 2.84]
≥ 3	0.32*** [0.22, 0.45]	1.47** [1.13, 1.91]	4.86*** [3.17, 7.44]
Comorbidity level by Charlson Comorbidity Index	Long-term (1 year) outcomes [$n=3605$]		
	Death unrelated to stroke	Death related to stroke	Nonfatal recurrence of stroke
0 (reference)	–	–	–
1	0.93 [0.63, 1.37]	0.94 [0.43, 2.05]	1.36 [0.71, 2.60]
2	1.47 [0.97, 2.24]	2.85* [1.18, 6.86]	1.67 [0.68, 4.10]
≥ 3	3.89*** [2.64, 5.73]	10.36** [5.09, 21.07]	3.38** [1.47, 7.77]

Covariates adjusted to include the initial NIHSS score at the index of the stroke event, patients' demographic characteristics (age in years and male gender), underlying health conditions, subtypes of ischemic stroke, and a dummy indicator for any complications at the onset of stroke. Details of covariate measurements are given in the text

*$p<0.1$, **$p<0.05$, ***$p<0.01$

Table 3 The effect of comorbidity on total healthcare cost: multivariate log-normal model

Comorbidity level by Charlson Comorbidity Index ($n=3605$)	Dependent variable: total healthcare cost (USD)	
	Coefficient (standard error) [95% confidence interval]	
	Short-term (3 months)	Long-term (1 year)
0 (reference)	–	–
1	985 (298) [400, 1571]	1265 (389) [501, 2028]
2	2463 (455) [1571, 3355]	3407 (613) [2204, 4610]
≥ 3	4376 (561) [3276, 5476]	7074 (794) [5517, 8630]

Covariates adjusted to include the initial NIHSS scores at the index of the stroke event, patients' demographic characteristics (age in years and male gender), underlying health conditions, subtypes of ischemic stroke, and a dummy indicator for any complications at the onset of stroke. Details of covariate measurements are given in the text

*$p<0.1$, **$p<0.05$, ***$p<0.01$

Decision model

Compared to the no-comorbidity group, patients in the severe comorbidity group had the largest excess cost (by 143 USD) per 1% point decrease of mRS 0–2 in the severe comorbidity group at 3 months. In contrast, the mild comorbidity group had the largest excess cost (by 1412 USD) per unit change in the probability of death at 3 months compared with the no-comorbidity group due to small variations in the incremental cost in comparison with the no-comorbidity group, and enormous variations in the incremental probability of mortality at 3 months across CCI levels. The excess cost per unit change in long-term mortality was the lowest for the severe comorbidity group (1051 USD per 1% point increase in mortality). For long-term mortality related to stroke, the severe comorbidity group also had the lowest excess cost (303 USD) per unit change in long-term mortality, despite a higher incremental mortality and higher cost compared with the no-comorbidity counterparts. Excess cost per unit change in long-term recurrence of nonfatal stroke remained relatively similar across comorbidity levels (Table 4).

The results of 10,000 simulations of excess cost and incremental outcome probability for each comorbidity level compared to the no-comorbidity group show a better incremental outcome and lower incremental cost for the lower comorbidity level for all outcomes of interest for 3 months (Fig. 2) and 1 year (Fig. 3). The difference for mortality and stroke recurrence by comorbidity level was apparent in both the short-term and long-term because the incremental cost and outcome were tightly distributed within a given comorbidity level, but were clearly separated across comorbidity levels.

Discussion

Although multi-morbidity in ischemic stroke patients commonly occurs in real clinical settings, guidelines addressing comorbidities are not well established. We demonstrated a relatively poorer prognosis of stroke and a larger total health expenditure for patients with a higher comorbidity level. Patients in the severe comorbidity group were less likely to have a good prognosis and spent larger amounts on healthcare cost in the short-term, compared with patients with no comorbidities in our data. However, we showed that the marginal increase in long-term mortality unrelated to stroke exhibited a greater variation according to comorbidity level than the marginal increase in total cost, which is likely attributable to fatal diseases, such as cancer.

There are no definite guidelines for comorbidities for stroke treatment. Indications for stroke treatment are based on randomized clinical trials with strict exclusion and inclusion criteria for patient selection. Since patients with severe or multi-morbidities are typically excluded in such clinical trials, there is a lack of clinical evidence for an appropriate indication concerning them in the guidelines, despite that such patients are common in the real world [26–28]. Building on the extant literature, we assessed real-world evidence for the comorbidity burden in stroke treatment, exploiting data from a stroke registry based on a large general hospital in Korea. In our study, the onset to admission time was 1.13 days on average (with standard deviation 1.66 days) and median 1.71 days (IQR 0.17–1.5 days). A total of 81.5% patients in the current dataset was admitted within 2 days from the stroke onset. Initial NIHSS score was 6.3 on average (with standard deviation 6.4) and median 3 (IQR 1–7.5), which was very similar to median 3 (IQR 1–8) in the data set of 27,851 patients from a Korean nationwide stroke registry [29].

A handful of previous studies have assessed a series of single comorbidities, such as atrial fibrillation, coronary artery disease, or diabetes, as risk factors for stroke prognosis, particularly for rehabilitation outcomes [30–32]. However, whether multiple comorbidities occurring together affect stroke outcomes is reported rather inconsistently in literature. For example, Turhan [11] used CCI for geriatric patients in Turkey and reported a negative correlation of CCI with rehabilitation outcomes. In contrast, Fischer [33] found that CCI did not have an independent effect on 3-month mRS when other factors, such as age, were adjusted for in a multivariate regression model. Schmidt [10] also reported that severe multi-morbidity (CCI $\geq$ 3) increased both 1-month and 5-year ischemic stroke mortalities by approximately 2.5-fold compared with no comorbidity.

We utilized an aggregate index of comorbidities based on CCI, a well-known standard, to represent the composite comorbidity level [34]. Using such a composite index to classify comorbidities is helpful in assessing the combined effects of multiple comorbidities [22], because stroke patients are likely to have several diseases with potential interactive effects on outcomes. However, we acknowledge that CCI was originally developed to predict the risk of 1-year mortality for patients in longitudinal studies [22]. Further studies on creating a more targeted comorbidity taxonomy for outcomes related to stroke in both the short-term and long-term would advance our understanding of the extent to which comorbidity level alters the outcomes and cost of stroke treatment.

Because multiple comorbidities may prevent a good outcome, our results imply that the decision to administer acute stroke treatments should be more personalized for patients who already have other illnesses and endured the consequent expenses. Our study may be helpful for developing an appropriate and cost-saving treatment protocol for this

Table 4 Excess cost and outcome probabilities for a given comorbidity group compared to the no-comorbidity group in the short- (3 months) and long- (1 year) term

Comorbidity level by Charlson Comorbidity Index (CCI)	Change in cost[a] (USD) (*A*)	Change in probability [a] (% points) (*B*)	Change in cost per unit change in probability (*A*/*B*)
Short-term (3 months) outcomes			
Modified RS = 0–2			
0 (reference)	–	–	–
1	1202 (249)	−8.39 (0.91)	−143 (24)
	[713, 1692]	[−10.18, −6.61]	[−190, −95]
2	1912 (361)	−14.63 (1.26)	−130 (20)
	[1204, 2621]	[317.11, −12.15]	[−170, −90]
≥3	4317 (390)	−20.87 (1.13)	−207 (16)
	[3550, 5084]	[−239, −174]	[−239, −174]
mRS = 3–5			
0 (reference)	–	–	–
CCI = 1	18 (113)	7.60 (0.72)	2 (15)
	[−204, 241]	[6.17, 9.02]	[−27, 32]
CCI = 2	833 (203)	10.19 (0.95)	81 (21)
	[435, 1232]	[9.32, 12.06]	[38, 124]
CCI ≥ 3	2253 (193)	7.74 (0.65)	290 (35)
	[1873, 2632]	[6.45, 9.03]	[220, 361]
mRS = 6			
0 (reference)	–	–	–
CCI = 1	1124 (154)	0.79 (0.17)	1412 (257)
	[821, 1428]	[0.44, 1.14]	[907, 1918]
CCI = 2	1857 (213)	4.44 (0.28)	418 (38)
	[1439, 2276]	[3.87, 5.00]	[342, 493]
CCI ≥ 3	2703 (231)	13.13 (0.51)	205 (17)
	[2248, 3157]	[12.12, 14.13]	[171, 240]
Long-term (1 year)			
Death not related to stroke			
0 (reference)	–	–	–
CCI = 1	1844 (194)	0.02 (0.06)	77,400 (4,248,801)
	[1462, 2227]	[−0.09, 0.13]	[−8,255,141, 8,409,942]
CCI = 2	3373 (220)	2.12 (0.12)	1591 (85)
	[2942, 3805]	[1.88, 2.35]	[1422, 1759]
CCI ≥ 3	6538 (52)	6.12 (0.22)	1051 (52)
	[948, 1154]	[5.68, 6.56]	[948, 1154]
Death related to stroke			
0 (reference)	–	–	–
CCI = 1	1981 (214)	0.59 (0.77)	3334 (126,000)
	[1559, 2402]	[−0.92, 2.11]	[−24,600, 24,700]
CCI = 2	3311 (282)	5.57 (1.32)	594 (235)
	[2756, 3866]	[2.97, 8.17]	[132, 1055]
CCI ≥ 3	4804 (404)	15.83 (1.45)	303 (48)
	[4011, 5596]	[12.94, 18.72]	[208, 398]
Nonfatal stroke recurrence			
0 (reference)	–	–	–
CCI = 1	1910 (213)	0.90 (0.04)	2102 (288)
	[1491, 2329]	[0.83, 0.98]	[1535, 2668]
CCI = 2	3851 (239)	1.18 (0.11)	3251 (281)
	[3381, 4322]	[0.96, 1.40]	[2699, 3803]
CCI ≥ 3	6638 (410)	2.56 (0.08)	2592 (189)
	[5834, 7443]	[2.38, 2.73]	[2220, 2964]

[a]No-comorbidity group (i.e., CCI = 0) is the comparison group in all calculations. Standard errors are in parentheses and 95% confidence intervals are in brackets

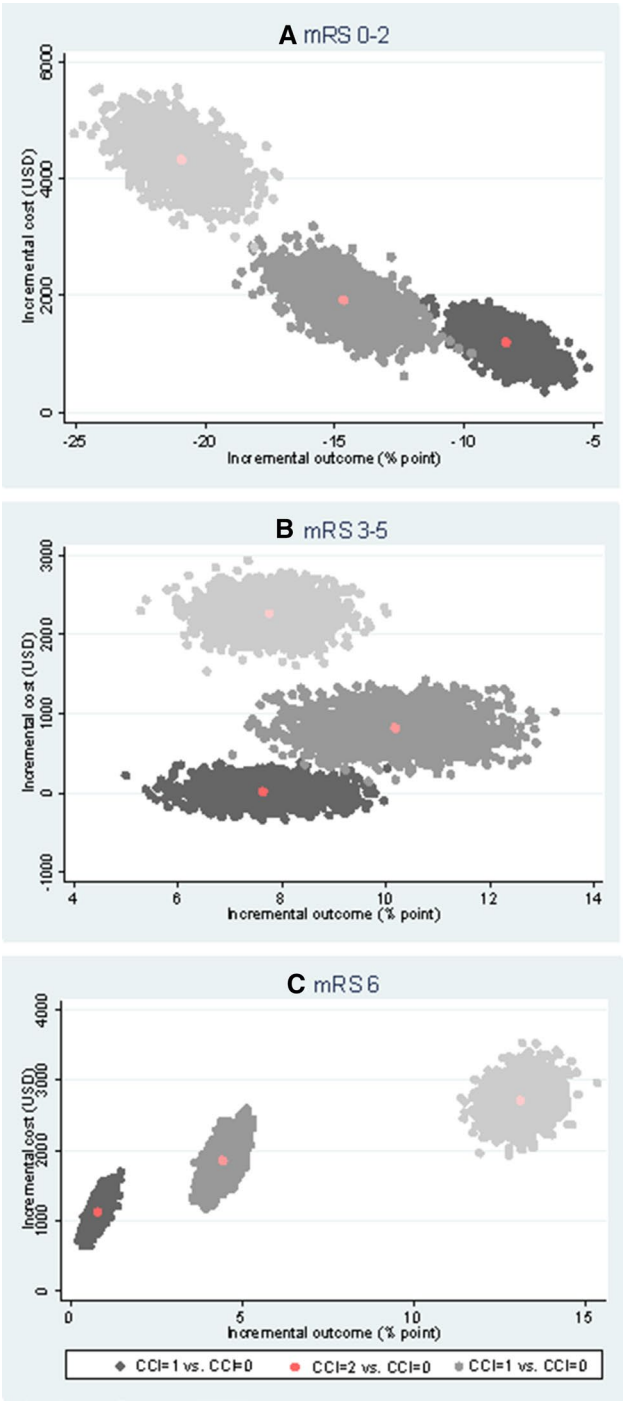

Fig. 2 Results of bootstrapping of extra cost and incremental probability of outcome by comorbidity level for short-term (3 months). *CCI* Charlson Comorbidity Index. *mRS* modified Rankin score. The *Y* axis represents incremental cost in USD, and the *x*-axis represents the incremental percent change in outcome probability for a given comorbidity level in comparison with the no-comorbidity group

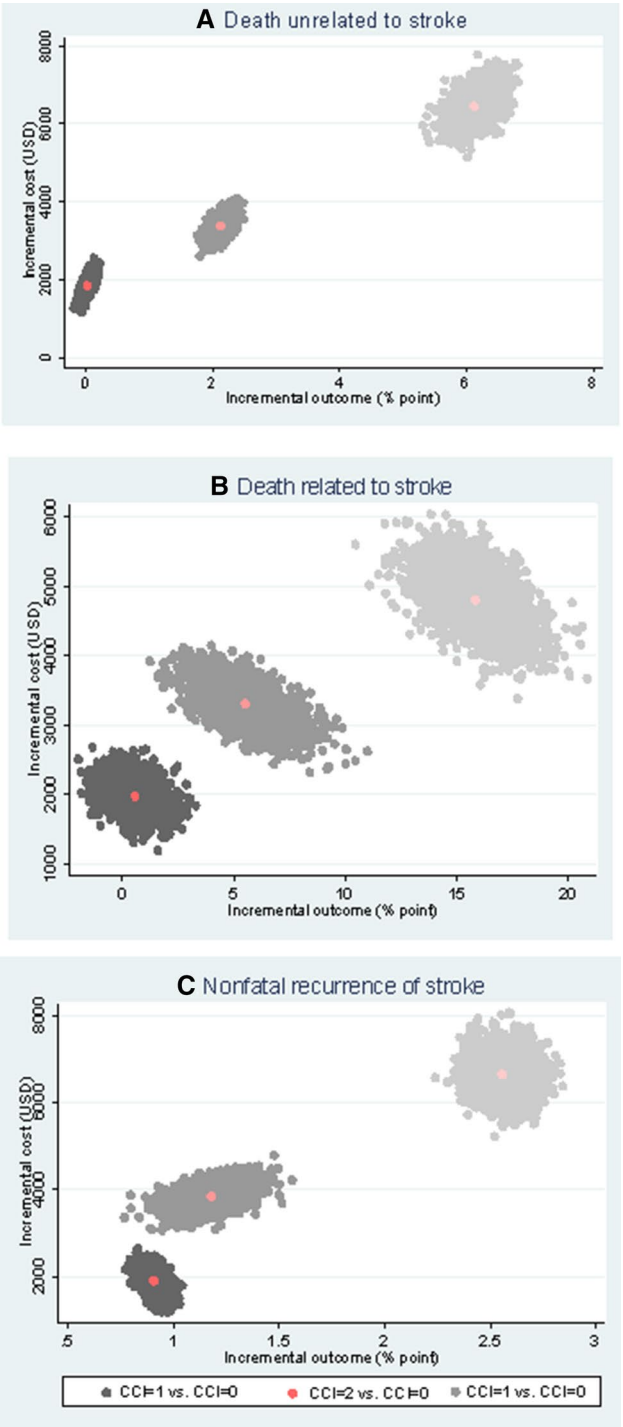

Fig. 3 Results of bootstrapping of extra cost and incremental probability of outcome by comorbidity level for long-term (1 year). *CCI* Charlson Comorbidity Index. *mRS* modified Rankin score. The *Y* axis represents incremental cost in USD, and the *x*-axis represents the incremental percent change in outcome probability for a given comorbidity level in comparison with the no-comorbidity group

purpose. Future study needs to identify patients who potentially have a poor prognosis, despite receiving various stroke treatments.

Conclusions

Our findings indicate that there is a relatively poorer prognosis for stroke and a larger total health expenditure for patients with a higher comorbidity, yielding the largest excess cost among patients in the severe comorbidity group, particularly in the short-term period.

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Compliance with ethical standards

Conflicts of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical standards The institutional review board of Severance Hospital, Yonsei University Health System, approved this study and waived the patients' informed consent because of a retrospective design and the observational nature of this study (4-2015-1196).

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