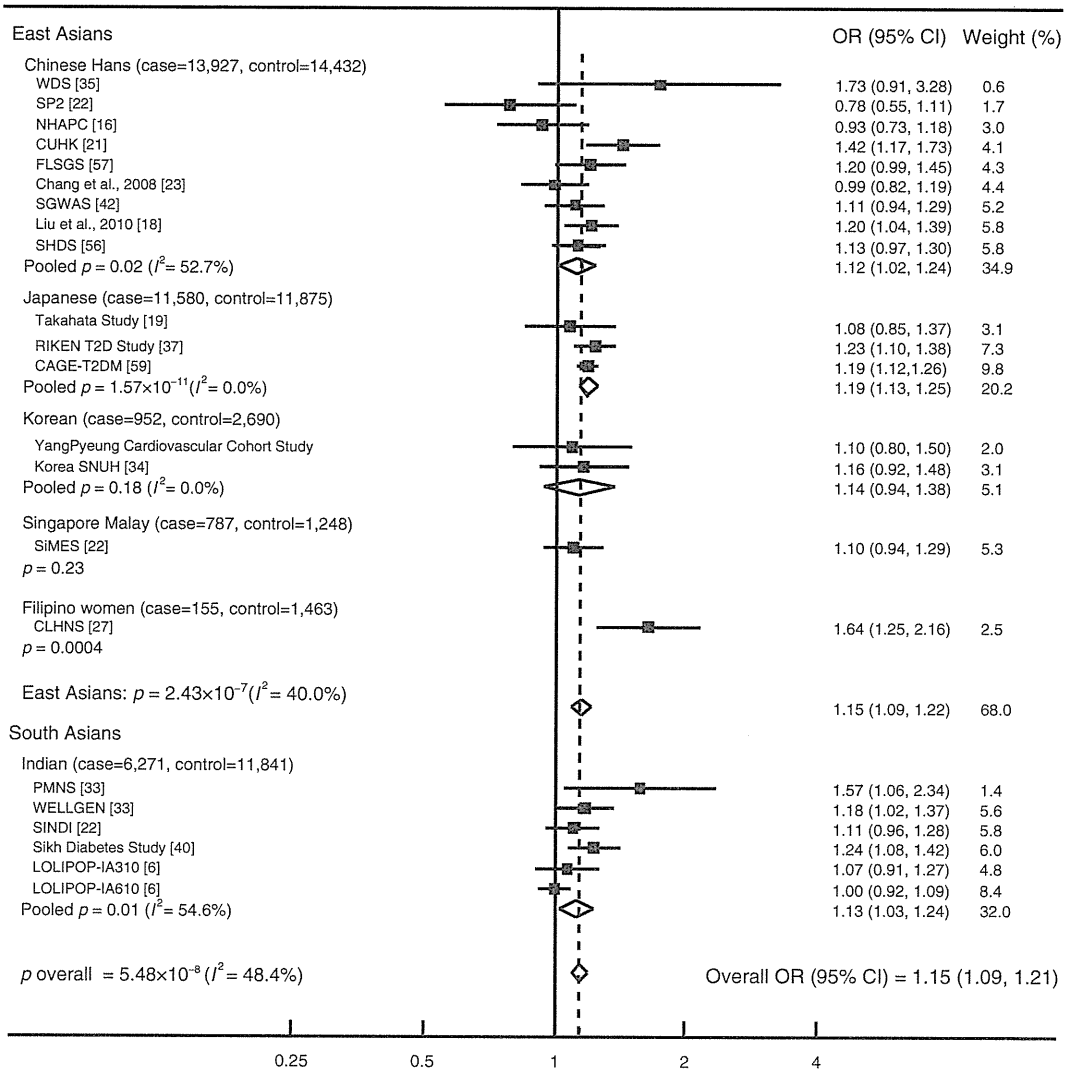

Fig. 3 Association of *FTO*-rs9939609 (or proxy) with type 2 diabetes. Study-specific association analyses assumed an additive genetic model adjusted for age and sex. Effect sizes were combined using random-effects meta-analyses (DerSimonian–Laird method)

similar to, or only somewhat smaller than, those reported for white Europeans. We furthermore confirm that variation in *FTO* is associated with increased risk of type 2 diabetes, an association that, unlike in white Europeans, is not abolished after adjustment for BMI in both East and South Asians.

Large-scale studies in individuals of white European descent have reported that each additional *FTO* minor allele increases the odds of obesity by 1.20–1.32-fold [1, 5, 7, 47]. The association with obesity observed in Asians in the present study was remarkably similar, with each additional minor allele increasing obesity risk by 1.25-fold (95% CI 1.19, 1.31), consistent with the association observed for obesity in previous literature-based meta-analyses of case–control studies in East and South Asians [18, 29, 30].

The association of the *FTO* variant with overweight was the same in East and South Asians (OR 1.13 per minor allele) and very similar to the effects (ORs ranging from 1.13 to 1.18) that have been reported in large-scale studies of white Europeans [1, 7, 47]. While the effect sizes observed for the influence of *FTO* on obesity and overweight in Asians are very similar to those of Europeans, it should be noted that the definitions of obesity and overweight are different, as BMI cut-offs are somewhat lower in Asians than in Europeans, consistent with the association of BMI with metabolic disease [48].

The *FTO* minor allele increases BMI by 0.26 kg/m^2 (equivalent to ~750 g/allele for a person 1.7 m tall) in Asians, with very similar results for East and South Asians. This observation suggests that the effect of *FTO* on BMI in Asians is substantially smaller than the effect observed in a meta-analysis of more than 125,000 white Europeans (0.39 kg/m^2 per minor allele, or 1,130 g per minor allele) [7]. This difference may be due to the fact that BMI in

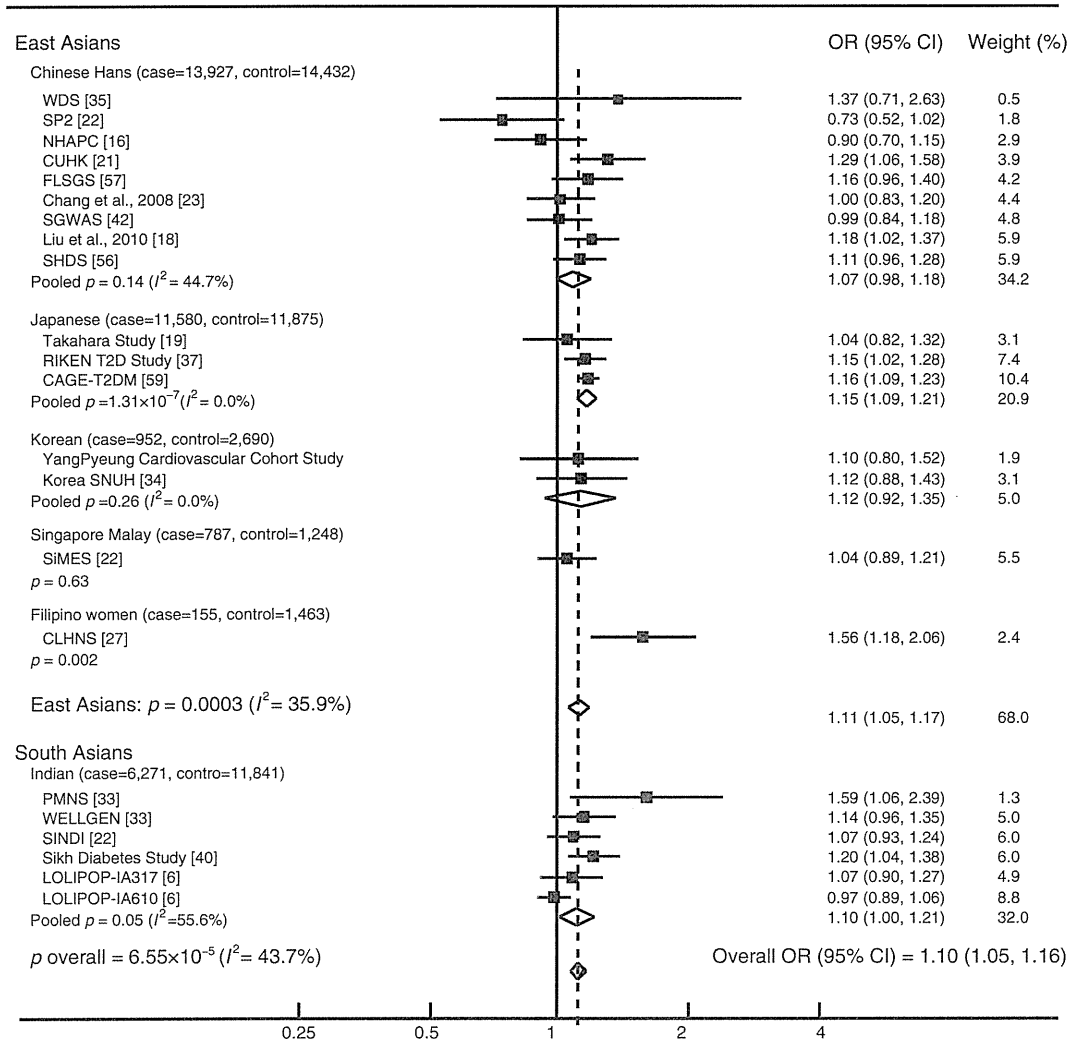

Fig. 4 Association of *FTO*-rs9939609 (or proxy) with type 2 diabetes adjusted for BMI. Study-specific association analyses assumed an additive genetic model adjusted for age, sex, and BMI. Effect sizes were combined using random-effects meta-analyses (DerSimonian–Laird method)

Asians does not represent exactly the same adiposity phenotype as in Europeans. However, given that other large-scale studies in white Europeans have reported effects for *FTO* on BMI that range between 0.26 and 0.39 kg/m^2, the comparison between Asians and Europeans should be made with caution [1, 3, 5, 15, 47]. The *FTO* variant also showed convincing association with measures of fat distribution such as waist and hip circumference and WHR in Asians. Despite the often described difference in abdominal obesity between East and South Asians, the effect sizes were very similar in the two groups. Consistent with the observations for BMI, the effect sizes tended to be somewhat smaller than those reported for white Europeans. For example, each additional *FTO* minor allele increased waist circumference by 0.51 cm in Asians, whereas large-scale studies in Europeans have reported an increase of 0.73–1.00 cm [1, 9, 47].

As the MAF of the *FTO* variant is substantially lower in Asians (East Asians, ~17%; South Asians, ~32%) than in white Europeans (~45%), and as the effect of this allele on obesity-related traits is similar or somewhat lower in Asians than in white Europeans, the overall contribution of genetic variation in *FTO* to obesity susceptibility will be lower in Asians, in particular East Asians. For example, the *FTO* variant explained less of the inter-individual variation in BMI in Asians (East Asians, 0.16%; South Asians, 0.20%) than in white Europeans (0.34%) [7]. Furthermore, the low risk allele frequency led to a lower PAR for the risk of obesity (East Asians, 8.3%; South Asians, 10.6%) and overweight (East Asians, 4.1%; South Asians, 7.8%) in Asians than in white Europeans (obesity, 20.4%; overweight, 12.7%) [1].

The *FTO* locus was first identified in a GWAS for type 2 diabetes in white Europeans, i.e. each minor allele

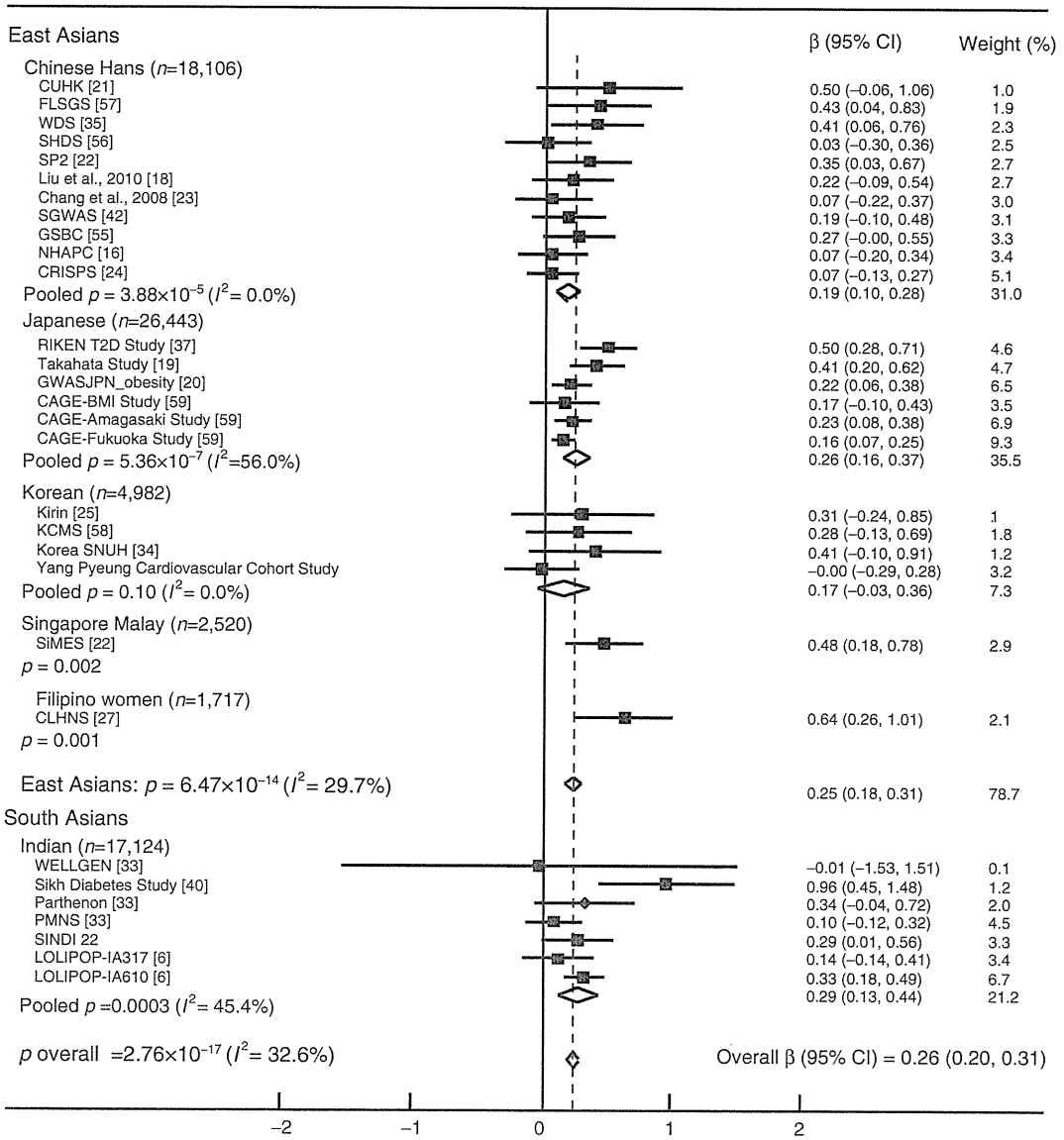

Fig. 5 Association of *FTO*-rs9939609 (or proxy) with BMI. Study-specific association analyses assumed an additive genetic model adjusted for age and sex. Effect sizes were combined using random-effect meta-analyses (DerSimonian–Laird method)

increased the odds of diabetes by 1.15-fold [1]. However, after adjustment for BMI, the association between the *FTO* variant and type 2 diabetes was completely abolished (OR 1.03), suggesting that *FTO* is primarily an obesity-susceptibility locus [1]. In our meta-analysis, we observed a similar effect of *FTO* on risk of type 2 diabetes, with each minor allele increasing the odds by 1.15-fold. Interestingly, adjustment for BMI did not abolish the association, but only slightly attenuated it to a 1.10-fold increased risk of type 2 diabetes for each additional minor allele. These observations were similar in East and South Asians, suggesting that the *FTO* locus influences the risk of type 2 diabetes, at least in part, independently of its effect on BMI. The reason for the discrepancy between the original observations in Europeans and our observations in Asians are not known, but may be due to the fact that *FTO* seems to have a smaller effect on BMI in Asians than in Europeans. It may also be due to the fact that BMI, as suggested above, represents a different adiposity phenotype in Asians than in Europeans because of differences in body composition. Although BMI is a marker for general adiposity, it does not distinguish between fat mass and fat-free mass and does not reflect regional fat distribution. Observational studies have suggested that, for a given amount of total body fat, East and South Asians have more abdominal fat and less muscle mass than white Europeans [49, 50]. However, while it has been generally believed that in white Europeans the association with type 2

diabetes is fully mediated by the effect of *FTO* on BMI, not all studies confirm this observation. A recent large-scale study in 41,504 Scandinavians found that the *FTO* minor allele indeed increased type 2 diabetes risk (OR 1.13), but this association remained present (OR 1.09) after adjustment for BMI, consistent with the observations in the present study. The biological pathways that underlie the independent association between *FTO* variation with obesity and type 2 diabetes remain unclear. However, results of gene expression studies have shown that *FTO* expression in human islets cells is not associated with BMI [51], whereas *FTO* mRNA and protein levels in muscle are increased in individuals with type 2 diabetes compared with non-diabetic obese individuals or healthy lean controls [52]. Furthermore, FTO overproduction in myotubes suggested a role for FTO in oxidative metabolism, lipogenesis and oxidative stress in muscle, a cluster of metabolic defects characteristic of type 2 diabetes [52].

Despite the fact that our meta-analyses included Asians with different genetic backgrounds, the overall heterogeneity of the association effects was generally only low to moderate. Interestingly, we found that the associations were generally very similar in East and South Asians, although these populations are known to have genetically different origins [53]. Furthermore, we found no differences between men and women, consistent with the observations in white Europeans [7]. We found some evidence that age may contribute to the heterogeneity of the association between *FTO* and BMI. Life course effects have been reported in white Europeans [54], and longitudinal analyses will be needed to establish this in Asian populations. Longitudinal studies are also more appropriate than cross-sectional studies for disentangling the intricate interplay between *FTO*, obesity and type 2 diabetes throughout life [15].

It should be noted that the association between *FTO* variation and obesity risk in Asians had been established in three earlier meta-analyses [18, 29, 30]. These meta-analyses were substantially smaller than the present ones and focused solely on case–control analyses of obesity and type 2 diabetes, while no continuous traits were studied. The meta-analysis by Liu et al [18] included individuals of East and South Asian origin, which were analysed together without comparison of effect sizes between the two populations. This study also examined the association with type 2 diabetes, but did not explore the association after adjustment for BMI [18]. Furthermore, the three previous meta-analyses were all literature-based and thus more prone to publication bias, whereas our meta-analysis was designed on the basis of a de novo analysis of data according to a standardised plan in all studies identified as having available data and agreement to participate. No evidence of publication bias was observed except for the associations with BMI and hip circumference. The analytical consistency across studies helped minimise between-study heterogeneity. Although our results are representative of individuals of Southeast Asian, East Asian and South Asian descent, the association of *FTO* with risk of obesity and type 2 diabetes in other Asian populations remains to be examined.

In summary, we have firmly established that genetic variation in the first intron of *FTO* is associated with increased risk of obesity and type 2 diabetes in Asians, with effect sizes similar to those in Europeans. Furthermore, we confirm that the association of *FTO* with risk of type 2 diabetes is partly independent of BMI.

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Contribution statement RJFL, HL and XL contributed to the conception and design of the study. CL and TOK performed the literature search, designed the analysis plan, performed the meta-analyses and researched the data. HL, TOK, CL and RJFL wrote the manuscript. HL, JZ, YL, CH, ZY, WZ, WB, SC, YW, TY, AS, BYC, CSY, DZ, FT, KY, JCC, KRM, LFB, MI, EN, NL, TF, SK, WW, CVJ, WL, YC, YX, YG, SL, YS, SHK, HDS, KSP, CHDF, JYK, PCS, KSLL, WZ, XS, HD, HI, GVK, DKS, LC, LL, RH, YK, MD, KH, WJ, JSK, JCC, GRC, RCM, SM, RD, MY, RT, NK, XL and RJFL collected study-specific data, analysed the study-specific data according to the standardised analysis plan, and reviewed and edited the manuscript. All authors have approved the final version of the manuscript to be published.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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Long-term prognosis of patients with lung cancer detected on low-dose chest computed tomography screening

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ABSTRACT

The effectiveness of lung cancer screening using low-dose chest computed tomography (CT) remains elusive. The present study examined the prognosis of patients with lung cancer detected on CT screening in Japanese men and women. Subjects were 210 patients with primary lung cancer identified on CT screening at two medical facilities in Hitachi, Japan, where a total of 61,914 CT screenings were performed among 25,385 screenees between 1998 and 2006. Prognostic status of these patients was sought by examining medical records at local hospitals, supplemented by vital status information from local government. The 5-year survival rate was estimated according to the characteristics of patients and lung nodule. A total of 203 (97%) patients underwent surgery. During a 5.7-year mean follow-up period, 19 patients died from lung cancer and 6 died from other causes. The estimated 5-year survival rate for all patients and for those on stage IA was 90% and 97%, respectively. Besides cancer stage, smoking and nodule appearance were independent predictors of a poor survival; multivariable-adjusted hazard ratio (95% confidence interval) was 4.7 (1.3, 16.5) for current and past smokers versus nonsmokers and 4.6 (1.6, 13.9) for solid nodule versus others. Even patients with solid shadow had a 5-year survival of 82% if the lesion was 20 mm or less in size. Results suggest that lung cancers detected on CT screening are mostly curative. The impact of CT screening on mortality at community level needs to be clarified by monitoring lung cancer deaths.

1. Introduction

Much attention has been paid to the effectiveness of low-dose chest computed tomography (CT) screening for lung cancer [1,2], which has poor prognosis. Screening with chest CT has been shown to have higher detection rate of lung cancer and, of cases identified, have higher curative resection rate than does screening with conventional chest X-ray [1–3]. However, data for the prognosis of lung cancer cases identified on CT screening are limited [4–6] and the effect of this screening procedure on mortality remains inconclusive. While several randomized controlled trials are ongoing [7–10], results of previous analyses [11–13] have not supported an effect of CT-based screening in lowering lung cancer mortality. Recently, however, the National Lung Screening Trial (NLST), a randomized trial targeted for current and former heavy smokers, found a 20% reduction in lung cancer death among participants screened with low-dose helical CT compared to participants screened with chest X-ray [14]. So far, screening lung cancer using CT has not been recommended in any set of guidelines except for research purpose [15,16].

In Hitachi Medical Area, a large-scale chest CT screening program for lung cancer has been introduced in two medical facilities since 1998 and 2001, respectively. We previously reported the characteristics of cancers detected on the CT screening [3,17]. In the present study, we followed 210 patients with lung cancer detected on the CT screening in collaboration with local hospitals and administrative office. The objectives of the present study were: (1) to estimate survival of prognosis of patients with lung cancer detected on CT screening and (2) to examine the prognosis of lung cancer patients according to a history of CT screening, patient characteristics, and the size and density of lung shadow on CT.

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2. Materials and methods

2.1. Study design and patients

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. Informed consent was obtained from each participant in both facilities prior to the examination. The protocol of the follow-up survey of patients whose cancer was detected on the CT screening has been approved by the ethics committee of Hitachi Health Care Center (1998–2001).

Detail of the screening procedure, the numbers of participants and patients with lung cancer, and clinical features of screen-detected cases in each facility has been described elsewhere [3,17]. In short, two readers independently interpreted the CT images. If they could not reach a consensus, the final decision was made at a reading conference. When we detected noncalcified solitary pulmonary nodules (SPNs) ≥8 mm (Hitachi Health Care Center) or those ≥5 mm (Hitachi Medical Center), a detailed CT scan was carried out 1 month later. For SPNs ≥11 mm in size, we recommended biopsy, thoracoscopy, thoracotomy, fine-needle aspiration, or a combination of these methods according to the standards of care at that time. For SPNs of 8–10 mm (Hitachi Health Care Center) or 5–10 mm (Hitachi Medical Center), detailed CT scans were performed at 3 months and 6 months. Further follow-up of SPNs was performed at referred hospitals according to the "Low-dose CT lung cancer screening guidelines for pulmonary nodules management" [18]. If there was a sign of growth in either scan, patients were recommended to receive confirmatory diagnostic tests as noted above. Among participants who underwent invasive diagnostic test, the number of false-positive cases was 14 and 5 for Hitachi Health Care Center and Hitachi Medical Center, respectively. Participants were given an advice on quitting smoking orally or using a leaflet at the time of screening if they were current smokers.

As of March 2006, a total of 61,914 CT screenings were performed among 25,385 screenees (Table 1). The characteristics of screening participants were different between the two facilities. For instance, screenees at Hitachi Health Care Center were on average younger than those at Hitachi Medical Center (57 years old versus 64 years old). Moreover, the proportion of those with a history of smoking was much higher in Hitachi Health Care Center than that in Hitachi Medical Center, reflecting a higher male-to-female ratio in Hitachi Health Care Center than in Hitachi Medical Center. Of all the screening participants, 169 cases of lung cancer were identified at the initial screening and 41 cases at repeat screenings. Mean (SD) diameter of the tumors identified was 17.5 mm (9.3 mm) and 178 (85%) were on stage IA. The observed difference in detection rate between the two facilities is probably ascribed to the differences of characteristics, especially age distribution, of screening participants as mentioned above. Of all the 210 lung cancer patients, 159 (76%) were residents of Hitachi city and 202 (96%) were referred to either Hitachi General Hospital (Hitachi Co Ltd) or Ibarakihigashi National Hospital.

Table 2 shows epidemiologic and clinical features of lung cancer cases detected on chest CT screening. Compared with patients whose cancer was detected at repeat screening, those whose cancer was detected at initial screening were more likely to be female and a nonsmoker, and tended to have a larger lesion in size. As regards histology, 195 (93%) were adenocarcinoma. Of all patients, 178 (85%) had stage IA cancer, 145 (81%) of which had a nodule of 20 mm or less in diameter. A total of 203 patients (97%) underwent surgery, 6 had unresectable lesion, and one refused any medical treatment. Mean time period between CT screening and initiation of medical therapy was 161 days.

2.2. Follow-up

We made a follow-up survey to determine prognostic status of the 210 patients with primary lung cancer detected on chest CT screening by examining medical records and log of screening participation, supplemented by vital status information from local government. We used two definitions of outcome: one for death from all causes and another for death from lung cancer. Censoring was made at either the date of death from causes other than lung cancer (if the outcome is death from lung cancer), the date of last contact, or 28 February 2010 (end of follow-up period), whichever came first. Follow-up period was calculated for each patient as time period from the date of initiation of medical therapy and the date of the occurrence of either outcome or censoring. We estimated

Table 1
Summary and results of thoracic CT screening in Hitachi Medical Area as of March 2006.

	Hitachi Medical Center	Hitachi Health Care Center
CT scanner	Multi detector row CT (mobile, 4 rows)	Single slice spiral CT
Screening participants	Local residents, 50 years or older	Employees, retired persons, and their spouses, 50–69 years old
Start of screening program	April 2001	April 1998
Baseline screening		
Participants	11,204	14,181
Lung cancer cases	109	60
Detection rate (%)	0.97	0.42
Mean diameter, mm	18.5	17.9
Stage IA (%)	83	83
Repeat screening		
Examinations	4387	32,142
Lung cancer cases	20	21
Detection rate (%)	0.46	0.07
Mean diameter, mm	13.1	15.1
Stage IA (%)	90	86

Table 2
Characteristics and outcome of lung cancer cases detected on CT screening according to the type of screening.

	Initial screening (n=169)	Repeat screening (n=41)	Total (n=210)
Age, years (mean ± SD)	62.2 ± 7.8	62.2 ± 7.5	62.4 ± 7.6
Sex (male/female)	76/93	25/16	101/109
Smoking history (%)	63 (37.3)	21 (51.2)	84 (40)
Nodule size, mm (mean ± SD)	18.3 ± 9.7	14.1 ± 7.0	17.5 ± 9.3
Nodule appearance in thin-section CT			
Nonsolid	61	14	75
Part-solid	69	11	80
Solid	39	16	55
Pathology			
Adenocarcinoma	159	36	195
Others	5	0	5
Stage[a]			
IA	142	36	178
IB	12	1	13
IIA to IV	6	2	8
Treatment			
Surgical resection	164	39	203
Other than surgery	4	2	6
No treatment	1	0	1
Time from screening to treatment, days (mean ± SD)	160 ± 147	164 ± 159	161 ± 149

[a] Disease stage was defined according to the UICC 5th edition of TNM staging system.

Table 3
Kaplan–Meier 5-year survival rate and hazard ratio of all cause death among patients with lung cancer detected on CT screening.

	n	Survival rate (95% CI)	*P*[a]	Age- and sex-adjusted HR (95% CI)	Multivariable adjusted HR (95% CI)[b]
All patients					
Total	210	90 (84, 93)			
Initial	169	91 (85, 94)	0.39	1 (reference)	
Repeat	41	84 (68, 93)		1.1 (0.4, 2.9)	
Women	109	97 (92, 99)	<0.001	1 (reference)	1 (reference)
Men	101	81 (72, 88)		5.9 (2.1, 17.3)	1.0 (0.3, 3.9)
Nonsmoker	126	98 (93, 99)	<0.001	1 (reference)	1 (reference)
Smoker[c]	84	77 (66, 85)		2.4 (0.7, 8.3)	4.7 (1.3, 16.5)
Nodule size, mm					
<11	52	98 (87, 100)	0.001	1 (reference)[d]	1 (reference)[d]
11 to <21	102	93 (85, 96)			
21+	56	76 (63, 86)		3.3 (1.5, 7.2)	1.9 (0.7, 5.1)
Nodule appearance					
Nonsolid	75	100	<0.001	1 (reference)[e]	1 (reference)[e]
Part-solid	80	96 (89, 99)			
Solid	55	66 (51, 77)		10.3 (3.7, 28.2)	4.6 (1.6, 13.9)
Stage IA					
Total	178	97 (92, 98)			
Initial	142	97 (92, 99)	0.69	1 (reference)	
Repeat	36	94 (79, 99)		1.2 (0.2, 6.1)	
Women	100	98 (92, 100)	0.35	1 (reference)	
Men	78	95 (86, 98)		2.0 (0.5, 8.5)	
Nonsmoker	112	99 (94, 100)	0.03	1 (reference)	1 (reference)
Smoker	66	92 (82, 97)		12.8 (1.4, 115.3)	3.4 (0.6, 18.8)
Nodule size, mm					
<11	52	98 (87, 100)	0.46	1 (reference)[d]	
11 to <21	93	96 (89, 98)			
21+	33	97 (79, 100)		0.6 (0.1, 4.7)	
Nodule appearance					
Nonsolid	74	100	0.03	1 (reference)[e]	1 (reference)[e]
Part-solid	72	97 (89, 99)			
Solid	32	87 (69, 95)		4.5 (1.0, 19.9)	3.2 (0.7, 14.1)

[a] Log-rank test.
[b] Variables adjusted for the multivariate model were sex, smoking, diameter of lesion, nodule appearance (which showed $P \leq 0.1$ in age- and sex-adjusted model), and cancer stage for all patients; smoking and nodule appearance (which showed $P \leq 0.1$ in age- and sex-adjusted model) for patients on stage IA.
[c] Including former and current smokers.
[d] Including nodules of <11 mm and 11 to <21 mm in size.
[e] Including nonsolid and part-solid nodules.

a 5-year survival rate for the 210 cases detected and according to the size of nodule (<11 mm, 11–<21 mm, or 21+ mm), features of nodule (solid, part-solid, or nonsolid), or the timing of detection (initial or repeat screening). Further, we examined clinical features of cases died from lung cancer detected on repeat screening.

2.3. Statistical analysis

Statistical analysis was done by using Stata version 10.0. Difference in continuous variable among groups was tested by *t* test or Mann–Whitney *U* test. Survival rate was estimated by using Kaplan–Meier method and its difference among groups was tested by using Log-rank test. Cox proportional hazard model was used to estimate hazard ratio and its 95 confidence interval. We calculated two types of hazard ratio: one using a model with adjustment of age and sex only and another using a model with adjustment of variables showing $P \leq 0.1$ in the age- and sex-adjusted model plus clinical stage of cancer. A two-sided *P* value of <0.05 was considered as statistically significant.

3. Results

The mean of follow-up period for all patients was 2076 days (5.7 years), with more than 70% of surviving patients being observed for at least 5 years. During the follow-up period, 25 (12%) died; 19 died from lung cancer and 6 died from other causes. Among 169 patients with lung cancer detected on initial screening, 19 (11%) died during follow-up period; of these, 14 died from the lung cancer detected. Causes of death other than lung cancer were colorectal cancer, esophageal cancer, ischemic heart disease (myocardial infarction), cerebrovascular infarction, and myeloid-fibrosis. Among 41 patients with lung cancer identified on repeat screening, 6 (15%) died; of these, 5 died from lung cancer and 1 from stomach cancer.

The estimated 5-year survival rate for death from all causes and hazard ratio and its 95% confidence interval were presented according to the characteristics of patients and nodule detected on screening (Table 3). Among all patients, the 5-year survival rate for death from all causes was 90%. The survival rate did not significantly differ between initial and repeat screenings (initial, 91%; repeat, 84%; $P = 0.39$). Male gender and smoking were each associated with a significantly poorer prognosis ($P < 0.001$ versus female gender and nonsmoking, respectively). Larger nodule and solid nodule on thin-section CT were significant predictors of lower survival. Patients with a lesion of 20 mm or smaller, compared with those with a lesion of 21 mm or larger in diameter, had a better prognosis (overall $P = 0.001$; Fig. 1). In age- and sex-adjusted model, a statistically significant increase in hazard of death was observed in association with male gender, smoking, larger nodule, and solid nodule. However, only smoking and solid nodule were associated with a statistically significantly increased hazard ratio after multivariate adjustment.

Patients with lung cancer on stage IA had a 5-year survival rate of 97% for death from all causes. Both solid nodule and smoking remained significant predictors of poor survival in this subgroup, whereas nodule size did not. Fig. 2 shows survival curves according to nodule density among patients with a lesion of 20 mm or smaller in diameter. Patients with a lesion of solid nodule had a 5-year

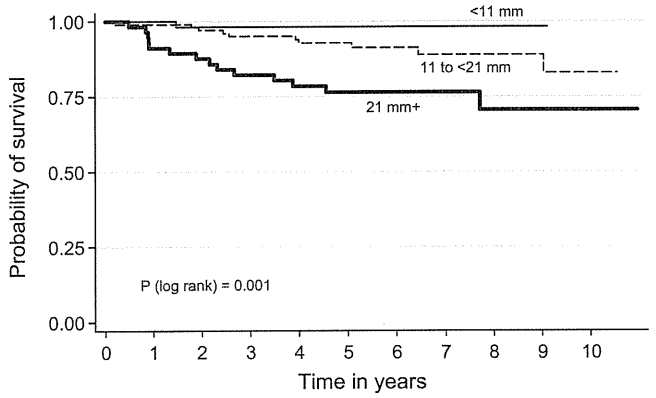

Fig. 1. Kaplan–Meier survival estimates for death from all causes by size of lung nodule.

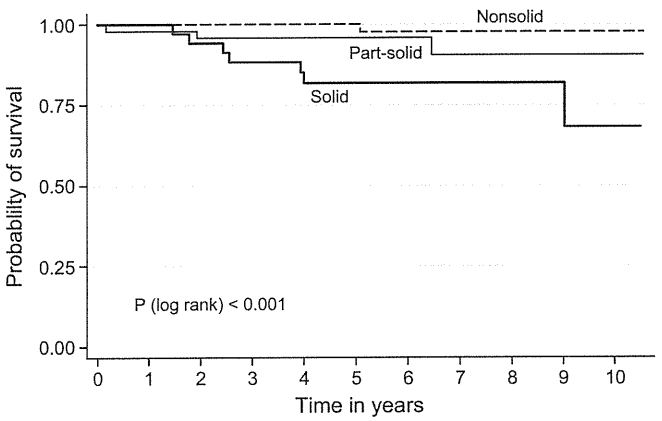

Fig. 2. Kaplan–Meier survival estimates for death from all causes in patients with small lung nodule (<21 mm in diameter).

survival of 82%, a value significantly lower than that among those with a lesion of combined nonsolid and part-solid shadow (98%; $P = 0.001$). In age- and sex-adjusted model, hazard ratio of death was statistically significantly increased in association with smoking and solid nodule. After multivariate adjustment, none of these variables remained statistically significant.

As smoking was a strong predictor of increased mortality among patients whose lung cancer was detected on CT screening, we presented background factors according to smoking status (Table 4). Smokers including past smokers were more likely to be male, had a larger nodule and a higher proportion of solid nodule, and tended to be on advanced clinical stage than nonsmokers.

Table 4
Clinical features of lung cancer detected on CT screening by smoking status.

	Smoker[b] ($n = 84$)	Nonsmoker ($n = 126$)	P[a]
Women	7 (8)	102 (81)	<0.001
Cancer stage			
IA	66 (79)	112 (89)	0.06
IB	9 (11)	4 (3)	
II to VI	9 (11)	10 (8)	
Mean (SD) nodule size, mm	19.4 (10.5)	16.2 (8.3)	0.01
Nodule appearance			
Nonsolid	19 (23)	56 (44)	<0.001
Part-solid	29 (35)	51 (40)	
Solid	36 (43)	19 (15)	

Figures in the table are number and percentage (in parenthesis) unless stated otherwise.

[a] Chi-square test for categorical variable and t-test for continuous variable.

[b] Including former and current smokers.

Among 14 deceased patients with lung cancer detected on baseline screening, the mean diameter of nodule was 32.1 mm and the proportion of advanced cancer showing solid shadow was high. Of these, 12 (86%) were male and 9 (64%) had a smoking history; 12 underwent surgical operation, 1 received chemotherapy, and 1 refused receiving medical therapy. Mean period from initiation of medical therapy to death was 3.0 years. Included in the 14 patients who subsequently died from lung cancer were one patient who chose alternative medicine and another patient who was under the care of physician due to interstitial pneumonia at the time of diagnosis. All five patients who died from the lung cancer detected on repeat screening were male, had a history of smoking, and showed a solid nodule. Of these, 4 had a lesion of 20 mm or smaller in diameter and only one had a nodule (4 mm in diameter and solitary) detectable at the time of initial screening.

4. Discussion

We investigated the prognosis of 210 patients with lung cancer detected on low-dose chest CT screening in two medical facilities in Hitachi City, Japan, with a 5.7-year mean follow-up period. Our study showed that lung cancer cases detected on CT screening had a fairly good prognosis, with a 5-year survival rate of 90%. A total of 19 patients, including 3 who refused or delayed medical therapy, died from lung cancer detected on the screening. No premature death was documented associated with therapeutic intervention. Patients with a lesion of solid shadow, indicative of invasive cancer, had a 5-year survival of 82% if the lesion detected was 20 mm or less in diameter.

The high survival rate among patients with lung cancer detected on CT screening observed in the present study is consistent with those in Japanese studies [4,6] as well as multi-country study [5]. However, lower survival rate have been reported in some Western studies [11,12], in which the proportion of stage I cancer of all cases detected was less than those in Japanese studies [2–4]. This may be attributed in part to the different characteristics of target population; Western studies have recruited persons with a history of smoking only, whereas Japanese studies also included persons without smoking experience. Moreover, there is ethnic difference in histological types of lung cancer; the proportion of adenocarcinoma among lung cancer patients in Japanese CT screening studies [2–4] is much higher than that observed in Western CT screening study [19]. Therefore, an extrapolation of findings obtained in Western populations to Japanese or vice versa requires caution. The analysis of data from an on-going Japanese cohort [20] using a simulation approach [21,22] may reveal the effectiveness of CT screening for lung cancer for Japanese populations.

We observed no measurable difference in survival rate between lung cancers detected on initial screening and those detected on repeat screening, similar to findings in previous studies [4–6]. Clinical characteristics of lung cancer cases differ according to whether the cancer was detected on initial or repeat examination [19]. At initial screening, not only cases showing small, vaguely delineated nodule but also those on advanced stage will be identified, leading to a wide variation in the nature of cancers ranging from non-invasive, slow-growing type to advanced one. High survival rate of patients with screening-detected cancer has been ascribed to well known bias; namely, lead time bias, length bias, and over-diagnose bias [23]. The effects of these types of bias are serious if cancers detected are mainly non-invasive and slow-glowing. However, given that 64% of patients with lung cancer detected at initial screening in the present study showed solid or part-solid nodule, which are likely invasive cancer [24], we believe that the observed high survival rate cannot fully be explained by these types of bias only. We should note that there was no death observed among patients with lung cancer with nonsolid nodule of 20 mm or less

in diameter at initial screening. More research is required to examine whether in-depth work-up for such a small, nonsolid nodule can be suspended until the next CT screening.

As regards repeat screening, lung cancers are detected due mainly to the emergence of new nodule or enlargement and change in concentration of CT image of the nodule detected on the previous screening. Although cancers detected on repeat screening are on average smaller than those detected on initial screening, they probably progress rapidly and thus are life-threatening if left untreated. In other words, the aforementioned bias inherent to the evaluation of screening may exert to a lesser extent in the survival of cases detected on repeat CT screening. Therefore, the present finding showing a good prognosis of these cases adds to evidence that repeat chest CT screening can prevent early death from lung cancer.

In the present study, smokers had a significantly poorer survival than nonsmokers even among stage IA patients, and all the three patients with small lung cancer (20 mm or less in diameter) detected on repeat screening who subsequently died from the lung cancer were current smokers. Poorer survival of smokers compared with nonsmokers is compatible with results of previous studies, including one among Japanese patients with CT-screen detected lung cancer [6]. These findings suggest that smoking-related lung cancers are likely aggressive and incurable even if detected on early stage, and thus underscore the importance of providing smoking cessation program at all settings including CT screening to decrease overall mortality [25].

Our study has several strengths including larger number of lung cancer patients who were detected on low-dose chest CT screening and longer follow-up period (mean 5.7 years) relative to most previous studies. In addition, the present study provided data not only for high-risk group (ever-smokers) but also for low risk group (lifetime nonsmokers), which makes it possible to compare survival of patients with lung cancer detected on CT screening between smokers and nonsmokers. The present study is limited due to bias inherent to screening studies of one arm design, as discussed above. Besides, we acknowledge two other limitations. First, our study was done only among patients whose cancer was detected at the time of CT screening and did not obtain any information about lung cancer diagnosed between the screenings. However, such interim cancers are probably few, and the inclusion of such cases may not greatly distort the result. Another limitation is that, as Hitachi CT screening program covered both ever-smokers and lifetime nonsmokers, overall result may not be applied to high-risk populations with a history of smoking.

CT screening for lung cancer has been performed at community and occupational settings in Hitachi City. If we assume 76% of screening participants (the proportion of residents in Hitachi City among lung cancer patients detected on CT screening) reside in Hitachi City, it is estimated that 18,115 residents (nearly 30% of residents aged 50–69 years [26]) of Hitachi City had participated into the CT screening program as of May 2006. The number of screening participants is increasing constantly, with some 700 individuals and another 2000 individuals receiving the screening at Hitachi Health Care Center and Hitachi Medical Center, respectively, each year. Given this wide-spread practice of CT screening in this community, it would be of interest whether lung cancer mortality among residents of Hitachi City will decrease more rapidly than that in other areas. Such time-trend analysis may provide valuable data for assessing the effectiveness of CT screening at population level.

5. Conclusion

Patients with lung cancer detected on low-dose CT screening had a fairly good prognosis, with the estimated 5-year survival rate for all patients and for those on stage IA being 90% and 97%, respectively. Besides cancer stage, smoking and nodule appearance were independent predictors of a poor survival. It is anticipated that chest CT screening program combined with anti-smoking campaign could effectively decrease risk of deaths from lung cancer. The impact of CT screening on mortality at community level needs to be clarified by monitoring lung cancer deaths.

6. Conflicts of interest

There are no conflicts of interest to disclose.

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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。
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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

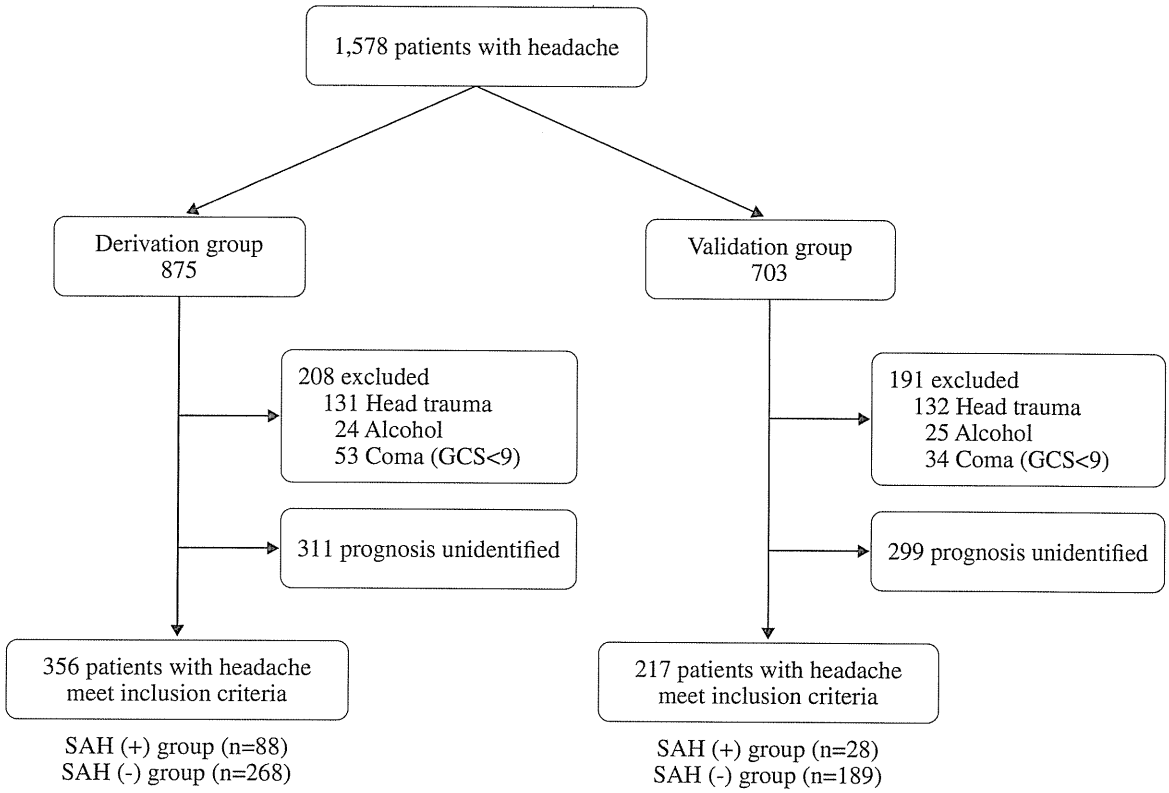

Fig. 1. Patients flow diagram.

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。

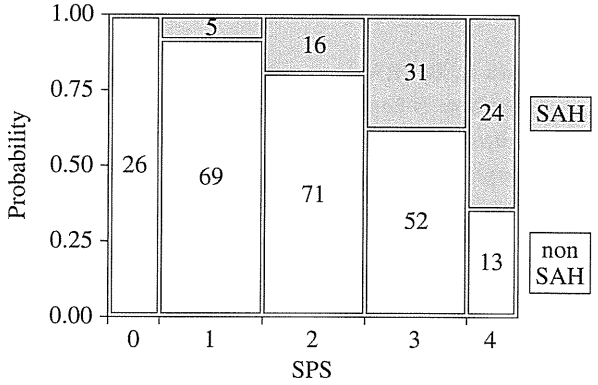

Fig. 2a. Subarachnoid hemorrhage prediction score (SPS) distribution map of subarachnoid hemorrhage (SAH) and non-SAH in derivation group.
The horizontal axis shows the SPS, while the vertical axis shows the proportions of SAH and non-SAH patients for each score. No patients with an SPS of 0 had SAH, and the proportion of patients with SAH increased proportionally with increasing SPS. A total of 64.9% of patients with an SPS of 4 had SAH.

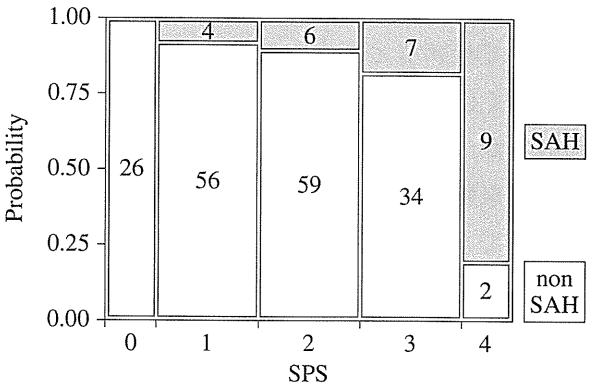

Fig. 2b. SPS distribution map of SAH and non-SAH in validation group.
As with Fig.2a, the horizontal axis shows the SPS, while the vertical axis shows the proportions of SAH and non-SAH patients for each score. As with the derivation group, no patients with an SPS of 0 had SAH, and the proportion of patients with SAH increased proportionally with increasing SPS.

Table 5. Clinical decision rule using SPS for patients with acute headache.

	CT scan	Response
High risk group SPS=4	Required	If SAH absent, consider CSF examination/ hospitalization
Moderate risk group 1≤SPS≤3		If SAH absent, Discharge and Telephone/outpatient follow-up
Low risk group SPS=0	Not required	Outpatient follow-up

SAH: subarachnoid hemorrhage, SPS: subarachnoid hemorrhage prediction score, CT: computed tomography

本研究では，クモ膜下出血群において有意に白血球値の上昇が認められたが，木村ら[7]も同様の報告を行っており，今回はこれを確認する結果となった。またFujiiら[8]によると，クモ膜下出血を含む脳内出血患者においてクモ膜下腔に出血が及ぶと白血球値が上昇するとのことであり，今回の研究データを裏付けるものであると考えられる。

また，カリウム値において，クモ膜下出血群にて有意な低下を認めた。これはクモ膜下出血によりカテコラミン分泌が促進され，細胞内にカリウムが取り込まれることによって血清カリウム値の低下を来しているものと考えられる[9-12]。

血糖値の上昇については血糖値上昇とSAHの関係について直接的な検証を行った研究はみられないがDouhoutら[13]によるとSAH罹患1-10日目の血糖値が高ければ高いほど予後が悪いと報告しており，加えてJenniferら[14]は，SAH後の高血糖は一般的であると唱えておりSAH罹患と血糖値上昇に何らかの関連があることが示唆されている。

また，血圧高値についてもSAHとの関係について検証を行った研究はないが高血圧自体がSAHのリスクであるとされている[15]。

現在，SAHが疑われる患者に対しては(とくに「突然の頭痛」を主訴に来院された患者に対しては)す

ぐに頭部CTが実施されている。確かに臨床の現場において症状などよりSAHが疑わしい場合においてはすぐに頭部CTを施行する必要があるかとは思われるが，「突然の頭痛」とは言えない頭痛を主訴として来院するSAH患者も多い。また，すぐにCTが撮影できない診療所や夜間の外来などでSAHを疑うべきか否かの判断に迫られる場面は往々にして存在する。こういった状況においても今回の判断基準はその一助になるものと考えられる。

最後に本研究の限界に言及しておく。本研究は，当施設のみでの過去の診療データを基に，後ろ向きに行ったケースコントロール研究である。よって，欠損値が多く存在し，コントロール群は初診でSAHではないと判断された患者のうち，その後何らかの理由で再度来院（もしくは当日別疾患で入院）し，その後SAHと診断されることのなかった患者としたため，症例数は大幅に減少した。加えて，救急車で来院した頭痛患者のみを対象としており，SPSの独歩来院患者に対する妥当性は確保されていない。よってSPSをより一般化するためには，様々な施設で独歩来院患者も含めて，前向き研究にて検証する必要があると思われる。

結　語

頭痛を主訴に救急車搬送された患者について，SAHを予測する数的因子を同定し，SAHの見逃し回避に重点を置いたスクリーニング目的にSPSを開発した。救急外来において見逃すことのできないSAHを予測する場合に，有力な判断基準となることが期待できる。

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ABSTRACT

Highly sensitive, subarachnoid hemorrhage prediction score for patients with acute headache

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Background: To ensure a good prognosis for subarachnoid hemorrhage (SAH), early diagnosis is essential. Although delayed diagnosis is associated with increased morbidity and mortality, it has been reported that 12% of cases of SAH are overlooked at initial assessment. Therefore, accurate prediction at the initial stage is necessary.
Objective: To identify objective predictive factors associated with SAH in patients admitted on an emergency basis with a chief complaint of a headache, and to propose a score for predicting the presence or absence of SAH by combining these factors.
Subjects and Methods: Among emergency patients brought by ambulance with a chief complaint of a headache during the nine-year period from 2001, a total of 573 patients were selected by excluding patients with trauma, drunkenness, or coma, as well as patients whose final outcome was unknown. Among these patients, those for whom data were obtained between January 1, 2001 and December 31, 2006 (356 cases) were used to derive a prediction rule and classified into the SAH group (n=88) and control (non-SAH) group (n=268) based on the diagnosis obtained on brain CT and lumbar puncture. Numerically expressed items such as vital signs and laboratory test values were investigated using univariate and multivariate logistic regression analyses in order to identify predictive factors, and an SAH prediction score (SPS) was created based on these factors. In addition, patient's data obtained between January 1, 2007 and December 31, 2009 (217 cases) were used to validate the SPS.
Results: In consideration of ease of use in clinical settings, the following factors and cutoff values were selected: white blood cell count >8,000/μl, blood glucose >130 mg/dl, serum potassium <3.5 mEq/l, systolic blood pressure >140 mmHg. By assigning points to these predictive factors, SPS was calculated for each group. No patients with an SPS of 0 had SAH. In addition, according to the derived prediction rule, the risk of SAH increased as SPS increased. Moreover, similar results were obtained for SPS in the validation.
Conclusion: The use of SPS may enable reliable prediction of SAH in initial assessment of patients with acute headache at emergency departments.
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