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.

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.
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.

**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.

**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
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 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.

| Reasons for PSA measurements | 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.
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

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.
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). |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 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 | 2,001 | 1,977 | 2,001 |
| PSA screening rates (B/A, %) | 8.5 | 13.1 | 13.5 | 13.8 | 13.1 | 11.8 | 11.4 | 11.0 | 11.3 | 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 | 176 | 164 | 174 | 132 | 93 | 82 |
| Positive PSA test rates (C/B, %) | 12.4 | 8.2 | 8.6 | 9.1 | 9.3 | 9.2 | 9.1 | 10.5 | 11.3 | 9.4 | 9.9 | 9.9 |
| Number of people who visited clinics for further examination (D) | 84 | 76 | 58 | 78 | 78 | 91 | 94 | 105 | 113 | 94 | 118 | 93 |
| Visiting rates for further examination (D/C, %) | 42.4 | 37.9 | 37.1 | 33.1 | 31.3 | 31.7 | 31.1 | 30.8 | 31.4 | 30.6 | 30.9 | 30.9 |
| Number of patients who were diagnosed with prostate cancer (E) | 33 | 27 | 12 | 13 | 17 | 21 | 10 | 13 | 17 | 14 | 17 | 14 |
| Cancer detection rates (E/B, %) | 2.07 | 1.07 | 0.46 | 0.48 | 0.48 | 0.54 | 0.59 | 0.82 | 0.85 | 0.71 | 0.61 | 0.57 |

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 rec‑
commended 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 overdiag‑
nosing 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 overdiag‑
nosis. 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
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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, ToY, 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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