



TITLE:

Association of coronary revascularisation after physician-referred non-invasive diagnostic imaging tests with outcomes in patients with suspected coronary artery disease: a post hoc subgroup analysis

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BMJ Open Association of coronary revascularisation after physician-referred non-invasive diagnostic imaging tests with outcomes in patients with suspected coronary artery disease: a post hoc subgroup analysis

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ABSTRACT

Objective We aimed to evaluate the association of the prognostic impact of coronary revascularisation with physician-referred non-invasive diagnostic imaging tests (single photon emission CT (SPECT) vs coronary CT angiography) for coronary artery disease.

Design A post hoc analysis of a subgroup from the patient cohort recruited for the Japanese Coronary-Angiography or Myocardial Imaging for Angina Pectoris Study.

Setting Multiple centres in Japan.

Participants From the data of 2780 patients with stable angina, enrolled prospectively between January 2006 and March 2008 in Japan, who had undergone physician-referred non-invasive imaging tests, 1205 patients with SPECT as an initial strategy and 625 with CT as an initial strategy were analysed. We assessed the effect of revascularisation (within 90 days) in each diagnostic imaging stratum and the interaction between the two strata.

Primary and secondary outcome measures Major adverse cardiac events (MACEs), including death, myocardial infarction, hospitalisation for heart failure and late revascularisation, were followed up for 1 year. The χ^2 test, Student's t-test, Kaplan-Meier analysis, log-rank test and multivariable Cox proportional hazard model were used in data analysis.

Results A total of 210 (17.4%) patients in the SPECT stratum and 149 (23.8%) in the CT stratum underwent revascularisation. Although in each stratum, the cumulative 1 year incidence of MACEs was significantly higher in patients who underwent revascularisation than in those who did not (SPECT stratum: 9.1 vs 1.2%, log-rank $p < 0.0001$; CT stratum: 6.1 vs 0.8%, log-rank $p = 0.0001$), there was no interaction between the risk of revascularisation and the imaging strata (SPECT stratum: adjusted HR (95% CI), 4.25 (1.86–9.72); CT stratum: 4.13 (1.16–14.73); interaction: $p = 0.97$).

Conclusion The association of revascularisation with the outcomes of patients with suspected coronary artery disease was not different between SPECT-first and CT-first strategies in a physician-referred fashion.

Strengths and limitations of this study

- The differences in the prognostic impact of coronary revascularisation with non-invasive diagnostic imaging tests (single photon emission CT (SPECT) vs coronary CT) remain to be elucidated.
- From the multicentre data of patients with stable angina enrolled prospectively between January 2006 and March 2008 in Japan, we analysed 1830 patients who had undergone physician-referred diagnostic imaging tests (SPECT 1205 patients; CT 625 patients) for initial assessment.
- We tested the interactions between the two strata and the impact of revascularisation therapy on their prognosis.
- One limitation of this study is that the imaging modality and the treatment strategy were chosen arbitrarily by the physicians.

INTRODUCTION

It is important to choose the appropriate initial diagnostic imaging modality to detect coronary artery disease (CAD) in symptomatic patient.^{1–4} Although the superiority of anatomical testing over functional testing has long been discussed, compared to initial functional testing, anatomical testing strategies using CT do not reduce the incidence of major adverse cardiac events (MACEs).^{1,2,4} Douglas *et al* reported that patients who had initial anatomic testing using CT underwent revascularisation more frequently than those who had initial functional testing. However, patients who had CT did not have reduced incidence of MACEs when compared with those who had functional testing.¹ In line with the evidence from the above-mentioned large

randomised trial, patients with CT and coronary angiography (CAG) were more likely to undergo revascularisation than those with single photon emission computed tomography (SPECT) in the original Japanese Coronary-Angiography or Myocardial Imaging for Angina Pectoris Study (J-COMPASS), a multicentre study.² Moreover, there was no difference in incidence of MACEs between those who had SPECT and those who had CT as the physician-referred initial tests for suspected stable CAD.³

Although patients who had initial CT underwent revascularisation more frequently than those who had initial functional tests, it has not yet been elucidated whether the prognostic impact of revascularisation is different between non-invasive diagnostic modalities for detecting CAD. In this post hoc analysis of a subgroup of patients recruited for the J-COMPASS study, we hypothesise that the prognostic impact of revascularisation is not different between patients with SPECT-first and CT-first strategies as the physician-referred initial non-invasive diagnostic test for CAD.

METHODS

Patient and public involvement

Patients and the public were not involved in the design or conduct of the study.

Study design and population

The design and main trial results of the J-COMPASS study has already been published.² From 81 centres in Japan with high-end diagnostic facilities (online supplementary appendix), 2870 consecutive patients with suspected stable angina who were followed up were enrolled prospectively between January 2006 and March 2008. Based on the results of initial tests and other clinical findings, well-trained cardiologists determined the initial diagnostic imaging modality to be used and the treatment strategy to be adopted without using any pre-specified criteria. In this post hoc sub-study, we excluded patients who had undergone an invasive modality (CAG: n=950). Thus, symptomatic patients who underwent SPECT

(n=1205) or CT (n=625) as the initial diagnostic test for suspected chronic CAD were enrolled (figure 1). The exclusion criteria of the original study were acute coronary syndrome at presentation or within a short period after the initial test and a history of myocardial infarction (MI) or revascularisation therapy.

Treatment strategy and outcome measures

Based on the results of initial diagnostic tests and other clinical findings, physicians chose the treatment strategy without using any pre-specified criteria.² The treatment strategies included (1) medical therapy, that is, therapy with the same medication at the same dose after the initial test; (2) escalation of medical therapy, that is, an increase in the dose of the same medication or introduction of new medication; and (3) early revascularisation that was defined within 90 days from the test with escalation of medical therapy.² The revascularisation and the medication strategies were selected at the discretion of the physicians. We divided the patients who had any of these diagnostic modalities into two groups: those who underwent early revascularisation (revascularisation group) and those who did not undergo early revascularisation (non-revascularisation group). The outcomes were MACEs: death, acute MI, hospitalisation for heart failure and late revascularisation (>3 months) in accordance with the original study.² One-year follow-up was performed with an allowance of 1 month.

Definition of obstructive CAD in coronary CT, functionally significant results in SPECT and comorbidities

We adopted the definitions used by the J-COMPASS study.^{2,4} On CT angiography, patients with one or more diseased vessel (>50% stenosis in segment 5, 6, 7, 11, 13, 1, 2 or 3) were considered to have significant stenosis.^{5,6} In the SPECT group, SPECT images were divided into 17 segments, each of which was scored on a 5-point scale under both stress and rest conditions (0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced; 4, absent) according to the American Heart Association criteria,⁷ and a Summed Stress Score (SSS) ≥ 2 was considered to be a functionally significant result.^{3,4} Comorbidities were determined based on the physician's evaluation. Cerebrovascular disease was defined as the occurrence of stroke or vascular disease requiring intervention by a neurosurgeon. Malignancy was defined as the presence of cancers or haematological neoplasms.

Statistical analysis

In this analysis, we (1) compared the baseline characteristics of patients who underwent early revascularisation and that of those who did not in each modality, (2) investigated the outcomes between the two groups in each modality and (3) investigated the interaction between the prognostic implication of early revascularisation and diagnostic modalities.

Categorical variables are expressed as numbers and percentages and were compared using the χ^2 test.

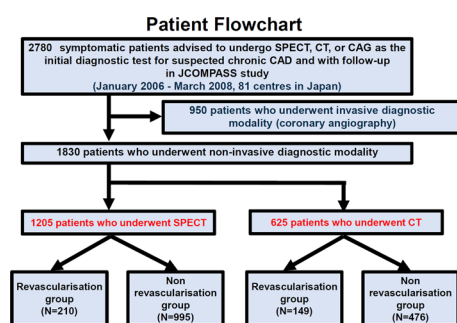


Figure 1 Patient flow chart. Revascularisation was defined as early revascularisation within 90 days from the initial diagnostic imaging test. CAG, coronary angiography; J-COMPASS, Japanese Coronary-Angiography or Myocardial Imaging for Angina Pectoris Study; SPECT, single photon emission CT.

Continuous variables are expressed as means (SD) or median and IQRs. Continuous variables were compared between the two groups using Student's t-test. Kaplan-Meier analysis was used to estimate the MACE rate between the revascularisation and non-revascularisation groups; the log-rank test was used to perform univariate comparisons. To compare risks between the revascularisation and non-revascularisation groups, a multivariable Cox proportional hazard model was developed for MACEs. The results are expressed as HRs and 95% CIs. There are several sources of bias in the processes of referral for angiography, performance of coronary revascularisation and revascularisation strategy, that could have influenced the risk of revascularisation in the patients who had SPECT and those who had CT. To overcome these sources of bias, we selected sixteen clinically relevant risk-adjusting variables as well as the severity of abnormal findings and the treatment strategies in each group: age ≥ 60 years; sex; body mass index (BMI); estimated glomerular filtration rate; the presence of hypertension, dyslipidaemia, diabetes, hyperuricaemia, chronic obstructive pulmonary disease and atrial fibrillation; Canadian Circulation Society class 2 or higher⁸; current smoking status; New York Heart Association functional class 2 or higher⁹ which is consistent with that used in our previous reports²⁻⁴; severity of abnormal findings (SSS ≥ 8 or three vessel disease); escalation of medical therapy; and early revascularisation (table 1). We then tested the interaction between the prognostic impact of early revascularisation and each diagnostic modality. Online supplementary table 1 compares the characteristics of patients who had SPECT and those who had CT.²

Statistical analysis was performed by the study biostatistician (YU) using SAS V.9.4 software (SAS Institute). All reported p values were two-tailed, and p values < 0.05 were considered statistically significant.

RESULTS

Patient characteristics

The characteristics of patients who underwent SPECT (n=1205) and those who underwent CT (n=625: online supplementary table 1) in the revascularisation and non-revascularisation groups are shown in table 1. There was a significant difference in the rate of early revascularisation between the SPECT and CT strata (17.4% and 23.8%, respectively, p=0.0012).

In the SPECT stratum, patients in the revascularisation group (n=210, 17.4%) were less likely to be women (30.5% vs 46.6%, p<0.0001) and had a higher BMI (mean: 24.3 vs 23.7, p=0.046); had greater prevalence of hypertension (66.7 vs 54.2%, p=0.0001), dyslipidaemia (56.7 vs 41.5%, p<0.0001) and diabetes (48.6 vs 23.8%, p<0.0001); and had more severe symptoms than those in the non-revascularisation group (n=995, 82.6%). There was a significant difference in abnormal SPECT (SSS >2) findings between the revascularisation and non-revascularisation groups (92.4 vs 35.6%, p<0.0001). The

severity of decreased perfusion or provoked ischaemia was greater in the revascularisation group than in the non-revascularisation group (table 1).

In the CT stratum, patients in the revascularisation group (n=149, 23.8%) were older (mean: 68.5 vs 65.2 years, p=0.0011); less likely to be women (34.9% vs 50.2%, p=0.0013); had a greater prevalence of hypertension (66.4 vs 55.0%, p=0.017), dyslipidaemia (59.1 vs 46.8%, p=0.011) and diabetes (41.6 vs 21.8%, p<0.0001); and had more severe symptoms than those in the non-revascularisation group (n=476, 76.1%). There was a significant difference in abnormal CT findings ($>50\%$ stenosis in segment 5, 6, 7, 11, 13, 1, 2 or 3) between the revascularisation and non-revascularisation groups (91.3 vs 28.6%, p<0.0001). The numbers of stenosed coronary arteries were greater in the revascularisation group than in the non-revascularisation group (table 1).

Association of revascularisation with outcomes in each stratum and an interaction

The 1 year follow-up rate was 97.6%. The cumulative 1 year incidence of MACEs was significantly higher in the revascularisation group than in the non-revascularisation group in each diagnostic imaging stratum (SPECT stratum: 9.1 vs 1.2%, log-rank p<0.0001 figure 2A; CT stratum: 6.1 vs 0.8%, log-rank p=0.0001 figure 2B). After adjusting for confounders, the risk of MACEs was significantly higher in the revascularisation group than in the non-revascularisation group (table 2). There was no significant interaction between the risk of MACEs in the revascularisation group relative to that in the non-revascularisation group and the diagnostic modality strata (SPECT stratum: adjusted HR (95% CI), 4.25 (1.86–9.72); CT stratum: 4.13 (1.16–14.73); interaction: p=0.97) (table 2).

DISCUSSION

The main findings of this study are as follows: (1) in both the SPECT and CT strata, patients who underwent revascularisation had a higher risk of atherosclerosis and abnormal findings on the initial diagnostic imaging, and (2) although the risk of MACEs in the revascularisation group remained significantly high compared to that in the non-revascularisation group, there was no interaction between the risk and diagnostic modalities.

Initial diagnostic imaging and early revascularisation

SPECT-first strategy introduces less revascularisation than the CT-first strategy, as previously reported in the J-COMPASS study.² This is in line with the result of the meta-analysis on non-invasive functional and anatomical testing.¹⁰ As anticipated, the prevalence of functional and anatomical abnormality was often observed in the revascularisation group in each diagnostic stratum. Therefore, the high incidence of MACEs in the revascularisation group is not surprising. The novelty of this study is that regardless of whether the non-invasive test was functional

Table 1 Patient population

	SPECT (n=1205)			CT (n=625)		
	Revascularisation (n=210)	Non-revascularisation (n=995)	P value	Revascularisation (n=149)	Non-revascularisation (n=476)	P value
Age	67.16	65.94	0.127	68.4	65.25	0.0011
Age ≥60 years old†	160	705	0.129	126	336	0.00059
Female	64	464	<0.0001	52	239	0.00133
Height (cm)	160.11	159.19	0.182	158.81	158.51	0.719
Weight (Kg)	62.58	60.43	0.016	61.74	60.06	0.116
BMI (kg/m ²)†	24.30	23.76	0.046	24.37	23.81	0.082
Systolic BP (mm Hg)	139.85	137.27	0.089	140.71	138.72	0.285
Diastolic BP (mm Hg)	77.13	78.49	0.146	77.24	78.32	0.355
Smoking	55	194	0.031	38	97	0.209
Hypertension†	140	539	0.001	99	262	0.017
Dyslipidaemia†	119	413	<0.0001	88	223	0.011
Diabetes†	102	237	<0.0001	62	104	<0.0001
Hyperuricaemia†	15	49	0.234	10	28	0.697
Familial history of CAD	32	110	0.099	28	67	0.190
Cerebrovascular disease	23	82	0.225	13	24	0.111
Peripheral artery disease	13	19	0.001	3	3	0.151
Atrial fibrillation	5	44	0.246	3	17	0.434
COPD†	3	10	0.483	0	6	0.344
Disease of aorta	4	22	1.000	2	2	0.242
Malignancy	6	23	0.621	3	8	0.729
eGFR (mL/min/1.73m ²)†	70.13	73.39	0.158	75.85	80.89	0.109
Abnormal findings†	194	354	<0.0001	136	136	<0.0001
SSS: 2~7	60	247	<0.0001	n/a	n/a	n/a
SSS: 8~†	134	107	10.8%	n/a	n/a	n/a
SDS:>=2	178	206	<0.0001	n/a	n/a	n/a
1VD	n/a	n/a	n/a	68	68	14.3%
2VD	n/a	n/a	n/a	43	35	7.4%
3VD†	n/a	n/a	n/a	25	15	3.2%

Continued

Table 1 Continued

	SPECT (n=1205)		CT (n=625)		P value	P value
	Revascularisation (n=210)	Non-revascularisation (n=995)	Revascularisation (n=149)	Non-revascularisation (n=476)		
CCS†						
Class 1	119	820	62	324	<0.0001	<0.0001
Class 2	85	165	74	125		
Class 3	6	7	9	6		
Class 4	0	3	4	21		
NYHAT						
I	169	938	109	395	<0.0001	0.0003
II	39	54	32	59		
III	2	3	4	7		
IV	0	0	4	15		
Subsequent CAG	210	197	149	66	<0.0001	<0.0001
Obstructive CAD	208	48	148	39	0.0016	<0.0001
Escalation of medical therapy	210	527	149	287	<0.0001	<0.0001

Values are number (%) or mean (SD).

P values were calculated from a χ^2 test for categorical variables, Continuous variables were expressed as means (SD). Continuous variables were compared using the Student's t-test between two groups.

*Body mass index was calculated as weight in kilograms divided by height in metres squared.

†Potential risk-adjusting variables selected for Cox proportional hazard models. CCS was adjusted for Class 2 or more, and NYHA functional class was adjusted for II or more.

‡Abnormal findings were defined as SSS >2 in SPECT and >50% stenosis in segments 5, 6, 7, 11, 13, 1, 2 or 3 in CT.

BP, blood pressure; BMI, body mass index; CAD, coronary artery disease; CAG, coronary angiography; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular rate; CCS, Canadian Circulation Society; NYHA, New York Heart Association; SPECT, single photon emission CT; CT, CT tomography angiography, SSS, Summed Stress Score; SDS, Summed Difference Score; n/a, not available.

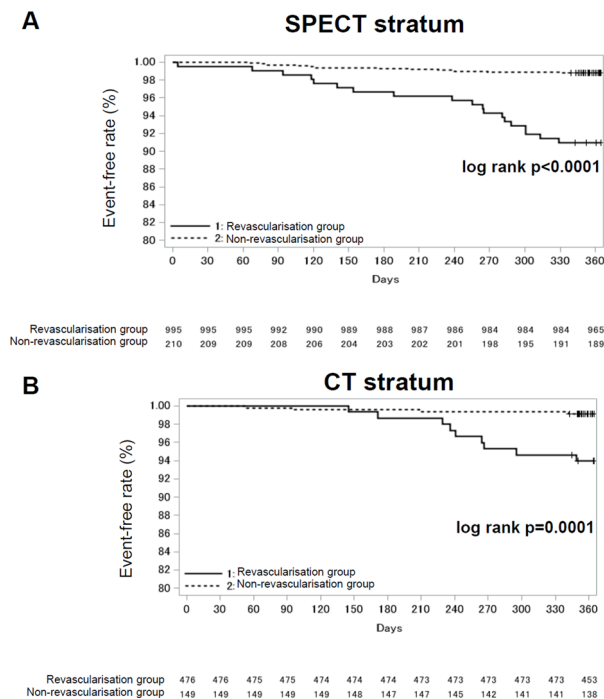


Figure 2 Crude Kaplan-Meier curve for major adverse cardiovascular events (MACEs) in the single photon emission CT (SPECT) (A) and CT (B) strata. MACEs were defined as death, acute myocardial infarction, heart failure hospitalisation and late revascularisation (>3 months).

or anatomical, the risk of MACE after revascularisation, that is, the effect of revascularisation, was not different between the two groups. Non-invasive imaging tests are essential in the diagnosis of suspected CAD and subsequent revascularisation to manage the symptoms and improve prognosis.^{11 12} In contemporary practice in Japan, the prognostic influence of revascularisation was not different between patients who underwent SPECT and those who underwent CT as initial tests. Interestingly, approximately 10% of patients in both initial non-invasive imaging groups who did not have abnormal test results were still revascularised early. They were referred to undergo subsequent other non-invasive imaging and ultimately referred to undergo CAG based on their clinical presentation or the result of previous imaging. Findings of CAG were comparable to those of SPECT and CT for the detection of CAD.¹³

Diagnostic and therapeutic strategy and outcomes

The standard of treatment for CAD has evolved over the years. Several studies have failed to show that revascularisation therapy was associated with the reduction of death in patients with stable CAD and objectively documented myocardial ischaemia.¹⁴⁻¹⁷ However, the FAME and FAME-2 trials provided strong evidence that percutaneous intervention improves prognosis when functional ischaemia is confirmed by fractional flow reserve (FFR).^{18 19} However, these studies were designed to select patients after invasive diagnostic catheterisation. In the original J-COMPASS study,² many patients with a high risk

Table 2 Clinical outcomes of patients in each diagnostic modality and an interaction

	Revascularisation		Non-revascularisation		Unadjusted HR	95% CI	P value	Interaction-p	Adjusted HR	95% CI	P value	Interaction-p
	N of patients with event/N of patients at risk	N of patients with event/N of patients at risk	N of patients with event/N of patients at risk	N of patients with event/N of patients at risk								
Entire	28/359 (7.8%)	16/1471 (1.1%)	6.50	4.29 to 9.85	<0.0001	4.23	2.04	8.76				
SPECT	19/210 (9.0%)	12/995 (1.2%)	7.75	3.76 to 15.96	<0.0001	4.25	1.86	9.72	0.97			
CT	9/149 (6.0%)	4/476 (0.8%)	7.33	2.26 to 23.80	0.0009	4.13	1.16	14.73				

SPECT, single photon emission CT.

of CAD were referred to CAG, that is, they were referred to more invasive than non-invasive diagnostic imaging modalities, such as SPECT and CT. In addition, there was a difference in the risk profile between the SPECT and CT groups. Patients in the SPECT group were more likely to have peripheral vascular/aortic disease and worse renal function, whereas those in the CT group were more likely to have a family history of CAD and more severe symptoms (online supplementary table 1). Overall, the SPECT group (21 of 1205, 2.5%) showed a slightly worse outcome than the CT group (13 of 625, 2.1%). The definite role of revascularisation in moderate-to-severe ischaemia is currently being investigated in the ISCHEMIA trial,²⁰ and the trial recently showed that the revascularisation of patients with stable CAD is neutral to cardiac events.²¹ When considering SPECT or CT as an initial test, knowing the coronary anatomy likely introduced selection bias to percutaneous coronary intervention and that may have diluted the potential to demonstrate the effect of revascularisation. However, in the present study, prognostic influence of revascularisation was not different between the SPECT and CT strata. The choice of diagnostic modalities in this study is based on the physician judgement; in addition, early revascularisation was performed without pre-defined criteria but was based on the physician judgement. Therefore, our results may support the appropriateness of diagnostic and therapeutic strategies for CAD. Physician-referred SPECT-first or CT-first strategies were not different in outcomes in the present study. Our data may be useful to cardiologist when considering the gatekeepers for invasive tests for CAD.

We observed a higher risk in patients who underwent coronary revascularisation; this was not consistent with the finding of the ISCHEMIA trial.²¹ There are two possible explanations for this discrepancy. First, the prevalence of atherosclerosis in the revascularisation group was significantly greater than that in the non-revascularisation group. This study is not a randomised study that tested the effect of revascularisation; thus, a substantial proportion of patients in the non-revascularisation group had no abnormal findings. In contrast, in the ISCHEMIA trial, randomly selected patients with moderate-to-severe ischaemia as proven by a stress test took part in the study. The higher risk of MACEs observed in the present study may point to an unmeasured confounding factor despite extensive statistical adjustment. Second, potentially incomplete revascularisation may have increased the risk of cardiovascular events in this cohort. We did not collect data on the completeness or method of revascularisation in this study. Instead, we focused on the role of the non-invasive diagnostic imaging modalities in terms of the effect of revascularisation on outcomes. Our data suggested that the non-invasive diagnostic imaging modalities were not related to the outcome of subsequent revascularisation.

Limitations

There are some limitations in the present study. First, information about why and how patient treatment

decisions were made, the cost of treatment,²² FFR in CAG, and the drugs administered was not analysed or collected. Detailed information on obstructive coronary disease in subsequent CAG was not collected either. Thus, data on the completeness of revascularisation were not taken into account in the cohort enrolled between January 2006 and March 2008, as this was before the advent of wide spread use of FFR in Japan. Second, although all centres had state of the art diagnostic facilities, we did not verify the quality of the diagnostic imaging modalities at each participating centre nor were they analysed in a core laboratory. Third, the use of CT is increasing annually, and functional flow reserve derived from CT is now being used clinically in Japan. Therefore, we should be careful when generalising the results of this study in future practice. Fourth, important factors associated with test selection (ability to exercise and ECG findings, such as left branch bundle block) were not included in the analyses of this study. Fifth, the present study was performed in Japan. Thus, the possible external validity of the result needs to be confirmed in non-Asian populations. Sixth, the impact of revascularisation on long-term prognosis is still unclear in our study population and needs to be elucidated. Finally, there might be several sources of bias that could not be corrected despite our extensive statistical adjustment due to the study design (observational study).

CONCLUSION

The influence of early revascularisation on the prognosis was not different between SPECT-first and CT-first strategies in a physician-referred fashion.

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Contributors TK had full access to all data in the study, and takes responsibility for the integrity of the data and accuracy of the data analysis. Study concept and design: TK, MN, MM, NM, SH, TN, TY, TS and NT. Acquisition, analysis or interpretation of data: TK, YU, MN, MN, MM, SH, TY, TN, ES, MI, TS and NT. Drafting of the manuscript: TK and YU. Critical revision of the manuscript for important intellectual content: TK, YU, MN, NM, MM, SH, TY, TN, ES, MI, TS and NT. Statistical analysis: YU. Administrative, technical or material support: ES, TS and NT. Study supervision: NT.

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Competing interests None declared.

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Patient consent for publication Not required.

Ethics approval All methods were performed according to the principles of the Declaration of Helsinki. The study protocol was approved by the institutional review board of Kitano Hospital (approval number: P16-01-005) and that of each participating center (online supplementary appendix).² All participants provided written or oral informed consent before being enrolled into this study.² We anonymized the patient records and information before commencing the analysis.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article or uploaded as supplementary information.

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