Population-based prostate-specific antigen screening for prostate cancer may have an indirect effect on early detection through opportunistic testing in Kusatsu City, Shiga, Japan

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Abstract. Prostate cancer is the most common genitourinary cancer in men. Population-based serum prostate-specific antigen (PSA) testing is used to screen men for the early detection of asymptomatic prostate cancer. The present study compared the features of patients with prostate cancer in Kusatsu City, the only municipality in Shiga Prefecture of Japan to implement organized PSA screening, with those in other municipalities. The target population for organized PSA screening by mail invitation was men ≥50 years. Patients were pathologically diagnosed via prostate biopsy because of elevated serum PSA. This multicenter observational study was subsequently conducted in 14 hospitals. The following information was extracted from patient records: age, reason for PSA testing, initial PSA level, Gleason score, clinical stage, and place of residence. Risk classification was defined as low, intermediate, high, and advanced. Each patient was stratified according to their city/town. A total of 984 patients diagnosed with prostate cancer in Shiga in 2012 and 2017 were analyzed, of which 955 (97%) were opportunistically tested, with the remaining 29 (3%) assessed by organized screening. In Kusatsu, 93 patients were diagnosed, of whom 26 (28%) were detected by organized screening. By contrast, only three of 891 patients (0.3%) were detected by organized screening in other municipalities. Of patients in Kusatsu, cases identified by opportunistic testing had a higher initial PSA value (P=0.010) than those identified by organized screening. However, patients detected through opportunistic testing in Kusatsu City were younger (P=0.034), had a lower PSA value (P=0.001), and improved risk classification (P<0.001) than those in other municipalities. It was concluded that more patients were diagnosed with early-stage cancer by organized PSA screening. Furthermore, population-based PSA screening in Kusatsu City may have indirectly affected early detection, even by opportunistic testing.

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Introduction

Prostate cancer is the most common genitourinary cancer in men. In 2020, 1,414,259 new cases and 375,304 deaths were estimated worldwide (1). Similarly, the incidence of prostate cancer is also the highest of male cancers in Japan, with the projected number of patients in 2021 being 95,400 (2). Serum

prostate-specific antigen (PSA) testing is the most important clinical test for the early detection of prostate cancer. Due to its simplicity, PSA testing is used to screen men for prostate cancer risk, with numerous industrialized countries having developed organized population-based PSA screening models. The European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) were large randomized controlled trials of PSA-based screening that were announced simultaneously in 2009 (3,4). Nine years of follow-up led to the mortality rate ratio in the screening group being reduced by 20% in the ERSPC trial. However, a difference in mortality rate ratios was not observed between screened or unscreened groups after 11.5 years of follow-up in the PLCO trial. Currently, population-screening for prostate cancer remains one of the controversial issues in this field (5).

In Japan, organized population-based PSA screening has been carried out since the early 1990s (6). However, by 2000, only 14.3% of municipalities in Japan ran screening programs. Nevertheless, by 2015, according to a Japanese Foundation for Prostate Research (JFPR) survey, population-based PSA screening systems could be found in 83.0% of municipalities (7). Currently, a population-based PSA screening system is present in over half of all cities and towns in all prefectures of Japan, except for Shiga Prefecture. According to the JFPR survey, in 2015, the implementation rate for organized PSA mass-screening in Shiga Prefecture was lowest (6.7% of municipalities). Moreover, the last city, Kusatsu, terminated population-based screening in 2017. Therefore, since 2018, no local governments in Shiga Prefecture have offered PSA screening, a situation that is quite exceptional in Japan.

Features of newly-diagnosed patients with prostate cancer in Shiga Prefecture were previously reported. A total of 97% of the patients were discovered through opportunistic PSA testing and showed worse clinical features than those patients diagnosed via an organized population-based screening (8). In the present study, a subanalysis was conducted to compare the characteristics of patients diagnosed with prostate cancer in 2012 and 2017 in Kusatsu City (Japan), the only municipality in Shiga Prefecture that implemented an organized population-based PSA screening, with those of patients in other municipalities in the prefecture.

Materials and methods

Patients. As a multicenter observational study, this investigation was conducted in 14 hospitals in Shiga Prefecture, Japan, as previously reported (8). Briefly, in 2012 and 2017, patients diagnosed with prostate cancer were surveyed. Cases were only included if they were pathologically diagnosed via prostate biopsy due to elevated serum PSA. Patients were excluded if they were incidentally diagnosed with T1a-b prostate cancer when operated on for benign prostate hyperplasia.

Data acquisition. Clinicopathological data of patients were extracted from their medical records by attending physicians in each hospital. In this survey, such data were collected, including patient's age, reasons for PSA measurement, initial PSA levels, Gleason score of prostate biopsy specimens, primary treatments selected, clinical stage (TNM classification 2009), and their place of residence. The reasons for PSA measurement were classified into six groups as follows: i) testing in general practice clinics, ii) testing in urologic clinics, iii) a repeat test due to elevated PSA earlier, iv) community-based PSA screening, v) investigation for metastatic disease of unknown origin, and vi) others. Risk classification was defined according to Arnsrud Godtman *et al* (9) as follows: Low risk=T1, not N1 or M1, with a Gleason score ≤6, and PSA <10 ng/ml. Intermediate risk=T1-2, not N1 or M1, with a Gleason score ≤7 and/or PSA <20 ng/ml. High risk=T1-4, not N1 or M1, with a Gleason score ≥8 and/or PSA <100 ng/ml. Advanced=N1 and/or M1 and/or PSA ≥100 ng/ml.

Approval (approval no. R2018-010) for the present study was granted by the Ethics Committee of Shiga University of Medical Science (Otsu, Japan) and by the ethics committee at each study center. The study was undertaken according to the provisions of the Declaration of Helsinki. Informed consent was obtained in the form of opt-out, and those who rejected were excluded.

Organized population-based PSA screening in Kusatsu City, Shiga. Kusatsu City initiated an annual prostate cancer screening program using serum PSA tests in 2004. The target population was limited to men ≥50 years old. Recommendations for prostate cancer screening were made to eligible persons by mail. The study participants visited family physicians or nearby hospitals with a recommendation letter and underwent a serum PSA test. The PSA cutoff value in this screening was set at 4.0 ng/ml. Kusatsu City collected final reports from hospitals where further prostate examinations were performed. This cancer screening program ceased in 2018 according to Kusatsu City policy. Data from this PSA screening program in Kusatsu City from 2004 to 2017 was kindly provided by the Division of Health Promotion, the Department of Health and Welfare, Kusatsu City, Japan.

Statistical analysis. We compared the clinical data of patients in Kusatsu City to those of other municipalities in Shiga Prefecture. IBM SPSS for Windows version 22.0 (IBM Corp.) was used to carry out statistical analyses. Differences between groups were analyzed using a Mann-Whitney U test and Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Demographics of patients. Within the institutions surveyed, 984 patients in total were diagnosed with prostate cancer made up of 431 in 2012 and 553 in 2017. According to the cancer registries of Shiga Prefecture, the number of cases of newly diagnosed prostate cancer were 616 and 896 in 2012 and 2017, respectively (10). Thus, the present study covered more than 60% of the total patient population. Since the community-based PSA screening program in Shiga Prefecture was similar between 2012 and 2017, data from the two years were combined and analyzed as a single group. The study population was divided into two groups according to the place of residence: Kusatsu City and other municipalities. Demographics of patients are shown in Table I.

Table I. Demographics of patients.

	Total	Kusatsu city	Other municipalities	P-value
Number of patients	984	93	891	
Median age, years	72 (44-92)	70 (50-88)	73 (44-92)	0.015
Median initial PSA (ng/ml)	11.27 (1.15-8684)	7.70 (3.488-8684)	11.80 (1.15-8138)	<0.001
Gleason score				
<8	596 (61%)	70 (75%)	526 (59%)	0.002
≥8	388 (39%)	23 (25%)	365 (41%)	
T stage				
T1c	263 (27%)	26 (28%)	237 (27%)	<0.001
T2	457 (46%)	56 (60%)	401 (45%)	
T3	200 (21%)	9 (10%)	191 (21%)	
T4	56 (6%)	0	56 (6%)	
Unknown	8 (1%)	2 (2%)	6 (1%)	
N stage				
N0	860 (87%)	87 (94%)	773 (87%)	0.047
N1	119 (12%)	5 (5%)	114 (13%)	
Unknown	5 (1%)	1 (1%)	4 (1%)	
M stage				
M0	846 (86%)	88 (95%)	758 (85%)	0.011
M1	130 (13%)	4 (4%)	126 (14%)	
Unknown	8 (1%)	1 (1%)	7 (1%)	

PSA, prostate-specific antigen.

The median age of patients in Kusatsu City was significantly younger than in other municipalities (70 vs. 73 years, P=0.015). The median initial PSA values of patients in Kusatsu City were also significantly lower than those of other municipalities (7.70 vs. 11.80 ng/ml, P<0.001). Worse prognostic factors, including a high Gleason Score (P=0.002), higher T-stage (P<0.001), higher rates of nodal (P=0.047) and distant metastasis (P=0.011), were found in other municipalities.

Differences in reasons for PSA measurements. The reasons for PSA measurements in each group are summarized in Table II. In Kusatsu City, 93 patients were diagnosed with prostate cancer in two sample years. A total of 26 men (28.0%) were diagnosed through community-based PSA screening. In comparison, in the other municipalities, only three of 891 patients (0.3%) were diagnosed via organized PSA screening (P=0.011). In other municipalities, the most common reason for PSA measurement was examination by general practitioners (42%). The specific reasons for why general physicians measured PSA in some patients could not be precisely identified because the referral forms showed incomplete information.

Clinicopathological differences between organized community-based PSA screening and opportunistic PSA measurement in patients of Kusatsu City. Of the patients in Kusatsu City, cases screened by opportunistic PSA test presented with a significantly higher median initial PSA value (P=0.01) and than values for those who underwent organized screening (Table III). In addition, a trend was noted toward more patients with higher T stage, nodal and distant metastases in the opportunistic screening group, although no statistically significant differences were evident.

Clinicopathological features in patients diagnosed through opportunistic PSA measurement. The characteristics of patients diagnosed opportunistically, excluding through organized PSA screening programs, were compared between Kusatsu and other municipalities in Table IV. Patients in Kusatsu were diagnosed at a younger age than in other municipalities (P=0.034). A lower median PSA value was revealed in the Kusatsu group compared with other municipalities (P=0.001). The proportion of worse risk classification (high to advanced risk) in the other municipality group was more prominent than in Kusatsu City (P<0.001; Fig. 1).

Discussion

Screening for PSA is helpful for the early detection of asymptomatic prostate cancer, although controversy still exists as to whether this reduces the rate of prostate cancer mortality. In the U.S., the PLCO Cancer Screening Trial has been performed since the 1990s (4). The PLCO Trial randomly assigned 76,693 men to undergo either annual screening (annual PSA testing for six years) or the usual care as control. After follow-up for 7 to 10 years, the death rate from prostate cancer was very low and showed no significant difference between the two study groups. Extended follow-up over a median of 15 years also indicated no difference in reduction in prostate cancer

Table II. Reasons for PSA measurements.

Reasons for PSA measurements	Kusatsu City (%)	Other municipalities (%)	P-value
Overall	93 (100)	891 (100)	
Organized screening (Community-based PSA screening)	26 (28)	3 (0.3)	0.011
General practice clinic	13 (14)	375 (42)	
Urologic clinic	24 (26)	251 (28)	
Repetitive measurement due to previous elevated PSA	15 (16)	137 (15)	
Investigation for metastatic disease of unknown origin	2 (2)	36 (4)	
Others	13 (14)	89 (10)	

PSA, prostate-specific antigen.

Table III. Clinicopathological differences by reasons for PSA measurement: Kusatsu City.

	Organized screening	Opportunistic measurement	P-value
Overall	26	67	
Median age	70 (61-80)	70 (50-88)	0.748
Median initial PSA (ng/ml)	5.16 (3.791-27.3)	9.1 (3.488-8684)	0.010
Initial PSA (ng/ml)			
<4	1 (4%)	1 (1%)	0.607
4-10	19 (73%)	41 (61%)	
10-20	5 (19%)	16 (26%)	
20-100	1 (4%)	5 (7%)	
≥100	0	4 (6%)	
Gleason score			
<8	20 (77%)	50 (75%)	1
≥8	6 (23%)	17 (25%)	
T stage			
<T3	26 (100%)	56 (86%)	0.056
≥T3	0	9 (14%)	
N stage			
N0	26 (100%)	61 (93%)	0.317
N1	0	5 (7%)	
M stage			
M0	26 (100%)	62 (94%)	0.574
M1	0	4 (6%)	
Risk classification			
Low risk	3 (12%)	8 (12%)	0.479
Intermediate risk	17 (65%)	36 (54%)	
High risk	6 (23%)	14 (21%)	
Advanced	0	7 (10%)	
Unknown	0	2 (3%)	

Low risk: T1, not N1 or M1, Gleason score ≤6, and PSA <10 ng/ml. Intermediate risk: T1-2, not N1 or M1, and Gleason score ≤7 and/or PSA <20 ng/ml. High risk: T1-4, not N1 or M1, and Gleason score ≥8 and/or PSA <100 ng/ml. Advanced: N1 and/or M1 and/or PSA ≥100 ng/ PSA, prostate-specific antigen.

mortality between intervention and control arms (11). Due to these results, the U.S. Preventive Services Task Force (USPSTF) recommended against PSA-based screening for prostate cancer in 2012. In contrast to the PLCO Trial, a statistically significant reduction (20%) was noted for prostate cancer mortality in the ERSPC study (3). After a 16-year follow-up,

Table IV. Clinicopathological features in patients diagnosed by an opportunistic PSA measurement.

	Kusatsu City	Other municipalities	P-value
Overall	67	888	
Median age	70 (50-88)	73 (44-92)	0.034
Median initial PSA (ng/ml)	9.1 (3.488-8684)	11.8 (1.15-8138)	0.001
Initial PSA (ng/ml)			
<4	1 (1%)	10 (11%)	0.003
4-10	41 (61%)	370 (42%)	
10-20	16 (26%)	195 (22%)	
20-100	5 (7%)	175 (20%)	
≥100	4 (6%)	138 (15%)	
Gleason score			
<8	50 (75%)	523 (59%)	0.014
≥8	17 (25%)	365 (41%)	
T stage			
<T3	56 (86%)	635 (72%)	0.013
≥T3	9 (14%)	247 (28%)	
N stage			
N0	61 (93%)	770 (87%)	0.250
N1	5 (7%)	114 (13%)	
M stage			
M0	62 (94%)	755 (86%)	0.064
M1	4 (6%)	126 (14%)	
Risk classification			
Low risk	8 (12%)	59 (7%)	<0.001
Intermediate risk	36 (54%)	345 (39%)	
High risk	14 (21%)	288 (32%)	
Advanced	7 (10%)	193 (22%)	
Unknown	2 (3%)	3 (0.3%)	

PSA, prostate-specific antigen.

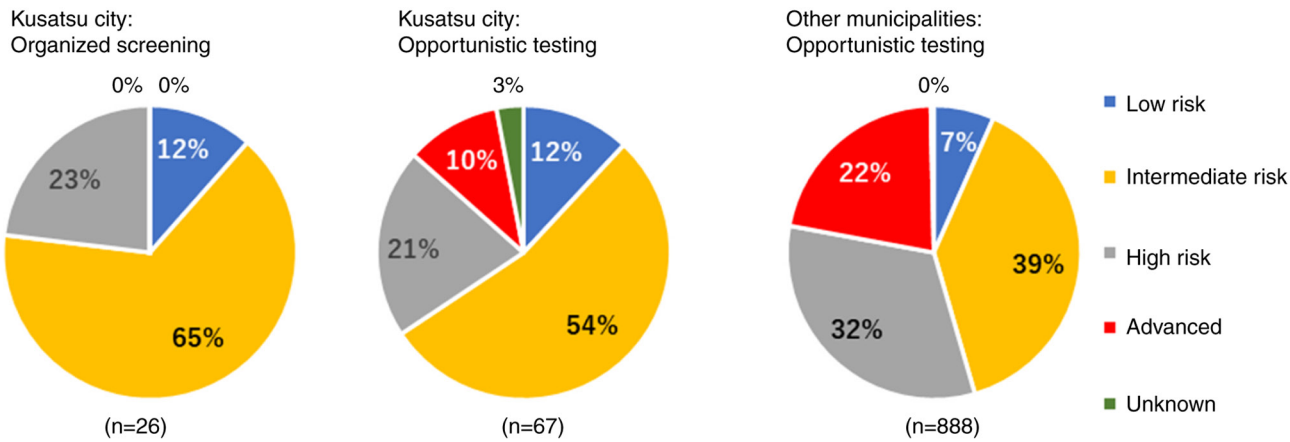

Figure 1. Proportion of the patients stratified by risk classification.

a significant reduction in cancer mortality continued, and the number of men required to be screened to prevent one prostate cancer death was reduced compared with that of previous reports from ERSPC (12). However, the PLCO Trial was flawed with a high contamination rate in the control arm (13). After a detailed review of various reports, USPSTF revised the recommendation that undergoing periodic PSA-based screening for prostate cancer is left to individual men aged

from 55 to 69 years (14). With the spread of PSA testing in clinical use, population-based PSA screening has expanded in Japan as well as the U.S. and Europe (6). In 2015, 1,189 of 1,432 (83.0%) municipalities in Japan had systems in place for population-based PSA screening according to a report by the JFPR (7). Despite this high implementation rate in Japan, only one city in Shiga Prefecture, Kusatsu City, undertook population-based PSA screening during our survey years.

In our study, patients in Kusatsu City who were detected not only by an organized population-based screening but also through opportunistic PSA testing showed a lower risk of prostate cancer than those in other municipalities. An exact explanation for this interesting result is not obvious but a possible reason may be related to the exposure rate of PSA screening. Organized mass screening using a serum PSA test by Kusatsu City was undertaken for 14 years (2004-2017). A summary of the data from PSA mass screenings in Kusatsu City are presented in Table V. A total of ~20,000 men, 50 years or older, were invited to the mass screening program each year, with uptake rates of 8.4-13.8%. Okihara *et al* (15) reported on the findings and quality control of prostate cancer screening performed serially for a decade in the Otokuni area, Kyoto, Japan. In the Otokuni program, candidates were part of a male population, 55 years or older, and the program involved ~22,000 men per year. In Otokuni, 39,213 men attended primary PSA screening over 10 years; thus, the mean yearly number of men screened was ~3,900. It was hypothesized by the authors that the exposure rate for PSA screening in the Otokuni area was 65%. The number of candidates for organized PSA screening in the Otokuni area was similar to that of Kusatsu City, but the rate of men attending PSA screening was two to three-fold that of Kusatsu City. Although we cannot calculate precisely the exposure rate for PSA screening in the men of Kusatsu City, it was assumed to be ~30%, which apparently seemed higher than that of other municipalities in Shiga Prefecture. Therefore, it was hypothesized that the higher exposure rates were caused by stage migration in newly diagnosed patients in Kusatsu City, even though this was opportunistic PSA testing, which is less effective compared with organized screening.

Further speculation relates to the awareness about prostate cancer screening using PSA measurements in general physicians as well as residents in Kusatsu City. Invitation letters were sent to individuals who were eligible for PSA screening. Therefore, this information may influence not only the response rate of PSA screening, but also awareness about prostate cancer and PSA testing in men in Kusatsu City. Furthermore, general physicians in Kusatsu may also tend to perform opportunistic PSA testing more frequently than in other municipalities in Shiga Prefecture. However, it is too difficult to prove this hypothesis in the present study.

The exact reason for the termination of the organized screening program for detecting prostate cancer by the Kusatsu City government is unknown. In Japan, prostate cancer is not included in cancer screening as a national program under the Health Promotion Act. The national committee in the Ministry of Health, Labor and Welfare do not recommend PSA-based screening for prostate cancer due to insufficient evidence of a reduction in mortality (16). According to a questionnaire by the JFPR, most cities and towns in Shiga Prefecture responded that they did not provide cancer screening because there is no

Table V. The results of PSA mass screenings organized by Kusatsu City (2004-2017).

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Male population of aged 50-years or older (A)	18,756	19,133	19,454	19,796	20,072	20,448	20,722	21,060	21,460	21,852	22,193	22,671	23,214	23,685
Number of men screened for PSA (B)	1,593	2,514	2,633	2,734	2,434	2,411	2,371	2,308	2,422	2,366	2,428	2,001	1,977	2,001
PSA screening rates (B/A, %)	8.5	13.1	13.5	13.8	12.1	11.8	11.4	11.0	11.3	10.8	10.9	8.8	8.5	8.4
Number of people with elevated PSA levels, 4.0 ng/ml or higher (C)	198	207	215	236	222	201	217	176	164	160	174	132	113	73
Positive PSA test rates (C/B, %)	12.4	8.2	8.2	8.6	9.1	8.3	9.2	7.6	6.8	6.8	7.2	6.6	5.7	3.6
Number of people who visited clinics for further examination (D)	84	76	58	78	91	94	113	105	99	99	118	93	82	45
Visiting rates for further examination (D/C, %)	42.4	36.7	27.0	33.1	41.0	46.8	52.1	59.7	60.4	61.9	67.8	70.5	72.6	61.6
Number of patients who were diagnosed with prostate cancer (E)	33	27	12	13	21	17	10	21	13	14	20	17	14	4
Cancer detection rates (E/B, %)	2.07	1.07	0.46	0.48	0.86	0.71	0.42	0.91	0.54	0.59	0.82	0.85	0.71	0.20

PSA, prostate-specific antigen.

legal basis for it (7). The present study showed not only the direct effects of cancer screening but also the indirect effects. In areas where cancer screening programs were continuously implemented, even patients who underwent opportunistic PSA testing were detected at an earlier stage than those in areas where cancer screening was not conducted. On basis of these results, the resumption of PSA screening in Kusatsu is appealing. Furthermore, it is considered that it is important to disseminate these data to other municipalities in Shiga Prefecture so that they consider initiating PSA screening to diagnose cancer in its early stages.

There are several limitations to the present study. First, these results only apply to a limited area in Japan and may not be applicable to other areas. Second, the present study could not prove the effectiveness of PSA mass screening with respect to cancer-specific mortality. Since the USPSTF recommended against PSA-based prostate cancer screening for all men in 2012, there has been a significant increase in the rate of metastatic disease at diagnosis in U.S. (17). After 20 years of a steady decline, prostate cancer mortality in the U.S. has also ticked upwards in the last few years (18). Based on the current situation in the U.S., it is possible that discontinuation of PSA screening in Kusatsu City may lead to a worsening of the mortality rate in prostate cancer. It is planned by the authors to conduct a new study on survival outcomes. Third, comments cannot be made on the prevalence of overdiagnosing by PSA testing since individual attending physicians likely have differing policies on diagnosis and treatment. Current progress in the development of multi-parametric magnetic resonance imaging (MRI) has played a major role in the diagnosis of prostate cancer. The PRECISION study showed that a multi-parametric MRI-based pathway increased the detection rate of clinically significant prostate cancer from 26 to 38% and decreased the detection rate of clinically insignificant cancer from 22 to 9%, compared with 12-core transrectal ultrasound-guided biopsy (19). In the near future, prostate-specific membrane antigen imaging may add value to the detection of clinically significant localized prostate cancer (20). Such diagnostic efforts should reduce overdiagnosis. However, in spite of such limitations, the present study yielded important information on the indirect influence of population-based PSA screening.

In conclusion, organized PSA screening leads to an increase in the number of men diagnosed with early-stage prostate cancer. Furthermore, population-based mass screening may indirectly affect early detection, even by opportunistic PSA testing in the community. Although the results of the present study were derived only from a small area, similar trends will likely be observed in more communities with continuous organized PSA screening.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The data are not publicly available due to privacy or ethical restrictions.

Authors' contributions

SK, YO, KN, ToY, SI, YaS and CJK designed the study. SK and YO confirm the authenticity of all the raw data, analyzed the data and drafted the manuscript. TI, RY, YA, ZN, HS, HU, YuS, YN, AW, MaN, TeY, MiN performed acquisition of clinical data. AK interpreted the data and supervised the study. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. R2018-010) by the Ethics Committee of Shiga University of Medical Science (Otsu, Japan) and by the ethics committee at each study center. The present study was undertaken according to the provisions of the Declaration of Helsinki. The participants were informed of the study by public notice using posters or websites. Informed consent was obtained in the form of opt-out, and those who rejected were excluded.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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