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Age-specific impact of diabetes mellitus on the risk of cardiovascular mortality: An overview from the evidence for Cardiovascular Prevention from Observational Cohorts in the Japan Research Group (EPOCH-JAPAN)

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ABSTRACT

Background: Diabetes mellitus is a strong risk factor for cardiovascular disease. However, the age-specific association of diabetes with cardiovascular risk, especially in the elderly, remains unclear in non-Western populations.
Methods: A pooled analysis was conducted using 8 cohort studies (mean follow-up period, 10.3 years) in Japan, combining the data from 38,854 individual participants without history of cardiovascular disease. In all, 1867 of the participants had diabetes, defined based on the 1998 World Health Organization criteria. The association between diabetes and the risk of death from cardiovascular disease, coronary heart disease (CHD), and stroke was estimated using a stratified Cox model, accounting for variability of baseline hazard functions among cohorts.
Results: During the follow-up, 1376 subjects died of cardiovascular disease (including 268 of coronary heart disease and 621 of stroke). Diabetes was associated with an increased risk of cardiovascular death after multivariable adjustment (hazard ratio [HR] 1.62; 95% confidence interval [CI], 1.35–1.94). Similarly, diabetes was a risk factor for CHD (HR 2.13; 95% CI, 1.47–3.09) and stroke (HR 1.40; 95% CI, 1.05–1.85). In the age-stratified analysis of the risk of cardiovascular death, the relative effects of diabetes were consistent across age groups (p for heterogeneity = 0.18), whereas the excess absolute risks of diabetes were greater in participants in their 70s and 80s than in younger subjects.
Conclusions: The management of diabetes is important to reduce the risk of death from cardiovascular disease, not only in midlife but also in late life, in the Japanese population.

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Introduction

The International Diabetes Federation (IDF) reported in the 7th Edition of the IDF Diabetes Atlas that the prevalence of diabetes had risen to 7.6% of the world population as of 2015 and was still climbing,[1] especially in Asian populations. Epidemiological studies, conducted mainly in Western countries, have accumulated evidence that diabetes is an independent risk factor for cardiovascular morbidity or mortality.[2–5] Recent meta-analyses have shown a two-fold elevated risk for cardiovascular death in people with diabetes.[6,7] The aging of the overall population is a significant driver of the diabetes epidemic. Although the burden of diabetes is often described in terms of its influence on middle-aged people, older people with diabetes are at substantial risk for cardiovascular disease. Recently, the Consensus Development Conference on Diabetes and Older Adults, which was convened by the American Diabetes Association, stated the necessity of epidemiological and clinical research focused on diabetes in older individuals.[8] The previous meta-analyses have reported that excess cardiovascular risk of diabetes was relatively modest in older subjects.[6,7] However, the association of non-communicable diseases, such as diabetes, with mortality and morbidity in individual countries, especially in Asia, is likely to be affected by their respective health care systems and demographic profiles, including such factors as age-distribution, life expectancy, availability of optimal care, and accessibility to hospitals. Therefore, it would be worthwhile to gather more reliable data on the age-specific association between diabetes and cardiovascular risk in countries having prolonged life expectancies and good health care systems for the elderly.

The Evidence for Cardiovascular Prevention From Observational Cohorts in JAPAN (EPOCH-JAPAN) study is a collaborative meta-analysis of individual participants' data from several community-based cohort studies in Japan, which is among the countries with relatively high proportions of elderly and prolonged life-expectancies.[9,10] The purpose of this study was to examine the age-specific association between diabetes and mortality from cardiovascular disease and its subtypes in the general Japanese population.

Methods

Study cohorts

The rationale, study design, and methods of the EPOCH-JAPAN study have been described elsewhere.[9–15] In brief, cohort studies were eligible for inclusion in this analysis if they met the following criteria: (1) collection of health examination measures, (2) at least 10 years of follow-up, and (3) greater than 1000 participants. Both nationwide and regional cohort studies were included. Individual records of 188,141 participants in 13 cohort studies were initially eligible for inclusion in this study. Quality control of the collected data was performed at the EPOCH-JAPAN Coordinating Center. Permission to submit data from each cohort to the EPOCH-JAPAN Study Coordinating Center was obtained from the relevant institutional review boards for ethical issues.

Of the 13 studies, three cohorts without codes for causes of death and two cohorts without information about diabetic status were excluded from the study. A total of 53,629 participants aged 40–90 years from the remaining 8 cohorts[16–24] were included in the present study to elucidate the association between diabetes and cardiovascular death. After excluding participants for whom examination data at baseline was unavailable and those with a history of CVD, the remaining 38,854 participants were enrolled in the present analyses.

Baseline assessment

Diabetic status was determined on the basis of World Health Organization (WHO) diagnostic criteria[25]: diabetes was considered present when fasting blood glucose was ≥7.0 mmol/L, non-fasting blood glucose was ≥11.1 mmol/L, or the subject was using an anti-diabetic agent. Blood pressure was measured with a standard sphygmomanometer in all cohorts. In several cohorts where blood pressure was measured twice or more, the average values were used for analysis. Body mass index was calculated as weight (kg) divided by height (m)^2. Measurement of serum total cholesterol was standardized in five cohorts such that values would be trackable to the Centers for Disease Control and Prevention reference method. Smoking status and alcohol intake were defined as current or not.

Outcomes

For each deceased subject, the primary underlying cause of death was coded according to the International Classification of Disease (ICD) for the National Vital Statistics based on the criteria proposed by WHO. Details on the causes of CVD mortality were sought using all available sources in each cohort study, and the findings were used to classify each case as either coronary heart disease (CHD), stroke, or other CVDs. In many studies, death certificates were reviewed and/or the National Vital Statistics were utilized after obtaining permission from the Ministry of Internal Affairs and Communications of Japan. Other sources utilized in some studies included autopsy, medical records, health examinations, and questionnaires. Causes of CVD mortality were coded based on either the ICD-9 or ICD-10 classification. Classification codes used in the study were as follows: death from CVD (390–459 in ICD-9 and I00-I99 in ICD-10), CHD (410–414 in ICD-9 and I20-I25 in ICD-10), and stroke (430–438 in ICD-9 and I60-I69 in ICD-10).

Statistical analysis

The SAS software package Version 9.13 (SAS Institute Inc., Cary, NC, USA) was used to perform all statistical analyses. Age- and sex-adjusted mean values of possible risk factors, taken as continuous variables, were computed using the analysis of covariance method stratified by diabetic status. The frequencies of risk factors, taken as binary variables, were adjusted for age and sex using the direct method. The differences in the mean values or the frequencies of risk factors were tested using analysis of covariance or logistic regression, respectively. The hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated using stratified Cox proportional hazards model, with accounting for the variability of baseline hazards among cohorts. For evaluating the difference in the association of diabetes with death from cardiovascular disease among cohorts, the heterogeneity across cohorts was tested using the Cochran Q test at a significance level of $p < 0.05$ and quantified by the I^2 statistic, where an I^2 of ≥50% was considered to be evidence of substantial heterogeneity and ≥75% considerable heterogeneity.[26] Since there was no evidence of heterogeneity in the associations, the pooled HRs and their CIs were calculated using a stratified Cox proportional hazards model, in which the difference in the HRs among the cohorts was considered as a fixed-effect in the meta-analysis. In the multivariable-adjusted analysis, adjustment was made for age, sex, systolic blood pressure, body mass index, total cholesterol, smoking habit, and alcohol intake.

The age-specific influence of diabetes on cardiovascular death was estimated using the sex-adjusted stratified Cox model in subgroups stratified by 10-year-interval age groups. The trend in the influence across age categories was tested by adding the

multiplicative interaction between diabetic status and ordinal age groups to the relevant Cox model. In each age group, absolute risk difference (ARD) of death from cardiovascular disease was calculated as the difference of crude mortality rate per 1000 person-years in patients without diabetes from that in those with diabetes.

Results

Table 1 shows the baseline characteristics of participants in each cohort.[11–19] Among all subjects, the mean age at study entry was 58 years, and the proportion of men was 43.9%. The frequency of diabetes at baseline was 4.8%. The baseline examinations were performed from 1977 to 1994. During an average follow-up of 10.3 years, a total of 4542 participants died. Of these, 1376 deaths were ascribed to cardiovascular disease.

Of the 38,854 participants, 1867 (4.8%) had diabetes at baseline (Table 2). Mean age, systolic blood pressure, diastolic blood pressure, total cholesterol, and body mass index were higher in participants with diabetes. The frequencies of male sex, current smoking, and alcohol intake were also higher in these participants.

Table 3 presents the HRs of diabetes for death from cardiovascular disease and its subtypes. The risk of death from cardiovascular disease was significantly higher in participants with diabetes than those without diabetes (age- and sex-adjusted HR 1.66; 95% CI, 1.40–1.98). With regard to the subtypes of cardiovascular disease, diabetes was significantly associated with an increased risk of death from coronary heart disease (age- and sex-adjusted HR 2.21; 95% CI, 1.54–3.16) and stroke (HR 1.47; 95% CI, 1.12–1.92). The risk of all-cause death was also higher in subjects with diabetes (HR 1.38; 95% CI, 1.24–1.52). After adjustment for systolic blood pressure, serum total cholesterol, body mass index, current smoking status, and habitual alcohol intake, these associations were not substantially changed. We tested the difference in the association between diabetes and death from cardiovascular disease among cohorts to check the validity of pooling the data. There was no evidence of heterogeneity in these associations among the included study cohorts (all P for heterogeneity >0.2; $Q = 5.2$, $I^2 = 0\%$ for cardiovascular disease; $Q = 4.0$, $I^2 = 0\%$ for coronary heart disease; and $Q = 4.0$, $I^2 = 0\%$ for stroke; and $Q = 9.6$, $I^2 = 27\%$ for all-cause death). In the subgroup analyses stratified by sex, the associations between diabetes and mortality from cardiovascular disease, stroke, and all-cause death were consistent between the sexes, without any evidence of heterogeneity in the influence (P for heterogeneity >0.05 for cardiovascular disease, stroke, and all-cause death). However, the magnitude of the association of diabetes with the risk of coronary heart disease was significantly greater in women than men (P for heterogeneity <0.05 for coronary heart disease).

Finally, we examined the age-specific association between diabetes and risk of cardiovascular death (Fig. 1). While there was no evidence of heterogeneity in the magnitude of the relative influence of diabetes on the cardiovascular risk across age groups in the sex-adjusted model (p for heterogeneity = 0.18) (HR 1.70; 95% CI, 0.53–5.43 for the 40–49 year age group, HR 2.02; 95% CI, 1.23–3.31 for the 50–59 year age group, HR 2.06; 95% CI, 1.53–2.76 for the 60–69 year age group, HR 1.38; 95% CI, 1.04–1.82 for the 70–79 year age group, and HR 1.72; 95% CI, 1.08–2.73 for the 80–89 year age group), the excess ARD of diabetes on cardiovascular death compared with non-diabetes was greater in participants in their 70s and 80s than in younger subjects (ARD per 1000 person-years: 0.5 for the 40–59 year age group, 1.7 for the 50–59 year age group, 4.2 for the 60–69 year age group, 4.8 for the 70–79 year age group, and 19.4 for the 80–89 year age group).

Discussion

The present pooled analysis of individual participants' data clearly demonstrated that diabetes was a significant risk factor for death from cardiovascular disease and all causes. With regard to cardiovascular subtypes, diabetes was associated with a doubled risk of coronary heart disease and a 40% increased risk of death from stroke. These associations remained robust even after adjustment for other confounding factors. Notably, the magnitude of the influence of diabetes on the mortality risk from cardiovascular disease was similar across age groups, without attenuation of the influence in older people in this study, whereas the excess ARD of diabetes on cardiovascular death increased with aging, reflecting higher cardiovascular mortality in older people. These findings provide robust evidence of the excess risk of cardiovascular disease in people with diabetes, not only in midlife but also in late life, among the general Japanese population.

Table 1
Characteristics of included studies.

Geographic region (Prefecture)	Cohort name	Year of baseline survey	Sample size	Mean (range) age, years	Men, %	DM[a], %	Mean follow-up period, years	Number of all-cause deaths	Number of CVD deaths	Number of CHD deaths	Number of stroke deaths
Hokkaido	Tanno-Sobetsu	1977	1808	50.7 (40–77)	46.5	2.9	18.2	217	76	18	34
Miyagi	Osaki	1994	15,758	62.2 (41–81)	42.1	4.6	6.0	796	237	59	112
Iwate	Ohasama	1987	775	58.7 (40–89)	33.8	5.4	10.1	90	17	4	9
Toyama	YKK workers	1990	3022	47.3 (40–65)	65.5	0.9	10.8	75	13	0	4
Hiroshima	RERF cohort	1986	2231	57.3 (40–89)	32.2	9.9	15.4	558	111	11	48
Fukuoka	Hisayama	1988	2625	59.0 (40–89)	42.2	8.8	11.0	473	138	24	57
Nationwide	NIPPON DATA 80	1980	6540	55.7 (40–89)	44.6	4.6	16.9	1661	598	114	285
Nationwide	NIPPON DATA 90	1990	6095	57.0 (40–89)	42.3	4.5	9.5	672	186	38	72
	Total		38,854	58.0 (40–89)	43.9	4.8	10.3	4542	1376	268	621

CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; RERF, Radiation Effects Research Foundation.
[a] Diabetes was defined as fasting blood glucose ≥7.0 mmol/L or casual blood glucose ≥11.1 mmol/L or use of diabetes medication.

Table 2
Baseline characteristics of the study sample by diabetic status.

Risk factors	Participants without diabetes (n = 36,987)	Participants with diabetes (n = 1867)	p value
Age, years	58 (0.1)	63 (0.3)	<0.001
Men, %	43.4	53.3	<0.001
Systolic blood pressure, mm Hg	132 (0.1)	136 (0.4)	<0.001
Total cholesterol, mmol/L	5.2 (0.01)	5.3 (0.02)	<0.001
Body mass index, kg/m^2	23.3 (0.02)	23.5 (0.07)	0.005
Current smoking, %	27.3	30.4	0.03
Current drinking, %	41.3	41.6	0.90

Values are reported as age- and sex-adjusted mean (standard error) or frequency. The statistical significance of the differences in the mean values or frequencies of risk factors was estimated by the analysis of covariance method or logistic regression, respectively.

Table 3
Influence of diabetes on the risk of death from cardiovascular disease.

	Number of participants	Number of events	Age- and sex-adjusted			Multivariable-adjusted		
			HR (95% CI)	P	I^2 (p heterogeneity)	HR (95% CI)	P	I^2 (p heterogeneity)
Overall								
Cardiovascular disease								
No diabetes	36,987	1227	1.00 (Reference)		0%	1.00 (Reference)		33.6%
Diabetes	1867	149	1.66 (1.40, 1.98)	<0.001	(0.52)	1.62 (1.35, 1.94)	<0.001	(0.17)
Coronary heart disease								
No diabetes	36,987	233	1.00 (Reference)		0%	1.00 (Reference)		0%
Diabetes	1867	35	2.21 (1.54, 3.16)	<0.001	(0.67)	2.13 (1.47, 3.09)	<0.001	(0.93)
Stroke								
No diabetes	36,987	561	1.00 (Reference)		0%	1.00 (Reference)		44.9%
Diabetes	1867	60	1.47 (1.12, 1.92)	0.0054	(0.41)	1.40 (1.05, 1.85)	0.02	(0.12)
All-cause death								
No diabetes	36,987	4114	1.00 (Reference)		26.9%	1.00 (Reference)		28.7%
Diabetes	1867	428	1.38 (1.24, 1.52)	<0.001	(0.21)	1.39 (1.25, 1.55)	<0.001	(0.20)
Men								
Cardiovascular disease								
No diabetes	16,072	620	1.00 (Reference)		0%	1.00 (Reference)		0%
Diabetes	966	79	1.60 (1.26, 2.02)	<0.001	(0.91)	1.41 (1.10, 1.82)	0.008	(0.62)
Coronary heart disease								
No diabetes	16,072	135	1.00 (Reference)		58.1%	1.00 (Reference)		33.8%
Diabetes	966	16	1.61 (0.95, 2.70)	0.08	(0.049)	1.42 (0.81, 2.48)	0.22	(0.20)
Stroke								
No diabetes	16,072	278	1.00 (Reference)		28.5%	1.00 (Reference)		53.8%
Diabetes	966	36	1.58 (1.12, 2.25)	0.01	(0.23)	1.33 (0.92, 1.94)	0.13	(0.07)
All-cause death								
No diabetes	16,072	2265	1.00 (Reference)		0%	1.00 (Reference)		0%
Diabetes	966	246	1.34 (1.17, 1.53)	<0.001	(0.89)	1.32 (1.15, 1.52)	<0.001	(0.93)
Women								
Cardiovascular disease								
No diabetes	20,915	607	1.00 (Reference)		0%	1.00 (Reference)		27.1%
Diabetes	901	70	1.77 (1.38, 2.28)	<0.001	(0.49)	1.96 (1.51, 2.55)	<0.001	(0.23)
Coronary heart disease								
No diabetes	20,915	98	1.00 (Reference)		0%	1.00 (Reference)		0%
Diabetes	901	19	3.23 (1.96, 5.32)	<0.001	(0.47)	3.45 (2.08, 5.70)	<0.001	(0.49)
Stroke								
No diabetes	20,915	283	1.00 (Reference)		0%	1.00 (Reference)		0%
Diabetes	901	24	1.35 (0.89, 2.05)	0.16	(0.93)	1.48 (0.97, 2.28)	0.07	(0.97)
All-cause death								
No diabetes	20,915	1849	1.00 (Reference)		42.8%	1.00 (Reference)		50.7%
Diabetes	901	182	1.44 (1.23, 1.68)	<0.001	(0.11)	1.53 (1.30, 1.80)	<0.001	(0.06)

CI, confidence interval; HR, hazard ratio.
In the stratified analyses of sex, the risk estimates were not adjusted for sex. Multivariable adjustment was made for age, sex, systolic blood pressure, body mass index, total cholesterol, smoking habits, and alcohol intake in the stratified Cox's proportional hazards model.
The p value for heterogeneity between the sexes was 0.53 for cardiovascular disease, 0.04 for coronary heart disease, 0.46 for stroke, and 0.55 for all-cause death in the age- and sex-adjusted model, and 0.09 for cardiovascular disease, 0.02 for coronary heart disease, 0.89 for stroke, and 0.21 for all-cause death in the multivariable-adjusted model.

The accumulated evidence in Western prospective studies has indicated that the risk of cardiovascular disease is two-to four-fold higher in individuals with diabetes compared with those without diabetes.[2–5] A recent meta-analysis of 97 cohort studies, 96% of which were conducted in Europe, North America, and Australasia, demonstrated that the average relative risk of diabetes for the risk of death from cardiovascular disease was 2.32.[6] In a pooled analysis of the Asian-Pacific region, subjects with diabetes had an approximately two-fold higher risk of fatal cardiovascular disease than those without diabetes.[7] With regard to cardiovascular subtypes, diabetes was also associated with an elevated risk of death from coronary heart disease[2–4,7] and stroke.[2,3,7,27,28] These findings were in accord with ours. Therefore, the present study confirms that, as

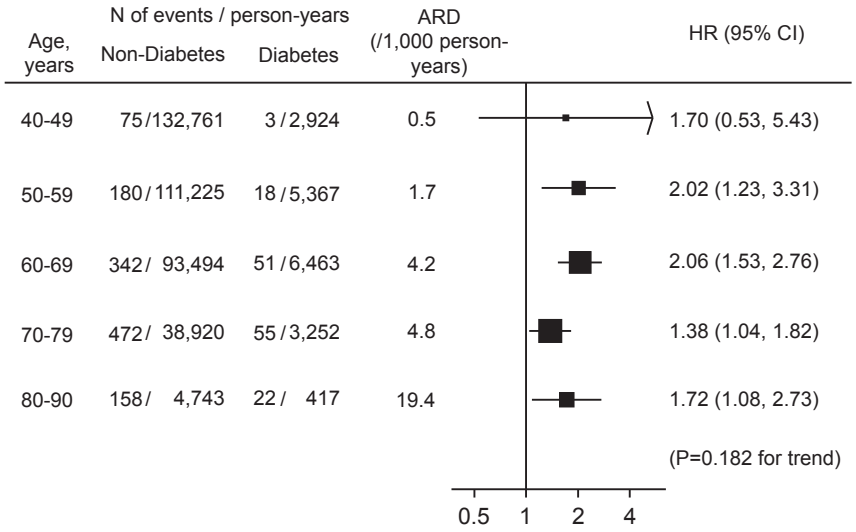

Fig. 1. Relative and absolute risk of death from cardiovascular disease associated with diabetes in each age group. The HRs and 95% CIs were calculated among age groups using the sex-adjusted stratified Cox model. The trend in the influence of diabetes on cardiovascular risk across age categories was tested by adding a multiplicative interaction term between diabetic status and ordinal age groups to the relevant Cox model. ARD, absolute risk difference; CI, confidence interval; HR, hazard ratio.

for Western populations, diabetes is a significant risk factor for cardiovascular mortality in the general Japanese population.

The influence of diabetes on cardiovascular death has been inconclusive in older people. In previous meta-analyses, the relative risk for cardiovascular death among diabetic subjects was reported to be reduced in older individuals.[6,7] In the present study, however, the magnitude of the association between diabetes and cardiovascular risk was consistent across age groups. The explanation for this discrepancy is uncertain, but the reduced influence of diabetes on the cardiovascular mortality and morbidity in older people in previous studies was likely affected by the higher mortality due to non-cardiovascular diseases (i.e., an increase in the competing risk for death) in older subjects. On the other hand, since the present study was conducted in Japan, a country with relatively prolonged life expectancy, the competing risk of death may have had less influence on cardiovascular death in older participants with diabetes in our study compared to studies in other populations. Our finding of a statistically significant interaction should be interpreted with the caveat that there might be actual attenuation of the effects in the elderly because of lower HRs and wider CIs in the elderly than in participants in their 60s.

In the present study, diabetes had a stronger impact on death from coronary heart disease in women than in men. This heterogeneity in the association between the sexes may be due to chance. However, a meta-analysis has reported that women had a 50% higher risk for fatal coronary heart disease associated with diabetes than men.[29] Previous cohort studies conducted in Japan,[30,31] one of which was included in the present pooled meta-analysis,[30] also showed that the risk of diabetes for the development of coronary heart disease was about three-fold higher in women than in men. Men may have a greater accumulation of cardiovascular risk factors, such as smoking and obesity, regardless of diabetes status, which would likely lead to a greater incidence of coronary heart disease even in non-diabetic men. Additionally, women without diabetes may have lower mortality from coronary heart disease compared to those with diabetes, which would lead to a greater relative effect of diabetes. Further investigation will be needed to clarify this issue.

The strengths of this study are its pooled analysis of prospective cohort studies, inclusion of a single ethnicity, a large sample size, and a sufficiently long follow-up period. Some limitations of this study should also be noted. First, selection bias may have been present, since the individual data of most cohort studies were collected from baseline surveys performed during community health examinations, and health-conscious participants were more likely to receive their health examinations. The influence of this limitation on the relative and absolute risks, however, would likely be slight, because all participants were Japanese and the difference in absolute risk between cohorts was small.

Our findings indicated that diabetes is an independent risk factor for death from cardiovascular disease in the Japanese population. This excess risk of death from cardiovascular disease associated with diabetes was substantially sustained even in late life, and the absolute risk increments in cardiovascular death from diabetes were greater in older people than in younger people. Therefore, the management of diabetes is important to reduce the risk of death from cardiovascular disease not only in midlife, but also in late life. In addition, since several factors, such as erratic nutritional intake, changes in mental status that impair the perception or response to hypoglycemia, and polypharmacy, predispose older diabetic patients to severe hypoglycemia, aggressive management of diabetes for older people requires careful consideration of the risks and benefits. Nevertheless, our findings underscore that careful management of diabetes has the potential to improve quality of life and increase life expectancy in older individuals with diabetes.

Conflicts of interest

None declared.

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Author contributions

Y.H. contributed to the study concept and design, analysis and interpretation of data, and drafting of manuscript. T.N. contributed to the study concept and design, analysis and interpretation of data, and critical revision of manuscript. Y.K. contributed to the study concept and design, acquisition of data, and critical revision of manuscript. Y.M. contributed to statistical analysis and critical revision of manuscript. S.S. contributed to acquisition of data and critical revision of manuscript. H.N. contributed to acquisition of data and critical revision of manuscript. A.O. contributed to acquisition of data and critical revision of manuscript. A.T. contributed to acquisition of data and critical revision of manuscript. K.S. contributed to acquisition of data and critical revision of manuscript. K.M. contributed to acquisition of data and critical revision of manuscript. H.U. contributed to acquisition of data and critical revision of manuscript. T.O. contributed to the study concept and design, acquisition of data, and critical revision of manuscript. All authors participated in the drafting and approval of the final manuscript and take responsibility for the content and integrity of this article.

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