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Association between serum ALT levels and incidence of new-onset diabetes in general population of Japanese: a longitudinal observational study (ISSA-CKD)

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ABSTRACT

Objective We aimed to clarify the relationship between serum alanine transaminase (ALT) levels and incidence of new-onset diabetes in a Japanese general population.

Setting Population-based retrospective cohort study using annual health check-up data for residents of Iki City, Nagasaki Prefecture, Japan.

Participants A total of 5330 Japanese individuals (≥30 years old) without diabetes at baseline were analysed.

Primary and secondary outcome measures Serum ALT levels were determined using an enzymatic method and were classified into gender-specific quartile groups as follows: group 1 (3–16 U/L in men and 3–13 U/L in women), group 2 (17–21 U/L in men and 14–16 U/L in women), group 3 (22–29 U/L in men and 17–22 U/L in women) and group 4 (30–428 U/L in men and 23–268 U/L in women). The study outcome was the incidence of diabetes (fasting glucose ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L, glycated haemoglobin ≥6.5% or use of glucose-lowering therapies).

Results After an average follow-up period of 5.0 years, 279 individuals developed diabetes. The incidence rate of diabetes increased with elevation of serum ALT levels (0.7% per 100 person-years in group 1, 0.9% in group 2, 0.9% in group 3 and 1.7% in group 4) (p<0.001 for trend). This association was significant after adjustment for other risk factors including age, sex, obesity, hypertension, dyslipidaemia, smoking, current daily alcohol intake and regular exercise (p<0.001 for trend). Comparable associations were observed between men and women (p=0.459 for interaction).

Conclusion Serum ALT levels were associated with future development of diabetes in the general Japanese population.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This large-scale observational study of the general Japanese population with long-term follow-up confirmed the findings from previous studies.
⇒ It is likely that the participants of this study, who attended health examinations, were more health conscious and were more likely to be engaged in healthier behaviours than those who did not attend health examinations.
⇒ In this study, there was no information on the causes of elevated serum alanine transaminase levels (fatty liver, alcoholic hepatitis, viral hepatitis, autoimmune diseases, thyroid dysfunction, etc).
⇒ Diabetes was not diagnosed using the 75 g oral glucose tolerance test and may be underestimated.

INTRODUCTION

In 2014, diabetes was estimated to affect 422 million adults worldwide (8.5% of the world total population). Furthermore, according to the 2012 data, 1.5 million people worldwide died as a direct result of diabetes. In addition, 2.2 million people die from cardiovascular disease, chronic kidney disease (CKD) and infectious diseases presumed to be caused by hyperglycaemia.[1 2] Effective prevention of diabetes, subsequent macrovascular and microvascular complications and deaths directly/indirectly related to diabetes requires strategies based on up-to-date knowledge on modifiable risk factors of new-onset diabetes.

Established modifiable risk factors of diabetes involve obesity,[3–5] glucose intolerance,[6–8] smoking,[9 10] alcohol intake,[11 12] inadequate diet[13 14] and physical inactivity.[15 16] Recently, several observational studies suggested that elevated serum alanine transaminase (ALT) levels are associated with increased risks of diabetes.[17–21] However,

findings of prior observational studies are still inconsistent particularly among Japanese.[22–24] The aim of the present analysis was to clarify the association between serum ALT levels and future development of diabetes in a large-scale longitudinal study of general Japanese population.

SUBJECTS AND METHODS

Study design and participants

We used data from the Iki City Epidemiological Study of Atherosclerosis and Chronic Kidney Disease (ISSA-CKD), which is a population-based retrospective cohort study of the residents of Iki City, Nagasaki Prefecture, Japan. Details of the ISSA-CKD study have been described previously.[14 25–28] Iki City is a city whose main administrative area is Iki Island in Nagasaki Prefecture. The total population of Iki City is approximately 26 000. Among them, approximately 11 000 residents were National Health Insurance subscribers (aged <75 years) and approximately 5000 residents were Latter-stage Elderly Health Insurance subscribers (aged 75 years or older). In Iki City, all National Health Insurance subscribers aged 30–74 years and all Latter-stage Elderly Health Insurance subscribers were invited to participate in annual specific health checkups each year. Between 2008 and 2017, a total of 7895 residents aged 30 years or older underwent annual health examinations conducted by the local government of Iki City at least once (range: 1–10 times) (annual participation rate ranged from 26.9% to 54.4%). We excluded 1898 residents with a follow-up duration of less than 1 year and 667 who had diabetes at baseline. Finally, a total of 5330 participants were included in the present analysis (figure 1). Consent of participants was obtained using opt-out approach. In detail, information of the study (title, objective, participants, data to be used in the study, contact information, etc) was published on the websites of the Iki City and Fukuoka University and the opportunity to refuse the usage of data for the study was provided to the participants of the study.

Data collection

Fasting or non-fasting blood and urine samples were collected and all samples were analysed at a single laboratory of CRC. Serum ALT levels were determined enzymatically using Beckman Coulter's autoanalyzer (AU5800, Brea, California, USA) with a data detection range of 2.2–1600 U/L, a reference range of 6–30 U/L and a coefficient of variation of 3%. Serum ALT levels were standardised using the Japan Society of Clinical Chemistry standardisation law method. Participants were classified into gender-specific quartile groups as follows: group 1 (3–16 U/L in men and 3–13 U/L in women), group 2 (17–21 U/L in men and 14–16 U/L in women), group 3 (22–29 U/L in men and 17–22 U/L in women) and group 4 (30–428 U/L in men and 23–268 U/L in women).

Serum low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride concentrations, serum aspartate aminotransferase (AST) levels and gamma-glutamyl transpeptidase (gamma-GTP) were determined enzymatically. Dyslipidaemia was defined by LDL cholesterol concentrations ≥3.62 mmol/L, HDL cholesterol concentrations <1.03 mmol/L, triglyceride concentrations ≥1.69 mmol/L or the use of lipid-lowering medication. Plasma glucose concentrations were determined using an enzymatic method and glycated haemoglobin (HbA1c) levels (mmol/mol, National Glycohemoglobin Standardisation Programme value) were determined using high-performance liquid chromatography. Urine protein was measured qualitatively and defined as + or greater.

At each health examinations, height, weight and waist circumference were measured with the participant wearing light clothes without shoes, and body mass index (BMI) was calculated. Obesity was defined as a BMI≥25 kg/m^2.[29] Blood pressure (BP) was measured twice by trained staff in the right upper arm using mercury, automatic or aneroid sphygmomanometer with appropriately sized cuff, after at least 5 min of rest in a sitting position. Average of the two BP values was used in the present analysis. Hypertension was defined as a BP level of ≥140/90 mm Hg or use of BP lowering medication.

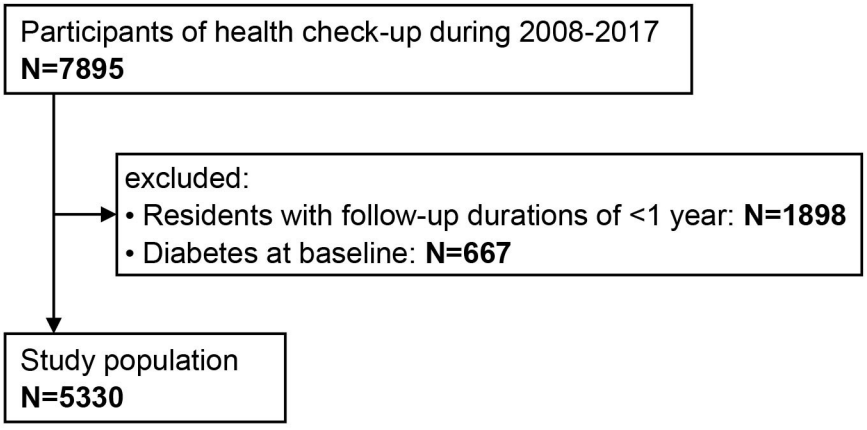

Figure 1 Flow chart of participants.

Information regarding the participants' smoking habits, alcohol intake, regular exercise and use of medications was obtained using the standard specific health check-up questionnaire defined by the Ministry of Health, Labour and Welfare, Japan.[30] Current smokers were defined as participants who had smoked 100 cigarettes or more, or those who had smoked regularly for more than 6 months at baseline, according to the guidance from the Ministry of Health, Labour and Welfare.[30] Alcohol intake was classified into current daily drinking or no daily drinking. Regular exercise was defined as regular exercise of ≥30 min per day, two times or more per week.

Follow-up and outcome

During the follow-up period from 2008 to 2017, we defined the first time when each participant received a medical examination as the baseline examination and followed the patients up to 2017. The outcome of the present analysis was development of new-onset diabetes (fasting glucose concentration ≥7.0 mmol/L, non-fasting glucose concentration ≥11.1 mmol/L, HbA1c ≥47 mmol/mol (6.5%) or use of glucose-lowering therapies). In order to avoid measurement error, participants whose blood test results suggested diabetes at a health examination but returned to normal level (fasting glucose <7.0 mmol/L, non-fasting glucose <11.1 mmol/L and HbA1c <47 mmol/mol (6.5%)) without initiation of any glucose-lowering therapies at the end of follow-up, were not regarded as incidence of new-onset diabetes. In other words, participants who developed diabetes at a follow-up examination and who were confirmed as having diabetes at the end of follow-up were diagnosed as incident diabetes.

Statistical analysis

Continuous variables were expressed as mean±SD or median and IQR and trends across quartile groups of serum ALT were tested using simple regression models or Jonckheere-Terpstra test. Categorical variables were expressed as the number of participants (percentage), and trends across groups were tested using logistic regression models. Incidence rates of diabetes were calculated using the person-year method. Crude and multivariable-adjusted HRs and their 95% CIs were estimated using

Table 1 Baseline characteristics according to quartile of serum alanine transaminase (ALT) levels

	Quartile of serum ALT levels*				
	Group 1 (n=1422)	Group 2 (n=1234)	Group 3 (n=1359)	Group 4 (n=1315)	P value for trend
Age, mean (SD), years	58.8 (11.5)	60.2 (10.6)	61.2 (9.2)	58.8 (10.5)	0.274
Men, n (%)	599 (42.1)	581 (47.1)	567 (41.7)	603 (45.9)	0.321
Smoking, n (%)	286 (20.1)	216 (17.6)	221 (16.3)	248 (18.9)	0.250
Current daily alcohol intake, n (%)	276 (21.3)	302 (26.8)	280 (23.1)	272 (23.0)	0.696
Regular exercise, n (%)	350 (26.4)	321 (28.1)	343 (27.1)	326 (26.6)	0.981
Body mass index, mean (SD), kg/m^2	22.4 (2.9)	23.0 (3.0)	23.8 (3.2)	25.1 (3.8)	<0.001
Obesity, n (%)	280 (19.7)	286 (23.2)	459 (33.8)	612 (46.5)	<0.001
Waist circumference, mean (SD), cm	80.4 (9.0)	82.1 (8.6)	84.3 (8.9)	87.3 (10.1)	<0.001
Systolic blood pressure, mean (SD), mm Hg	126.5 (18.6)	129.4 (18.3)	130.1 (19.2)	130.7 (17.9)	<0.001
Diastolic blood pressure, mean (SD), mm Hg	73.7 (11.0)	74.7 (11.1)	75.3 (10.7)	76.3 (11.2)	<0.001
Use of blood pressure lowering medications, n (%)	345 (24.3)	312 (25.4)	391 (28.8)	417 (31.7)	<0.001
Hypertension, n (%)	549 (38.7)	523 (42.4)	621 (45.7)	645 (49.1)	<0.001
Use of lipid lowering medications, n (%)	121 (8.5)	110 (9.0)	203 (15.0)	195 (14.9)	<0.001
Low-density lipoprotein cholesterol, mean (SD), mmol/L	3.04 (0.77)	3.14 (0.79)	3.27 (0.81)	3.23 (0.90)	<0.0001
High-density lipoprotein cholesterol, mean (SD), mmol/L	1.64 (0.46)	1.66 (0.42)	1.63 (0.50)	1.53 (0.44)	<0.001
Triglyceride, median (IQR), mmol/L	2.22 (1.63–3.05)	2.38 (1.76–3.23)	2.64 (1.89–3.78)	3.00 (2.12–4.32)	<0.001
Dyslipidaemia, n (%)	467 (32.8)	460 (37.3)	650 (47.8)	682 (51.9)	<0.001
Aspartate aminotransferase, mean (SD), U/L	18.9 (4.1)	21.8 (4.3)	24.3 (5.5)	36.0 (22.1)	<0.001
Gamma-glutamyl transpeptidase, median (IQR), U/L	18 (14–26)	22 (16–35)	27 (19–43)	42 (25–76)	<0.001
HbA1c NGSP, mean (SD), %	5.0 (0.3)	5.0 (0.4)	5.1 (0.4)	5.1 (0.4)	<0.001
Proteinuria, n (%)	57 (4.0)	60 (4.9)	52 (3.8)	67 (5.1)	0.371

*Group 1=3–16 U/L in men and 3–13 U/L in women, group 2=17–21 U/L in men and 14–16 U/L in women, group 3=22–29 U/L in men and 17–22 U/L in women, group 4=30–428 U/L in men and 23–268 U/L in women.
HbA1c, glycated haemoglobin; NGSP, National Glycohemoglobin Standardisation Programme.

Table 2 Risk of diabetes mellitus to quartile of the alanine transaminase (ALT) value

	Quartile of serum ALT levels*				
	Group 1 (n=1422)	Group 2 (n=1234)	Group 3 (n=1359)	Group 4 (n=1315)	P value for trend
N of events/person-years	47/7020	56/6164	64/6819	112/6643	
Annual incidence rate	0.7%	0.9%	0.9%	1.7%	
Crude HR	1.00	1.35	1.40	2.53	<0.001
(95% CI)	(Reference)	(0.92 to 2.00)	(0.96 to 2.04)	(1.80 to 3.56)	
Adjusted HR (model 1)†	1.00	1.24	1.37	2.11	<0.001
(95% CI)	(Reference)	(0.80 to 1.91)	(0.90 to 2.07)	(1.43 to 3.12)	

*Group 1=3–16 U/L in men and 3–13 U/L in women, group 2=17–21 U/L in men and 14–16 U/L in women, group 3=22–29 U/L in men and 17–22 U/L in women, group 4=30–428 U/L in men and 23–268 U/L in women.
†Adjusted for age, sex, smoking, current daily alcohol intake, regular exercise, obesity, hypertension and dyslipidaemia.

the Cox proportional hazards model. The multivariate Cox model included all available factors considered to be biologically plausible and clinically important (ie, age, sex, smoking, current daily alcohol intake, regular exercise, obesity, hypertension and dyslipidaemia) as covariates without any mathematical selection of variables. Sensitivity analysis was performed using serum ALT levels as a continuous variable in Cox proportional hazards models. Because of skewed distribution of serum ALT levels, serum ALT levels were log-transformed and HRs per 1 increase in log-transformed ALT levels were calculated. Sensitivity analysis excluding participants with serum ALT levels of >50 U/L (top 5 percentile), using BMI (instead of obesity) as a covariate in multivariable analysis and using alcohol intake as 5 categories (no drinkers, occasional drinkers or daily drinkers (average alcohol intake <22 g/day, 22–43 g/day or ≥44 g/day)) in multivariable analysis were also conducted. The effect of serum ALT levels on the development of diabetes was compared between subgroups defined by gender, current daily alcohol intake and obesity by adding interaction items (interaction between serum ALT categories and sex for subgroup analysis by gender, interaction between serum ALT categories and alcohol intake for subgroup analysis by alcohol intake, and interaction between serum ALT levels and obesity for subgroup analysis of obesity). A two-tailed p<0.05 was considered statistically significant. All data analyses were carried out using SAS V.9.4.

Patient and public involvement

ISSA-CKD study was conducted in collaboration between Fukuoka University and Iki City. This study was originally designed to prevent incidence and progression of CKD using existing data obtained by the Iki City because of priorities of the public, but the Iki City was not involved in design of this paper. The results will be disseminated to the Iki City through public seminars after publication of this paper.

RESULTS

Online supplemental figure 1 shows scatterplot of serum ALT levels among participants who developed diabetes and those who did not.

Table 1 shows the baseline characteristics according to quartile groups of serum ALT. Participants with higher ALT value had higher waist circumference, higher levels of BMI, BP, LDL cholesterol, triglyceride, AST, gamma-GTP and HbA1c, and lower levels of HDL cholesterol and more used antihypertensive and lipid-lowering medications.

During follow-up mean 5.0 years (SD 2.65 years), 279 participants developed new-onset diabetes. Table 2 shows the risks of new-onset diabetes according to quartile groups of serum ALT. The incidence rates of diabetes increased with elevation of serum ALT levels: 0.7 per 100 person-years in quartile group 1, 0.9% in quartile group 2, 0.9% in quartile group 3 and 1.7% in quartile group 4) (p<0.001 for trend). This association was significant after adjustment for other risk factors including age, sex, smoking, current daily alcohol intake, regular exercise, obesity, hypertension and dyslipidaemia: multivariable-adjusted HRs 1.24 (95% CI 0.80 to 1.91) for quartile group 2, 1.37 (0.90–2.07) for quartile group 3 and 2.11 (95% CI 1.43 to 3.12) for quartile group 4 compared with the reference group of quartile 1 (p<0.001 for trend). Sensitivity analysis using log-transformed ALT levels as a continuous variable demonstrated HR of 1.93 (95% CI 1.52 to 2.43) per 1 increase in log-transformed ALT (p<0.001). Another sensitivity analysis excluding participants with serum ALT levels of >50 U/L (top 5 percentile) demonstrated similar findings: multivariable-adjusted HR 1.22 (95% CI 0.79 to 1.88) for quartile group 2 was, 1.36 (95% CI 0.90 to 2.06) for quartile group 3 and 1.93 (95% CI 1.28 to 2.90) for quartile group 4 compared with quartile group 1 (p<0.001 for trend). Sensitivity analysis using BMI (instead of obesity) as a covariate in multivariable analysis found similar findings: multivariable-adjusted HR 1.18 (95% CI 0.77 to 1.83) for quartile group 2 was, 1.29 (95% CI 0.85 to 1.95) for quartile group 3 and 1.83 (95%

Table 3 Risk of new-onset diabetes mellitus according to quartile of serum alanine transaminase (ALT) levels in subgroups quartile of serum ALT levels in subgroups

		Quartile of serum ALT levels*				
		Group 1 (n=1422)	Group 2 (n=1234)	Group 3 (n=1359)	Group 4 (n=1315)	P value for interaction
Gender						
Men	(n=2350)	1.00	1.27	1.30	1.79	0.249
		(Reference)	0.74–2.16	0.76–2.21	1.08–2.98	
Women	(n=2980)	1.00	1.14	1.41	2.63	
		(Reference)	0.54–2.43	0.72–2.76	1.40–4.93	
Current daily alcohol intake						
Yes	(n=1130)	1.00	1.75	1.64	2.00	0.567
		(Reference)	0.78–3.96	0.72–3.71	0.89–4.48	
No	(n=3690)	1.00	1.06	1.27	2.14	
		(Reference)	0.62–1.78	0.79–2.06	1.37–3.33	
Obesity						
Yes	(n=1637)	1.00	1.53	2.19	3.03	0.203
		(Reference)	0.66–3.55	1.04–4.60	1.50–6.14	
No	(n=3691)	1.00	1.13	1.05	1.73	
		(Reference)	0.68–1.89	0.61–1.80	1.04–2.90	

Values are HRs (95% CIs) adjusted for age, sex (except for subgroup analysis by sex), smoking, current alcohol intake (except for subgroup analysis by current alcohol intake), regular exercise, obesity (except for subgroup analysis by obesity), hypertension and dyslipidaemia. Obesity: body mass index of ≥25 kg/m^2.
*Group 1=3–16 U/L in men and 3–13 U/L in women, group 2=17–21 U/L in men and 14–16 U/L in women, group 3=22–29 U/L in men and 17–22 U/L in women, group 4=30–428 U/L in men and 23–268 U/L in women.

CI 1.23 to 2.73) for quartile group 4 compared with quartile group 1 (p<0.001 for trend). Sensitivity analysis using alcohol intake as five categories (no drinkers, occasional drinkers or daily drinkers (average alcohol intake <22 g/day, 22–43 g/day or ≥44 g/day)) in multivariable analysis also found similar findings: multivariable-adjusted HR 1.25 (95% CI 0.81 to 1.93) for quartile group 2 was, 1.37 (95% CI 0.91 to 2.08) for quartile group 3 and 2.12 (95% CI 1.44 to 3.13) for quartile group 4 compared with quartile group 1 (p<0.001 for trend).

Subgroup analysis (table 3) demonstrated that there were no clear differences in the effects of serum ALT levels on new-onset diabetes between subgroups defined by gender, current daily alcohol intake and obesity (all p>0.2 for interaction).

DISCUSSION

In the present longitudinal study of general Japanese population, elevated serum ALT levels were associated with increased risks of new-onset diabetes mellitus. This association remained significant after controlling for the effects of other confounding factors such as age, sex, smoking, current daily alcohol intake, regular exercise, obesity, hypertension and dyslipidaemia. There were no clear differences in the associations between serum ALT levels and incident diabetes between men and women, and also between subgroups defined by obesity and alcohol intake.

Several previous cohort studies have reported an association between elevated serum ALT levels and risk of diabetes. In a prospective cohort study of 6928 Hispanic Americans,[17] participants in the highest quartile of serum ALT had 1.51-times higher risks of developing diabetes compared with those in the lowest quartile. With regard to Asian population, the Namwon study of 6926 Koreans[19] demonstrated that incidence of diabetes was significantly higher in the highest quartile group of serum ALT than in the lowest quartile group. In a study of 132 377 general Taiwanese aged 35–79,[20] elevated serum ALT levels were significantly associated with increased risks of diabetes both among men and women. In Japan, a worksite-based prospective study of 2775 male civil servants conducted from 2002 to 2014[22] found 1.7-fold higher risks of developing type 2 diabetes in the group with the highest tertile of serum ALT levels compared with the lowest tertile. In the Hisayama study,[24] which is a prospective cohort study of 1804 general residents followed-up from 1988 to 1998, the cumulative incidence of diabetes in the fourth quartile of serum ALT was significantly higher than that in the first quartile in both men and women. The present population-based longitudinal study of 5330 Japanese followed-up from 2008 to 2017 confirmed the findings from the previous observational studies and clearly

demonstrated significant associations between serum ALT levels and incidence of new-onset diabetes in general population of current Japan.

The exact mechanisms underlying the association between elevated serum ALT levels and development diabetes has not yet been clarified, but there are a number of possible ones. Factors associated with increase in serum ALT levels involve (1) non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), (2) alcoholic liver disease, (3) viral hepatitis etc. With regard to (1) NAFLD/NASH, ectopic fat accumulation in the liver has been shown to be associated with enhancement of insulin resistance in the liver.[31–34] Excessive fat accumulation in the liver also causes activation of macrophages and result in further enhancement of insulin resistance in the liver.[3 35] With regard to (2) alcoholic liver disease, alcohol intake has been shown to be associated with enhancement of insulin resistance in the liver as well as in peripheral tissues.[36 37] (3) With regard to viral hepatitis, hepatitis C virus has been shown to impair insulin signalling and to cause insulin resistance in the liver.[38] Insulin resistance in the liver (and peripheral tissues), which is associated with various liver diseases described above, can cause hyperinsulinaemia and subsequent development of diabetes.

Strengths of the study involve longitudinal design, large sample size and the fact that participants were general Japanese people. However, there are several limitations. First, it is likely that the participants of this study, who attended health examinations, were more health conscious and were more likely to be engaged in healthier behaviours than those who did not attend health examinations. Second, in this study, there was no information on the causes of elevated serum ALT levels (fatty liver, alcoholic hepatitis, viral hepatitis (B, C, etc) autoimmune diseases, thyroid dysfunction, etc). Future research should take aetiology of elevated serum ALT levels into account. Third, diabetes was not diagnosed using the 75 g oral glucose tolerance test and may be underestimated. Forth, there was no information on waist-to-hip ratio, gestational diabetes, non-HDL cholesterol and microalbuminuria.

CONCLUSION

In the present longitudinal study of general Japanese population, elevated serum ALT levels were significantly associated with increased risks of diabetes. High-risk prevention strategies based on serum ALT levels might provide further protection against emerging burden of diabetes.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Fukuoka University Medical Ethics Review Board (No. U19-05-003). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The datasets generated and/or analysed during the current study are not publicly available due to the property of the Iki CIty, Nagasaki, Japan and cannot be made public as it may result in violation of the Act on the Protection of Personal Information of the Japanese government but are available from the corresponding author on reasonable request.

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