intercept and coefficients are determined by versions of the Abbreviated Injury Scale (AIS) [5, 6] required for ISS calculation. The RTS is calculated using the Glasgow Coma Scale (GCS) score, the systolic blood pressure (SBP), and the respiratory rate (RR). The formula is a linear equation of their coded values (c):

$$RTS = 0.9368^{*}cGCS + 0.7326^{*}cSBP + 0.2908^{*}cRR.$$

However, in our previous study [7], we demonstrated that logistic regression models with direct use of the actual AY provide a better fit than the TRISS model using the categorized (coded) AY, because a rapid increase in mortality is not observed around the AY of 55 in Japan. Moreover, a model without the RR information can be made with only a slight reduction in accuracy, and it can be feasible for Ps prediction if the RR data are missing.

This study aimed to modify the TRISS model in order to obtain better survival prediction for blunt trauma (BT) victims in Japan and Thailand, and to pursue the possibility of Ps estimation without RR information on admission.

Methods

Study design, population, and settings

We conducted a retrospective observational study to create Ps prediction models for BT victims in Japan and in Thailand. The protocol of the study was approved by the ethics committee of the National Center for Global Health and Medicine.

Once approval was obtained from the Trauma Registry Committee of the Japanese Association for the Surgery of Trauma, we used deidentified anonymous data from the JTDB [8], with which 144 Japanese hospitals have been involved since 2004. From 2005 to 2008, 25,310 patients who had suffered BT were registered in the JTDB. For analyses, we collected data on 15,524 patients without missing both outcome information on survival and information on the predictors for Ps calculation by the TRISS method using the 1990 revision of AIS (AIS90) [5].

From 2005 to 2008, 6,667 patients who had experienced BT in the Khon Kaen District in Thailand were registered in the Khon Kaen Regional Hospital Trauma Registry, where data have been collected since 1997. The hospital is one of the World Health Organization (WHO) collaborating centers for injury prevention and safety promotion, and has been providing outstanding contributions. With the permission of the hospital, we analyzed data on 6,411 patients, including items necessary for Ps calculation by the TRISS method using the 1985 version of the AIS (AIS85) [6] and information on survival at discharge.

Analyses

We performed logistic regression analyses in order to establish models. Maximum likelihood estimation was used as the method of coefficient estimation for each model. In addition to the RTS, AY, ISS, GCS, SBP, and RR, we used their coded values (cAY, cGCS, cSBP, cRR), defined in Table 1, as predictor variables. The outcome variable was survival (=1) with non-survival (=0) at discharge. We used the likelihood ratio χ^2 test for evaluating independence of variables. The statistically significant level was considered to be <0.05.

For model selection, we used Akaike's Information Criterion (AIC) [9], defined as:

$$AIC = -2^{*}\log(\text{maximum likelihood}) + 2^{*}(\text{number of adjusted parameters}).$$

Table 1 Demographics of each data set and distribution of variables

	Coded value	JTDB data	Khon Kaen data
Number		15,524	6,411
Gender (male %)		69.2	74.1
Age (years) mean (SD)		48.5 (23.2)	31.6 (18.9)
<55	0	55.0%	87.6%
≧55	1	45.0%	12.4%
RTS mean (SD)		6.78 (2.13)	7.47 (1.08)
SBP			
>89 mmHg	4	86.3%	95.9%
76–89 mmHg	3	3.2%	1.6%
59–75 mmHg	2	2.4%	1.1%
1–49 mmHg	1	1.3%	0.2%
No pulse	0	6.8%	1.2%
GCS score			
13–15	4	73.8%	89.4%
9–12	3	7.3%	3.0%
6–8	2	5.9%	4.6%
4–5	1	2.2%	1.1%
<4	0	10.8%	1.9%
RR			
10–29/min	4	77.9%	92.1%
>29/min	3	14.3%	0.2%
6–9/min	2	0.4%	0.02%
1–5/min	1	0.2%	0.2%
0/min	0	7.2%	7.5%
ISS mean (SD)		17.9 (13.6)	9.5 (10.1)
Survival (%)		85.0	95.9

JTDB Japan Trauma Data Bank, *ISS* Injury Severity Score, *RTS* Revised Trauma Score, *SBP* systolic blood pressure, *GCS* Glasgow Coma Scale score, *RR* respiratory rate

The AIC was used to identify the model that best explains the data with a minimum of free parameters. The model having the lower AIC is considered to be the better model.

We compared the area under the receiver operating characteristic curve (AUROCC) (which distinguishes between survival and non-survival, and varies between 0.5 and 1 [1 = perfect discrimination]), and accuracy (the proportions of survivors with Ps $\geq$ 0.5 and proportions of non-survivors with Ps < 0.5) among the models.

The JMP 9.0 (SAS Institute Inc., Cary, NC) and SAS 9.1 (SAS Institute Inc., Cary, NC) software packages were used for statistical analyses.

Results

Table 1 shows the demographics of each data set, including the distributions of predictor variables and the proportions of survivors. The JTDB seems to have data of older and more severely injured BT patients than the Khon Kaen Trauma Registry. The proportions of patients whose RRs were more than 29/min or 6–9/min were quite low in the Khon Kaen data.

The survival proportion of younger patients (AY < 55, cAY = 0) was 88.13%, which was slightly higher than the survival proportion (81.25%) of the older patients (AY $\geq$ 55, cAY = 1) in the JTDB data. In the Khon Kaen data, the difference can hardly be recognized between the survival proportion (95.86%) of the older patients (AY $\geq$ 55, cAY = 1) and the survival proportion (95.92%) of the younger patients (AY < 55, cAY = 0).

Table 2 shows the AIC of each model. The AIC of the model using AY was lower than that of the model using cAY (used by the TRISS method). In both data groups, the model using ISS, AY and cGCS, cSBP, and cRR instead of the RTS demonstrated the lowest AIC, 4,305 and 1,105, respectively. In the Khon Kaen data, no additional reduction of the AIC was shown in the model with the cRR variable compared with the model without cRR.

The estimated coefficients of the logistic regression models derived from the JTDB data are shown with the original TRISS coefficients in Table 3. As discussed in previous reports [10], each coefficient of cSBP, cGCS, and cRR on the TRISS line of the table is obtained by multiplying by the coefficient of RTS, namely 0.8085, in the TRISS equation using the AIS90. All estimated coefficients were significant. However, the intercept of the model using the ISS, AY, cSBP, and cGCS was not significant.

Table 2 AIC for each model

Regression model	AIC Japan	AIC Khon Kaen
ISS, RTS, cAY	4,372	1,120
ISS, RTS, AY	4,305	1,109
ISS, AY, cSBP, cGCS, cRR	4,305	1,105
ISS, AY, cSBP, cGCS	4,347	1,105

Regression models are represented by their predictor variables

AY age year, *cAY* coded value of AY, *cSBP* coded value of systolic blood pressure, *cGCS* coded value of Glasgow Coma Scale score, *cRR* coded value of respiratory rate

Table 3 Coefficients of logistic regression models of Japanese data

Regression model	Intercept	βISS	βRTS	βAY	βcAY	βcSBP	βcGCS	βcRR
TRISS (AIS90)	−0.4499	−0.0835	0.8085	×	−1.743	0.5923	0.7574	0.2351
ISS, RTS, cAY	−1.9502*	−0.0679*	1.0096*	×	−1.492*	×	×	×
	(0.1812)	(0.00310)	(0.024)		(0.086)			
	[115.85]	[479.6]	[1,723]		[297.6]			
ISS, RTS, AY	−0.76266*	−0.0710*	1.0256*	−0.0379*	×	×	×	×
	(0.2011)	(0.00316)	(0.024)	(0.00198)				
	[14.38]	[504.7]	[1,718]	[367.1]				
ISS, AY, cSBP, cGCS, cRR	−1.0723*	−0.0711*	×	−0.0383*	×	0.7370*	0.9318*	0.4243*
	(0.2616)	(0.00317)		(0.00199)		(0.0496)	(0.0281)	(0.0604)
	[16.79]	[502.2]		[369.9]		[221.2]	[1096.9]	[49.3]
ISS, AY, cSBP, cGCS	−0.3375	−0.0707*	×	−0.0369*	×	0.9017*	0.9814*	×
	(0.2059)	(0.00314)		(0.00196)		(0.0410)	(0.0273)	
	[2.69]	[508.6]		[354.4]		[483.3]	[1,290]	

Regression models are represented by their predictor variables

β regression coefficients

AIS abbreviated injury scale, *ISS* Injury Severity Score, *RTS* Revised Trauma Score, *AY* age year, *cAY* coded value of AY, *cSBP* coded value of systolic blood pressure, *cGCS* coded value of Glasgow Coma Scale score, *cRR* coded value of respiratory rate

* $p < 0.05$ (standard error) [χ^2 value]

The estimated coefficients of the logistic regression models derived from the Khon Kaen data are shown with the original TRISS coefficients in Table 4. Each coefficient of cSBP, cGCS, and cRR is obtained by multiplying by 0.9544, that is, the coefficient of RTS of the TRISS equation using the AIS85. The variable of cRR had a very low χ^2 value, and was not significant ($p = 0.06$). The intercepts of the models using ISS, AY, cSBP, and cGCS with or without cRR were not significant.

All models, including the models without the cRR variables, had AUROCCs > 0.95 in both data sets (Table 5). The model using AY, ISS, and RTS provided better AUROCC than the model with the variables of cAY, ISS, and RTS in both groups of data.

Discussion

Tables 3 and 4 reveal that the χ^2 value of cAY is much smaller than that of AY. Therefore, categorization (coding) of AY with a cut-off value of 55 reduces the amount of information and the discriminative abilities in both countries. This seems to be due to no obvious increase in mortality above the AY of 55 in the registry data of both Japan and Thailand, unlike that seen in the Major Trauma Outcome Study (MTOS) of the United States, from which the TRISS model was derived [1, 2]. Thus, we recommend the use of AY instead of cAY as a predictor variable in Asian countries. From the results of their M-statistic score calculation, Fujita et al. [11] concluded that the trauma population of a particular trauma center in Tokyo that has been participating in the JTDB differed significantly from that of the MTOS. Fujita et al. pointed out that modified TRISS coefficients should be adapted for outcome assessment based on the location of the injured population.

Our previous study [7] revealed that information on RR was missing in up to 18.8% of the JTDB data (2004–2007). In applying the model using only ISS, AY, cSBP, and cGCS, the Ps could be estimated in 38.1% of the patient data from which Ps was not calculated by the TRISS method. The model had sufficiently high discriminative ability (AUROCC = 0.923). Bouamra et al. [12] reported that a successful model (AUROCC = 0.947) using only GCS instead of RTS dramatically reduced the number of missing cases in the United Kingdom. However the equation of Bouamra et al. was more complicated than that of the TRISS method. Our recent study [13] demonstrated that simpler models using cGCS or cSBP with cAY and maximum AIS (or its coded value) showed high AUROCCs of >0.94, which seems to be suitable in more resource-constrained countries.

We found no additional reduction of the AIC in the model using cRR than the model without cRR in the Khon Kaen data. Moreover, multivariate analysis failed to show cRR as an independent predictor variable (Table 4). Information bias about collecting RR data might exist in

Table 4 Coefficients of logistic regression models of Khon Kaen data

Regression model	Intercept	βISS	βRTS	βAY	βcAY	βcSBP	βcGCS	βcRR
TRISS (AIS 85)	−1.2470	−0.0768	0.9544	×	−1.9052	0.6992	0.8941	0.2775
ISS, RTS, cAY	−0.7241	−0.0710*	0.8128*	×	−0.583*	×	×	×
	(0.3502)	(0.00548)	(0.0487)		(0.2509)			
	[4.27]	[168.2]	[278.5]		[5.40]			
ISS, RTS, AY	−0.2377*	−0.0707*	0.8215*	−0.0184*	×	×	×	×
	(0.3741)	(0.00550)	(0.0489)	(0.00463)				
	[0.4038]	[165.3]	[281.8]	[15.74]]				
ISS, AY, cSBP, cGCS, cRR	−0.1130	−0.0710*	×	−0.0177*	×	0.4458*	0.9669*	0.0960
	(0.4738)	(0.00562)		(0.00469)		(0.1019)	(0.0828)	(0.0606)
	[0.0569]	[159.8]		[14.29]		[19.13]	[136.4]	[2.515]
ISS, AY, cSBP, cGCS	−0.1565	−0.0731*	×	−0.0174*	×	0.4392*	1.0525*	×
	(0.4747)	(0.00546)		(0.00469)		(1.843)	(282.4)	
	[0.1087]	[179.0]		[13.80]		[18.43]	[282.4]	

Regression models are represented by their predictor variables

β regression coefficients

AUROCC area under receiver-operating characteristic curve, *AIS* abbreviated injury scale, *ISS* Injury Severity Score, *RTS* Revised Trauma Score, *AY* age year, *cAY* coded value of AY, *cSBP* coded value of systolic blood pressure, *cGCS* coded value of Glasgow Coma Scale score, *cRR* coded value of respiratory rate

* $p < 0.05$ (standard error) [χ^2 value]

Table 5 AUROCC and accuracy of models

Regression model	AUROCC Japan	Accuracy Japan (%)	AUROCC Khon Kaen	Accuracy Khon Kaen (%)
TRISS (USA)	0.9625	92.74	0.9628	96.33
ISS, RTS, cAY	0.9598	94.16	0.9657	96.60
ISS, RTS, AY	0.9624	94.38	0.9666	96.56
ISS, AY, cSBP, cGCS, cRR	0.9624	94.37	0.9667	96.66
ISS, AY, cSBP, cGCS	0.9617	94.25	0.9667	93.77

Regression models are represented by their predictor variables

AUROCC area under receiver-operating characteristic curve, *AIS* abbreviated injury scale, *ISS* Injury Severity Score, *RTS* Revised Trauma Score, *AY* age year, *cAY* coded value of AY, *cSBP* coded value of systolic blood pressure, *cGCS* coded value of Glasgow Coma Scale score, *cRR* coded value of respiratory rate

the Khon Kaen Trauma Registry, because the proportions of patients whose RR was >29/min or 6–9/min were quite small (Table 1). Thus, utilization of the model without cRR is recommended. In the model without cRR, the intercept can be zero for simplification because it was not statistically significant (Tables 3 and 4).

Finally, we should mention the limitations of the present study. Because of large amount of missing data for the TRISS predictors and outcome in the JTDB data, we could develop the models using 61.3% from registered BT patients. Recently, Tohira et al. [14] revealed that only 58.2% of the registered data of the JTDB from 2004 to 2008 had sufficient data on the TRISS Ps estimation and outcome, and that statistically significant differences existed in mean AY (74.8 vs. 51.2), in mean RTS (6.90 vs. 6.68), and in mean ISS (15.1 vs. 17.3) between outcome missing data and non-outcome missing data. They pointed out that selection bias may exist in research outputs gained from the extracted data from the JTDB by excluding patients with missing outcome and the TRISS predictors. However, we could demonstrate almost the same results with the Khon Kaen Trauma Registry data, which are substantially different from the JTDB in AY, RTS, and ISS. Thus, the assumable selection bias might not be important for interpretation of the results. At present, the tendency of the logistic regression models revealed in this study is observed only in the JTDB and the Khon Kaen Trauma Registry in Thailand. For generalization, our results must be verified by data from other Asian countries.

The JTDB has been using the AIS 90 [5], and The Khom Kaen trauma registry has been using the AIS 85 [6]. Both of these are out of date and insufficient for contemporary coding of injuries. Japan and Thailand has been preparing for utilization of AIS 2005 update 2008 [15], but implementation of nationwide coding under that version is not realized in either country. In the future, we should conduct this kind of research once again under the newest measure for quality assurance of our results.

Conclusions

For better prediction of Ps, the real number of AY should be used as a predictor variable instead of the coded value of AY in the TRISS method. The logistic regression model with the predictor variables of ISS, AY, and the coded value of SBP, GCS, and RR estimates the best prediction.

Information about RR seems to be less important for BT victims in Asian countries than in the United States, where the TRISS method was developed. The logistic regression model without cRR can provide the Ps with almost the same discriminative ability as the model that uses RR.

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Conflict of interest None.

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A decrease in lung cancer mortality following the introduction of low-dose chest CT screening in Hitachi, Japan

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ABSTRACT

Recent US clinical trial demonstrated that CT screening prevents lung cancer death among high risk individuals. However, it remains unclear whether wide implementation of low-dose CT screening for lung cancer can decrease mortality in the community. Among residents in Hitachi City (Japan), where nearly 40% of inhabitants aged 50–69 years were estimated to have participated in the screening at least once from 1998 through 2009, the trend of lung cancer mortality was described in relation to the timing of implementation of the CT screening. Cancer mortality data were obtained from regional cancer registry and standardized mortality ratio (SMR) of lung cancer was calculated for each 5-year period during 1995–2009. In both men and women aged 60 years or older, age-specific lung cancer mortality rates were generally lower during 2005–2009 as compared with those during 1995–2004. For combined men and women aged 50–79 years, SMR was nearly unity prior to or during introductory phase of CT screening and during early period of implementation; however, it was significantly decreased during 2005–2009, well after the implementation of CT screening, with SMR (95% confidence interval) being 0.76 (0.67–0.86). Results suggest that wide implementation of low-dose chest CT screening may decrease lung cancer mortality in the community 4–8 years after introduction of the screening.

1. Introduction

Screening for lung cancer using low dose computed tomography (CT) can detect smaller size of lung nodule than can chest radiography and thus has been expected to decrease lung cancer mortality. In June 2011, the National Lung Screening Trial (NLST) study group reported a 20% reduction in lung cancer mortality among persons randomly allocated to low dose CT screening compared with controls [1]. Based on a systematic review including the NLST study, the American College of Chest Physicians (ACCP) and the American Society of Clinical Oncology (ASCO) have released a clinical practice guideline, in which CT screening for lung cancer is recommended for high risk individuals [2]. In Japan, where CT screening for lung cancer was initiated first in the world [3] and has been implemented at community and workplace settings [4], evidence on the effectiveness of the CT screening is sparse and thus research is required to elucidate whether CT screening for lung cancer can decrease mortality.

Hitachi (Ibaraki prefecture), where low dose CT screening for lung cancer was initiated in the workplace in 1998 [5,6], is among areas with the largest number of the screening performed in Japan. Using data from a follow-up survey of 210 patients with lung cancer, 85% of which were on stage IA, detected on CT screening at Hitachi Medical Center and Hitachi Health Care Center, we reported an excellent survival (5-year survival of 90%) of these patients [7]. As of March 2006, nearly 30% of Hitachi citizens aged 50–69 is estimated to have received at least one CT lung cancer screening at either of the two medical facilities [7]. It would thus be of interest

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Table 1
The number of participants in low-dose chest CT screening in the two facilities[a] in Hitachi, Japan (as of March 2009).

Age (year)	Men	Women	Total
50–54	10,108	5131	15,239
60–64	6223	6363	12,586
70–74	1775	1826	3601
80 or older	167	146	313
Total	18,273	13,466	31,739

History of smoking: men 74.1%, women 8.3%; total 46.2%.
[a] Hitachi Health Care Center and Hitachi Medical Center.

whether CT screening for lung cancer had any impact on mortality at community level. Here, we report the trend of lung cancer mortality among Hitachi citizens in relation to the timing of screening implementation.

2. Materials and methods

In Hitachi Health Care Center (Hitachi Ltd., Hitachi), chest CT screening for lung cancer has been conducted for ages 50–69 years for employees, retired persons, and their spouse since in 1998. In Hitachi Medical Center (Hitachi) also initiated chest CT screening for lung cancer for community dwellers aged 50 years or older in 2001. Details of the screening procedure, the numbers of participants and patients with lung cancer, and clinical features of screen-detected cases in each facility have been described elsewhere [5–7].

Table 1 shows the number of participants of the chest CT screening by sex and age as of March 2009. A total of 31,739 participants received the screening at least once (total 83,342 screenings, mean 2.6 times) at Hitachi Medical Center or Hitachi Health Care Center. The majority of the participants (men 89%, women 85%) were in ages 50–69, with the mean age of all participants being 57 years. Because we did not obtain information on address of screening participants, we assumed that the proportion of Hitachi residents among total screening participants was the same as that among participants with screen-detected lung cancer (76%). Based on this assumption, 36% Hitachi residents aged 50–79 (men 43%, women 30%) and 40% Hitachi residents aged 50–69 (men 47%, women 33%) were estimated to have received the screening program as of March 2009. Of these, 14,661 were current or past smokers, and more than a half (54%) had never smoked cigarette in their lifetime.

First, we examined time trend of lung cancer mortality and incidence in Hitachi. For this purpose, we obtained from the Ibaraki Cancer Registry data on lung cancer death and incidence by sex- and 5-year age-group for each Hitachi City and Ibaraki prefecture each year from 1995 to 2009 (1995 to 2007 for incidence). We also collected sex- and age-specific population statistics, which were derived from residential registry, in Hitachi City during the same period. Using these data, we calculated lung cancer mortality rate and its exact 95% confidence interval, based on the binomial distribution, by sex and 10-year age group in Hitachi City for three 5-year periods (1995–1999, 2000–2004, 2005–2009), each representing "stage of no or the beginning of CT screening program", "early stage of implementation", and "later stage of implementation".

Next, we compared the lung cancer mortality in Hitachi City with that for overall Japan. We first calculated the expected number of death from lung cancer by multiplying the sex- and age (5 years interval)-specific number of residents in Hitachi City by their corresponding mortality rate of lung cancer in Japan, and then summed. We then calculated standardized mortality ratio (SMR) as the observed number of death divided by the expected number of death as well as its exact 95% confidence interval based on the Poisson distribution. We repeated this analysis by using sex- and age-specific mortality data of Ibaraki prefecture. We also calculated age-standardized incidence rate of lung cancer in Hitachi for each year from 1995 to 2007 (standard population, the 1985 model population of Japan). All analyses were done with Stata version 10.1 (StataCorp, College Station, TX).

3. Results

Table 2 shows lung cancer mortality rate for each 5-year period by sex and age group. In men between ages 60 and 74, lung cancer mortality was slightly lower during the second period of 2000–2004 (early stage of CT screening), whereas it showed a large reduction during the third period of 2005–2009 (stable stage of CT screening) as compared with that during 1995–1999 (no CT screening or its introductory stage). Men aged 75–79 also showed a large reduction in mortality in the third period. Similarly, women aged 60 or older showed a decreasing trend of lung cancer mortality during the course of time.

Fig. 1 shows the time trend of age-standardized lung cancer mortality ratio (ages 50–79 year) for men and women combined in Hitachi using sex- and 5-year age group-specific lung cancer mortality statistics of whole population of Japan for calculation, together with that of age-standardized lung cancer incidence rate (ages 50–79 year). This analysis was limited to those aged 50–79 years, the majority (>99%) of CT screening participants in Hitachi. During the period of 1995–1999, when CT screening was not provided or has just introduced in Hitachi area, lung cancer mortality was comparable to that of national and prefectural levels; SMR (95% CI) was 0.95 (0.83, 1.08). There was also no material difference in mortality during the second period representing early stage of CT screening implementation; SMR (95% CI) was 0.97 (0.86, 1.09). During the third period (2005–2009), which corresponds to 4–8 years after the implementation of CT screening in both medical facilities in Hitachi, we observed a statistically significant, 24% reduction in lung cancer mortality; SMR (95% CI) was 0.76 (0.67, 0.86). Similar results were obtained when sex- and age-specific lung cancer mortality data of Ibaraki prefecture were used in calculating the expected number of lung cancer death in Hitachi; SMR (95% CI) was 1.04 (0.91, 1.17), 1.04 (0.92, 1.16), and 0.79 (0.69, 0.89) for 1995–1999, 2000–2004, and 2005–2009, respectively. In contrast, age-standardized incidence rate of lung cancer in Hitachi appears to increase after the introduction of CT screening in Hitachi Health Care Center (1998) and Hitachi Medical Center (2001).

To further examine which sex- and age-group showed reduction in lung cancer mortality, we repeated the above analysis for each sex- and/or age (10-year interval)-group using sex- and age (5-year interval)-specific lung cancer mortality of overall Japan (Table 3). For all the three age groups combined, a statistically significant decrease in SMR during the third period of 2005–2009 was observed in both men and women (men 24%, women 26%). A statistically significant decrease in lung cancer mortality was observed during the third period in men in 60s (32%), men in 70s (24%), and women in 70s (33%). Women in 60s also showed a decrease (25%), albeit statistically non-significant, in lung cancer mortality during that period.

4. Discussion

In the present study, we examined chronological changes of lung cancer mortality among residents of Hitachi City, where chest CT screening has been widely implemented as a community preventive service. As a result, we found a significant reduction in lung cancer mortality among target age groups 4–8 years after introduction of CT screening.

Table 2
Lung cancer mortality rate by sex, age, and period in Hitachi, Japan.

Age (year)	Period	Men			Women		
		Lung cancer death	Total population[a]	Lung cancer mortality rate (95% CI), per 100,000	Lung cancer death	Total population	Lung cancer mortality rate (95% CI), per 100,000
50–79	1995–1999	194	155,034	125 (108, 142)	57	166,975	34 (26, 44)
	2000–2004	228	169,910	134 (117, 153)	57	179,002	32 (24, 41)
	2005–2009	203	187,636	108 (94, 124)	53	194,686	27 (20, 36)
50–59	1995–1999	24	75,647	32 (20, 47)	11	74,608	15 (7, 26)
	2000–2004	31	71,952	43 (29, 61)	9	74,167	12 (6, 23)
	2005–2009	29	70,589	41 (28, 59)	10	71,128	14 (7, 26)
60–69	1995–1999	75	53,376	140 (111, 176)	18	53,451	34 (20, 53)
	2000–2004	80	66,153	121 (96, 150)	19	63,347	30 (18, 47)
	2005–2009	61	72,528	84 (64, 108)	18	73,492	24 (15, 39)
70–79	1995–1999	95	26,011	365 (296, 446)	28	38,916	72 (48, 104)
	2000–2004	117	31,805	368 (304, 441)	29	41,488	70 (47, 100)
	2005–2009	113	44,519	254 (209, 305)	25	50,066	50 (32, 74)

CI, confidence interval.
[a] The sum of the population each year.

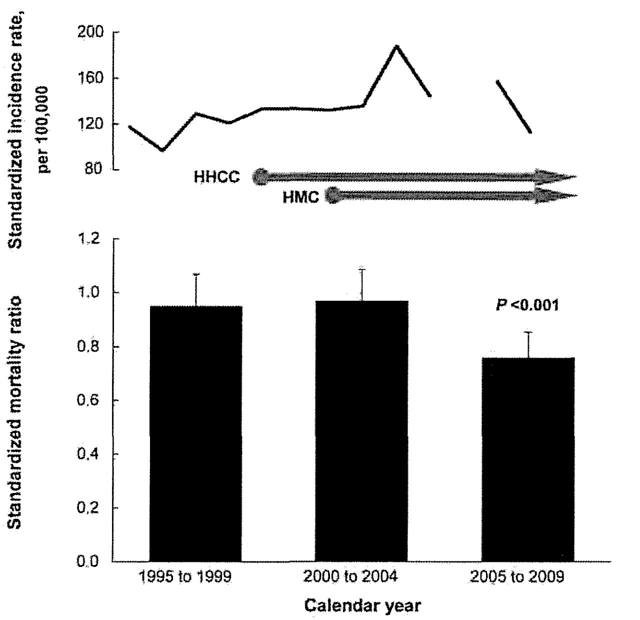

Fig. 1. Time trend of standardized mortality ratio (based on sex- and age (5-year interval)-specific lung cancer mortality in Japan) and standardized incidence rate (standard population is the 1985 model population of Japan. Data for 2005 is not shown due to a flaw in registration system) of lung cancer among residents aged 50–79 years in Hitachi, Japan. HHCC, Hitachi Health Care Center; HMC, Hitachi Medical Center. Arrows indicate implementation period of CT screening. Error bar indicates 95% confidence interval.

A recent finding from NLST provided strong evidence supporting the effect of low-dose CT screening in decreasing lung cancer mortality among those with a history of smoking [1]. Protective effect of the CT screening on lung cancer mortality was also supported from a prognostic investigation of patients with lung cancer detected on CT screening in the US [8]. Similarly, we previously reported an excellent long-term survival of patients with lung cancer detected on the CT screening in Hitachi area [7]. Lung cancer mortality in a cohort of smokers who received CT screening for lung cancer in New York State was compared with two unscreened cohorts (CPS-II and CARET), with adjustment for age, sex, and smoking history [9]. The authors found a significant reduction of deaths from lung cancer (36% and 64% for CPS-II and CARET, respectively). Our present finding is in line with these results and provides further evidence to support that community-wide implementation of CT screening can contribute to the reduction of lung cancer mortality in the community.

In the present observation among residents of Hitachi City, a significant reduction of lung cancer mortality was observed during 2005–2009, which corresponds to 4–8 years after introduction of chest CT screening in both facilities. The timing of reduction in lung cancer mortality observed in the present study agrees well with that in the New York State cohort [9], in which the two rounds of screening provided a mortality reduction starting in the 6th–8th year after enrollment.

It remains unclear whether chest CT screening for lung cancer can decrease mortality among nonsmokers. However, given that more than a half of participants in CT screening for lung cancer at the two facilities in Hitachi City were nonsmokers and that 60% of lung cancer patients detected on that screening (as of March 2006) were nonsmokers, it may be reasonable to infer that observed reduction in lung cancer mortality among Hitachi residents may be due, at least in part, to the effect of CT screening on lung cancer mortality among nonsmokers. In fact, we also observed a significant reduction in lung cancer mortality for women, majority of whom are never smokers, during the third period (2005–2009), suggesting that CT screening is also effective in preventing lung cancer death among nonsmokers. Moreover, data from an ongoing cohort study of CT-screening participants including nonsmokers in Japan showed a reduction in lung cancer mortality [10]. The ACCP and ASCO guideline stated, based on available evidence, that CT screening for lung cancer should not be performed for low risk individuals [2]. However, given that nearly one-fourth of lung cancer in the world are unrelated to smoking [11] and in Japan, 31% and 80% of lung cancer deaths for men and women, respectively, are probably not related to smoking [12], the effectiveness of CT screening for lung cancer among nonsmokers should be evaluated in future studies.

The limitations of the present study warrant mention. The present analysis based on community level data, compared with cohort or randomized control studies, is more likely to suffer from bias. As a major concern, decreasing trend in lung cancer mortality observed in this population might be ascribed to factors other than chest CT screening. Of such factors, smoking is potentially important. Although long-term, representative data are not available on smoking prevalence in Hitachi, recent statistics on health indicators showed no material difference in smoking prevalence between Hitachi City and Ibaraki Prefecture [13]. In addition, no reduction

Table 3
Standardized mortality ratio[a] and its 95% confidence interval by sex, age, and period.

Age (year)	Men			Women		
	1995–1999	2000–2004	2005–2009	1995–1999	2000–2004	2005–2009
Total (50–79)						
O/E	194/201.4	228/227.6	203/267.1	57/61.8	57/65.2	53/71.3
SMR	0.96 (0.83, 1.11)	1.00 (0.88, 1.14)	0.76 (0.66, 0.87)	0.92 (0.70, 1.19)	0.87 (0.66, 1.13)	0.74 (0.56, 0.97)
50–59						
O/E	24/28.9	31/28.5	29/29.1	11/10.7	9/11	10/10.2
SMR	0.83 (0.53, 1.23)	1.09 (0.74, 1.54)	1.00 (0.67, 1.43)	1.03 (0.52, 1.85)	0.82 (0.38, 1.56)	0.98 (0.47, 1.81)
60–69						
O/E	75/76.2	80/82.5	61/89.2	18/18.2	19/21.1	18/24.0
SMR	0.98 (0.77, 1.23)	0.97 (0.77, 1.21)	0.68 (0.52, 0.88)	0.99 (0.59, 1.56)	0.90 (0.54, 1.40)	0.75 (0.45, 1.19)
70–79						
O/E	95/96.3	117/116.6	113/148.8	28/33	29/33.1	25/37.2
SMR	0.99 (0.80, 1.21)	1.00 (0.83, 1.20)	0.76 (0.63, 0.91)	0.85 (0.56, 1.23)	0.88 (0.59, 1.26)	0.67 (0.44, 0.99)

O, observed number of death; E, expected number of death; SMR, standardized mortality ratio.
[a] The expected number of lung cancer death was estimated using mortality data for whole population of Japan.

in SMR for cardiac disease, another smoking related disease, was observed during 2005–2009 in Hitachi (1.15 and 1.11 for men and women, respectively [13]). These data argue against smoking cessation as a plausible explanation for the reduction of lung cancer mortality observed among Hitachi residents. An increase of the incidence of lung cancer after the implementation of CT screening in the two medical facilities in Hitachi provides an additional support for the specific effect of CT screening, rather than other factors, in decreasing lung cancer mortality. Finally, we are uncertain whether the present finding in Hitachi could be generalized to other communities in Japan or other countries, which have different background in terms of risk factors for lung cancer as well as availability of medical service for patients with lung cancer detected on the screening.

5. Conclusion

In Hitachi City, a significant reduction in lung cancer mortality was observed 4–8 years after introduction of low-dose CT screening for lung cancer, suggesting that wide implementation of CT screening can decrease lung cancer mortality at community level. To enhance the benefit of CT screening and minimize its harm, future studies should be designed to address issues including clinical work-up of in-determined nodules, cost-effectiveness, and integration of smoking cessation practices [14].

Conflicts of interest

There are no conflicts of interest to disclose.

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原著論文

軽症頭部外傷患者における頭部CT適応基準の作成と検証

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要旨 【目的】入院経過観察あるいは外科的治療を必要とするような頭蓋内出血性病変を有する軽症頭部外傷患者を見逃すことなく（感度100%を保ち），なおかつ可及的に特異度の高い頭部CT撮影の判断基準を作成すること。【方法】2006年1月1日から2010年3月31日までに当病院救急科を受診した軽症頭部外傷患者（来院時GCSスコア15を満たす）を対象に予測因子候補11項目を設定し後方視的に調査した。対象を16歳以上60歳未満の若年群と60歳以上の高年齢群の2群に分けて解析を行った。2006年1月1日から2007年12月31日をDerivation期間とし，この11項目に関し頭部CT陽性例と陰性例にて単変量解析を行った。有意差が認められた項目のみを選択し，これらを候補とし2進再帰分割法を行い，予測因子を決定し頭部CT撮影の必要性に重点を置いた臨床判断基準を作成した。2008年2月1日から2010年3月31日をValidation期間とし，Derivation dataで導き出された予測因子について2進再帰分割法を行い，その妥当性を検証した。【結果】若年群では抗凝固薬あるいは抗血小板薬の内服歴，一過性意識消失あるいは健忘，鎖骨より頭側の創傷の3項目のどれかを有すれば頭部CT所見陽性に対する感度が100%となった。高年齢群では抗凝固薬あるいは抗血小板薬の内服歴，全汎性頭痛，一過性意識消失あるいは健忘の3項目のどれかを有すれば頭部CT所見陽性に対する感度が100%になった。【考察】このように年齢別の判断基準を作成することで，これまでの研究より少ない項目数の予測因子で臨床的に重要な頭蓋内損傷を有する軽症頭部外傷患者を見逃すことなく頭部CT撮影数を減少させうる。
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はじめに

頭部外傷患者のうち来院時の意識状態が良好な患者群（来院時のGlasgow coma scale（GCS）スコアが14あるいは15）は軽症頭部外傷患者と分類され，全頭部外傷患者の約80%を占めており[1]，救急外来でよくみる疾患の一つとなっている。その中でも来院時のGCSスコアが15の頭部外傷患者をminor head injuries（以下MHI）として，その診断と治療に関して1980年以降活発に議論[2-5]されている。

これまでに各国で軽症頭部外傷患者に対する頭部CT撮影基準を含めた診断と治療のガイドラインが作成されている[6,7]が，頭部CT異常所見を有する患者に対する感度・特異度の両者とも高い数値を満たし，世界的に統一された頭部CT撮影基準は未だ存在しない。

これまでの研究成果[3-7]を踏まえ，本研究ではMHIを対象としてリスク因子の有無および頭部CT所見を調査した。頭蓋内病変のリスクを持つ患者の臨床所見の重要度を解析し，ハイリスク患者を予測しう

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る因子を同定し，その結果を用いて，臨床上重要な頭蓋内病変を有する軽症頭部外傷患者を見逃すことなく，かつ，より効率的な頭部CT撮影基準を作成することを目的とした。すなわち感度100%を達成し，なおかつ可及的に高い特異度を達成する新しい頭部CT撮影基準を作成することが本研究の目的である。また，これまでの主要な論文[3-5]において，60-65歳以上の患者はハイリスクグループであるとの結果が得られているため，対象を60歳以上の高齢者とそれ以外の若年者に分類し，個々のグループでCT撮影の必要性に重点を置いた臨床判断基準を作成することとした。

方　法

1. 対象患者

2006年1月1日から2010年3月31日までに当病院の救急科を受診した来院時GCSスコア15の軽症外傷患者を対象とした。2006年1月1日から2007年12月31日をDerivation dataの期間に，2008年2月1日から2010年3月31日をValidation dataの期間とした。

本研究の参入基準は，1）16歳以上のGCSスコア15の軽症頭部外傷患者，2）救急車にて搬送された患者，3）来院時頭部CT撮影が施行された患者，4）翌日患者本人に電話連絡が取れたもの，とした。

また除外基準は，Haydelら[3]の報告に基づいて作成し，1）痙攣，2）何らかの意識消失にて転倒し頭部外傷を受傷した患者，3）受傷後24時間以上経過した患者，4）頭部の他にAIS（abbreviated injury scale）3以上の外傷を有する患者，5）妊娠中の女性，とした。更に16歳以上60歳未満の患者群を若年群，60歳以上の患者群を高年齢群とした。

2. 調査項目と定義

2001年から当施設にて採用している軽症頭部外傷CT撮影基準とHaydelらが報告している頭部CT撮影基準[3]を参考にして，予後予測因子候補11項目を設定した（Table 1）。「一過性意識消失あるいは健忘」は，頭部を受傷した直後に意識消失を伴ったがその後意識回復した患者，あるいは頭部を受傷した直後からの記憶を一時的に失っている患者と定義した。「全汎性頭痛」は，創傷部位に限局しない頭部全体の疼痛を伴う患者と定義した。鎖骨より頭側の創傷は，擦過傷・挫創など処置を要する創傷を鎖骨より頭側の部位に伴う患者と定義した。

Table 1. Eleven factors predict severe head trauma.

①taking alcohol and/or medication influence on consciousness
②transient loss of consciousness and/or amnesia
③diffuse headache
④having history of neurosurgical operation
⑤receiving oral anticoagulant and/or antiplatelet therapy
⑥vomit more than 2 times
⑦vomit once
⑧nausea
⑨wound over clavicular to head
⑩JCS 2 or more on EMS arrival
⑪impaired hearing after injury

JCS: Japan coma scale, EMS: emergency medical service

Table 2. Protocol for head CT abnormality.

①loss of vadum
②exclusion of interpeduncular cistern/midline shift
③over 1cm/mass effect subdural/epidural hematoma
④pneumocephalus
⑤more 2 places/diffuse traumatic subarachnoid hemorrhage
⑥hemorrhage in both hemisphere
⑦over 1cm/multiple contusion
⑧cerebral hernia
⑨hemorrhage in posterior cranial fossa
⑩depressed fracture
⑪diffuse brain swelling
⑫diffuse axonal injury

*Having 1 or more factor → head CT abnormality (+)
*No factor → head CT abnormality (-)

3. 頭部CT陽性所見の定義

頭部CTの陽性所見は，Atzemaら[8]の報告に基づいて設定した（Table 2）。頭部CT上これらの所見を1項目以上認めた患者を頭部CT所見陽性とした。

4. 解析方法

Table 1にあげた11項目に関して，頭部CT陽性例

Table 3. Univariate analysis (16-59 years old).

Prediction factor	Positive % (n=47)	Negative % (n=1,158)	p value
receiving oral anticoagulant and/or antiplatelet therapy	34.0	12.8	<0.001
diffuse headache	25.5	5.1	<0.001
transient LOC and/or amnesia	27.6	6.9	<0.001
wound over clavicular to head	8.5	4.9	<0.001
vomit more than 2 times	4.2	0.9	<0.001
impaired hearing after injury	23.4	12.9	<0.001
having history of neurosurgical operation	8.5	3.7	<0.001
JCS 2 or more on EMS arrival	57.4	22.5	<0.001
taking alcohol and/or medication influence on consciousness	12.7	11.5	0.08
vomit once	2.1	2.8	0.92
nausea	6.3	5.9	0.91

LOC: loss of consciousness, JCS: Japan coma scale, EMS: emergency medical service

と陰性例にて単変量解析を行った。有意差が認められた項目のみを選択し，これらを予測因子候補として2進再帰分割法を行った。単変量解析の検定にはχ^2検定を用いた。2進再帰分割法では，対数尤度比χ^2が大きい因子から順に分割させた。検定における有意水準を0.05未満とした。統計解析ソフトウエアにはJMP 6.0（SAS社）を用いた。

結　果

1. 対象患者についての記述

2006年1月1日から2010年3月31日に当病院の救急科を受診した来院時GCSスコア15の軽症頭部外傷患者3,134例から，本研究の参入基準を満たした患者2,990例を研究対象とし，除外項目を満たす患者を除いた2,787例を解析対象とした。平均年齢は49歳（範囲は16-97歳，標準偏差15），男女比は57：43である。また，緊急脳神経外科手術を要した患者は0.28%（8例）で全て60歳以上であり，死亡例はなかった。

2. 判断基準の作成

Derivation dataの期間において解析対象患者数は1,440例であり，16歳以上60歳未満は1,205例，60歳以上は235例であった。

1）若年群

16歳以上60歳未満の患者群1,205例において単変量解析を行い，抗凝固薬あるいは抗血小板薬の内服歴，全汎性頭痛，一過性意識消失・健忘，鎖骨より頭側の創傷，2回以上の嘔吐，外傷後難聴，脳外科手術の既往，救急隊到着時JCS 2以上の8項目で有意差を認めた（**Table 3**）。有意差のなかった3項目は予測因子候補から外した。

次に，これら8項目について2進再帰分割法を行い，抗凝固薬あるいは抗血小板薬の内服歴，一過性意識消失あるいは健忘，鎖骨より頭側の創傷の3項目でふるい分けをすることで全ての頭部CT所見陽性群を選択することができ，この3項目のいずれかを有する場合，頭部CT所見陽性に対する感度が100%に達するとの結果（**Table 5a**）を得た。

2）高年齢群

次に60歳以上の患者群235例を対象とした。単変量解析において，抗凝固薬あるいは抗血小板薬の内服歴，全汎性頭痛，一過性意識消失・健忘，2回以上の嘔吐，救急隊到着時JCS（Japan coma scale）2以上，外傷後難聴の6項目で有意差を認め（**Table 4**），有意差のない5項目は予測因子候補から外した。

この6項目を候補として2進再帰分割法を行い，抗凝固薬あるいは抗血小板薬の内服歴，全汎性頭痛，一過性意識消失あるいは健忘の3項目でふるい

Table 4. Univariate analysis (≥ 60 years old).

Prediction factor	Positive % (n=9)	Negative % (n=226)	p value
receiving oral anticoagulant and/or antiplatelet therapy	66.6	12.8	<0.001
diffuse headache	22.2	4.0	<0.001
transient LOC and/or amnesia	44.4	7.1	<0.001
wound over clavicular to head	22.2	3.1	<0.001
vomit more than 2 times	11.1	8.8	0.0019
impaired hearing after injury	11.1	6.2	0.0201
having history of neurosurgical operation	55.5	39.4	0.0878
JCS 2 or more on EMS arrival	33.3	23.5	0.4655
taking alcohol and/or medication influence on consciousness	11.1	4.4	0.2189
vomit once	11.1	2.2	0.7892
nausea	11.1	6.2	0.8932

LOC: loss of consciousness, JCS: Japan coma scale, EMS: emergency medical service

Table 5a. Sensitivity and specificity with combinations of factors (16-59 years old) - Derivation.

Prediction factor	Sensitibity %	Specificity %
receiving oral anticoagulant and/or antiplatelet therapy	84.3	79.1
receiving oral anticoagulant and/or antiplatelet therapy and/or transient LOC and/or amnesia	96.8	34.9
receiving oral anticoagulant and/or antiplatelet therapy and/or transient LOC and/or amnesia and/or wound over clavicular to head	100	18.9

LOC: loss of consciousness

Table 5b. Sensitivity and specificity with combinations of factors (≥ 60 years old) - Derivation.

Prediction factor	Sensitibity %	Specificity %
receiving oral anticoagulant and/or antiplatelet therapy	73.9	80.7
receiving oral anticoagulant and/or antiplatelet therapy and/or transient LOC and/or amnesia	78.5	31.8
receiving oral anticoagulant and/or antiplatelet therapy and/or transient LOC and/or amnesia and/or diffuse headache	100	21.4

LOC: loss of consciousness

分けをすることで全ての頭部CT所見陽性群を選択することができ，この3項目のいずれかを有する場合，頭部CT所見陽性に対する感度が100%に達するとの結果（Table 5b）を得た。

3. 判断基準の検証

Validation dataの期間において解析対象患者数は1,347例であり，16歳以上60歳未満は1,127例，60歳以上は219例であった。

1）若年群

16歳以上60歳未満の患者群1,127例において抗凝固薬あるいは抗血小板薬の内服歴，一過性意識消失あるいは健忘，鎖骨より頭側の創傷の3項目を候補として2進再帰分割法を行うことにより，全ての頭部CT所見陽性群を選択することができ，この3項目のどれか1項目以上を有する場合，頭部CT所見陽性に対する感度が100%になった（Table 6a）。

Table 6a. Sensitivity and specificity with combinations of factors (16-59 years old) - Validation.

Prediction factor	Sensitibity %	Specificity %
receiving oral anticoagulant and/or antiplatelet therapy	85.7	74.1
receiving oral anticoagulant and/or antiplatelet therapy and/or LOC and/or amnesia	92.1	33.2
receiving oral anticoagulant and/or antiplatelet therapy and/or LOC and/or amnesia and/or wound over clavicular to head	100	19.2

LOC: loss of consciousness

Table 6b. Sensitivity and specificity with combinations of factors (≥ 60 years old) - Validation.

Prediction factor	Sensitibity %	Specificity %
receiving oral anticoagulant and/or antiplatelet therapy	79.2	68.4
receiving oral anticoagulant and/or antiplatelet therapy and/or LOC and/or amnesia	100	20.8

LOC: loss of consciousness

2）高年齢群

次に60歳以上の患者群219例を対象とした。抗凝固薬あるいは抗血小板薬の内服歴，一過性意識消失あるいは健忘，全汎性頭痛の3項目を候補として2進再帰分割法を行うことにより，全ての頭部CT所見陽性群を選択することができ，抗凝固薬あるいは抗血小板薬の内服歴，一過性意識消失あるいは健忘の2項目のいずれかを有する場合，CT所見陽性に対する感度が100%になった（**Table 6b**）。

考　察

来院時GCSが14点以下の患者に対しては入院治療や頭部CT撮影の有用性が示されているが，多くの論文が指摘しているようにMHIにおいて頭部CTにて臨床上重要な異常所見を認める頻度は10%以下であり，更に外科的治療を必要とする頻度は1%以下[3]と非常に少ない。つまり，多くの患者は積極的な医学的介入を必要としないが，稀に致死的な頭部外傷を有し、脳神経外科手術を含めた治療を必要とする患者が存在する。重症化する頭蓋内病変を有する患者を見逃すことはあってはならないが，救急医・脳神経外科医・放射線科医・放射線技士の負担やコスト面からは頭部CT撮影数や入院患者数の削減が望ましく，このように相反するニーズが存在するため，MHIの診断と治療に関しては慎重に考慮する必要がある。

日本神経外傷学会ガイドライン第2版にて軽症頭部外傷患者に対する頭部CT撮影基準[9]が作成された。それを検証した研究は未だ少ないため，これまでの研究の結果や各国での頭部CT撮影基準を踏まえ，本研究ではMHIを対象としてリスク因子の有無および頭部CT所見を調査し，頭蓋内病変のリスクを持つ患者の臨床所見の重要度を解析し，重症化する可能性のあるハイリスク患者を予測しうる因子を同定することに成功した。導かれた判断基準は日本神経外傷学会ガイドラインの頭部CT撮影基準と矛盾せず，臨床での利用を考慮できるものとなった。

本研究では，まず対象とする患者を年齢により2群に分けた点が，これまでにない試みであるといえる。既知の解析結果[3]から60歳以上の患者はリスクを有することがすでに予測されており，高年齢者と若年者では異なる徴候が存在するならば，それぞれの病態に合ったCT適応基準が必要である。本研究ではそれを明らかにしたといえる。

このように年齢別の判断基準を作成することで，これまでの研究[3,4]より少ない予測因子で臨床的に

重要な頭蓋内損傷を有する軽症頭部外傷患者を見逃すことなく，頭部CT撮影数を減少させうる。

本研究の限界点としては，後ろ向き研究であること，単独施設の研究であること，高年齢群での頭部CT所見陽性患者数が少ないことなどが挙げられる。その結果，Validation期間内の高年齢群で「抗凝固薬あるいは抗血小板薬の内服歴」と「一過性意識消失あるいは健忘」の2項目のみで感度100%を達成しており，Validation dataの患者数が不十分であったことは否めない。しかしながら，より少ない予測因子で感度100%に達したことはDerivation dataの期間で得られた結果に含まれるものであり，それを否定するものではない。

今後，本研究の結果の客観性を高め，広く臨床の現場で利用されるためには，前向きの多施設研究を行う必要があると考える。

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ABSTRACT

Clinical decision rules for the indication of computed tomography in adults with minor head injury

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Objective: The objective of the present study is to create clinical decision rules for head computed tomography (CT) that enable highly sensitive detection of intracranial hemorrhage requiring hospitalization or surgery, and highly specific diagnosis.
Methods: Patients with Minor Head Injuries (MHI) who presented with Glasgow coma scale (GCS) score of 15 who visited the emergency department of our center between January 1, 2006 and March 31, 2010 were retrospectively investigated with regard to 11 predictor candidates. Patients were divided into younger (16 to 59 years of age) and elderly (360 years of age) groups for analysis. Using the period from January 1, 2006 to December 31, 2007 as the derivation period, univariate analysis was performed for the 11 predictor candidates using positive (CT abnormality present) and negative (absent) results on head CT as the outcome. Factors with significant differences were identified and recursive partitioning analysis was used to determine the smallest combination of prognostic factors that yielded a sensitivity of 100% for positive results on head CT. Based on the results, clinical decision rules focusing on the necessity of CT were created. In addition, using the period from February 1, 2008 to March 31, 2010 as the data validation period, the validity of the prognostic factors derived above was determined using recursive partitioning.
Results: In the younger group, sensitivity for positive results on head CT was 100% when they have any of the following three predictors: receiving oral Anticoagulant and/or Antiplatelet therapy, transient loss of consciousness (LOC) and/or amnesia, and Wound over clavicular to head. In the elderly group, sensitivity for positive results on head CT was 100% when they have any of the following three predictors: receiving oral Anticoagulant and/or Antiplatelet therapy, transient LOC and/or amnesia, and diffuse headache.
Discussion: By creating age-specific clinical decision rules, it may be possible to reduce the number of head CT taken for MHI without overlooking patients who have clinically important intracranial injuries using fewer predictors than in previous studies.
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Keywords: predictor, oral anticoagulant therapy, oral antiplatelet therapy, transient loss of consciousness
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原著論文

頭痛患者におけるクモ膜下出血の見逃し回避を目指した予測スコア（subarachnoid hemorrhage prediction score）の開発

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要旨　**背景**：クモ膜下出血（subarachnoid hemorrhage; SAH）の予後は早期診断に依存し，診断の遅れはmorbidityやmortalityを悪化させる。しかしながら，初診の段階で12%のSAHが見逃されているとの報告もあり，発症初期における高精度の予測が必要とされている。**目的**：頭痛を主訴に救急搬送された症例でSAHを疑わせる客観的予測因子を同定し，これらを組み合わせてSAHの有無を予測するスコアを策定すること。**対象と方法**：2001年より9年間で頭痛を主訴に救急搬送された症例のうち，外傷，酩酊，昏睡の症例や，最終転帰不明の症例を除いた573例を対象とした。このうち2001年1月1日～2006年12月31日の356例について頭部CT，腰椎穿刺でSAHと診断されたSAH群（n=88）と認めなかった対照群（n=268）に分け，バイタルサインや検査値など数値で表される項目を調査し，単変量並びに多変量ロジスティック解析を施行して予測因子を決定し，それらを基にSAH予測スコア（SPS）を作成した。次に2007年1月1日～2009年12月31日の217例を用いて，作成された予測スコアを検証した。**結果**：臨床の場面での使い易さを踏まえ，白血球数>8,000(/μl)，血糖値>130(mg/dl)，血清K値<3.5(mEq/l)，収縮期血圧>140(mmHg)という因子とカットオフ値が導き出された。これらの予測因子に点数を定め，SPSとして各群に点数付けを行った。SPS=0点の患者において，SAHは存在しなかった。更にSPSが上昇するに従いSAHのリスクも高まった。また，検証群においてもSPSについて同様の結果を得た。**結語**：SPSを用いることにより，救急外来において，見逃し回避を重視したSAH予測が可能となる。
（日救急医会誌. 2011; 22: 305-11）
キーワード：収縮期血圧，血糖値，カリウム値，白血球数，臨床意思決定

背景と目的

SAHは発症すると40%から60%もの人が何らかの障害を負うか，死亡に至るといわれている[1-3]。更にその予後は早期診断に強く依存している[2,3]。にもかかわらず，SAHは初診の段階で12%もの見逃しがあるといわれている[3]。SAHを疑うきっかけとしてはしばしば「突然の頭痛」といわれるが，そういった典型的な頭痛ではないSAHの患者もいる[1]。また「突然の頭痛」の強弱や性状について定義があるわけではなく典型的と考えられるような訴えに頼った検索方法ではSAHの見逃しにつながると考えられる。加えて頭痛以外の症状（意識消失，嘔気・嘔吐，項部硬直など）も，SAHでない頭痛患者に一般的に認められるもの[4]であり非特異的である。頭痛を含めこういった所見は臨床現場におけるSAH診断の判断材料としては非常に重要ではあるが，これらのみに頼った判断では観察者の主観が影響することも考えられ，客観性に欠ける部分がある。

また，診断のための検査として多くの論文[1,2,5]がSAHを疑った場合，まず頭部CTを行う，としてい

Highly sensitive, subarachnoid hemorrhage prediction score for patients with acute headache
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る。しかし，SAHを疑う指標としては上述したような数値で表せないものがほとんどであり，SAHのスクリーニングの根拠となる明確な指標は現時点では存在しない。最近，SAHに対するclinical decision ruleが発表された[6]が，頭痛の種類を限定しておりinclusion criteriaが厳しくルール自体も単独ではないため，臨床現場で使用しにくい印象がある。またルールが導き出された群以外での検証が行われておらず，その外的妥当性に関して十分な検証がなされているわけではない。

そこで，本研究において我々は，SAHを示唆する予測因子を客観性の高い数値にて同定し，これらの因子を組み合わせてSAHの予測スコアを作成し，その検証を試みた。

対象と方法

1. 患　者

2001年1月1日から2009年12月31日までの9年間に頭痛を主訴に救急車で搬送され，頭部CTを施行された1,578名を対象とし，当センター救急科診療録，電子カルテ等を用い後ろ向き研究を行った。2001年1月1日～2006年12月31日に来院した875名をderivation群，2006年1月1日～2009年12月31日に来院された703名をvalidation群として検証を行った。derivation群について外傷（n=131），アルコール（n=24）など頭痛の原因が明らかであった症例や，主訴は頭痛であったが搬送時に既に昏睡状態（GCS<9）であった症例（n=53）は除外した。また受診当日に頭部CT等にてSAHでないと診断された症例のうち翌日以降に入院・来院がなく後日SAHでなかったことが確認できなかった症例（n=310）は除外とした。最終的なderivation群は計356名であり，これらをクモ膜下出血群（SAH+群）88名とコントロール群（SAH-群）268名に分け，検証を行った。SAHの確定診断は頭部CTにてクモ膜下出血を認めるもの，もしくは腰椎穿刺にてSAHと診断されたものとした（Fig. 1）。

2. 予測因子の抽出とスコアリング

両群において，救急外来にて簡便に用いやすいと考えられた①性別，②年齢，③収縮期血圧（systolic blood pressure; SBP）（mmHg），④脈拍，⑤呼吸数，⑥体温（℃），⑦白血球数（white blood cell; WBC）（/μl），⑧ヘマトクリット（%），⑨血糖値（blood sugar; BS）（mg/dl），⑩血清ナトリウム（Na）値（mEq/l），⑪血清カリウム（K）値（mEq/l），⑫血清クロール（Cl）値（mEq/l）などの数値として表わせる客観性の高い因子を過去の救急部診療録，電子カルテより調査した。その後，患者データは，匿名かつ非連結化し，解析を進めた。上記項目に対し2群間で単変量解析を用いて比較検討を行った。単変量解析にて有意であった因子についてreceiver-operating characteristic（ROC）曲線を描き，感度と1-特異度が最も良いとされる値に近く，臨床現場で用いやすいことを考慮してカットオフ値を設定した。このカットオフ値を基に予測因子を名義変数化し，SAHの有無を目的変数としてロジスティック回帰分析を行った。有意であった予測因子について点数を与え，SAH予測スコア（subarachnoid hemorrhage prediction score; SPS）を作成した。このSPSをderivation群にあてはめ，SPSの検証を行った。ここで，derivation群について欠損値のある症例（n=49）はスコア付けができず除外したため，最終的なSPS検証を行ったderivation群は307例となった。また，validation群についても除外されずに残った数は217例であったが欠損値のある症例（n=14）を除外したところ，最終的に203名が対象となった。

3. 統計解析

名義変数についてはχ^2検定を，連続変数についてはt検定を用いた。ロジスティック回帰式の係数は，最尤推定法に求め，予測因子ついては，尤度比χ^2検定を行った。有意水準は$p<0.05$とした。解析ソフトウエアにはJMP6.0（SAS社）を用いた。

結　果

derivation群とvalidation群のプロフィールについ

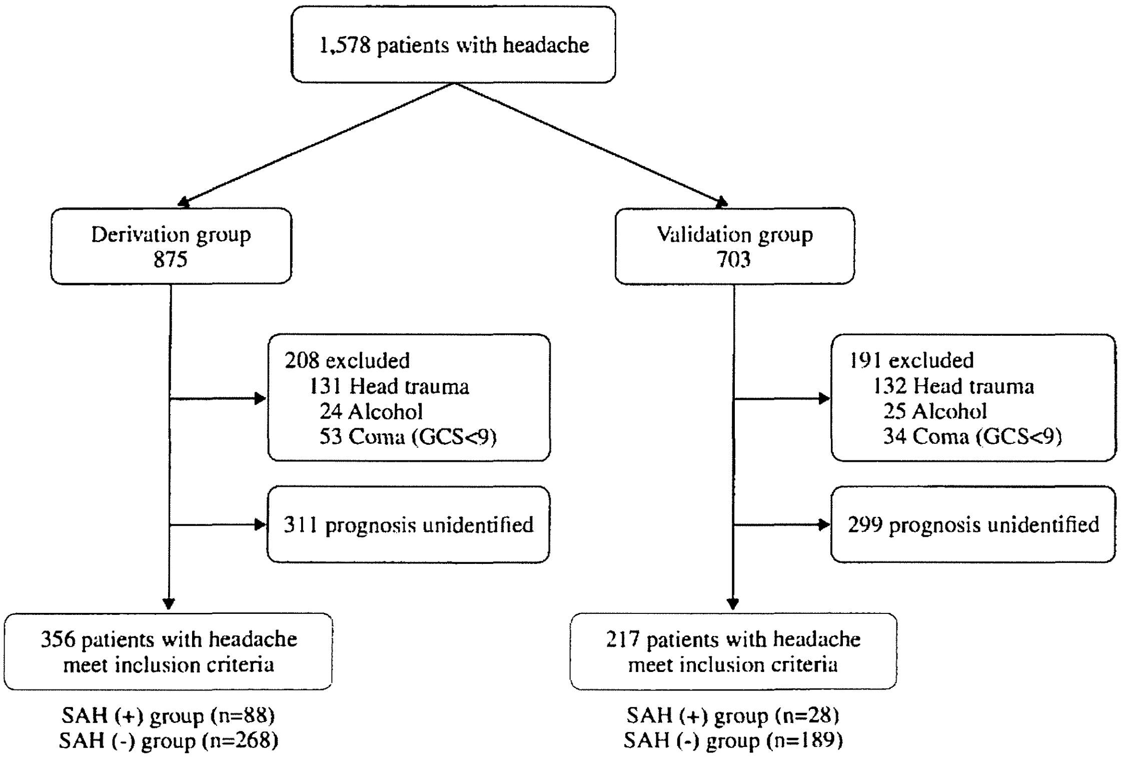

Fig. 1. Patients flow diagram.

て，年齢についてはとくに有意な差は認められなかった（derivation群56±18歳，validation群56±19歳）。SAHの割合についてはderivation群が24.7%（88/356），validation群が12.9%（28/217）でありderivation群の方がSAHが多い傾向にあった。

derivation群において，単変量解析では，SAH+群（88例）とSAH-群（268例）に間で，年齢，SBP，体温，WBC，CRP，BS，Na，K，Clに有意差が認められた（Table 1）。

これらの各々についてROC曲線を描き，臨床で用いやすい値を踏まえて求めたカットオフ値をTable 2に示す。

これらを基にロジスティック回帰分析を行ったところ，WBC >8000（μl），BS >130（mg/dl），K <3.5（mEq/l），SBP >140（mmHg）が有意な予測因子とされた（Table 3）。このロジスティック回帰式の各因子について点数をつけ，SPSを作成した（Table 4）。すなわち，SPSの最高点は4点となり，最低点は0点となる。

SPSをderivation群にあてはめたところ，SPS=0点においてはSAHの患者は存在しなかった。また，SPSが増加するにつれSAHである可能性が高くなることも明らかとなった。SPS=4の患者の64.9%にSAHが存在した（Fig. 2a）。そしてSPSをvalidation群にあてはめたところ，ほぼ同様の結果を得ることができた（Fig. 2b）。

考　察

救急外来において頭痛を主訴に来院される患者は多い[1,2]。なかでもクモ膜下出血は死亡，もしくは重度障害を負う可能性がとても高い疾患である[1-3]。また，その予後は早期診断により改善されることが示されており[2,3]，初診の段階で見逃すことのできない疾患の一つである。しかし，もっとも特徴的な症状とされる「突然の頭痛」は多くのクモ膜下出血患者で認められるものではあるが，クモ膜下出血でない患者にも同様に認められることがまれではな

Table1. Univariate analyses between subarachnoid hemorrhage (SAH) group and control group.

Profile	SAH (n=88)	Controls (n=268)	p value
Male : Female	32:56	118:147	0.21
Age (years)	60±15	55±19	<0.01
Systolic blood pressure (mmHg)	176±34	167±43	<0.01
Pulse rate (/min)	81±16	81±18	0.75
BT (°C)	36.0±0.8	36.3±1.0	<0.01
WBC (/μl)	9,900±3,800	8,300±3,800	<0.01
Hematocrit (%)	39.7±4.9	40.0±5.6	0.84
C-reactive protein (mg/dl)	0.47±1.0	0.82±2.3	<0.01
BS (mg/dl)	159±35	140±56	<0.01
Na (mEq/l)	140±2	139±4	0.02
K (mEq/l)	3.4±0.4	3.7±0.4	<0.01
Cl (mEq/l)	104±3	103±4	<0.01

BT: body temperature, WBC: white blood cell, BS: blood sugar

Table 2. Cut-off points of candidates of predictor valuables.

Variables	AUC	Cut-off point
Age (years)	0.5640	50
BT (°C)	0.5922	35.5
SBP (mmHg)	0.5878	140
WBC (/μl)	0.6358	8,000
BS (mg/dl)	0.7143	130
Na (mEq/l)	0.5513	140
K (mEq/l)	0.6828	3.5
Cl (mEq/l)	0.5710	105

AUC: area under the curve, BT: body temperature, SBP: systolic blood pressure, WBC: white blood cell, BS: blood sugar

Table 3. Multivariate logistic regression analysis.

Variables	β	Standard error	χ^2	p value
BS>130	0.62	0.17	14.15	<0.01
SBP>140	0.67	0.22	9.20	<0.01
K<3.5	0.56	0.15	13.72	<0.01
WBC>8,000	0.40	0.15	6.86	<0.01

BS: blood sugar, SBP: systolic blood pressure, WBC: white blood cell

Table 4. Subarachnoid hemorrhage prediction score.

Variable	Score
BS>130	1
SBP>140	1
K<3.5	1
WBC>8,000	1

max: 4 points
min: 0 point
BS: blood sugar, SBP: systolic blood pressure, WBC: white blood cell

い[4]。また，そのほかの症状として一過性意識消失，嘔気・嘔吐，項部硬直などが挙げられるが「突然の頭痛」を含め，どれも非特異的であり[4]，観察者の主観も介入することが考えられる。先の論文[6]においても上記のような非特異的な症状等が観察項目に入っており客観性を保ったままルールが使用できるかどうか明らかではない。

本研究において我々は，救急外来にてよく遭遇する頭痛を主訴に来院した患者を対象に，観察者の主観の介入を受けない数的因子のみを用いて，SPSを作成した。このような数的予測因子のみを用いてクモ膜下出血についての予測スコアを作成したのは今回が初めてであると考えられる。SPSについて，0点においてはSAHを否定することができた。それに対してSPS=4点の患者についてはSAHである可能性が非常に高かった。また，その間の点数では，SAHの可能性はあまり高くないが，否定はできなかった。以上よりSPSを用いて，頭痛患者をSAHの高リスク，中リスク，低リスクと分類し，各々リスクに見合ったマネージメントを示したTable 5を提唱する。