Pandemic-resistant target setting in colorectal cancer screening for vulnerable older population

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Abstract

Background: Colorectal cancer screening (CRCS) needs to be pandemic-resilient to avoid long-lasting shutdowns; however, realistic participation target remains unelucidated. This study aimed to identify the lowest acceptable participation rate in CRCS during a pandemic, focusing on vulnerable older populations who require urgent intervention.

Methods: This nationwide cross-sectional study included 80,946 inpatients aged 70–85 years who were first diagnosed with colorectal cancer (CRC) after 70 years of age, between April 1, 2014 and March 31, 2019, in Japan. To evaluate the association between area-level CRCS participation rate and individual early CRC detection, a multilevel logistic regression model was constructed. The mandatorily implemented screening rates were converted to the total screening rate equivalents (TSREs), which reflect the remaining contributions of voluntarily provided screenings.

Results: Early detections during stages 0–I were significantly observed when primary screening rate was \( \geq 38\% \) (TSRE) and combined follow-up rate was \( \geq 85\% \). For early detection during Tis–T1, primary screening rate \( \geq 38\% \) (TSRE) and combined follow-up rate \( \geq 90\% \) were necessary. For follow-up rates \( \geq 70\% \) or \( \geq 75\% \), there were cases where missed detection of Tis–T1 were observed.

Conclusion: The results indicate that, even during pandemic, CRCS should achieve a primary screening rate of 38% and follow-up rate of 85% for vulnerable older populations. These values, lower than the current desirable rates, suggest the maximum possible compromise in balancing the resources between cancer screening and pandemic measures. Moreover, they also indicate the minimum target for shifting to fecal immunochemical test-focused program. Further explorations with varied CRCS settings are necessary for verification.

Keywords: cancer screening, colorectal cancer, COVID-19, early detection, pandemic, participation rate
LAY SUMMARY

- Colorectal cancer screening requires pandemic-resilience to avoid long-lasting shutdown.
- This study revealed that, for pandemic-vulnerable older populations, participation rates ≥38% for the primary screening and ≥85% for the follow-up should be achieved, even during pandemics, to sustain early detection of colorectal cancer.
- This can help pandemic-resilient target setting by serving as a foundation for balancing the resources between cancer screening and pandemic measures, or a minimum target for shifting to a stool test focused program.

1 | INTRODUCTION

Colorectal cancer screening (CRCS) was disrupted during the COVID-19 pandemic in 2020.1–3 Globally, the decline in screening rates ranged from 28% to 100%.4 The impacts appeared greater for regions where screening programs were paused for longer periods of time, and for pandemic-vulnerable segments of society, such as older populations.5 Given that colorectal cancer (CRC) is the second most deadly cancer worldwide, it is vital to build pandemic-resilient CRCS, especially for vulnerable populations.

Our approach was to clarify the lowest acceptable limit for the screening rate. It was expected that the lowest limit screening rate indicates what percentage of screening rate should be achieved (to what extent screening rate can be compromised) during pandemic. The lowest limit for screening rate by fecal immunochemical test (FIT) can also suggest what level of screening rate is necessary for shifting to FIT-focused program effectively. In addition, we recognize that the older population is the segment requiring urgent intervention. This is because: (1) healthcare access is disproportionately affected in this population (the COVID-19 case fatality rate of 9.7% in those aged ≥70 years6 could have led to a 5-year low per capita medical expenditure specifically for those aged ≥75 years in Japan7); (2) CRCS backlogs for those aged ≥70 years increased considerably during the 2020 pandemic. In the municipal-run CRCS program in Japan alone, the screening completion fell by 405,571 from 2019 to 20208; (3) delayed CRC diagnosis is more critical in them9; (4) the importance of cancer prevention is still insufficiently focused in this group10,11 (those aged >76 years are beyond the CRCS eligibility limits in most countries, despite the recommendation of up to 85 years in the United States12 and the full eligibility in Japan); and (5) the impacts on CRCS incidence (and, hence, medical expenditure) is substantial in this age group (those aged ≥70 years account for 58.9% of CRC incidence in Japan13).

To clarify the lowest limit, a threshold screening rate needs to be identified, above which early detection of CRC is achieved at the area level. However, no studies have specifically examined a threshold screening rate owing to the limited attention of this viewpoint, until the COVID-19 pandemic. Among a few related studies, Smith et al.14 reported that a screening rate of 25.04% did not differ in stage distribution (stage I–II vs. III–IV) between screening and clinically detected patients with CRC aged 50–74 years. Levin et al.15 reported that a rise in stool test screening rate of up to 32.0% resulted in a peak of early detection of CRC (earlier than stage III–IV) in patients aged 51–75 years. Although these findings imply the existence of a threshold screening rate for area-level early detection at stage I–II, the exact value remains unclear and is almost unknown for stage 0–I or for those aged >75 years. Therefore, this study aimed to identify the threshold for CRCS rate that achieves early detection during stage 0–I, focusing on the pandemic-vulnerable older population as our initial target. To our knowledge, this is the first study to examine pandemic-resilient target setting for CRCS.

2 | MATERIALS AND METHODS

2.1 | Study design

In this nationwide cross-sectional study, we analyzed the association between area-level CRCS rates and individual stages at diagnosis. We regarded that the CRCS process has worked as expected when the combined participation in primary screening and diagnostic follow-up leads to the early detection of CRC during stages 0–I at the area level. Based on this recognition, the threshold participation rate (TPR) was identified as the combination of the lowest screening and follow-up rates that are significantly associated with early detection.

2.2 | CRCS program

Japan’s population-based two-step CRCS program recommends primary screening by a two-sample annual FIT for healthy, asymptomatic individuals aged ≥40 years (no age limit), and diagnostic follow-up by colonoscopy for those with a positive FIT result.16 CRCS is provided under two types of schemes: mandatory (municipal-run) and voluntary (employment-based and private). Municipal-run CRCS is provided free of charge, employment-based CRCS is delivered in line with employee welfare benefits, and private CRCS is provided as a for-profit service. A key challenge in CRCS in Japan is the unachieved target rate, a major cause of the unreduced mortality rate.8 As of 2016, among those aged 40–69 years, the primary screening rate was 41.4% compared to the desired level of 50%,17 and the follow-up rate was 69.5% compared to the target of 90%.18
Data accessibility is a key issue; complete statistical data are available only for municipality-managed programs. Therefore, the primary screening rate is not an aggregated value calculated by statistical data but an estimated value based on the national sampling survey. Data access is even more limited for the follow-up; there are no accessible national statistical data for voluntarily provided follow-ups.

### 2.3 Total screening rate equivalent

A linear regression model was constructed to translate the municipal-run screening rate to the total screening rate equivalent (TSRE), by comparing the municipal-run screening rate and the survey-based total screening rate by sex, age group, and prefecture (Figure 1).

### 2.4 Study population

We used an anonymized dataset extracted from the Diagnosis Procedure Combination/Per-Diem Payment System (DPC/PDPS) database, a medical claim-based national database. The DPC/PDPS database includes information on individual patients, such as age, sex, International Statistical Classification of Diseases, Tenth Revision (ICD-10) code, stage at diagnosis, medical procedures, insurance type, and postal code. As of April 1, 2018, the DPC/PDPS covered 1730 hospitals and 488,563 beds, and Japan’s acute inpatients were regarded as almost fully accommodated. This study included 1165 DPC/PDPS member and 98 nonmember hospitals.

A total of 174,469 inpatients were identified through DPC/PDPS dataset who (1) were aged 70–85 years; (2) completed hospitalization between April 1, 2014 and March 31, 2019; (3) were first diagnosed with CRC (ICD10 codes: C18.0–C18.9 and C26.0 for colon, and C19.9 and C20.9 for rectal cancer); (4) had not been hospitalized for cancers until 70 years of age as an acute admission; and (5) not partaking in a clinical trial. Excluded patients were those with (1) unavailable data for body mass index (BMI) and Brinkman index (BI); (2) unmatched municipal codes and missing screening or follow-up rate; and (3) were from municipalities with small population sizes (the number of follow-up candidates by sex and age group was estimated to be <30). Consequently, 80,946 records (468 municipalities or administrative districts) were extracted for our main analyses (Figure 2).

Selection bias was tested for the stage distribution between the study and excluded populations, because multiple imputation could not be performed, since the proportion of excluded records appeared to exceed the applicability limit. The sample representativeness of the study population was also evaluated by comparison with the national averages. Upon validation, chi-square tests were applied to assess the significance of stage distribution.

### 2.5 Primary outcome

The primary outcome of this study was early detection of CRC during stages 0–I. This was mainly because the detection of CRC during stages 0–I, where the survival rate remains over 90% (91.6–94%), is crucial for mortality reduction. Besides, as the probability of main lymph node metastases remains <1% for these earlier stages, first-line therapies (endoscopic or surgical treatment) are less invasive and hence, less costly. Cancer staging was based on the Japanese Classification of Colorectal, Appendiceal, and Anal Carcinoma developed consistent with the Union Internationale Contre le Cancer staging system.

### 2.6 Variables

The main explanatory variable was the combined primary screening and follow-up participation rate. The combined participation rate was dichotomized at the candidate TPRs: 10%, 15%, 20%, and 25% for municipal-run primary screening rate.
screening and 70%, 75%, 80%, 85%, and 90% for follow-up (Figure 3). Independent variables included age, sex, cancer site, BMI,27,28 BI,29 and Charlson comorbidity index (CCI).30,31 Other risk factors, such as diet, alcohol consumption, genetic polymorphisms, family history, and past screening behavior and test results were not available in the DPC/PDPS database. As a socioeconomic predictor of health disparity,32 individual income level was also used.

### 2.7 Statistical analyses

A multilevel multivariate logistic regression model was used to evaluate the odds ratios (ORs) of the combined participation rate for early detection of CRC at stages 0–I and Tis–T1 (intraclass correlation coefficients were 0.023 and 0.031, respectively). ORs and 95% confidence intervals (CIs) were adjusted for age group, sex, cancer site, BMI, BI, CCI, and income level. We regarded the interaction term (i.e., combined participation rate) to be significant if P for interaction < 0.2. The model was tested through sensitivity analyses with assumed area-level confounders, such as regional healthcare access and employment. Statistical analyses were conducted using R version 4.1.2 and EZR version 1.54.33 The dataset was made mainly by Tableau Prep Builder version 2020.3.3.

### 3 RESULTS

#### 3.1 TSRE

A linear regression model was constructed to estimate TSRE with an intercept of 0.138 (95% CI [0.117–0.159], p < 0.001); coefficient of 1.22 (95% CI [1.10–1.34], p < 0.001); and an adjusted $R^2 = 0.68$. By adapting this model, the examined TPRs for the primary screening of 10%, 15%, 20%, and 25% were converted to the TSRE-based values of 26%, 32%, 38%, and 44%, respectively.
3.2 | Patient demographics

Municipalities with a population ≥ 70,000 (77% of the total population) were included in the study population, which corresponded to an estimated number of follow-up candidates ≥ 30, using a linear regression model with an intercept: 0, coefficient: 0.435 (95% CI [0.433–0.437], p < 0.001), and adjusted $R^2 = 0.59$. In testing for selection bias, the differences in the proportion of early-stage cases were ≤ 0.6 percentage points between the study and excluded populations (Table S1). Regarding sample representativeness, the average screening rate of the study population was 36.9% (TSRE; 70–85 years) against the national average of 37.0% (70–84 years). Likewise, the obtained average follow-up rate was 71.1% (70–85 years) compared with the national average of 67.7% (≥70 years). Chi-square tests applied to the stage distributions (Table 1) showed that higher percentages of stages 0–I cases were constantly observed, when combined participation rates were higher than the TPRs: 38% or 44% for primary screening and 70%, 80%, and 90% for combined follow-up (32.8–36.0%), compared with the overall percentage of stages 0–I cases (30.9%).

3.3 | TPR

With the candidate TPRs of screening rate ≥ 38% and follow-up rate ≥ 90% (the case with the lowest P for interaction), multilevel logistic regression models (Table 2) revealed that the combined higher participation rates were significantly associated with earlier detection at stages 0–I (OR: 0.84, 80% CI [0.71–0.99], p = 0.003) and Tis–T1 (OR: 0.79, 80% CI [0.66–0.96], p = 0.002). The analyses for seeking the TPR revealed that the combination of the lowest screening and follow-up rates that were significantly associated with early detection at stages 0–I was 38% (TSRE) for primary screening and 85% for follow-up (Figure 4; the data are provided in Table S2). In the sensitivity analyses (Table S3), we obtained the same results with a nonhierarchical model with a 95% confidence level (Figure S1). Further, a similar tendency was observed in the analyses adjusted for the potential confounders, except for some cases, such as those adjusted for municipal population size and income per capita. In the analyses of Tis–T1/T2–4, the significance of early detection at Tis–T1 persisted only when the primary screening rate was ≥ 38% (TSRE) and follow-up rate was ≥ 90%. Moreover, increased ORs (later detection at T2–4) were observed for some cases with the candidate TPR for follow-up rate at 70% or 75%.

4 | DISCUSSION

By defining the older population as a segment requiring urgent intervention in the ongoing COVID-19 pandemic, we reported here that the screening rate ≥ 38% and combined follow-up rate ≥ 85% are necessary to sustain the area-level early detection of CRC (stage 0–I). Below these threshold values, the two-step CRCS may not perform as expected. Therefore, importantly, it is suggested that the screening rate of 38% and combined follow-up rate of 85% be regarded as the lowest acceptable limits to be achieved, even during pandemics.

The lowest acceptable limits present a reasonable fit with the currently set target rates. The primary screening rate of 38% was found to be moderately lower than the desired rate in Japan (50%), and considerably lower than the EU and Canadian desirable levels (65% and 60%, respectively). An 85% follow-up rate lies below the common desirable level in Japan and the EU (90%). These relationships imply that the lowest acceptable limits can help pandemic-resilient target setting because the participation targets can be made more flexible with a clear, maximum compromise of 12–27% for the primary screening rate and 5% for the combined follow-up rate to optimize balanced pandemic measures.

Unexpected issues were observed in comparisons with the current screening rates. The threshold screening rate of 38% is comparable with Japan’s current screening rate for those aged 70–84 years (37.0%). Also, the 38% rate has not been achieved in some regions, such as France (34.3%, 2008–2009), Czech Republic (22.7%, 2000–2011), Croatia (19.9%, 2007–2011) in the EU, and Prince Edward Island (33%), New Brunswick (30%), and Newfoundland and Labrador (20.4%) in Canada (2017). These facts primarily indicate that the lowest acceptable limits might serve as immediate targets for regions where current screening rates are not sufficiently high. Regarding the follow-up rate, the results require more careful interpretation. Despite the decreased colonoscopy capacity during the pandemic for safety reasons, the threshold follow-up rate (85%) is, for some regions, considerably higher than the currently used acceptable level (e.g., 70% in Japan). Although it may be unlikely for follow-up rates to be higher during a pandemic than in normal times, it is implied that follow-up rate should not be easily compromised even in such an extraordinary situation. Therefore, feasible approaches should be considered, such as focusing on people with higher risk of advanced CRC (e.g., higher FIT level) or with lower risk of COVID-19 fatality (e.g., no or few basic diseases). Alternatively, a more rational interpretation might be that follow-up compliance should be sufficiently enhanced during normal times. Some of the
**TABLE 1  Patient demographics by CRC stage at diagnosis**

|                      | Stage 0, I versus II, III, IV | Tis, T1 (N0, M0) versus T2, 3, 4 |
|----------------------|-------------------------------|----------------------------------|
|                      | Total  | n    | %    | n    | %    | p*    | Total  | n    | %    | n    | %    | p*    |
| Overall              | 80,946 | 25,037 | 30.9 | 55,909 | 69.1 | 74,167 | 17,043 | 23.0 | 57,124 | 77.0 |        |
| Age b                |        |       |      |        |      |        |        |      |        |      |        |
| 70–79 years          | 57,723 | 18,459 | 32.0 | 39,264 | 68.0 | <0.001 | 53,009 | 12,780 | 24.1 | 40,229 | 75.9 | <0.001 |
| 80–85 years          | 23,223 | 6578   | 28.3 | 16,645 | 71.7 |        | 21,188 | 4263   | 20.1 | 16,895 | 79.9 |        |
| Sex                  |        |       |      |        |      |        |        |      |        |      |        |
| Male                 | 44,312 | 14,018 | 31.6 | 30,394 | 68.4 | <0.001 | 40,640 | 9794   | 24.1 | 30,846 | 75.9 | <0.001 |
| Female               | 36,634 | 11,019 | 30.1 | 25,615 | 69.9 |        | 33,527 | 7249   | 21.6 | 26,278 | 78.4 |        |
| Cancer site          |        |       |      |        |      |        |        |      |        |      |        |
| Colon                | 55,574 | 17,450 | 31.4 | 38,124 | 68.6 | <0.001 | 50,735 | 12,156 | 24.0 | 38,579 | 76.0 | <0.001 |
| Rectum               | 25,372 | 7587   | 29.9 | 17,785 | 70.1 |        | 23,432 | 4887   | 20.9 | 18,545 | 79.1 |        |
| BMI, kg/m²           |        |       |      |        |      |        |        |      |        |      |        |
| <21.5                | 33,496 | 8787   | 26.2 | 24,709 | 73.8 | <0.001 | 30,295 | 5853   | 19.3 | 24,442 | 80.7 | <0.001 |
| 21.5–24.9 c          | 29,968 | 9887   | 33.0 | 20,081 | 67.0 |        | 27,701 | 6785   | 24.5 | 20,916 | 75.5 |        |
| ≥24.9                | 17,482 | 6363   | 36.4 | 11,119 | 63.6 |        | 16,171 | 4405   | 27.2 | 11,766 | 72.8 |        |
| BI, cigarette year   |        |       |      |        |      |        |        |      |        |      |        |
| <800                 | 68,242 | 21,143 | 31.0 | 47,099 | 69.0 | 0.459  | 62,482 | 14,304 | 22.9 | 48,178 | 77.1 | 0.197  |
| ≥800 d               | 12,704 | 3894   | 30.7 | 8810   | 69.3 |        | 11,685 | 2739   | 23.4 | 8946   | 76.6 |        |
| CCI                  |        |       |      |        |      |        |        |      |        |      |        |
| <3                   | 64,974 | 23,124 | 35.6 | 41,850 | 64.4 | <0.001 | 60,723 | 15,854 | 26.1 | 44,869 | 73.9 | <0.001 |
| ≥3                   | 15,972 | 1913   | 12.0 | 14,059 | 88.0 |        | 13,444 | 1189   | 8.8  | 12,255 | 91.2 |        |
| Income level         |        |       |      |        |      |        |        |      |        |      |        |
| ≥Average e           | 6895   | 2463   | 35.7 | 4432   | 64.3 | <0.001 | 6320   | 1694   | 26.8 | 4626   | 73.2 | <0.001 |
| <Average             | 74,051 | 22,574 | 30.5 | 51,477 | 69.5 |        | 67,847 | 15,349 | 22.6 | 52,498 | 77.4 |        |
| Screening rate (TSR) |        |       |      |        |      |        |        |      |        |      |        |
| ≥26%                 | 60,714 | 19,414 | 32.0 | 41,300 | 68.0 | <0.001 | 55,540 | 13,168 | 23.7 | 42,372 | 76.3 | <0.001 |
| <26%                 | 20,232 | 5623   | 27.8 | 14,609 | 72.2 |        | 18,627 | 3875   | 20.8 | 14,752 | 79.2 |        |
| ≥38%                 | 32,835 | 11,002 | 33.5 | 21,833 | 66.5 | <0.001 | 30,012 | 7520   | 25.1 | 22,492 | 74.9 | <0.001 |
| <38%                 | 48,111 | 14,035 | 29.2 | 34,076 | 70.8 |        | 44,155 | 9523   | 21.6 | 34,632 | 78.4 |        |
| ≥44%                 | 21,387 | 7325   | 34.2 | 14,062 | 65.8 | <0.001 | 19,539 | 4978   | 25.5 | 14,561 | 74.5 | <0.001 |
| <44%                 | 59,559 | 17,712 | 29.7 | 41,847 | 70.3 |        | 54,628 | 12,065 | 22.1 | 42,563 | 77.9 |        |
| Follow-up rate       |        |       |      |        |      |        |        |      |        |      |        |
| ≥70%                 | 50,079 | 15,341 | 30.6 | 34,738 | 69.4 | 0.020  | 46,141 | 10,621 | 23.0 | 35,520 | 77.0 | 0.744  |
| <70%                 | 30,867 | 9696   | 31.4 | 21,171 | 68.6 |        | 28,026 | 6422   | 22.9 | 21,604 | 77.1 |        |
| ≥80%                 | 26,719 | 8081   | 30.2 | 18,638 | 69.8 | 0.003  | 24,655 | 5592   | 22.7 | 19,063 | 77.3 | 0.173  |
| <80%                 | 54,227 | 16,956 | 31.3 | 37,271 | 68.7 |        | 49,512 | 11,451 | 23.1 | 38,061 | 76.9 |        |
| ≥90%                 | 5542   | 1582   | 28.5 | 3960   | 71.5 | <0.001 | 5113   | 1085   | 21.2 | 40,288 | 78.8 | 0.002  |
| <90%                 | 75,404 | 23,455 | 31.1 | 51,949 | 68.9 |        | 69,054 | 15,958 | 23.1 | 53,096 | 76.9 |        |
| Stage 0, I versus II, III, IV | Tis, T1 (N0, M0) versus T2, 3, 4 |
|--------------------------------|----------------------------------|
| **Total** | **Tis, T1** | **T2, 3, 4** |
| **n** | **n** | **n** | **p** | **n** | **n** | **p** |
| Combined rate<sup>a</sup> (TSRE) | | | | | | |
| ≥26% and ≥70% | 36,407 | 24,903 | <0.001 | 33,440 | 25,556 | <0.001 |
| <26% or <70% | 44,539 | 31,006 | 0.086 | 40,727 | 31,568 | 0.175 |
| ≥26% and ≥80% | 18,291 | 12,539 | 0.619 | 16,819 | 12,889 | 0.247 |
| <26% or <80% | 62,655 | 43,370 | <0.001 | 57,348 | 44,255 | <0.001 |
| ≥26% and ≥90% | 2715 | 1887 | 0.086 | 2462 | 1920 | 0.175 |
| <26% or <90% | 78,231 | 54,022 | 0.002 | 71,705 | 55,204 | 0.002 |
| ≥38% and ≥70% | 18,003 | 12,090 | <0.001 | 16,585 | 12,527 | <0.001 |
| <38% or <70% | 62,943 | 43,819 | <0.001 | 57,582 | 44,597 | <0.001 |
| ≥38% and ≥80% | 8643 | 5777 | <0.001 | 8001 | 6031 | <0.001 |
| <38% or <80% | 72,303 | 50,132 | 0.002 | 66,166 | 51,093 | 0.002 |
| ≥38% and ≥90% | 1079 | 696 | 0.001 | 1003 | 731 | <0.001 |
| <38% or <90% | 79,867 | 55,213 | <0.001 | 73,164 | 56,393 | <0.001 |
| ≥44% and ≥70% | 10,844 | 7216 | <0.001 | 10,018 | 7539 | <0.001 |
| <44% or <70% | 70,102 | 48,693 | <0.001 | 64,149 | 49,585 | <0.001 |
| ≥44% and ≥80% | 5324 | 3522 | <0.001 | 4945 | 4714 | <0.001 |
| <44% or <80% | 75,622 | 52,387 | <0.001 | 69,222 | 53,410 | <0.001 |
| ≥44% and ≥90% | 688 | 440 | 0.004 | 635 | 464 | <0.001 |
| <44% or <90% | 80,258 | 55,469 | <0.001 | 73,532 | 56,660 | <0.001 |

Abbreviations: BI, Brinkman index; BMI, body mass index; CCI, Charlson comorbidity index; CRC, colorectal cancer; TPR, threshold participation rate; TSRE, total screening rate equivalent.<sup>a</sup>Chi-square tests.

<sup>b</sup>Dichotomized according to cancer screening behavior (screening rate decreases for aged ≥80 years).

<sup>c</sup>Defined as the desirable range for aged ≥65 years by the Japanese government.

<sup>d</sup>Dichotomized according to the risk of CRC incidence.

<sup>e</sup>The average income level for couple household of active generation estimated by the Japanese government.

<sup>f</sup>Municipal-run primary screening rates of 10%, 20%, and 25% are converted to TSRE-based values of 26%, 38%, and 44%, respectively. Municipal-run screening rate of ≥30% (50% on TSRE basis) was not analyzed due to insufficient sample size.

<sup>g</sup>Two-way interaction between primary screening and follow-up rate, both dichotomized at the candidate TPRs: 26%, 38%, and 44% for primary screening and 70%, 80%, and 90% for follow-up.
currently used acceptable levels, which might serve not as literal values but as viable milestones toward the desirable rates, might have to be replaced by the lowest acceptable limits. Interestingly, if our methods are verified and scaled to wider age groups, evidence regarding where the missing true acceptable level should lie may be achieved. EU guidelines recommend CRCS to achieve a favorable
stage distribution in screening-detected cancers compared with clinically diagnosed cancers. However, the threshold screening rates are not identified. Also, Japan's acceptable screening rates are based more on macro benchmarks, such as actual screening rates in the reference countries, than their influence on stage distribution.

In the discussion of a pandemic-resilient CRCS, our results may suggest new fundamental elements. Currently examined solutions are mainly regarding: (1) enhancing the participation rate (mailed FIT program\textsuperscript{37} and shift toward a more FIT-focused CRCS\textsuperscript{38}); and (2) improving efficiency for an increased yield (readjustment of the cutoff value of FIT and risk-stratified colonoscopy based on FIT result\textsuperscript{39}). However, solutions for avoiding a shutdown of cancer screening are not explicitly discussed. The lowest acceptable limits might address this missing point. Moreover, for regions with screening colonoscopy-centered CRCS, such as the United States, the lowest acceptable FIT screening rate might serve as a minimum target in shifting to a FIT-focused program.

Our findings appeared consistent with, or did not contradict, previous findings. First, regarding stage distribution, the proportion of patients at stage 0–II in this study was 55.6\% (70–85 years), whereas in situ and local cancers accounted for 61.6\% (\geq 65 years; 2012–2014) in a cancer registry-based study by Toyoda et al. (Osaka, Japan).\textsuperscript{40}
These values appear roughly consistent, considering the differences in datasets and target regions. Second, given that diagnosis at stages 0–I or Tis–T1 was significantly associated with combined colonoscopy (Table 2), FIT appeared less sensitive for those earlier stages. This observation is supported by previous works.31,32 Third, the obtained TPR of 38% (TSRE) for screening and 85% for follow-up (Figure 4) appeared within the limits of related studies. Evidently, the screening rate of 25.04%, which did not affect the stage distribution in the work by Smith et al.,14 is expectedly lower than the TPR of 38%. It is seemingly discrepant that Levin et al. found a peak of early detection when the FIT-centered screening rate increased to 32.0% (still < 38%) with a follow-up colonoscopy rate of 72.2% (also lower than the 85%).15 Nevertheless, this can be explained by the difference in the definition of early stage. The definition by Levin et al. included stage II, for which FIT has a higher sensitivity. Finally, male sex and higher income level were associated with early detection, consistent with previously reported findings.40,43 Because municipal-run CRCS is free of charge, the association between CRC stage at diagnosis and individual income level is thought to be due to differences in patients’ health behaviors rather than a disparity in CRCS access. For further verification, it is expected that our methods are applied to the CRCS eligible population aged <70 years or other cancers using an integrated dataset of area-level screening rates and individual stage at diagnosis data and that comparisons are made between obtained TPRs and current metrics.

4.1 Limitations

This study had some limitations. First, it was a cross-sectional study; thus, we could not evaluate timeline factors, such as the effect of delayed follow-up after a positive FIT result.44,45 Second, some predictors for CRC incidence were not included, such as diet, alcohol consumption, genetic polymorphisms, family history, and past screening behavior and test results. Third, outpatients were not included, hence a considerable number of potential early-stage cases could have been omitted in our study, given that endoscopic mucosal resections in outpatient settings accounted for 64.4% and 25.7% for adenomatous polyps <2 and ≥2 cm, respectively (2018).46 Underestimated ORs for early detection might have raised the bar for the lowest acceptable screening rates. Fourth, CRCS false positive cases could act as a confounder for the analysis of stages 0–I, because it was not possible to fully exclude T0 cancer, which is regarded as non-invasive, due to missing TNM classification data. However, since the analyses were focused on inpatients for whom CRC was a main disease in terms of resources utilization, the influence of potential T0 case is thought to be limited. Fifth, our model used area-level variables along with latent confounders. Based on the findings when adjusted for the assumed area-level confounders in the sensitivity analyses (Table S3), the model appeared robust for municipal-level healthcare access indicators (density of hospital, clinic, and gastroenterologist). The model appeared more affected by the variation of municipal population size (≥120,000) and income per capita, indicating that these factors are associated with a higher share of employment-based or private CRCS, which could undermine the applicability of TSRE. For practical use by public health administrators, further verification is needed. Finally, access to the statistical data of voluntarily provided CRCS was limited. TSRE did not reflect municipal-level variations of voluntarily provided CRCS. Furthermore, the follow-up rate remained untranslated because no statistical data were available for estimating TSRE.

5 CONCLUSION

CRCS needs to have a pandemic-resilient target setting option to avoid the long-lasting shutdown. Our results suggest that, even during a pandemic, CRCS should achieve a primary screening rate ≥38% and follow-up rate ≥85% to sustain the early detection of CRC (stages 0–I) in the pandemic-vulnerable older population. For policymakers, these values suggest the extent to which the CRCS rate can be compromised to balance cancer screening and implementation of pandemic measures and serve as evidence for securing continuity of CRCS during pandemics. The obtained screening rates can also be used as an immediate target or an acceptable level for regions with insufficient screening rates or as the minimum target for shifting to FIT-focused CRCS in regions with screening colonoscopy-centered programs. To verify our findings, future studies in varied CRCS settings and eligible populations are warranted.

AUTHOR CONTRIBUTIONS

Toshiaki Shibata: Conceptualization, data curation, methodology, formal analysis, and writing—original draft. Daisuke Shinjo: Methodology, and writing—review and editing. Junichi Takahashi: Conceptualization and writing—review. Kiyohide Fushimi: Supervision, resources, writing—review, and funding acquisition.

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CONFLICT OF INTEREST
No relevant financial or nonfinancial interests to disclose.

DATA AVAILABILITY STATEMENT
The data availability is not applicable due to an ethical restriction. However, upon reasonable request to the corresponding author, the data can be made available by the DPC research group for researchers who meet the necessary confidential criteria.

ETHICS APPROVAL
This study was approved by the institutional review board at the Tokyo Medical and Dental University.

PRECIS
Colorectal cancer screening requires pandemic-resilience to avoid a long-lasting shutdown. This nationwide study, focusing on pandemic-vulnerable older population indicates that colorectal cancer screening should achieve a primary screening rate ≥38% and follow-up rate ≥85%, which serves as a foundation for balancing the resources between cancer screening and pandemic measures or as the minimum target for shifting to fecal immunochemical test focused program.

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REFERENCES
1. Croswell JM, Corley DA, Lafata JE, et al. National Cancer Institute population-based research to optimize the screening process (PROSPR) II Consortium. Cancer screening in the U.S. through the COVID-19 pandemic, recovery, and beyond. Prev Med. 2021;151:106595. doi:10.1016/j.ypmed.2021.106595
2. Kortlever TL, de Jonge L, Wisse PHA, et al. The national FIT-based colorectal cancer screening program in The Netherlands during the COVID-19 pandemic. Prev Med. 2021;151:106643. doi:10.1016/j.ypmed.2021.106643
3. Campbell C, Sommerfield T, Clark GRC, et al. COVID-19 and cancer screening in Scotland: a national and coordinated approach to minimising harm. Prev Med. 2021;151:106606. doi:10.1016/j.ypmed.2021.106606
4. Mazidimoradi A, Tiznobaik A, Salehiniya H. Impact of the COVID-19 pandemic on colorectal cancer screening: a systematic review. J Gastrointest Cancer. 2021;18:1-15. doi:10.1007/s12029-021-00679-x
5. Walker MJ, Meggetto O, Gao J, et al. Measuring the impact of the COVID-19 pandemic on organized cancer screening and diagnostic follow-up care in Ontario, Canada: a provincial, population-based study. Prev Med. 2021;151:106586. doi:10.1016/j.ypmed.2021.106586
6. Visualizing the data: information on COVID-19 infections. Ministry of Health, Labour and Welfare, Government of Japan. Published December 14, 2021. Accessed January 3, 2022. https://covid19.mhlw.go.jp/en/
7. Survey on the Trend of Medical Care Expenditures. (2020). Ministry of Health, Labour and Welfare, Government of Japan. Accessed December 15, 2021. https://www.stat.go.jp/english/data/handbook/index.html
8. Cancer Mortality Database, World Health Organization. Accessed November 12, 2021. https://covid19.mhlw.go.jp/en/
9. Loveday C, Sud A, Jones ME, et al. Prioritisation by FIT to mitigate the impact of delays in the 2-week wait colorectal cancer referral pathway during the COVID-19 pandemic: a UKmodelling study. Gut. 2021;70(6):1053-1060. doi:10.1136/gutjnl-2020-321650
10. Klabunde CN, Zheng Y, Quinn VP, et al. Influence of age and comorbidity on colorectal cancer screening in the elderly. Am J Prev Med. 2016;51(3):e67-e75. doi:10.1016/j.amepre.2016.04.018
11. Kudo SE, Kudo T. The necessity of colorectal cancer screening for elderly patients. Transl Gastroenterol Hepatol. 2017;2:19. doi:10.21037/gh.2017.03.03
12. US Preventive Services Task Force, Davidson KW, Barry MJ, et al. Screening for colorectal cancer: US preventive services task force recommendation statement. Jama. 2021;325(19):1965-1977. doi:10.1001/jama.2021.6238
13. Cancer Statistics. Cancer information service, National Cancer Center, Japan (National Cancer Registry, Ministry of Health, Labour and Welfare). Published October 11, 2021. Accessed December 15, 2021. https://ganjoho.jp/reg_stat/statistics/data/dl/en.html
14. Smith HA, Scarffe AD, Brunet N, et al. Impact of colorectal cancer screening participation in remote northern Canada: a retrospective cohort study. World J Gastroenterol. 2020;26(48):7652-7663. doi:10.3748/wjg.v26.i48.7652
15. Levin TR, Corley DA, Jensen CD, et al. Effects of organized colorectal cancer screening on cancer incidence and mortality in a large community-based population. Gastroenterology. 2018;155(5):1383-1391.e5. doi:10.1053/j.gastro.2018.07.017
16. Ministry of Health, Labour and Welfare. Report on regional public health services and health promotion services (2016). Comprehensive Survey of Living Conditions. Accessed November 12, 2021. https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkouyoku/0000111662.pdf [in Japanese]
17. Ministry of Health, Labour and Welfare, Government of Japan. (2016). Comprehensive Survey of Living Conditions. Accessed November 12, 2021. https://www.mhlw.go.jp/english/database/db-hss/cslc-report2016.html
18. Ministry of Health, Labour and Welfare. Report on regional public health services and health promotion services (2016). Accessed November 12, 2021. https://www.mhlw.go.jp/english/database/db-hss/rphshps.html
19. Shinjo D, Matsumoto K, Terashima K, et al. Volume effect in paediatric brain tumour resection surgery: analysis of data from the Japanese national inpatient database. Eur J Cancer. 2019;109:111-119. doi:10.1016/j.ejca.2018.12.030
20. Hayashida K, Murakami G, Matsuda S, Fushimi K. History and profile of diagnosis procedure combination (DPC): development of a real data collection system for acute inpatient care in Japan. J Epidemiol. 2021;31(1):1-11. doi:10.2188/jen.E20200288
21. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020 May;70(3):145-164. doi:10.3322/caac.21601
22. e-Stat, The Portal Site of Official Statistics of Japan, Statistics Bureau, Ministry of Internal Affairs and Communications. Accessed December 9, 2021. https://www.e-stat.go.jp/en/regional-statistics/ssdsvIEW/municipality

23. Demirtas H, Hedeker D. An imputation strategy for incomplete longitudinal ordinal data. Stat Med. 2008;27(20):4086-4093. doi:10.1002/sim.3239

24. Watanabe T, Muro K, Ajikura Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol. 2018;23(1):1-34. doi:10.1007/s10147-017-1101-6

25. Japanese Society for Cancer of the Colon and Rectum. Japanese Classification of Colorectal, Appendiceal, and anal carcinoma: the 3D English edition [secondary publication]. J Anus Rectum Colon. 2019;3(4):175-195. doi:10.23922/jarc.2019-018

26. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 8th ed. John Wiley & Sons; 2017.

27. Dietary Reference Intakes for Japanese. Comprehensive Survey of Living Conditions. Ministry of Health, Labour and Welfare, Government of Japan; 2015.

28. Li H, Boakye D, Chen X, Hofmeyr M, Brenner H. Association of body mass index with risk of early-onset colorectal cancer: systematic review and meta-analysis. Am J Gastroenterol. 2021;116(11):2173-2183. doi:10.14309/ajg.0000000000001393

30. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43(11):1130-1139. doi:10.1097/01.mlr.0000182534.19832.83

33. Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. Bone Marrow Transplant. 2013;48(3):452-458. doi:10.1038/bmt.2012.244

34. Moss S, Ancelle-Park R, Brenner H, International Agency for Research on Cancer. European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis. First Edition—Evaluation and Interpretation of Screening Outcomes. Endoscopy. 2012;44(Suppl 3):SE49-SE64. doi:10.1055/s-0032-1309788

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

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