EMJ Online First, published on February 28, 2013 as 10.1136/emermed-2012-202058

OPEN ACCESS

Mortality and morbidity after high-dose methylprednisolone treatment in patients with acute cervical spinal cord injury: a propensity-matched analysis using a nationwide administrative database

Hirotaka Chikuda,[1] Hideo Yasunaga,[2] Katsushi Takeshita,[1] Hiromasa Horiguchi,[2] Hiroshi Kawaguchi,[1] Kazuhiko Ohe,[3] Kiyohide Fushimi,[4] Sakae Tanaka[1]

[1]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, Tokyo, Japan
[2]Department of Health Management and Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[3]Department of Medical Informatics and Economics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[4]Department of Health Care Informatics, Tokyo Medical and Dental University, Tokyo, Japan

Correspondence to
Dr Hirotaka Chikuda, Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; chikuda-tky@umin.ac.jp

Received 8 October 2012
Revised 18 December 2012
Accepted 19 December 2012

To cite: Chikuda H, Yasunaga H, Takeshita K, *et al*. *Emerg Med J* Published Online First: [*please include* Day Month Year] doi:10.1136/emermed-2012-202058

ABSTRACT

Objective To examine the magnitude of the adverse impact of high-dose methylprednisolone treatment in patients with acute cervical spinal cord injury (SCI).

Methods We examined the abstracted data from the Japanese Diagnosis Procedure Combination database, and included patients with ICD-10 code S141 who were admitted on an emergency basis between 1 July and 31 December in 2007–2009. The investigation evaluated the patients' sex, age, comorbidities, Japan Coma Scale, hospital volume and the amount of methylprednisolone administered. One-to-one propensity-score matching between high-dose methylprednisolone group (>5000 mg) and control group was performed to compare the rates of in-hospital death and major complications (sepsis; pneumonia; urinary tract infection; gastrointestinal ulcer/bleeding; and pulmonary embolism).

Results We identified 3508 cervical SCI patients (2652 men and 856 women; mean age, 60.8±18.7 years) including 824 (23.5%) patients who received high-dose methylprednisolone. A propensity-matched analysis with 824 pairs of patients showed a significant increase in the occurrence of gastrointestinal ulcer/bleeding (68/812 vs 31/812; p<0.001) in the high-dose methylprednisolone group. Overall, the high-dose methylprednisolone group demonstrated a significantly higher risk of complications (144/812 vs 96/812;OR, 1.66; 95% CI 1.23 to 2.24; p=0.001) than the control group. There was no significant difference in in-hospital mortality between the high-dose methylprednisolone group and the control group (p=0.884).

Conclusions Patients receiving high-dose methylprednisolone had a significantly increased risk of major complications, in particular, gastrointestinal ulcer/bleeding. However, high-dose methylprednisolone treatment was not associated with any increase in mortality.

INTRODUCTION

Methylprednisolone is one of the most investigated agents for its neuroprotective potential, and remains the only drug used worldwide for acute spinal cord injury (SCI). The beneficial effect of high-dose methylprednisolone was initially reported in a series of National Acute Spinal Cord Injury Studies (NASCIS) in the 1990s.[1 2] Specifically, NASCIS-2 compared 24 h of high-dose methylprednisolone (given as a bolus of 30 mg/kg over 15 min followed by a continuous infusion of 5.4 mg/kg/h) with placebo in acute SCI patients.[1] Patients receiving methylprednisolone within 8 h of injury were reported to have greater neurologic improvement at 6 months. Results of NASCIS-3 further indicated slightly more recovery following 48 h of treatment than after 24 h.[2] Following publication of the NASCIS trials, the regimen of these trials was rapidly adopted worldwide; however, subsequent debate over the efficacy and safety of high-dose methylprednisolone treatment[3–5] has led to serious differences of opinion in the medical community, and considerable variations in current practice.[6–9]

According to a recent Cochrane review,[10] NASCIS-2 showed a weak trend towards an increase in complications, including wound infection (OR 2.11; 95% CI 0.81 to 5.49) and gastrointestinal haemorrhage (OR 1.48; 95% CI 0.48 to 4.56). The high-dose methylprednisolone group showed slightly lower 180-day mortality than the control group (7/162 vs 12/171; OR 0.62 95% CI 0.25 to 1.53). On the other hand, NASCIS-3, comparing 24 h and 48 h methylprednisolone administration, found a trend towards increased rates of severe pneumonia (OR 2.25; 95% CI 0.71 to 7.15) and sepsis (OR 4.00; 95% CI 0.45 to 35.38) in the 48 h treatment group. Mortality was not significantly different between the two groups.

Although many studies following the NASCIS trials reported a trend toward increased complications after high-dose methylprednisolone treatment,[11–15] the magnitude of its negative impact remains unclear. The reported incidence of complications after high-dose methylprednisolone administration varied greatly between studies, primarily because of small sample sizes and bias in selection of the study population. In addition, it is unknown whether high-dose methylprednisolone negatively affects the survival of SCI patients. Despite widespread use of this treatment, information from high-level evidence about the risks associated with high-dose methylprednisolone administration is lacking. We therefore conducted a retrospective observational study based on a propensity score-matched analysis of data from a nationwide administrative database to examine the risk of high-dose methylprednisolone treatment after acute cervical SCI.

METHODS

Diagnosis Procedure Combination database

The Diagnosis Procedure Combination (DPC) is a case-mix patient classification system which was

launched in 2002 by the Ministry of Health, Labour and Welfare of Japan, and was linked with a lump-sum payment system.[16] All 82 university teaching hospitals are obliged to adopt this system, but adoption by community hospitals is voluntary. The survey in the participating hospitals is conducted between 1 July and 31 December each year by the DPC research group, in collaboration with the Ministry of Health, Labour and Welfare. In 2009, the number of participating hospitals was 818 and the number of patients included was 2.57 million, which represented approximately 40% of all inpatient admissions to acute care hospitals in Japan. The database includes administrative claims data and the following data: unique identifiers of hospitals; patient age and sex; diagnoses, comorbidities at admission and complications after admission recorded with text data in the Japanese language and the International Classification of Diseases, 10th Revision (ICD-10) codes; consciousness level at admission measured with the Japan Coma Scale (JCS; see Appendix); discharge status; and drugs administered.[17] In the DPC database, complications that occur after admission are clearly differentiated from comorbidities that already present at admission. To optimise the accuracy of the recorded diagnoses, physicians in charge are obliged to record the diagnoses with reference to medical charts. Because of the anonymous nature of the data, informed consent was waived when this study was approved by the institutional review board at The University of Tokyo.

Patient selection and data

Using the DPC database, we identified patients who had an emergency admission to the participating hospitals with a diagnosis of cervical SCI (ICD-10 code, S141) between July and December, 2007–2009. Patients who were transferred from other hospitals were excluded. Although we were unable to confirm the presence of a neurological deficit in each patient, miscoding is relatively unlikely because the DPC data are coded by physicians and subjected to an audit. The list of drugs used during hospitalisation was reviewed for each patient, and we identified patients who started high-dose methylprednisolone treatment for acute cervical SCI at admission and received a total of ≥5000 mg methylprednisolone infusion. In Japan, many elderly patients who sustain a cervical SCI are lean. For a 40 kg person, the total dosage amounted to 6168 mg in the NASCIS-2 protocol. Therefore, we set a cut-off value of 5000 mg. As a control group, we identified cervical SCI patients who did not receive methylprednisolone, or those who received less than 500 mg methylprednisolone during hospitalisation. We selected this cut-off value according to the definition of 'high-dose' adopted by Sauerland *et al*[18] (>15 mg/kg (600 mg for a 40 kg person) or >1000 mg).

We assessed patient background, including age, sex, JCS score and Charlson Comorbidity Index (CCI). JCS 0 indicates patients with alert consciousness; JCS one-digit codes (1–3) indicate patients who are drowsy but awake without any stimuli; JCS two-digit codes (10–30) indicate patients with somnolence who can be aroused with some stimuli; JCS three-digit codes (100–300) indicate coma.[19] The JCS and the Glasgow Coma Scale assessments are well correlated. The CCI is a prognostic index as a means for quantifying the prognosis of patients enrolled in a large cohort, and is used widely to measure the case-mix with administrative data. This index is based on a point scoring system (from 0 to 40) for the presence of specific associated diseases. Quan *et al*[20] provided a validated chart showing how each comorbidity corresponds to a set of ICD-10 codes.[20] Based on Quan's protocol, each ICD-10 code of comorbidity was converted into a score, and was summed for each patient to determine CCI. Hospital volume was defined as the annual number of patients with cervical SCI at each hospital.

Clinical outcomes included in-hospital deaths and major complications (sepsis (ICD-10 codes: A40, A41), respiratory complications (pneumonia (J12-J18), postprocedural respiratory disorders (J95) or respiratory failure (J96)), pulmonary embolism (I26), gastroduodenal ulcer/bleeding (K25, K26), urinary tract infection (N10, N30, N390)).

Statistical analyses

We performed a one-to-one matching of patients in the high-dose methylprednisolone group and the control group on the basis of estimated propensity scores of each patient.[21] The propensity-score approach addresses selection bias that is inherent in retrospective observational studies, where outcomes can reflect a lack of comparability in treatment groups rather than the effects of treatment. This approach tries to construct a randomised experimental-like situation where treatment groups being contrasted are comparable for observing prognostic factors. Application of propensity-score matching involves estimation of the propensity score followed by matching of patients according to their estimated propensity score and comparison of outcomes in matched patients. To estimate the propensity score, we fitted a logistic regression model for the receipt of high-dose methylprednisolone treatment as a function of patient demographic and hospital factors, including age, sex, JCS score, CCI, receipt of cervical spinal surgery and hospital volume. The C-statistic for evaluating the goodness-of-fit was calculated. Each patient in the high-dose methylprednisolone group was matched with a patient in the control group with the closest estimated propensity on the logit scale within a specified range (≤0.6 of the pooled SD of estimated logits) to reduce differences between treatment groups by at least 90%.[21]

Descriptive statistics of the patient population included proportions to describe categorical variables and the median and IQR values to describe continuous variables. The χ^2 test was used to compare categorical data and the Wilcoxon rank sum test to compare continuous variables. Fisher's exact test was used to compare in-hospital mortality and major complication rates between the high-dose methylprednisolone group and the control group. A logistic regression analysis for major in-hospital complications was performed in the propensity score-matched patients to analyse the adjusted effects of various factors, while also adjusting for clustering of patients within hospitals using a generalised estimating equation. The threshold for significance was a p value<0.05. All statistical analyses were conducted using IBM SPSS V.19.0 (IBM SPSS, Armonk, New York, USA).

RESULTS

We identified 3508 cervical SCI patients (2652 men and 856 women; mean±SD age, 60.8±18.7 years) who had an emergency admission direct to the participating hospitals. Among them, we identified 824 (23.4%) patients who received ≥5000 mg methylprednisolone with initiation on the day of admission (high-dose methylprednisolone group). We also identified 2101 patients treated without methylprednisolone, or with <500 mg methylprednisolone during hospitalisation (the control group). By one-to-one propensity-score matching, 812 pairs of the high-dose methylprednisolone and control groups were selected. The C-statistic for goodness-of-fit was 0.630 in the propensity-score model, which suggested a moderately good fit.

Table 1 shows the patient demographics of the unmatched and propensity-matched groups. In the unmatched groups,

Table 1 Patient demographics in unmatched and propensity score-matched groups

	Unmatched group			Propensity-matched group		
	Control (n=2101)	High-dose methyl-prednisolone (n=824)	p Value	Control (n=812)	High-dose methyl-prednisolone (n=812)	p Value
Sex (males, n (%))	1570 (74.7)	645 (78.3)	0.044	650 (80.0)	634 (78.1)	0.329
Age (years, n (%))						
≤59	786 (37.4)	318 (38.6)	0.022	292 (36.0)	313 (38.5)	0.674
60–69	513 (24.4)	219 (26.6)		218 (26.8)	216 (26.6)	
70–79	456 (21.7)	198 (24.0)		213 (26.2)	195 (24.0)	
≥80	346 (16.5)	89 (10.5)		89 (11.0)	88 (10.8)	
Charlson Comorbidity Index (n (%))						
1	1414 (67.3)	456 (55.3)	<0.001	464 (57.1)	456 (56.2)	0.638
2	508 (24.2)	287 (34.8)		279 (34.4)	276 (34.0)	
≥3	179 (8.5)	81 (9.8)		69 (8.5)	80 (9.9)	
Japan Coma Scale at admission (n (%))						
0 (alert)	1811 (86.2)	689 (83.6)	0.085	692 (85.2)	681 (83.9)	0.622
1–3 (drowsy)	200 (9.5)	99 (12.0)		95 (11.7)	97 (11.9)	
10–30 (somnolence)	36 (1.7)	20 (2.4)		15 (1.8)	18 (2.2)	
100–300 (coma)	54 (2.6)	16 (1.9)		10 (1.2)	16 (2.0)	
Cervical spinal surgery	221 (10.5)	189 (22.9)	<0.001	192 (23.6)	178 (21.9)	0.408
Preoperative length of stay (days, median (IQR))	8 (1–17)	8 (1–18)	0.838	8 (2–18)	8 (1–17)	0.683
Use of tracheostomy	55 (2.6)	51 (6.2)	<0.001	38 (4.7)	48 (5.9)	0.268
Hospital volume (per year, median (IQR))	7 (4–12)	8 (4–13)	0.004	7 (4–13)	7.5 (4–13)	0.188

patients who were male, younger, or with higher CCI were more likely to receive high-dose methylprednisolone treatment. The high-dose methylprednisolone patients were admitted to hospitals of significantly higher volume than the control group. The high-dose methylprednisolone group was significantly more likely to receive cervical spinal surgery. After propensity-score matching, patient distributions were closely balanced between the high-dose methylprednisolone and the control groups.

Table 2 shows the in-hospital mortality and major complication rates in the unmatched and propensity-matched groups. Fisher's exact test in the propensity-matched groups showed no significant difference in in-hospital mortality between the high-dose methylprednisolone and control groups (2.8% vs 3.0%, p=0.884). There was a significant difference in gastrointestinal ulcer/bleeding (8.4% vs 3.8%, p=0.001) between the groups. The high-dose methylprednisolone group demonstrated a significantly higher risk of overall major complications than the control group (17.7% vs 11.8%, p=0.001). Table 3 shows the results of logistic regression analysis for the occurrence of major complications. After adjustment for the measured confounders, the high-dose methylprednisolone group was significantly more likely to have major complications than the control group (OR, 1.66; 95% CI 1.23 to 2.24; p=0.001).

DISCUSSION

In this retrospective study using a national administrative database, patients receiving high-dose methylprednisolone after cervical SCI had a significantly higher risk of complications than those without high-dose methylprednisolone treatment. A propensity score-matched analysis revealed an increased risk of gastrointestinal ulcer/bleeding and overall major complications in the high-dose methylprednisolone group. However, high-dose methylprednisolone treatment was not associated with any increase in mortality.

Strengths and weaknesses of the study

The major strength of this study is the large size of our study sample. With a study population of 3508 patients with cervical SCI, the current analysis is the largest to examine risks associated with high-dose methylprednisolone administration. Use of the

Table 2 In-hospital mortality and major complication rates in unmatched and propensity score-matched groups

	Unmatched group			Propensity-matched group		
	Control (n=2101)	High-dose methylprednisolone (n=824)	p Value	Control (n=812)	High-dose methylprednisolone (n=812)	p Value
In-hospital mortality (n (%))	71 (3.4)	23 (2.8)	0.485	24 (3.0)	23 (2.8)	0.884
Major complications (n (%))	191 (9.1)	151 (18.3)	<0.001	96 (11.8)	144 (17.7)	0.001
Respiratory complications	84 (4.0)	53 (6.4)	0.006	39 (4.8)	49 (6.0)	0.324
Urinary tract infection	52 (2.5)	29 (3.5)	0.133	32 (3.9)	29 (3.6)	0.698
Sepsis	16 (0.8)	10 (1.2)	0.273	6 (0.7)	10 (1.2)	0.330
Gastrointestinal ulcer/bleeding	66 (3.1)	71(8.6)	<0.001	31 (3.8)	68 (8.4)	<0.001
Pulmonary embolism	1 (0.05)	4 (0.5)	0.024	1 (0.1)	4 (0.5)	0.218
Length of stay (median (IQR))	16 (6–37)	27 (10–52)	<0.001	23 (8–46)	26 (10–52)	<0.001

Table 3 Logistic regression analysis of the occurrence of major complications in the propensity score-matched groups

	OR	95% CI	p
Treatment			
Control	Reference		
High-dose methylprednisolone	1.66	1.23 to 2.24	0.001
Sex			
Male	Reference		
Female	0.57	0.38 to 0.86	0.007
Age			
≤59	Reference		
60–69	1.49	1.04 to 2.12	0.029
70–79	1.81	1.26 to 2.62	0.002
≥80	2.07	1.27 to 3.39	0.004
Charlson Comorbidity Index			
1	Reference		
2	1.41	1.04 to 1.92	0.027
≥3	1.95	1.26 to 3.02	0.003
Japan Coma Scale at admission			
0 (alert)	Reference		
1–3 (drowsy)	1.51	0.99 to 2.31	0.059
10–30 (somnolence)	1.75	0.74 to 4.09	0.200
100–300 (coma)	4.55	2.06 to 10.06	<0.001
Cervical spinal surgery	1.95	1.44 to 2.64	<0.001
Hospital volume (per year)	1.01	0.99 to 1.03	0.550

DPC database, which covers approximately 40% of all acute hospitalisations in Japan, enabled us to conduct a nationwide investigation. In addition, the propensity score-matched analysis allowed us to evaluate the risks of high-dose methylprednisolone treatment while controlling for confounding variables, an assessment that prior studies have been unable to make.

Certain characteristics of the study subjects warrant mention. First, the mean age of the patients in this study was substantially higher than in other SCI studies, which may be explained by the rapid aging of our society. Currently, the geriatric population (those 65 years of age or older) accounts for approximately 23% of the Japanese population. Second, the surgery rate reported in this study was markedly lower compared with that of North American or European countries. The low surgery rate likely reflects differences in patient demographics and treatment strategy. In Japan, approximately 70% of patients sustain a cervical SCI without bone injury, such as fracture or dislocation (mostly elderly patients), and conservative treatment is recommended for these patients.

Our study has several limitations. First, as is common in studies using administrative data, coded diagnoses and outcomes are less well validated than prospective surveys. A degree of misclassification or under-reporting of outcome might have occurred in this study. Second, the DPC database does not provide important clinical data, such as severity of paralysis (ie, Frankel classification) at admission, patient disability at discharge, and cause of death. We could not confirm whether the administration of methylprednisolone conformed to the NASCIS protocol. Specifically, administrative databases such as the DPC database and National Inpatient Sample provide only limited information on the baseline neurological status, which is one of the most important factors that affect morbidity after SCI. It is possible that the high-dose methylprednisolone group included patients with more severe impairment than the control group, which would have created a bias toward overestimating the adverse effect of the high-dose methylprednisolone. Finally, although propensity-score adjustment is currently recognised as the best analytical approach for retrospective observational data, unmeasured confounders might have caused a hidden selection bias.

Comparison with other studies

Most published studies following the NASCIS trials indicated an increased overall complication rate after high-dose methylprednisolone treatment.[11–15] Regarding specific complications, pneumonia,[11–13 15] infection,[11 12] and gastrointestinal bleeding[13] are the most common complications reported in the literature, in patients receiving high-dose methylprednisolone. However, available evidence on the adverse effects of high-dose methylprednisolone is mixed, with substantial variation in reported incidences, and even conflicting results. There are several studies reporting lower complication rates in high-dose methylprednisolone groups.[22 23] Major drawbacks of these previous studies were small sample size and lack of adjustment for confounding variables, which considerably limits the validity of their conclusion.

In the present study, we first analysed the possible adverse impact of high-dose methylprednisolone treatment in SCI patients using a large nationwide database. We then performed propensity score-matched analysis to adjust for potential confounding factors. High-dose methylprednisolone was associated with a significantly higher risk of complications (17.7% vs 11.8%, $p=0.001$) than control after adjustment for confounding variables. Specifically, we found a significant increase in the occurrence of gastrointestinal ulcer/bleeding (8.4% vs 3.8%, $p<0.001$) in the high-dose methylprednisolone group.

In this study, we observed slightly lower in-hospital mortality in patients receiving high-dose methylprednisolone (2.8% in the methylprednisolone group vs 3.0% in the control group after propensity-score matching). The impact of high-dose methylprednisolone on patient survival remains unclear. The CRASH trial,[24] a randomised trial which examined the efficacy of high-dose methylprednisolone in the treatment of head injury patients, was prematurely terminated because of increased 2-week mortality in the high-dose methylprednisolone group (21.1% vs 17.9%). However, it remains to be determined whether these findings are generalisable to patients sustaining acute SCI. In fact, reported mortalities in SCI patients in the literature have been slightly more favourable in those with high-dose methylprednisolone treatment,[12 15 23] although sample bias played a substantial role. Similarly, a meta-analysis[18] of 51 randomised trials of high-dose methylprednisolone in elective and trauma surgery found reduced mortality compared with controls (1.7% vs 2.7%), although it was not statistically significant. In our propensity score-matched analysis, no significant difference in mortality was observed between the groups in spite of a significant increase in complication rate in patients receiving high-dose methylprednisolone, which may be partly attributable to advances in intensive care and increased physician awareness of steroid-related complications.

Implications for future research

We believe that the findings of our study will provide a basis for future research to re-examine the net benefit of high-dose methylprednisolone treatment described in the NASCIS trials. The main criticism of the NASCIS trials is two-fold: (1) there was no significant difference in the primary comparison; a significant but small benefit (ie, five points in motor score) was found only after posthoc subgroup analysis; (2) there was a trend toward an increase in adverse events, including

pneumonia, infection and gastrointestinal bleeding in patients receiving high-dose methylprednisolone. For the reasons stated above, current guidelines classify this treatment only as a therapeutic 'option', leaving the decision to adopt or avoid this treatment up to individual physicians. Despite the apparent need for a randomised study of better design with sufficient power to examine whether the beneficial effect of high-dose methylprednisolone is reproducible, no such study has been conducted mainly because of ethical and safety concerns. With a dearth of effective alternative therapeutic options, we believe that a strong case exists for a randomised placebo-controlled trial re-examining the potential benefit of high-dose methylprednisolone in patients sustaining SCI. The results of our study showed that high-dose methylprednisolone treatment was not associated with any increase in in-hospital mortality, despite a significant increase in complications, a finding that further justifies future randomised trials in carefully selected patient population. To minimise the heterogeneity of the study population, future trials should focus on patients with incomplete SCI, in whom a beneficial effect was observed in the NASCIS trial. According to an estimate by the International Campaign for Cures of Spinal Cord Injury Paralysis,[25] it would require about 450 subjects with incomplete motor cervical SCI in each arm of the study to show a statistically significant difference of five American Spinal Injury Association motor points between the experimental and control groups. It would clearly require a multi-institution collaboration to carry out this project.

CONCLUSION

Despite controversies lingering for more than two decades since the publication of the NASCIS trial, risks and benefits of high-dose methylprednisolone treatment remain unclear with limited high-level evidence. In this study, we focused on safety concerns of high-dose methylprednisolone treatment, and first clarified the magnitude of its adverse impact by using a large nationwide database. There was a significantly increased risk of major complications, in particular, gastrointestinal ulcer/bleeding, with high-dose methylprednisolone, but no increase in in-hospital mortality. We believe that the findings of our study provides critical information on the risks associated with high-dose methylprednisolone administration in patients with SCI, and thus, may help physicians make a more informed decision on the use of this highly controversial treatment.

Contributors HC, HY, KT, HK and ST contributed to the conception and design of the study. HH, KO, KF contributed to the analysis, and all authors contributed to the interpretation. HC drafted the article; all authors revised it critically for important intellectual content and approved the final version submitted for publication. HC is the guarantor. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding This study was funded by a Grant-in-Aid for Research on Policy Planning and Evaluation from the Ministry of Health, Labour and Welfare, Japan (Grant number: H22-Policy-031), by a Grant-in-Aid for Research on Intractable Diseases from the Ministry of Health, Labour and Welfare, Japan (Grant number: H23-Nanchi-032), by a Grant-in-Aid for Scientific Research B (No. 22390131) from the Ministry of Education, Culture, Sports, Science and Technology, and by the Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST programme) from the Council for Science and Technology Policy, Japan (Grant number: 0301002001001). The researchers were independent from the funders. Sponsors played no role in the study design; the collection, analysis, and interpretation of data; the writing of the article; or the decision to submit it for publication.

Competing interests All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) none has company support for the submitted work; (2) the authors have no relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouse, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) the authors have no non-financial interests that may be relevant to the submitted work.

Ethics approval The Institutional Review Board at The University of Tokyo approved the study.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Bracken MB, Shepard MJ, Collins WF, *et al*. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Eng J Med* 1990;322:1405–11.
2 Bracken MB, Shepard MJ, Holford TR, *et al*. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA* 1997;277:1597–604.
3 Sayer FT, Kronvall E, Nilsson OG. Methylprednisolone treatment in acute spinal cord injury: the myth challenged through a structured analysis of published literature. *Spine J* 2006;6:335–43.
4 Hurlbert RJ. The role of steroids in acute spinal cord injury: an evidence-based analysis. *Spine (Phila Pa 1976)* 2001:S39–46.
5 Short DJ, El Masry WS, Jones PW. High dose methylprednisolone in the management of acute spinal cord injury—a systematic review from a clinical perspective. *Spinal Cord* 2000;38:273–86.
6 Eck JC, Nachtigall D, Humphreys SC, *et al*. Questionnaire survey of spine surgeons on the use of methylprednisolone for acute spinal cord injury. *Spine (Phila Pa 1976)* 2006;31:E250–3.
7 Frampton AE, Eynon CA. High dose methylprednisolone in the immediate management of acute, blunt spinal cord injury: what is the current practice in emergency departments, spinal units, and neurosurgical units in the UK? *Emerg Med J* 2006;23:550–3.
8 Molloy S, Price M, Casey AT. Questionnaire survey of the views of the delegates at the European Cervical Spine Research Society meeting on the administration of methylprednisolone for acute traumatic spinal cord injury. *Spine (Phila Pa 1976)* 2001;26:E562–4.
9 Rozet I. Methylprednisolone in acute spinal cord injury: is there any other ethical choice? *J Neurosurg Anesthesiol* 2008;20:137–9.
10 Bracken MB. Steroids for acute spinal cord injury. *Cochrane Database Syst Rev* 2012;1:CD001046.
11 Ito Y, Sugimoto Y, Tomioka M, *et al*. Does high dose methylprednisolone sodium succinate really improve neurological status in patient with acute cervical cord injury?: a prospective study about neurological recovery and early complications. *Spine (Phila Pa 1976)* 2009;34:2121–4.
12 Suberviola B, González-Castro A, Llorca J, *et al*. Early complications of high-dose methylprednisolone in acute spinal cord injury patients. *Injury* 2008;39:748–52.
13 Matsumoto T, Tamaki T, Kawakami M, *et al*. Early complications of high-dose methylprednisolone sodium succinate treatment in the follow-up of acute cervical spinal cord injury. *Spine (Phila Pa 1976)* 2001;26:426–30.
14 Pointillart V, Petitjean ME, Wiart L, *et al*. Pharmacological therapy of spinal cord injury during the acute phase. *Spinal Cord* 2000;38:71–6.
15 Gerndt SJ, Rodriguez JL, Pawlik JW, *et al*. Consequences of high-dose steroid therapy for acute spinal cord injury. *J Trauma* 1997;42:279–84.
16 Matsuda S, Ishikawa K, Kuwabara K, *et al*. Development and use of the Japanese case-mix system. *Eurohealth* 2008;14:27–30.
17 Chikuda H, Yasunaga H, Horiguchi H, *et al*. Mortality and morbidity in dialysis-dependent patients undergoing spinal surgery: analysis of a national administrative database in Japan. *J Bone Joint Surg Am* 2012;94:433–8.
18 Sauerland S, Nagelschmidt M, Mallmann P, *et al*. Risks and benefits of preoperative high dose methylprednisolone in surgical patients: a systematic review. *Drug Saf* 2000;23:449–61.
19 Ono K, Wada K, Takahara T, *et al*. Indications for computed tomography in patients with mild head injury. *Neurol Med-Chir* 2007;47:291–7.
20 Quan H, Sundararajan V, Halfon P, *et al*. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130–9.
21 Ayanian JZ, Landrum MB, Guadagnoli E, *et al*. Specialty of ambulatory care physicians and mortality among elderly patients after myocardial infarction. *N Engl J Med* 2002;347:1678–86.

22 Tsutsumi S, Ueta T, Shiba K, *et al*. Effects of the Second National Acute Spinal Cord Injury Study of high-dose methylprednisolone therapy on acute cervical spinal cord injury-results in spinal injuries center. *Spine (Phila Pa 1976)* 2006;31:2992–6.
23 George ER, Scholten DJ, Buechler CM, *et al*. Failure of methylprednisolone to improve the outcome of spinal cord injuries. *Am Surg* 1995;61:659–63.
24 Roberts I, Yates D, Sandercock P, *et al*. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet* 2004;364:1321–8.
25 Fawcett JW, Curt A, Steeves JD, *et al*. Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials. *Spinal Cord* 2007;45:190–205.

Appendix Japan Coma Scale for grading of impaired consciousness[19]

Grade	Consciousness level
1-digit code	The patient is awake without any stimuli, and is:
1	Almost fully conscious
2	Unable to recognise time, place and person
3	Unable to recall name or date of birth
2-digit code	The patient can be aroused (then reverts to previous state after cessation of stimulation):
10	Easily by being spoken to (or is responsive with purposeful movements, phrases, or words)*
20	With loud voice or shaking of shoulders (or is almost always responsive to very simple words like yes or no, or to movements)*
30	Only by repeated mechanical stimuli
3-digit code	The patient cannot be aroused with any forceful mechanical stimuli, and:
100	Responds with movements to avoid the stimulus
200	Responds with slight movements including decerebrate and decorticate posture
300	Does not respond at all except for change of respiratory rhythm

'R' and 'I' are added to the grade to indicate restlessness and incontinence of urine and faeces, respectively: for example; 100-R and 30-RI.
*Criteria in parentheses are used in patients who cannot open their eyes for any reason.

Mortality and morbidity after high-dose methylprednisolone treatment in patients with acute cervical spinal cord injury: a propensity-matched analysis using a nationwide administrative database

Hirotaka Chikuda, Hideo Yasunaga, Katsushi Takeshita, et al.

Emerg Med J published online February 28, 2013
doi: 10.1136/emermed-2012-202058

Topic Collections

Articles on similar topics can be found in the following collections

Open access (38 articles)
Spinal cord (22 articles)
Spinal cord injury (17 articles)
Trauma (949 articles)
Trauma CNS / PNS (265 articles)
Coma and raised intracranial pressure (147 articles)
Pneumonia (infectious disease) (66 articles)
Pneumonia (respiratory medicine) (55 articles)
Pulmonary embolism (88 articles)
TB and other respiratory infections (141 articles)
Urinary tract infections (23 articles)
Urinary tract infections (23 articles)
Venous thromboembolism (131 articles)

Notes

Chikuda et al. BMC Musculoskeletal Disorders 2013, 14:173
http://www.biomedcentral.com/1471-2474/14/173

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

Impact of age and comorbidity burden on mortality and major complications in older adults undergoing orthopaedic surgery: an analysis using the Japanese diagnosis procedure combination database

Hirotaka Chikuda[1*], Hideo Yasunaga[2], Hiromasa Horiguchi[2], Katsushi Takeshita[1], Shurei Sugita[1], Shuji Taketomi[1], Kiyohide Fushimi[3] and Sakae Tanaka[1]

Abstract

Background: The purpose of this study was to examine how complications in older adults undergoing orthopaedic surgery vary as a function of age, comorbidity, and type of surgical procedure.

Methods: We abstracted data from the Japanese Diagnosis Procedure Combination database for all patients aged ≥ 50 who had undergone cervical laminoplasty, lumbar decompression, lumbar arthrodesis, or primary total knee arthroplasty (TKA) between July 1 and December 31 in the years 2007 to 2010. Outcome measures included all-cause in-hospital mortality and incidence of major complications. We analyzed the effects of age, sex, comorbidities, and type of surgical procedure on outcomes. Charlson comorbidity index was used to identify and summarize patients' comorbid burden.

Results: A total of 107,104 patients were identified who underwent cervical laminoplasty (16,020 patients), lumbar decompression (31,605), lumbar arthrodesis (18,419), or TKA (41,060). Of these, 17,339 (16.2%) were aged 80 years or older. Overall, in-hospital death occurred in 121 patients (0.11%) and 4,448 patients (4.2%) had at least one major complication. In-hospital mortality and complication rates increased with increasing age and comorbidity. A multivariate analysis showed mortality and major complications following surgery were associated with advanced age (aged ≥ 80 years; odds ratios 5.88 and 1.51), male gender, and a higher comorbidity burden (Charlson comorbidity index ≥ 3; odds ratio, 16.5 and 5.06). After adjustment for confounding factors, patients undergoing lumbar arthrodesis or cervical laminoplasty were at twice the risk of in-hospital mortality compared with patients undergoing TKA.

Conclusions: Our data demonstrated that an increased comorbid burden as measured by Charlson comorbidity index has a greater impact on postoperative mortality and major complications than age in older adults undergoing orthopaedic surgery. After adjustment, mortality following lumbar arthrodesis or cervical laminoplasty was twice as high as that in TKA. Our findings suggest that an assessment of perioperative risks in elderly patients undergoing orthopaedic surgery should be stratified according to comorbidity burden and type of procedures, as well as by patient's age.

Keywords: Orhopaedic surgery, Spine surgery, Arthroplasty, Complication, Mortality, Database, Charlson comorbidity index, Elderly patients

* Correspondence: chikuda-tky@umin.ac.jp
[1]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
Full list of author information is available at the end of the article

Background

Orthopaedic surgery for degenerative spine or limb joints is widely performed with the aim of improving patients' quality of life. In the United States, about 400,000 spinal arthrodesis and 600,000 total knee arthroplasty (TKA) operations are completed annually [1,2]. Orthopaedic surgery for elderly patients, even octogenarians and nonagenarians, is becoming more common as the population ages. This trend is particularly evident in Japan, where 23% of the population are 65 years or older [3,4].

Despite the rapid increase of surgical treatment in elderly patients, the impact of advanced age on the risk arising from orthopaedic surgery is not fully understood. Although age has long been considered as a major risk factor for perioperative mortality and morbidity, chronological age is not the sole determinant of surgical risk. Risk factors vary considerably among individuals and depend on multiple variables including severity of disease, comorbid conditions, and type of surgical procedure. Further understanding of each factor's contribution would allow surgeons to better evaluate perioperative risk to elderly patients. However, few large studies, in particular those using a national database, has examined this issue [1,5-10].

In this analysis of nationwide inpatient claim data, we investigated mortality and morbidity in older adults undergoing one of the following operations: cervical laminoplasty; lumbar decompression; lumbar arthrodesis; and primary TKA to examine how complications vary as a function of age, comorbid conditions, and type of surgical procedure.

Methods

Data source

The Diagnosis Procedure Combination (DPC) is a case-mix patient classification system launched in 2002 by the Ministry of Health, Labour and Welfare of Japan, and linked with a lump-sum payment system [11-14]. All 82 university teaching hospitals are obliged to use this system, but adoption by community hospitals is voluntary. The DPC Research Group surveys participating hospitals between July 1 and December 31 each year in collaboration with the Ministry of Health, Labour and Welfare. In 2010, 926 hospitals participated and provided data for 2.9 million patients, approximately 45% of all inpatient admissions to acute care hospitals in Japan. The database includes the International Classification of the Diseases 10th Revision (ICD-10) codes for primary and secondary diagnoses; comorbid conditions that existed at admission; and complications that occurred after admission. To optimize the accuracy of the recorded diagnoses, physicians in charge are obliged to record the diagnoses with reference to medical charts.

The Institutional Review Board at The University of Tokyo approved the study design and waived informed consent because the data is anonymous.

Patients

We included all patients aged 50 years or older who had undergone one of the following operations from 2007 to 2010: cervical laminoplasty, lumbar decompression, lumbar arthrodesis, and primary TKA. These procedures were chosen because they are predominantly performed for degenerative conditions commonly seen in the elderly. Although these procedures might be conducted in an urgent manner, this study did not exclude emergency cases. We excluded total hip arthroplasty (THA) from our analysis because of demographic and etiologic differences; the majority of Japanese patients present with osteoarthritis secondary to dysplasia of the hip joint, which is not necessarily the case in other parts of the world.

The variables abstracted from the DPC database were: age, sex, comorbid conditions that existed at admission, surgical site, length of stay, and postoperative adverse outcomes. To evaluate the impact of multiple comorbidities, we used Charlson comorbidity index (CCI) base on Quan's protocol [15,16], a weighted index that takes into account the number and the seriousness of comorbid conditions. In calculation of the CCI, patients' comorbid conditions are classified into following 17 categories: myocardial infarction; congestive heart failure; peripheral vascular disease; cerebrovascular disease; dementia; chronic pulmonary disease; peptic ulcer diease; mild liver disease; diabetes without chronic complication; diabetes with chronic complication; hemiplesia or paraplegia; renal disease; any malignancy, including leukemia and lymphoma; moderate or severe liver disease; metastatic solid tumor; and AIDS/HIV. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with the condition. Scores are then summed to provide a total score of the CCI. In the present study, coded comorbidities in the DPC database were converted to designated points according to Quan's protocol.

Outcomes

Primary outcomes included in-hospital death or any of the following complications: surgical site infection (ICD10 code: T793, T814), sepsis (A40, A41), cardiac events (acute coronary events [I21-I24] or heart failure [I50]), respiratory complications (pneumonia [J12-J18], post procedural respiratory disorders [J95] or respiratory failure [J96]), pulmonary embolism (I26), stroke (cerebral infarction or hemorrhage [I60-I64]), acute renal failure [N17].

Statistical analysis

We used analysis of variance or Kruskal-Wallis tests to compare continuous data; Chi-square tests to compare categorical data; Fisher's exact test to compare in-hospital mortality and major complication rates between subgroups; logistic regression to analyze concurrent effects of factors on the occurrence of in-hospital deaths and postoperative

complications, and a generalized estimating equation to adjust for the clustering of patients within hospitals. In the regressions, in-hospital deaths and postoperative complications were modeled as functions of age, sex, CCI, and surgical procedure [17]. The threshold for significance was < 0.05.

Results

A total of 107,104 patients were identified (45,044 men and 62,060 women; mean ± SD age, 70.1 ± 10.7 years): cervical laminoplasty (16,020 patients); lumbar decompression (31,605); lumbar arthrodesis (18,419); or primary TKA (41,060). Of these, 17,339 (16.2%) were aged ≥ 80 years. Diabetes was the most common comorbid condition that existed at admission (found in 16.0% of the patients) followed by chronic pulmonary disease (2.6%), chronic renal failure (1.9%), malignancy (1.7%), and congestive heart failure (1.6%). Table 1 shows the characteristics of the patients according to surgical procedures.

One-hundred and twenty-one patients died in-hospital following surgery (0.11%), and 4,448 patients (4.2%) experienced at least one major complication (Table 2). The most common major complication was surgical site infection (about 2% of patients) followed by cardiac events and respiratory complications. As expected, in-hospital mortality and complication rate increased with age and comorbid burden (Table 2). Patient receiving cervical laminoplasty showed the highest mortality (0.20%) and major complication rate (4.7%).

Mortality and major complication following surgery were associated with advanced age (aged ≥ 80 years; odds ratios [OR], 5.88 and 1.51 respectively), male gender, and increasing comorbidity (CCI ≥ 3; OR, 16.5, and 5.06 respectively) (Table 3). We note the risk of in-hospital death following lumbar arthrodesis or cervical laminoplasty was twice that in TKA.

Discussion

Overall, our results confirmed that mortality following current orthopaedic surgery was low (0.11%). Although these results support previous reports [18], there was a marked difference in risk profile among patient subgroups. The multivariate analysis showed that postoperative mortality and morbidity were modestly associated with advanced age and strongly with the comorbidity burden as measured by the CCI. An increased CCI was the greatest risk factor for both in-hospital mortality and the occurrence of major complications. In addition, the use of lumbar arthrodesis and cervical laminoplasty were associated with increased risk of in-hospital mortality compared with TKA.

Strengths and weaknesses of the study

This study is the largest (study population of 107,104) that analyzes the risks associated with current orthopaedic surgery in older adults. The DPC database is a large administrative database similar to National Inpatient Sample in the United States, and the data allows nationwide investigation and comparison of mortality and morbidity between stratified subgroups. In addition, the DPC database allows us to assess perioperative complications by differentiating comorbidities at admission and complications after admission.

In common with other studies using administrative data, a degree of misclassification or underreporting

Table 1 Characteristics of the study population according to surgical procedures

	Overall (n = 107,104)	Cervical laminoplasty (n = 16,020)	Lumbar decompression (n = 31,605)	Lumbar arthrodesis (n = 18,419)	Total knee arthroplasty (n = 41,060)	p
Age, years; mean [SD]	70.1 [10.7]	66.2 [11.6]	68.9 [11.3]	65.7 [12.1]	74.6 [6.9]	< 0.001
≤ 64	25,927 (24.2)	6,534 (40.8)	8,898 (28.2)	6,976 (37.9)	3,519 (8.6)	
65–79	63,838 (59.0)	7,678 (47.9)	18,166 (57.5)	10,060 (54.6)	27,394 (68.0)	
≥ 80	17,339 (16.2)	1,808 (11.3)	4,541 (14.4)	1,383 (7.5)	9,607 (23.4)	
Sex						
Men	45,044 (42.1)	11,050 (69.0)	18,735 (59.3)	8,456 (45.9)	6,803 (16.6)	< 0.001
Women	62,060 (57.9)	4,970 (31.0)	12,870 (40.7)	9,963 (54.1)	34,257 (83.4)	
Charlson comorbidity index						
0	68,931 (64.4)	9,518 (59.4)	20,234(64.0)	11,971 (65.0)	27,208 (66.3)	< 0.001
1	24,068 (22.5)	3,481 (21.7)	7,060(22.3)	3,825 (20.8)	9,702 (23.6)	
2	9,656 (9.0)	1,885 (11.8)	2,928(9.3)	1,747 (9.5)	3,096 (7.5)	
≥ 3	4,449 (4.2)	1,136 (7.1)	1,383(4.4)	876 (4.8)	1,054 (2.6)	
Postoperative length of stay, day, median [IQR]	21 [15–30]	18 [14–26]	15 [12-21]	20 [15–28]	27 [21–36]	< 0.001

SD standard deviation, *IQR* interquartile range.

Table 2 Mortality and major complications following surgery according to age groups

	Cervical laminoplasty (n = 16,020)	Lumbar decompression (n = 31,605)	Lumbar arthrodesis (n =18,419)	Total knee arthroplasty (n = 41,060)	p
Inhospital death, n (%)	32 (0.20)	35 (0.11)	27 (0.15)	27 (0.066)	< 0.001
Age ≤ 64 years	5(0.077)	4 (0.045)	3 (0.043)	1 (0.028)	
65–79	17(0.22)	20 (0.11)	17 (0.17)	15 (0.055)	
≥ 80	10(0.55)	11 (0.24)	7 (0.51)	11 (0.11)	
Postoperative complications, n (%)					
Surgical site infection	320 (2.0)	511 (1.6)	362 (2.0)	636 (1.5)	< 0.001
Sepsis	25 (0.16)	53 (0.17)	53 (0.29)	61 (0.15)	0.002
Cardiac events	279 (1.7)	508 (1.6)	302 (1.6)	677 (1.6)	0.754
Respiratory complications	96 (0.60)	104 (0.33)	88 (0.48)	196 (0.48)	< 0.001
Pulmonary embolism	16 (0.10)	31 (0.10)	31 (0.17)	167 (0.41)	< 0.001
Stroke	71 (0.44)	74 (0.23)	42 (0.23)	92 (0.22)	< 0.001
Acute renal failure	1 (0.006)	8 (0.025)	7 (0.038)	15 (0.037)	0.227
At least one complication, n (%)	757 (4.7)	1,197 (3.8)	808 (4.4)	1,686 (4.1)	< 0.001
Age ≤ 64 years	264 (4.0)	254 (2.9)	248 (3.6)	106 (3.0)	
65–79	384 (5.0)	716 (3.9)	467 (4.6)	1,114 (4.1)	
≥ 80	109 (6.0)	227 (5.0)	93 (6.7)	466 (4.9)	

of outcome might have occurred. Although we could not verify data for each patient, we presume the level of miscoding is low because DPC data are coded by physicians and subject to an audit. Data are limited as the DPC database does not record some important clinical data, such as the severity of the disease, levels of the arthrodesis, or type of implant used. Despite these limitations, the results presented here provide important national estimates of inpatient morbidity and mortality after orthopaedic surgery.

Table 3 Adjusted risk of adverse outcomes after surgery

	Inhospital death			Postoperative complications		
	OR	95% CI	p	OR	95% CI	p
Age						
≤ 64	Reference			Reference		
65–79	2.58	1.36 – 4.89	0.004	1.22	1.09 – 1.36	0.001
≥ 80	5.88	2.93 – 11.8	<0.001	1.51	1.31 – 1.75	< 0.001
Sex						
men	Reference			Reference		
women	0.60	0.39 – 0.92	0.018	0.88	0.82 – 0.95	0.001
Charlson comorbidity index						
0	Reference			Reference		
1	1.60	0.89 – 2.87	0.116	2.42	2.17 – 2.71	< 0.001
2	6.58	3.99 – 10.8	<0.001	3.42	2.92 – 4.01	< 0.001
≥ 3	16.50	10 – 27.2	<0.001	5.06	4.2 – 6.1	< 0.001
Surgical procedure						
Total knee arthroplasty	Reference			Reference		
Cervical laminoplasty	2.15	1.23 – 3.77	0.008	1.02	0.81 – 1.28	0.865
Lumbar decompression	1.38	0.79 – 2.4	0.253	0.87	0.72 – 1.04	0.117
Lumbar arthrodesis	2.23	1.21 – 4.06	0.009	1.07	0.92 – 1.24	0.397

OR odds ratio, *CI* confidence interval.

Comparison with other studies

The values for mortality for spine surgery (0.11%–0.20%) and primary TKA (0.066%) are similar to those reported in other large database studies [6-9,19-21]. In the present study, comorbidity burden (CCI ≥ 3) had the greatest impact both on in-hospital mortality and occurrence of major complications. In the National Surgical Quality Improvement Program, which examined outcomes for 3,475 patients undergoing spine surgery, identified age, and contaminated or infected wounds as independent predictors of mortality [10]. Pumberger et al. reported the highest odds for perioperative mortality for patients undergoing lumbar arthrodesis were among patients aged 75 years or older (OR, 4.35; reference: 45–46 years) and those with the comorbidities of congestive heart failure, coagulopathy, and liver disease [9]. Similarly, Memtsoudis et al. found that risk factors for mortality following TKA and THA included age (≥ 75 years; OR, 3.70), male gender, ethnicity, emergency admission, and comorbidity [8].

In these previous studies, each comorbid condition was analyzed separately. In the present study, we used the CCI because in elderly patients often present with multiple coexisting conditions. Our data demonstrate that presentation with coexisting conditions has a striking impact on postoperative adverse outcomes.

Risk profile also varies among surgical procedures. After adjusting for age, sex, and comorbidities, the risk for in-hospital death following lumbar arthrodesis or cervical laminoplasty was twice as high as the risk following TKA. There was no significant difference between lumbar decompression and TKA. Few previous studies have examined procedure-related risk differences among orthopaedic procedures. Memtsoudis et al. reported that TKA has a slightly lower risk of mortality than THA [8]. Deyo et al. demonstrated that lumbar arthrodesis, in particular complex fusion, compared with decompression alone, increased risk of 30-day mortality [5]. Although unadjusted factors may influence mortality rates, surgeons should be aware of the different risk profile among surgical procedures.

Conclusions

Our findings suggest that an assessment of perioperative risks in elderly patients undergoing orthopaedic surgery should be stratified according to comorbidity burden and type of procedures, as well as by patient's age. We believe that the findings of our study provide critical information for individual treatment recommendations for elderly patients.

Abbreviations

DPC: Diagnosis procedure combination; TKA: Total knee arthroplasty; THA: Total hip arthroplasty; CCI: Charlson comorbidity index; OR: Odds ratios.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HC, HY, KT, and ST contributed to the conception and design of the study. HH, SS, ST, and KF contributed to the analysis, and all authors contributed to the interpretation. HC drafted the article; all authors revised it critically for important intellectual content and approved the final version submitted for publication. All authors read and approved the final manuscript.

Acknowledgements

This study was funded by grants from the Ministry of Health, Labour and Welfare, Japan (Research on Policy Planning and Evaluation grant number: H22-Policy-031); (Research on Intractable Diseases grant number: H23-Nanchi -032); the Ministry of Education, Culture, Sports, Science and Technology, Japan (Scientific Research B, No. 22390131); and the Council for Science and Technology Policy, Japan (Funding Program for World-Leading Innovative R&D on Science and Technology (FIRST program-grant number: 0301002001001). The funders have played no role in design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author details

[1]Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. [2]Department of Health Management and Policy, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. [3]Department of Health Care Informatics, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan.

Received: 4 March 2013 Accepted: 23 May 2013
Published: 28 May 2013

References

1. Cram P, Lu X, Kates SL, Singh JA, Li Y, Wolf BR: **Total knee arthroplasty volume, utilization, and outcomes among Medicare beneficiaries, 1991–2010.** *JAMA* 2012, **308**:1227–1236.
2. Rajaee SS, Bae HW, Kanim LE, Delamarter RB: **Spinal fusion in the United States: analysis of trends from 1998 to 2008.** *Spine (Phila Pa 1976)* 2012, **37**:67–76.
3. Muramatsu N, Akiyama H: **Japan: super-aging society preparing for the future.** *Gerontologist* 2011, **51**:425–432.
4. Nakamura K: **A "super-aged" society and the "locomotive syndrome".** *J Orthop Sci* 2008, **13**:1–2.
5. Deyo RA, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG: **Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults.** *JAMA* 2010, **303**:1259–1265.
6. Kalanithi PS, Patil CG, Boakye M: **National complication rates and disposition after posterior lumbar fusion for acquired spondylolisthesis.** *Spine (Phila Pa 1976)* 2009, **34**:1963–1969.
7. Li G, Patil CG, Lad SP, Ho C, Tian W, Boakye M: **Effects of age and comorbidities on complication rates and adverse outcomes after lumbar laminectomy in elderly patients.** *Spine (Phila Pa 1976)* 2008, **33**:1250–1255.
8. Memtsoudis SG, Pumberger M, Ma Y, Chiu YL, Fritsch G, Gerner P, Poultsides L, Valle AG: **Epidemiology and risk factors for perioperative mortality after total hip and knee arthroplasty.** *J Orthop Res* 2012, **30**:1811–1821.
9. Pumberger M, Chiu YL, Ma Y, Girardi FP, Vougioukas V, Memtsoudis SG: **Perioperative mortality after lumbar spinal fusion surgery: an analysis of epidemiology and risk factors.** *Eur Spine J* 2012, **21**:1633–1639.
10. Schoenfeld AJ, Ochoa LM, Bader JO, Belmont PJ Jr: **Risk factors for immediate postoperative complications and mortality following spine surgery: a study of 3475 patients from the National Surgical Quality Improvement Program.** *J Bone Joint Surg Am* 2011, **93**:1577–1582.
11. Chikuda H, Yasunaga H, Horiguchi H, Takeshita K, Kawaguchi H, Matsuda S, Nakamura K: **Mortality and morbidity in dialysis-dependent patients undergoing spinal surgery: analysis of a national administrative database in Japan.** *J Bone Joint Surg Am* 2012, **94**:433–438.
12. Kadono Y, Yasunaga H, Horiguchi H, Hashimoto H, Matsuda S, Tanaka S, Nakamura K: **Statistics for orthopedic surgery 2006–2007: data from the Japanese Diagnosis Procedure Combination database.** *J Orthop Sci* 2010, **15**:162–170.
13. Masuda K, Chikuda H, Yasunaga H, Hara N, Horiguchi H, Matsuda S, Takeshita K, Kawaguchi H, Nakamura K: **Factors affecting the occurrence of pulmonary embolism after spinal surgery: data from the national administrative database in Japan.** *Spine J* 2012, **12**:1029–1034.

14. Chikuda H, Yasunaga H, Takeshita K, Horiguchi H, Kawaguchi H, Ohe K, Fushimi K, Tanaka S: **Mortality and morbidity after high-dose methylprednisolone treatment in patients with acute cervical spinal cord injury: A propensity-matched analysis using a nationwide administrative database.** *Emerg Med J* 2013. doi:10.1136/emermed-2012-202058.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR: **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.** *J Chronic Dis* 1987, **40**:373–383.
16. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA: **Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data.** *Medical Care* 2005, **43**:1130–1139.
17. Hubbard AE, Ahern J, Fleischer NL, Van der Laan M, Lippman SA, Jewell N, Bruckner T, Satariano WA: **To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health.** *Epidemiology* 2010, **21**:467–474.
18. Bhattacharyya T, Iorio R, Healy WL: **Rate of and risk factors for acute inpatient mortality after orthopaedic surgery.** *J Bone Joint Surg Am* 2002, **84**:562–572.
19. Fu KM, Smith JS, Polly DW Jr, Perra JH, Sansur CA, Berven SH, Broadstone PA, Choma TJ, Goytan MJ, Noordeen HH, Knapp DR Jr, Hart RA, Zeller RD, Donaldson WF 3rd, Boachie-Adjei O, Shaffrey CI: **Morbidity and mortality in the surgical treatment of 10,329 adults with degenerative lumbar stenosis.** *J Neurosurg Spine* 2010, **12**:443–446.
20. Patil PG, Turner DA, Pietrobon R: **National trends in surgical procedures for degenerative cervical spine disease: 1990–2000.** *Neurosurgery* 2005, **57**:753–758.
21. Sansur CA, Reames DL, Smith JS, Hamilton DK, Berven SH, Broadstone PA, Choma TJ, Goytan MJ, Noordeen HH, Knapp DR, Hart RA, Zeller RD, Donaldson WF, Polly DW, Perra JH, Boachie-Adjei O, Shaffrey CI: **Morbidity and mortality in the surgical treatment of 10,242 adults with spondylolisthesis.** *J Neurosurg Spine* 2010, **13**:589–593.

doi:10.1186/1471-2474-14-173
Cite this article as: Chikuda *et al.*: Impact of age and comorbidity burden on mortality and major complications in older adults undergoing orthopaedic surgery: an analysis using the Japanese diagnosis procedure combination database. *BMC Musculoskeletal Disorders* 2013 **14**:173.

Osteoarthritis and Cartilage 21 (2013) 783–788

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Associations between radiographic lumbar spinal stenosis and clinical symptoms in the general population: the Wakayama Spine Study

Y. Ishimoto †, N. Yoshimura ‡, S. Muraki ‡, H. Yamada †, K. Nagata †, H. Hashizume †, N. Takiguchi †, A. Minamide †, H. Oka ‡, H. Kawaguchi ‡, K. Nakamura §, T. Akune †, M. Yoshida †*

† *Wakayama Medical University, Japan*
‡ *The University of Tokyo, Japan*
§ *Rehabilitation Services Bureau, National Rehabilitation Center for Persons with Disabilities, Japan*

ARTICLE INFO

Article history:
Received 19 September 2012
Accepted 24 February 2013

Keywords:
Lumbar spinal stenosis
Prevalence
Cohort
Magnetic resonance imaging

SUMMARY

Objective: Many asymptomatic individuals have radiographic lumbar spinal stenosis (LSS), but the prevalence of symptoms among individuals with radiographic LSS has not yet been established. The purpose of this study was to clarify the association between radiographic LSS and clinical symptoms in the general population.

Methods: In this cross-sectional study, data from 938 participants (308 men, 630 women; mean age, 66.3 years; range, 40–93 years) were analyzed. The severity of radiographic LSS, including central stenosis, lateral stenosis, and foraminal stenosis, was assessed by mobile magnetic resonance imaging and rated qualitatively. Assessment of clinical symptoms was based on the definition of symptomatic LSS in the North American Spine Society guideline.

Results: We found that 77.9% of participants had more than moderate central stenosis and 30.4% had severe central stenosis. Logistic regression analysis after adjustment for age, sex, body mass index, and severity of radiographic LSS showed that severe central stenosis was related to clinical symptoms. However, only 17.5% of the participants with severe central stenosis were symptomatic.

Conclusion: Although radiographic LSS was common in our cohort, which resembled the general Japanese population, symptomatic persons were relatively uncommon.

Introduction

Radiographic lumbar spinal stenosis (LSS) is defined as a narrowing of the lumbar canal with encroachment of neural structures by surrounding bone and soft tissue[1]. Symptomatic LSS, which requires both the presence of clinical symptoms and radiographic LSS[2], is usually associated with impaired walking and other disabilities in the elderly[1,3] and is the most frequent indication for spinal surgery in patients older than 65 years[4]. Because of the high number of elderly persons in Japan, there is an urgent need for evidence-based data regarding radiographic LSS occurring as a result of degenerative changes. However, little information is available regarding the epidemiology of radiographic LSS. This is because previous studies on radiographic LSS have not included subjects who were part of the general population[5–7]. Furthermore, for radiographic LSS to be diagnosed, the detection of minute changes of the intervertebral discs and ligaments using a tool like magnetic resonance imaging (MRI) is essential[8,9], but to the best of our knowledge, no studies of radiographic LSS among the general population have been performed using MRI.

LSS symptoms include a range of possible clinical presentations resulting from dilatation of the intrinsic vessels of the nerve roots[10]. However, inconsistent with this observation, severe radiographic LSS is often present in asymptomatic patients[7], and little is known of the prevalence of symptoms among individuals with radiographic LSS. Previous studies have reported on the relationship between radiographic LSS and quality of life, function, and pain due to symptoms in symptomatic patients[11–14]. To the best of our knowledge, there has been no study on the association between radiographic LSS and clinical symptoms among the general population, which includes both symptomatic and asymptomatic individuals.

In this study, we aimed to determine the prevalence of radiographic LSS assessed by MRI and its association with clinical symptoms using mobile MRI in a population-based cohort.

* Address correspondence and reprint requests to: M. Yoshida, Orthopedic Surgery, Wakayama Medical University, 811-1 Kimidera, Wakayama 641-8509, Japan. Tel: 81-(0)-73-447-2300; Fax: +81-(0)-73-448-3008.
E-mail address: sekitui@wakayama-med.ac.jp (M. Yoshida).

1063-4584/$ – see front matter © 2013 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.joca.2013.02.656

Methods

Participants

The present study, entitled The Wakayama Spine Study, assessed a subcohort drawn from Research on Osteoarthritis/Osteoporosis Against Disability (ROAD), which is a large-scale, prospective study of bone and joint diseases among population-based cohorts established in several communities throughout Japan. As the detailed profile of the ROAD study is described elsewhere, only a brief summary is provided here[15–18]. A database including baseline clinical and genetic information relating to 3,040 inhabitants (1,061 men, 1,979 women) with a mean age of 70.6 years (range, 23–95 years) has been created. We recruited individuals listed in resident registrations in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. All participants provided written, informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Participants completed an interviewer-administered questionnaire that included 400 items covering lifestyle information, and they underwent anthropometric measurements and assessments of physical performance. Blood and urine samples were collected for biochemical and genetic examinations.

The ROAD study team made a second visit to the mountainous region of Hidakagawa and the coastal region of Taiji between 2008 and 2010. Of the inhabitants who participated in this second visit, 1,063 volunteers were recruited for MRI. Fifty-two of these declined to attend the examination, and the remaining 1,011 were registered in the Wakayama Spine Study. All participants provided their written, informed consent for the MRI examination. Participants who had sensitive implanted devices (such as a pacemaker) or other disqualifiers were excluded. In total, 977 participants underwent lumbar spine MRI. Ten participants who had undergone a previous lumbar operation for LSS were excluded, and 29 participants who were younger than 40 years were excluded because LSS is a degenerative disease. Thus, MRI results were available for 938 participants (308 men and 630 women) with an age range of 40–93 years (mean, 68.3 years for men and 66.9 years for women).

Similar to the baseline study, the second ROAD study included an interviewer-administered questionnaire that included 400 items that covered lifestyle information such as smoking habits, alcohol consumption, family history, past history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, bilateral grip strength, and body mass index (BMI) (kg/m^2). Co-morbidities were defined according to blood data (diabetes: HbA1c $>$ 6.5%[19], hyperuricemia: uric acid $>$ 7.0 mg/dL[20], hyperlipidemia: high-density lipoprotein cholesterol $<$ 40 mg/dL[21]). The ankle-brachial index (ABI) of all participants was measured using PWV/ABI (OMRON Co., Kyoto, Japan).

MRI

All participants underwent total spinal MRI with a mobile MRI unit (Excelart 1.5 T; Toshiba, Tokyo, Japan) on the same day as the examination. MRI exclusion criteria included the presence of a cardiac pacemaker, claustrophobia, or other reasons. The participants were supine during the MRI, and those with rounded backs used triangular pillows under their head and knees. The imaging protocol included sagittal T2-weighted fast spin echo (FSE) (repetition time [TR]: 4,000 ms/echo, echo time [TE]: 120 ms, field of view [FOV]: 300 mm $\times$ 320 mm) and axial T2-weighted FSE (TR: 4,000 ms/echo, TE: 120 ms, FOV: 180 mm $\times$ 180 mm). Sagittal images were taken of the entire spine, but axial images were taken at each lumbar intervertebral level (L1/2–L5/S1) parallel to the vertebral endplates.

Qualitative ratings

The severity of radiographic LSS was qualitatively assessed after all examinations were completed. An experienced orthopedic surgeon (YI) without knowledge of the participants' symptom status examined the images, which were provided on films. The features assessed included the severity of central, lateral recess, and foraminal stenosis, rated on a four-grade scale. We used Fardon and Millette's[22] definition of lateral recess: a recess extending from the medial edge of the facet to the edge of the neuroforamen. We also applied the classification included in a general guideline[2] in which mild stenosis was defined as narrowing of one-third of the normal area or less, moderate stenosis as narrowing of between one- and two-thirds, and severe stenosis as narrowing of more than two-thirds of the area. Central stenosis and lateral recess stenosis were rated on the axial images and foraminal stenosis on the sagittal images. For lateral and foraminal stenosis, the rating for the side with the worst score was used. To evaluate the intraobserver variability of the severity rating, 50 randomly selected lumbar MRI films were scored by the same observer more than 1 month after the first reading. Fifty other lumbar MRI films were also scored by two experienced orthopedic surgeons (YI & KN) to determine the interobserver variability. The intraobserver variabilities in severity rating were confirmed by kappa analysis to be sufficient for the assessment of central, lateral, and foraminal stenosis (0.82, 0.71, and 0.66, respectively); interobserver variability was also sufficient (0.77, 0.66, and 0.66, respectively).

Assessment of clinical symptoms

An experienced orthopedic surgeon (YI) took the medical history and performed the physical examination of all the participants. The history included information about the presence of lower back pain, buttock pain, and leg pain; areas of pain or other discomfort; the presence of intermittent claudication (IC) and its distance; and items on a modified Zurich Claudication Questionnaire[23] (except six items about satisfaction and a history of lumbar surgery for symptomatic LSS). Physical examination included assessments to determine whether any symptoms could be induced by lumbar extension or were improved or induced by lumbar flexion, floor finger distance (cm), and peripheral circulation (good or poor); a straight-leg raising test; manual muscle testing of both the upper and lower extremities; tendon reflex testing for both the upper and lower extremities; and Babinski reflex testing. In addition, an MRI study of the entire spine was performed for all participants on the same day as the physical examination.

Assessment of clinical symptoms in the present study was based on the LSS definition in the North American Spine Society (NASS) guideline[24] and required one or more of the following symptoms: pain, numbness and neurological deficits in the lower extremities and buttocks, and bladder/bowel dysfunction. In addition, the above symptoms were required to be induced or exacerbated by walking or prolonged standing and relieved by lumbar flexion, sitting, and recumbency.

Statistical analysis

All statistical analyses were performed using JMP, version 8 (SAS Institute Japan; Tokyo, Japan). Differences between men and women in age, height, weight, and BMI were examined using non-paired Student's *t* test., co-morbidities, and clinical symptoms were compared between men and women with the chi-square test. The chi-square test was also used to determine the association between radiographic LSS and age stratum. Logistic regression analysis was performed stratified for sex to determine the effect of age and BMI

on severe stenosis of all locations or the severest stenosis in each area, with the latter as an objective variable and age and BMI as explanatory factors. A further logistic regression analysis was performed stratified for sex to determine the effect of age, BMI, and each level of severity of central stenosis with clinical symptoms, using radiographic LSS as an objective variable and age, BMI, and each severity level as explanatory factors. We constructed a set of two dummy variables defining the three different central stenosis groups (none/mild, moderate, and severe).

Results

Table I summarizes characteristics of the 938 participants (308 men and 630 women; mean age 67.3 years, range 40–93 years), including age and anthropometric measurements. Two-thirds of them were women. Mean age was not significantly different between men and women. BMI was significantly lower in women than in men.

For all locations except central L1/2 and L2/3, several MRIs were found to be inadequate for interpretation; in particular, the sample for qualitative analysis of foraminal L1/2 was reduced to 907 (Table II). Regarding both central and lateral canal stenosis, the prevalence of severe stenosis was highest at L4/5, followed by L3/4. One-third of the participants had severe canal stenosis of at least one level. On the other hand, the distribution of the prevalence of severe foraminal stenosis was entirely different from that of central and lateral severe stenosis. The level with the highest prevalence of severe foraminal stenosis was L5/S1, followed by L4/5. There were few participants with more than moderate stenosis at the upper levels of the foramen. Concerning severe stenosis in all locations, multiple logistic regression analysis after adjustment for age and BMI revealed that more men had severe stenosis at lateral L2/3, L3/4, and L4/5 than women (odds ratios [ORs] and 95% confidence intervals [CIs] for lateral stenosis were 2.05, 1.13–3.73 at L2/3; 1.95, 1.34–2.86 at L3/4; and 1.52, 1.11–2.08 at L4/5). To identify factors related to the severest stenosis at each location, we performed a further multiple logistic regression analysis with age, BMI, and sex as explanatory variables. Age was significantly associated with severe stenosis at all locations for both sexes (ORs and 95% CIs were 1.06, 1.04–1.07 for central stenosis; 1.09, 1.07–1.10 for lateral stenosis; and 1.11, 1.08–1.15 for foraminal stenosis). BMI was also significantly associated with severe central stenosis in the overall cohort and in men, but not in women (overall: 1.06, 1.02–1.10; men: 1.08, 1.00–1.17; women: 1.05, 0.99–1.10). There was no significant difference in the prevalence of central stenosis of more than moderate severity between agricultural/forestry/fishery workers or not ($P = 0.60$). There was also no significant difference in radiographic LSS between persons with diabetes, hyperuricemia, and hyperlipidemia or not, each (Diabetes: $P = 0.21$, hyperuricemia: $P = 0.65$, hyperlipidemia: $P = 0.71$).

Table I
Characteristics of participants

	Total	Men	Women
No. of participants	**938**	**308**	**630**
Age group (years)			
<49	96	26	70
50–59	175	59	116
60–69	222	65	157
70–79	258	87	171
≧80	187	71	116
Demographic characteristics			
Age, years	67.3 ± 12.4	68.3 ± 12.5	66.9 ± 12.3
Height, cm	155.7 ± 9.3	164.4 ± 6.9**	151.4 ± 7.1
Weight, kg	56.7 ± 11.4	64.3 ± 11.3**	53.0 ± 9.4
BMI, kg/m^2	23.3 ± 3.6	23.7 ± 3.3*	23.1 ± 3.6
Job titles, no.			
Clerical workers/technical experts	197	79	118
Agricultural/forestry/fishery workers	105	62	43
Factory/construction workers	48	23	25
Others	588	144	444
Co-morbidities, no.			
Diabetes	48	23*	25
Hyperuricaemia	71	54**	17
Hyperlipidemia	41	30**	11

A non-paired *t*-test was used to determine differences in demographic characteristics and measurements of physical performance between men and women. Values are the means ± standard deviation. *$P < 0.05$, **$P < 0.01$.

Fig. 1 shows the prevalence of moderate and severe radiographic LSS for the severest stenosis identified in each area and classified by age and sex. Both central and lateral stenosis of more than moderate severity were quite common among the elderly, but foraminal stenosis of more than moderate severity was less common. The prevalence of severe stenosis at each location was significantly higher with increasing age stratum in both sexes (central, men: $P = 0.008$; central, women: $P < 0.0001$; lateral, both: $P < 0.0001$; foraminal, both: $P < 0.0001$ [all by chi-square test]).

There were 105 individuals with clinical symptoms (men: 35, women: 70). There was no significant difference between sexes in the prevalence of clinical symptoms ($P = 0.91$). Fifty-four of the 105 participants identified as having clinical symptoms had IC. Five of these 54 participants presented with an ABI <0.9. However, these five participants also had symptomatic LSS, and their leg symptoms were dependent on position. These five cases were unspecified IC, caused by both neurogenic and vascular claudication. We used cases of central stenosis to clarify the association between radiographic LSS and clinical symptoms. The prevalence of clinical symptoms significantly increased with increasing severity of central stenosis, for both sexes, according to chi-square test (men: $P = 0.009$; women: $P = 0.004$). Furthermore, to clarify the relationship between individuals with clinical symptoms and each grade of severity, we performed a logistic regression analysis to estimate the OR and 95% CI after adjustment for age, BMI, sex, and severity of radiographic LSS, and we constructed a set of two dummy variables defining the three central stenosis groups (none/mild, moderate, and severe). Severe central stenosis was confirmed to be related to symptomatic individuals, but moderate stenosis was not (men, severe vs none/mild: 4.42, 1.44–17.0; men, moderate vs none/mild: 1.53, 0.49–5.86; women, severe vs none/mild: 2.50, 1.44–17.0; women, moderate vs none/mild: 1.83, 0.82–4.66). Among symptomatic persons ($n = 105$), there were 16 taking painkillers, seven taking trigger injections, and 13 in rehabilitation. We added these treatment statuses to the multivariate model and logistic regression analysis for the association between radiographic LSS and clinical symptoms, but the result was unchanged (Table III).

Discussion

In this study, we evaluated the prevalence of radiographic LSS assessed by MRI and its association with clinical symptoms in the general population. The intervertebral level with the highest prevalence of both severe central stenosis and severe lateral stenosis was L4/5; the prevalence of severe foraminal stenosis was greatest at L5/S. The prevalence of moderate or severe central stenosis was 64.0% in patients in their 50s and 93.1% in those in their 80s. There was a significant association between the severity of central stenosis and the presence of clinical symptoms. Of those with severe central stenosis, 17.5% had clinical symptoms. In addition, logistic regression after adjustment for age, BMI, sex, and severity of radiographic LSS revealed that severe central stenosis was related to clinical symptoms.

The most frequent intervertebral level of severe stenosis was consistent with the intervertebral location of severe stenosis that is most frequently seen in clinical settings. However, to the best of our

Table II
Prevalence of central, lateral, and foraminal stenosis

	L1/2	L2/3	L3/4	L4/5	L5/S1	Severest
Central stenosis						
No. of total†	938	938	937	937	936	938
None	112 (11.9)	57 (6.1)	36 (3.8)	31 (3.3)	163 (17.4)	13 (1.4)
Mild	606 (64.6)	435 (46.4)	305 (32.6)	276 (29.5)	580 (62.0)	194 (20.7)
Moderate	205 (21.9)	389 (41.5)	445 (47.5)	406 (43.3)	161 (17.2)	446 (47.5)
Severe	15 (1.6)	57 (6.1)	151 (16.1)	224 (23.9)	32 (3.4)	285 (30.4)
Lateral stenosis*						
No. of total†	933	933	929	931	925	938
None	439 (47.1)	199 (21.3)	80 (8.6)	29 (3.1)	333 (36.0)	11 (1.2)
Mild	393 (42.1)	454 (48.7)	347 (37.4)	251 (27.0)	414 (44.8)	205 (21.9)
Moderate	90 (9.6)	231 (24.8)	359 (38.6)	368 (39.5)	126 (13.6)	380 (40.5)
Severe	11 (1.2)	49 (5.0)	143 (15.4)	283 (30.4)	52 (5.6)	342 (36.5)
Foraminal stenosis*						
No. of total†	907	915	930	930	926	937
None	676 (74.5)	535 (58.5)	316 (34.0)	154 (16.6)	265 (28.6)	84 (9.0)
Mild	210 (23.2)	335 (36.6)	513 (55.2)	524 (56.3)	421 (45.5)	474 (50.6)
Moderate	18 (2.0)	42 (4.6)	90 (9.7)	220 (23.7)	202 (21.8)	313 (33.4)
Severe	3 (0.3)	3 (0.3)	11 (1.2)	32 (3.4)	38 (4.1)	66 (7.0)

Number (%). Percentage shows the prevalence at the same location.
* The rating of the most severely affected side was used.
† Participants were omitted if interpretation of their MRI was difficult because of poor image quality at each level.

knowledge, there has been no study on the prevalence of radiographic LSS assessed by MRI among the general population. We found a differential distribution in the prevalence of canal stenosis (including central and lateral stenosis) and foraminal stenosis, which may be partly explained by the difference in anatomy between these two locations. Canal stenosis consists of a bulging disk, thickening of the ligamentum flavum, and hypertrophy of the facet joints, whereas loss of disk height, disk protrusion, and facet joint osteoarthritis (OA) lead to foraminal stenosis[1]. The difference in anatomy between canal stenosis and foraminal stenosis (in terms of compression of the nerve root) may be related to the differential distribution of prevalence.

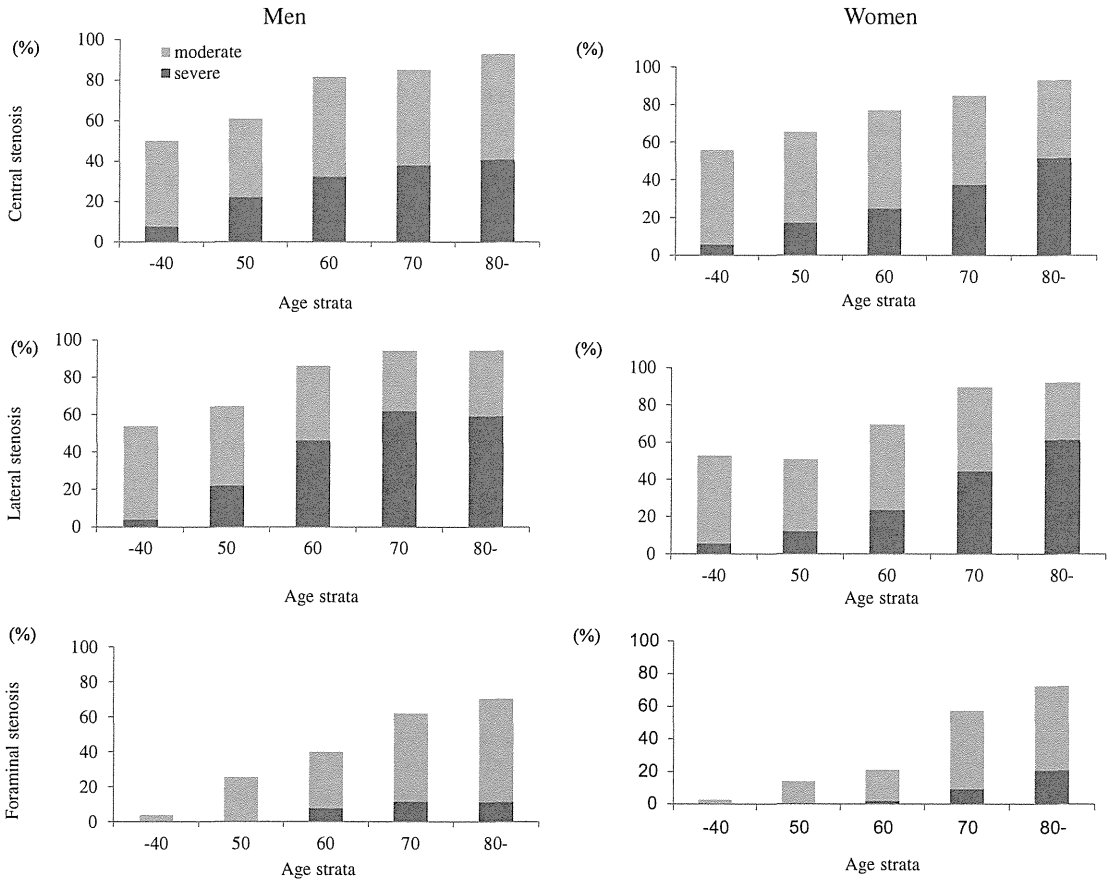

Fig. 1. Prevalence of severe central stenosis, severe lateral stenosis, and compressing foraminal stenosis classified by age and sex for 938 participants from a community cohort in Japan.

Table III
The association of radiographic LSS with clinical symptoms

	None/Mild	Moderate	Severe	Total
Men				
Radiographic LSS*	66	144	98	308
Clinical symptoms	4 (6.1)	12 (8.3)	19 (19.4)	35 (11.4)
Women				
Radiographic LSS*	141	302	187	630
Clinical symptoms	7 (5.0)	32 (10.6)	31 (16.6)	70 (11.1)
Total				
Radiographic LSS*	207	446	285	938
Clinical symptoms	11 (5.3)	44 (9.9)	50 (17.5)	105 (11.2)

Number (%).
* Radiographic LSS means central stenosis.

Many participants had radiographic LSS, although most were asymptomatic: 77.9% had more than moderate central stenosis and about 30.4% had severe central stenosis. Boden *et al.*[7] reported that 21% of 14 asymptomatic volunteers who were over 60 years of age had spinal stenosis, but their criteria for spinal stenosis (loss of epidural fat with compression of neural tissue within the canal) were different from ours. To our best knowledge, there is no report on the prevalence of radiographic LSS using MRI in a large population-based cohort. These findings indicate that radiographic LSS is quite common among the elderly.

We found that severe central stenosis was significantly associated with clinical symptoms, but only 17.5% of participants with severe central stenosis were symptomatic. Previous studies of the relationship between disabilities and radiographic LSS have yielded varied results[11–14]. One study with a 12-year follow-up[11] period showed a clear association between Oswestry Disability Index (ODI) and degree of stenosis. The subjects were assessed by myelography, but only 56.0% (75/134) were followed up and the ODI was determined by telephone interview. Ogikubo *et al.*[12] reported an association between the cross-sectional area of the lumbar spine and walking distance and pain among patients who subsequently underwent surgery. On the other hand, Amundsen *et al.*[13] found no relationship between the degree of stenosis measured by myelography and computed tomography (CT) and clinical symptoms in 100 symptomatic patients. Lohman *et al.*[14] also found no relationship between cross-sectional areas of the canal measured by CT and clinical symptoms in 117 patients who were referred from a primary health service because of chronic lower back pain and clinical suspicion of spinal stenosis. Jenson *et al.*[25] noted that abnormal MRI findings in individuals with lower back pain may frequently be coincidental. Thus, although one would expect that associations between radiographic LSS and symptoms or other disabilities due to LSS would be related to the degree of stenosis, previous studies have yielded varied results. In this study, severe central stenosis was related to clinical symptoms, but less than 20% of those with severe central stenosis were symptomatic. It thus seems to be impossible to clarify the cause of clinical symptoms by imaging alone; an expert clinician's opinion of both clinical assessment and imaging studies is essential for interventions such as surgery in symptomatic individuals.

There were several limitations to the present study. First, our participants may not represent the general population, as they were recruited from only two areas. However, anthropometric measurements were compared between the participants and the general Japanese population, and no significant differences in BMI were found (men: 23.71 [3.41] vs 23.95 [2.64], women: 23.06 [3.42] vs 23.50 [3.69])[26]. In addition, the proportions of current smokers and current drinkers (those who regularly smoked or drank more than one drink per month) in the general Japanese population were compared with those in the study population. The proportions of current smokers and drinkers (men) and current drinkers (women) were significantly higher in the general Japanese population than in the study population (smokers, men: 32.6% of the Japanese population vs 25.2% of the study participants; smokers, women: 4.9% of the Japanese population vs 4.1% of the study participants; drinkers, men: 73.9% of the Japanese population vs 56.8% of the study participants; drinkers, women: 28.1% of the Japanese population vs 18.8% of the study participants). This suggests the study participants (both men and women) likely had healthier lifestyles than the general Japanese population. Second, this was a cross-sectional study, so it does not provide conclusive evidence of any causal relationship between radiographic LSS and clinical symptoms. Third, this study only represented the Japanese population, and the prevalence in other countries may be quite different. Fourth, this study investigated elderly participants who lived independently rather than those who lived in institutional settings, so the calculated prevalence may be an underestimate. Fifth, we excluded 10 subjects who had already had surgery for LSS, and this could have influenced the results. However, LSS surgery is a major intervention that interferes with radiographic assessment of LSS, because it involves decompression and instrumentation that could produce artifacts. Finally, concerning facet OA and disc degeneration, which are important factors for radiographic LSS, we reported the prevalence of radiographic lumbar spondylosis assessed by Kellgren/Lawrence grading elsewhere[15,17]. We did not assess facet OA in this MRI study. We have been assessing disc degeneration in this cohort and will have results to report about this important investigation in the near future.

Nevertheless, this is the first trial to evaluate the prevalence of radiographic LSS and its association with clinical symptoms in the general population using MRI. In addition, the Wakayama Spine Study is a longitudinal survey, so future results will help to elucidate any causal relationships.

In conclusion, the present study evaluated the prevalence of radiographic LSS and clarified its association with clinical symptoms in a population-based cohort. Many participants had radiographic LSS, but few had clinical symptoms. The prevalence of clinical symptoms increased with increasing severity of radiographic LSS.

Contributors

All authors worked collectively to develop the protocols and methods described in this paper. YI, SM, KN, NO, HO, TA, and NY were the principal investigators responsible for the fieldwork in the Wakayama Spine Study. YI and SM performed the statistical analysis. YI, HY, SM, KN, HH, HO, TA, MY, and NY contributed to the analysis and interpretation of results. YI wrote the report. All authors read and approved the final report.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Role of the funding source

The study sponsors played no role in the study design, the collection, analysis, and interpretation of data, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data and had the final decision to submit for publication.

Acknowledgments

This study was supported by a Grant-in-Aid for Scientific Research (B20390182, B23390357, C20591737, C20591774), for Young Scientists (A18689031) and for Exploratory Research

(19659305) from the Japanese Ministry of Education, Culture, Sports, Science and Technology, H17-Men-eki-009, H18-Choujyu-037, and H20-Choujyu-009 from the Ministry of Health, Labour and Welfare, Research Aid from the Japanese Orthopaedic Association, a Grant from the Japanese Orthopaedics and Traumatology Foundation, Inc. (No. 166, No.256), and a Grant-in-Aid for Scientific Research, Scientific Research (C22591639), from the Japanese Society for the Promotion of Science. The sponsors had no role in study design, data collection, data analysis, data interpretation, or in the writing of the report.

The authors wish to thank Mrs. Tomoko Takijiri and other members of the Public Office in Hidakagawa Town, and Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, and other members of the Public Office in Taiji Town, for their assistance in locating and scheduling participants for examinations.

References

1. Katz JN, Harris MB. Lumbar spinal stenosis. N Engl J Med 2008;358:818–25.
2. Suri P, Rainville J, Kalichman L, Katz JN. Does this older adult with lower extremity pain have the clinical syndrome of lumbar spinal stenosis? JAMA 2010;304:2628–36.
3. Cadogan MP. Lumbar spinal stenosis. Clinical considerations for older adults. N Engl J Med 2011;37:8–12.
4. Ciol MA, Deyo RA, Howell E, Kreif S. An assessment of surgery for spinal stenosis: time trends, geographic variations, complications, and reoperations. J Am Geriatr Soc 1996;44:285–90.
5. Roberson GH, Llewellyn HJ, Taveras JM. The narrow lumbar spinal canal syndrome. Radiology 1973;107:89–97.
6. Johnsson KE. Lumbar spinal stenosis. A retrospective study of 163 cases in southern Sweden. Acta Orthop Scand 1995;66: 403–5.
7. Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990;72:403–8.
8. Bischoff RJ, Rodriguez RP, Gupta K, *et al.* A comparison of computed tomography-myelography, magnetic resonance imaging, and myelography in the diagnosis of herniated nucleus pulposus and spinal stenosis. J Spinal Disord 1993;6: 289–95.
9. Jia LS, Shi ZR. MRI and myelography in the diagnosis of lumbar canal stenosis and disc herniation. A comparative study. Chin Med J (Engl) 1991;104:303–6.
10. Olmarker K, Rydevik B, Holm S, Bagge U. Effects of experimental graded compression on blood flow in spinal nerve roots. A vital microscopic study on the porcine cauda equina. J Orthop Res 1989;7:817–23.
11. Hurri H, Slätis P, Soini J, Tallroth K, Alaranta H, Laine T, *et al.* Lumbar spinal stenosis: assessment of long-term outcome 12 years after operative and conservative treatment. J Spinal Disord 1998;11:110–5.
12. Ogikubo O, Forsberg L, Hansson T. The relationship between the cross-sectional area of the cauda equina and the preoperative symptoms in central lumbar spinal stenosis. Spine 2007;32:1423–8.
13. Amundsen T, Weber H, Lilleås F, *et al.* Lumbar spinal stenosis. Clinical and radiologic features. Spine 1995;20:1178–86.
14. Lohman CM, Tallroth K, Kettunen JA, Lindgren K- A. Comparison of radiologic signs and clinical symptoms of spinal stenosis. Spine 2006;31:1834–40.
15. Muraki S, Oka H, Akune T, *et al.* Prevalence of radiographic lumbar spondylosis and its association with low back pain in the elderly of population-based cohorts: the ROAD study. Ann Rheum Dis 2008;68:1401–6.
16. Muraki S, Oka H, Akune T, *et al.* Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthritis Cartilage 2009;17:1137–43.
17. Yoshimura N, Muraki S, Oka H, *et al.* Prevalence of knee osteoarthritis, lumbar spondylosis and osteoporosis in Japanese men and women: the Research on Osteoarthritis/Osteoporosis against Disability (ROAD) study. J Bone Miner Metab 2009;27:620–8.
18. Yoshimura N, Muraki S, Oka H, *et al.* Cohort profile: research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study. Int J Epidemiol 2010;39:988–95.
19. Japan Diabetes Society. Treatment Guide for Diabetes 2007.
20. Japanese Society of Gout and Nucleic and Metabolism. Guideline for the management of hyperuricemia and gout. Ver. 2.
21. Japan Atherosclerosis Society. Japan Atherosclerosis Society guidelines for prevention of atherosclerotic cardiovascular diseases.
22. Fardon DF, Milette PC. Nomenclature and classification of lumbar disc pathology. Recommendations of the combined task forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Spine 2001;26:93–113.
23. Stucki G, Daltroy L, Liang MH, Lipson SJ, Fossel AH, Katz JN. Measurement properties of a self-administered outcome measure in lumbar spinal stenosis. Spine 1996;21:796–803.
24. North American Spine Society Clinical Guidelines. III. Definition and natural history of degenerative lumbar spinal stenosis11.
25. Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. New Engl J Med 1994;331:69–73.
26. Ministry of Health, Labour and Welfare. The Report of National Health and Nutrition Survey. http://www.mhlw.go.jp/bunya/kenkou/eiyou07/01.html.