



# PREVALENCE OF POSITIVE FECAL OCCULT BLOOD TEST RESULTS IN COLORECTAL CARCINOMA SCREENING IN THE CATCHMENT AREA OF TOMONI PRIMARY HEALTH CENTER THROUGH THE EMPOWERMENT OF POSBINDU PTM AND POSYANDU LANSIA

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## ABSTRACT

**Background.** Colorectal carcinoma is the third most common malignancy worldwide, with a rapidly rising burden in Southeast Asia, whereas organized screening coverage in Indonesia remains highly limited and most cases are diagnosed at an advanced stage. Fecal occult blood testing is the most feasible first-line screening modality in resource-limited primary care settings; however, community-level data on the prevalence of positive results from eastern Indonesia are virtually non-existent.

**Objective.** To determine the prevalence of positive fecal occult blood test results in a community-based colorectal carcinoma screening program in the catchment area of Tomoni Primary Health Center and to analyze its association with age, sex, and village/urban-ward distribution.

**Methods.** An analytical observational study with a population-based cross-sectional design was conducted among 181 adult participants from 12 villages and 1 urban ward, mobilized through the empowerment of Posbindu PTM and Posyandu Lansia. The prevalence of positive results was expressed as a proportion with 95% confidence intervals (CI) calculated using the Wilson, Wald, and Clopper–Pearson methods, together with cluster design effect correction. Bivariate analysis employed Pearson's chi-square test, Fisher's exact test, the Cochran–Armitage test for trend, and the Mann–Whitney test. Multivariable analysis employed binary logistic regression, supplemented by age-stratified Mantel–Haenszel odds ratios, tests of inter-village heterogeneity (Cochran's Q and  $I^2$ ), receiver operating characteristic curve analysis, and sensitivity and statistical power analyzes.

**Results.** Of 181 participants (mean age  $63.7 \pm 7.0$  years; 50.6% male), 30 tested positive, yielding a prevalence of 16.6% (95% Wilson CI 11.9–22.7). Prevalence was higher in men than in women (22.0% vs 11.2%; crude odds ratio 2.23; 95% CI 0.98–5.07;  $p = 0.071$ ) and reached statistical significance after adjustment for age (adjusted odds ratio 2.51; 95% CI 1.03–6.08;  $p = 0.042$ ) and in the Mantel–Haenszel stratified analysis (odds ratio 2.51; 95% CI 1.03–6.14). Age was not associated with a positive result, whether analyzed as a continuous variable (odds ratio 1.00 per year; 95% CI 0.94–1.06;  $p = 0.947$ ), across age groups ( $p = 0.375$ ), or by trend testing ( $Z = 0.279$ ;  $p = 0.780$ ), with an area under the curve of 0.494 (95% CI 0.377–0.612). No inter-village heterogeneity in prevalence was observed ( $Q = 2.77$ ;  $p = 0.993$ ;  $I^2 = 0.0\%$ ; permutation  $p = 0.993$ ).

**Conclusion.** The 16.6% prevalence of positive fecal occult blood test results substantially exceeds the positivity rates of organized

screening programs in high-income countries, with male sex emerging as the sole independent determinant. These findings support the feasibility of empowering Posbindu PTM and Posyandu Lansia as channels for screening mobilization, while underscoring the urgent need to strengthen the colonoscopy referral pathway so that the benefits of screening do not end at the detection stage.

**Keywords:** fecal occult blood test; colorectal carcinoma; Posbindu PTM; Posyandu Lansia; community-based screening.

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## INTRODUCTION

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### Background

Colorectal carcinoma represents one of the foremost oncological challenges of the present century. Global estimates indicate more than 1.9 million new cases and approximately 930,000 deaths attributable to this malignancy in 2020, ranking it as the third most common malignancy and the second leading cause of cancer-related death worldwide. Demographic projections anticipate an increase to 3.2 million new cases and 1.6 million deaths by 2040, whereas estimates based on 2022 data project 2.36 million new cases by 2050. This burden is unevenly distributed: age-standardized incidence rates have declined in high-income North America but have risen consistently across Asia, with Southeast Asia exhibiting a substantial positive average annual percentage change over the past three decades.<sup>1,2</sup>

In Southeast Asia, colorectal cancer has become the leading malignancy among men in several countries and is projected to increase in case numbers by 89.2% in men and 65.6% in women by 2050 relative to 2022. Analyses of the global burden of gastrointestinal disease likewise show that the age-standardized incidence rate of colorectal carcinoma continues to rise, in contrast to esophageal and gastric malignancies, which tend to decline. This increase was predicted two decades ago as a consequence of lifestyle transition, westernization of dietary patterns, population aging, and improvements in cancer registration in Asia.<sup>3,4,5</sup>

Indonesia faces an even more complex situation. An eleven-year retrospective analysis at a national referral hospital demonstrated a significant annual percentage change in colorectal carcinoma cases of 2.38% per year among patients aged 50 years and older, accompanied by a surge in colon cancer among young patients of 9.24% per year. The mean patient age was only 53.2 years, and 38.1% were classified as early-onset, a profile considerably younger than that observed in Western countries. Most patients in lower-middle-income countries present at an advanced stage, when curative options have narrowed and survival outcomes have deteriorated substantially.<sup>6,7</sup>

Evidence that fecal occult blood–based screening reduces colorectal carcinoma mortality has been well established for more than three decades. The Minnesota randomized controlled trial reported a 33% reduction in 13-year cumulative mortality with annual screening, and 30-year follow-up confirmed the durability of this effect, with a relative risk of 0.68 for annual and 0.78 for biennial screening. The Nottingham and Funen trials demonstrated mortality reductions of 15% and 18%, respectively, with biennial screening. A Cochrane synthesis of four randomized controlled trials involving more than 320,000 participants concluded a 16% relative reduction in mortality, increasing to 25% among those who actually attended at least one screening round. Contemporary network meta-analyses and systematic reviews have confirmed the consistency of this effect.<sup>8,9,10,11,12,13,14</sup>

On the basis of this evidence, the United States Preventive Services Task Force recommends colorectal carcinoma screening for all adults aged 50 to 75 years as a grade A recommendation and for those aged 45 to 49 years as a grade B recommendation. The supporting evidence review showed that the fecal immunochemical test has a pooled sensitivity of 0.74 and specificity of 0.94 for carcinoma detection, whereas high-sensitivity guaiac-based testing has a sensitivity of 0.50 to 0.75 with a specificity of 0.96 to 0.98. The third Asia-Pacific consensus affirms that stool-based screening remains the principal strategy in most countries of the region, and the first consensus explicitly positioned fecal occult blood testing as the first-line option in resource-constrained countries. The joint guideline of the Asian Pacific Association of Gastroenterology and the Asian Pacific Society of Digestive Endoscopy subsequently provided detailed guidance on the use of non-invasive markers for the detection of colorectal neoplasia.<sup>15,16,17,18,19</sup>

Nevertheless, fecal occult blood test positivity rates vary widely across settings. A global systematic review and meta-analysis of 93 studies encompassing nearly 90 million person-tests reported a pooled positivity rate of 7.28% with a carcinoma detection rate of 0.28%. In organized European programs, positivity rates range from 2.4% to 10.7%, depending on the fecal hemoglobin threshold, sex, and screening round. Conversely, a community-based study in Nigeria reported a positivity rate of 21% with a positive predictive value for invasive carcinoma of only 1.1%, raising concern about a disproportionate colonoscopy burden in resource-limited settings. A scoping review

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of colorectal carcinoma screening implementation in low- and middle-income countries found uptake ranging from 14% to 100% and highlighted that face-to-face recruitment strategies and community education-based interventions most consistently achieved coverage above 65%.<sup>20,21,22</sup>

Experience from a community-based program in Shanghai showed that initial screening can achieve very high coverage, with 97.7% of 828,302 registered residents completing initial screening. However, only 39.8% of participants with positive results agreed to undergo colonoscopy, and this proportion declined with increasing age and lower educational attainment. This phenomenon underscores that the success of a screening program is determined not by the detection stage alone but by the integrity of the entire care continuum through to diagnostic confirmation.<sup>23</sup>

In the Indonesian context, the primary care system already possesses community infrastructure that is theoretically well suited to screening mobilization, namely the Integrated Development Post for Non-Communicable Diseases (Pos Pembinaan Terpadu Penyakit Tidak Menular, Posbindu PTM) and the Integrated Service Post for the Elderly (Posyandu Lansia). A mixed-methods evaluation of 54,224 participants at 475 Posbindu sites showed that 95.1% of attendees had their blood pressure measured at the first visit, yet fewer than 25% were interviewed regarding non-communicable disease risk factors and fewer than 15% underwent blood cholesterol testing, with limited resources and time as the principal barriers. A satisfaction survey of 1,263 participants across three provinces identified dissatisfaction primarily with service availability and infrastructure and recommended integrating Posbindu into existing community-based activities. Access to Posbindu has been associated with better knowledge of hypertension, although its association with attitudes and practices has been inconsistent. Most pertinent to the present study, an analysis of 277 adults with abnormal screening results in Aceh Besar found that fewer than half (42.2%) completed follow-up at primary care facilities.<sup>24,25,26,27</sup>

Empowering community cadres as the spearhead of screening is supported by a robust evidence base. Three Community Guide systematic reviews of 76 studies concluded that interventions engaging community health workers increased colorectal carcinoma screening by a median of 10.5 percentage points, an effect that was consistent irrespective of race, ethnicity,

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income, or insurance status. A systematic review of randomized controlled trials in low- and middle-income countries likewise demonstrated that community health workers are effective in the primary prevention of non-communicable diseases. The Asia-Pacific Colorectal Screening risk stratification framework, which incorporates age, sex, family history, and smoking status, has been validated for prioritizing screening candidates among asymptomatic Asian populations.<sup>28,29,30</sup>

### **Research Gap**

The evidence gap underpinning this study can be delineated at four levels. First, despite the increasing burden of colorectal carcinoma in Indonesia and its clinicopathological profile differing from that of Western populations, virtually no estimates exist of the prevalence of positive fecal occult blood test results derived from Indonesian community populations, let alone from primary health center catchment areas outside Java. Nearly all positivity data used as clinical references originate from organized programs in Europe, North America, and East Asia, whose demographic characteristics, risk exposures, background gastrointestinal disease, and health system configurations differ fundamentally. Second, the literature on Posbindu PTM and Posyandu Lansia in Indonesia has thus far been dominated by studies of hypertension, diabetes mellitus, and cardiometabolic risk factors; consequently, the capacity of these two platforms to serve as channels for mobilizing cancer screening has never been tested or quantitatively reported.<sup>6,20,24,25</sup>

Third, the demographic determinants of fecal occult blood positivity in Southeast Asian populations remain uncharacterized. Sex differences in positivity are a highly consistent finding in European populations, yet the magnitude of this effect in the Indonesian population—with its distinct age structure, body mass index, prevalence of *Helicobacter pylori* infection, and patterns of non-steroidal anti-inflammatory drug use—remains unknown. Fourth, no Indonesian study has explicitly situated prevalence estimates of positive results within a service capacity planning framework, that is, translating positivity rates into projections of colonoscopy burden, number needed to screen, and implications for district-level referral readiness.<sup>37,38,39,46</sup>

### **Novelty**

This study offers several novel contributions. First, to the best of the authors' knowledge based on the literature search, this is the first report to measure the prevalence of positive fecal

occult blood test results in a community-based colorectal carcinoma screening program within a primary health center catchment area in South Sulawesi, and one of the first in eastern Indonesia. Second, this study is the first to evaluate the simultaneous empowerment of Posbindu PTM and Posyandu Lansia as a mechanism for mobilizing participants for cancer screening, thereby expanding the functional scope of both platforms from cardiometabolic risk factor screening to oncological screening.<sup>24,25,28</sup>

Third, this study applies a more comprehensive analytical approach than conventional prevalence reports, encompassing confidence interval estimation using three comparative methods together with cluster design effect correction, directional trend testing with the Cochran–Armitage test, quantification of inter-village heterogeneity using Cochran's Q and I<sup>2</sup> statistics supplemented by a permutation test, multivariable modeling with Hosmer–Lemeshow calibration assessment, and post-hoc statistical power analysis. Fourth, this study introduces a scenario analysis that translates positivity rates into projected colonoscopy yields and numbers needed to screen based on the range of positive predictive values reported in the global literature, so that the epidemiological findings can be directly applied as a basis for planning referral service capacity at the district level.<sup>20,21,23</sup>

### **Research Objectives**

The general objective of this study was to determine the prevalence of positive fecal occult blood test results in a community-based colorectal carcinoma screening program in the catchment area of Tomoni Primary Health Center implemented through the empowerment of Posbindu PTM and Posyandu Lansia.

The specific objectives of this study were: (1) to estimate the prevalence of positive fecal occult blood test results with 95% confidence intervals in the screened population; (2) to describe the demographic characteristics of screening participants, including the distribution of age, sex, and village/urban ward of origin; (3) to analyze the association between age, as both a continuous and a categorical variable, and a positive fecal occult blood test result; (4) to analyze the association between sex and a positive fecal occult blood test result, both crude and after adjustment for age; (5) to evaluate geographical variation in the prevalence of positive results across villages/urban wards and to test for heterogeneity; (6) to identify independent determinants of a positive result through

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binary logistic regression modeling; and (7) to project the downstream diagnostic burden in terms of confirmatory colonoscopy requirements and the number needed to screen under various positive predictive value scenarios.

### **Significance of the Study**

The theoretical contribution of this study lies in enriching the body of knowledge on colorectal carcinoma epidemiology in Indonesia with prevalence data on positive screening results obtained directly from a community population, rather than from referral hospital populations that are heavily affected by selection bias. These data provide a comparative reference for similar studies in other regions and an input for future cost-effectiveness modeling of a national screening program.

The practical benefit for primary care providers is the availability of quantitative estimates of the workload generated by a community-based screening program, including the proportion of participants requiring further referral and the projected colonoscopy demand. These estimates enable evidence-based logistical planning, budgeting, and strengthening of referral networks. For district- and provincial-level policymakers, the results of this study provide a rationale for integrating colorectal carcinoma screening into the existing service packages of Posbindu PTM and Posyandu Lansia and for preparing referral endoscopy capacity.

The benefit for the community is increased awareness of the importance of early detection of colorectal carcinoma and the availability of access to non-invasive screening close to their place of residence. For future researchers, this study provides a methodological framework and working hypotheses that can be tested in a prospective cohort design with colonoscopic confirmation as the gold standard.

### **Research Hypotheses**

The first null hypothesis states that the prevalence of positive fecal occult blood test results in the screened population does not differ from the pooled positivity rate of global screening programs of 7.28%. The alternative hypothesis states that the prevalence in this population differs significantly from this reference rate.<sup>20</sup>

The second null hypothesis states that there is no association between sex and a positive fecal occult blood test result. The alternative hypothesis, based on consistent evidence of higher fecal hemoglobin concentrations in men, states that the prevalence of positive results is higher in men than in women.<sup>37,38,39</sup>

The third null hypothesis states that there is no association between age and a positive fecal occult blood test result. The alternative hypothesis states that the prevalence of positive results increases with advancing age. The fourth null hypothesis states that there is no heterogeneity in the prevalence of positive results across villages/urban wards in the catchment area of Tomoni Primary Health Center, whereas the alternative hypothesis states that there is significant geographical variation. All hypotheses were tested two-sided at a 5% significance level.<sup>41,46</sup>

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## METHODS

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### Study Design

This was an analytical observational study with a population-based cross-sectional design utilizing data from a colorectal carcinoma screening program conducted by the Technical Implementation Unit (UPTD) of Tomoni Primary Health Center. A cross-sectional design was selected because the primary aim of the study was to estimate the prevalence of positive fecal occult blood test results at a single point in time and to examine the association between demographic characteristics and screening outcomes, rather than to assess incidence or temporal cause-and-effect relationships. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies.

### Study Setting and Period

The study was conducted throughout the catchment area of UPTD Tomoni Primary Health Center, East Luwu Regency, South Sulawesi Province, which comprises twelve villages and one urban ward, namely Bayondo, Bangun Karya, Tadulako, Lestari, Beringin Jaya, Mulyasri, Bangun Jaya, Mandiri, Kalpataru, Rantemario, Ujung Baru, and Sumber Alam villages, and Tomoni urban ward (Kelurahan Tomoni). The area is predominantly agrarian with an ethnically heterogeneous population, comprising both indigenous Sulawesi inhabitants and transmigrant settlers, and

endoscopy services are available only at district- or provincial-level referral facilities. Data were collected during the period in which the screening program was being conducted.

### **Population and Sample**

The target population comprised all average-risk adult residents of the catchment area of Tomoni Primary Health Center. The accessible population comprised adult residents registered with and actively participating in Posbindu PTM and/or Posyandu Lansia activities in the twelve villages and one urban ward. The study sample comprised all participants who met the eligibility criteria, consented to participate, and successfully submitted an adequate stool specimen for examination during the study period.

Total sampling of all screening program participants meeting the inclusion criteria was employed; hence, neither randomization nor quota restriction per village was applied other than the available logistical testing capacity. This approach reflects the nature of the study as a service program evaluation rather than an experimental trial. The final sample size successfully analyzed was 181 participants.

### **Inclusion and Exclusion Criteria**

The inclusion criteria were: (1) adults residing in the catchment area of Tomoni Primary Health Center; (2) average risk for colorectal carcinoma, defined as no prior history of colorectal carcinoma, no history of confirmed adenomatous polyps, and no history of established inflammatory bowel disease; (3) no overt gastrointestinal bleeding in the form of hematochezia or melena within the preceding six months; (4) willingness to participate in the screening program and provision of informed consent; and (5) ability to submit a stool specimen independently or with the assistance of a companion.

The exclusion criteria were: (1) participants with alarm symptoms requiring direct diagnostic referral without screening, such as overt rectal bleeding, significant unintentional weight loss, or a palpable abdominal mass; (2) participants with a complete colonoscopy within a period still valid according to the surveillance interval; (3) female participants menstruating at the time of specimen collection, who were rescheduled at least three days after the end of menstruation; (4) participants with severe medical conditions rendering diagnostic follow-up infeasible; and (5)

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specimens unsuitable for examination owing to inadequate volume, contamination with urine or water, or delayed submission beyond the assay stability limit.

### Study Variables and Operational Definitions

The dependent variable was the fecal occult blood test result, dichotomized as positive or negative based on interpretation of the test strip according to the manufacturer's instructions. The independent variables were age, sex, and village/urban ward of origin. The operational definition of each variable is presented in Table 1.

**Table 1. Operational definitions of study variables**

| Variable                       | Operational definition                                                                                                                                                                          | Measurement method                                                                  | Scale                                                                                                |
|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Fecal occult blood test result | Detection of hemoglobin in the stool specimen above the detection threshold of the test device used; considered positive when a test line appeared according to the manufacturer's instructions | Laboratory examination at the primary health center by a trained laboratory analyst | Dichotomous nominal (positive/negative)                                                              |
| Age                            | Participant's age in completed years at the time of specimen collection, verified against civil registration documents                                                                          | Interview and verification of identity card                                         | Ratio; categorized as <50, 50–59, 60–69, 70–79, and ≥80 years, and dichotomized as <60 and ≥60 years |
| Sex                            | Participant's biological sex as recorded in civil registration documents                                                                                                                        | Observation and verification of identity card                                       | Dichotomous nominal (male/female)                                                                    |
| Village/urban                  | Administrative area in which                                                                                                                                                                    | Participant                                                                         | Nominal (13                                                                                          |

|      |                                                                                 |                        |             |
|------|---------------------------------------------------------------------------------|------------------------|-------------|
| ward | the participant resided and attended Posbindu PTM or Posyandu Lansia activities | registration by cadres | categories) |
|------|---------------------------------------------------------------------------------|------------------------|-------------|

Note: Age grouping follows the decade-based grouping commonly used in colorectal carcinoma screening programs, with a dichotomous cut-off of 60 years representing the target age threshold of organized screening programs in most Asia-Pacific countries.

## Data Collection Procedures

### Community Mobilization Phase

Participant mobilization was carried out through the empowerment of two existing community-based health platforms, namely Posbindu PTM and Posyandu Lansia. These platforms were selected because both already possess a structure of trained cadres, regular monthly activity schedules, participant databases, and social legitimacy at the village level, enabling them to function as recruitment channels at low marginal cost. A face-to-face recruitment approach through community cadres was chosen because a scoping review of colorectal carcinoma screening implementation in low- and middle-income countries showed that face-to-face strategies, either alone or in combination, consistently achieved coverage above 65%.<sup>22,28,29</sup>

Posbindu PTM and Posyandu Lansia cadres received training on the basic concepts of colorectal carcinoma, the rationale for screening, participant eligibility criteria, correct stool specimen collection procedures, and communication skills to address cultural barriers related to stool specimen collection. The training was delivered by medical personnel and primary health center laboratory analysts using lectures, demonstrations, and return demonstrations. The cadres subsequently conducted outreach during routine Posbindu and Posyandu Lansia activities, delivered group health education, performed initial eligibility screening, distributed specimen containers with pictorial instructions, and scheduled specimen return.<sup>25,28</sup>

### Specimen Collection and Examination Phase

Participants were instructed to collect a stool specimen independently at home in the morning using the clean container provided, with emphasis on avoiding contamination with urine or water. Specimens were returned to the cadres or directly to the primary health center laboratory on

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the same day and examined as soon as possible to minimize hemoglobin degradation, given that delayed specimen submission has been shown to increase the proportion of false-negative results. Specimens that could not be examined immediately were stored at a controlled temperature in accordance with the test manufacturer's instructions.<sup>74</sup>

Fecal occult blood testing was performed at the laboratory of UPTD Tomoni Primary Health Center by trained laboratory analysts using a rapid test device. Results were interpreted visually within the reading time window specified by the manufacturer. A test was considered positive when lines appeared in both the test and control zones, negative when a line appeared only in the control zone, and invalid when the control line failed to appear. All invalid tests were repeated using a new test device on the same specimen.

It should be emphasized that the choice of test modality has important methodological implications for the positivity rate. Immunochemical tests are specific for human globin and are therefore unaffected by dietary peroxidases or by blood from the upper gastrointestinal tract, whose globin has been denatured, whereas guaiac-based tests detect the pseudoperoxidase activity of heme and are thus more susceptible to false-positive results due to consumption of red meat and certain vegetables. A randomized comparison in a screening population showed a positivity rate of 2.4% for the guaiac test compared with 5.5% for the immunochemical test. Furthermore, qualitative immunochemical tests have a much higher positivity rate than quantitative immunochemical tests at conventional thresholds, namely 12.86% versus 5.87%, with a lower positive predictive value for carcinoma. Performance differences between brands of immunochemical test devices are also substantial, with up to a fourfold variation in positivity rates, ranging from 3.9% to 16.4%.<sup>31,32,33,34</sup>

### **Management of Results Phase**

Participants with negative results received an explanation of the meaning of the result, the limitations of the test including the possibility of a false-negative result, and advice on periodic repeat screening in accordance with the program protocol. Participants with positive results received individual counseling, an explanation that a positive result does not constitute a diagnosis of malignancy, and referral for colonoscopic evaluation at the available referral facility. Participants with positive results were also assessed for gastrointestinal complaints, a history of hemorrhoids, a

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history of peptic ulcer, and the use of non-steroidal anti-inflammatory drugs and anticoagulants as part of further clinical assessment. It should be stressed that fecal occult blood testing is validated only as a population screening tool and not as a diagnostic tool for clinical indications such as iron deficiency anemia, since a systematic review showed a sensitivity of only 0.58 for predicting the cause of iron deficiency anemia on endoscopic examination. The complete participant flow is presented in Figure 1.<sup>53</sup>

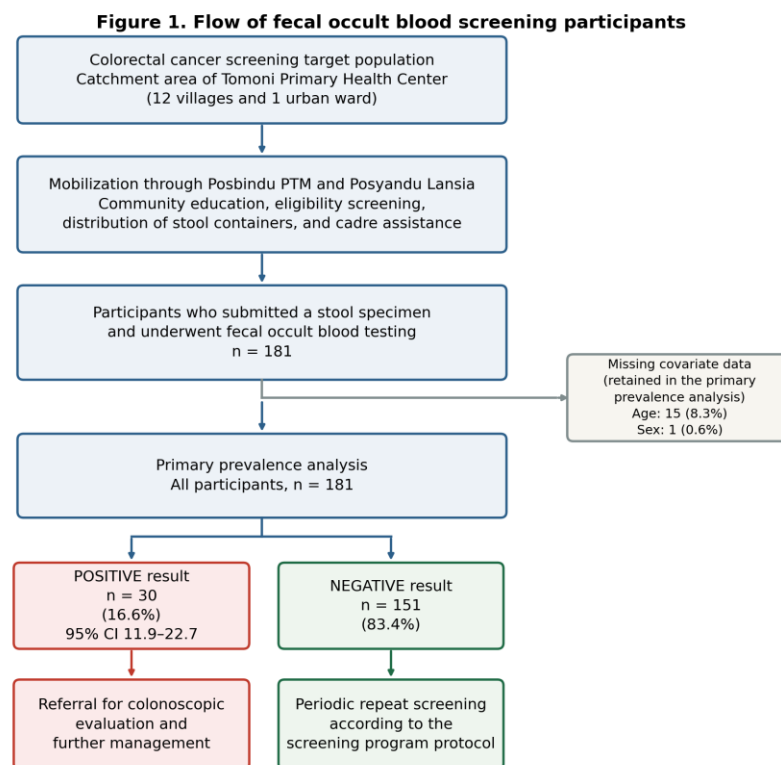


Figure 1. Flow diagram of participants in fecal occult blood screening in the catchment area of Tomoni Primary Health Center. Mobilization was carried out through the empowerment of Posbindu PTM and Posyandu Lansia in twelve villages and one urban ward. All 181 participants who submitted adequate specimens were included in the primary prevalence analysis without exclusion, including those with incomplete covariate data.

## Data Management

Primary test result data were recorded on village-specific registration forms containing name, age, sex, and test result, and were subsequently tabulated into separate electronic spreadsheet files for each village. All files were merged into a single analytical database with the addition of a village identification variable. Data cleaning included standardization of result category entries (removal of excess spaces and standardization of capitalization), verification of plausible age ranges, and identification of invalid sex entries. One sex entry consisting of an uninterpretable character was coded as missing. All participant names were removed from the analytical database and replaced with sequential identification numbers before analysis.

Missing data were handled using an available-case analysis approach. Age data were missing for 15 participants (8.3%) and sex data for 1 participant (0.6%). All participants, including those with incomplete covariate data, were retained in the primary prevalence analysis because the outcome variable was complete for all 181 participants. Analyses involving age and sex were performed on the subset with complete data, and the consistency of results was examined through sensitivity analysis comparing prevalence estimates in the full population and the complete-case population.

### **Statistical Analysis**

All statistical analyses were performed using Python version 3.12 with the pandas, NumPy, SciPy, statsmodels, and scikit-learn libraries. The significance level was set at  $\alpha = 0.05$  with two-sided testing. Categorical variables are presented as frequencies and percentages, whereas numerical variables are presented as mean with standard deviation if normally distributed, or median with interquartile range if not normally distributed. The normality of the age distribution was assessed using the Shapiro–Wilk test, supplemented by examination of the skewness and kurtosis coefficients.

The prevalence of positive results was calculated as the proportion of participants with positive results among all participants tested. The 95% confidence intervals were calculated using three comparative methods, namely the Wilson score method as the primary estimator owing to its superior performance for moderate proportions with moderate sample sizes, the Wald normal approximation method, and the Clopper–Pearson exact method. Given that participants were

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recruited in clusters by village, the cluster design effect was quantified by means of the intraclass correlation coefficient calculated using the analysis of variance method, and an alternative design effect–corrected confidence interval is presented as a sensitivity analysis.

Comparisons of prevalence between categorical groups were performed using Pearson's chi-square test with Yates' continuity correction for 2×2 tables, and Fisher's exact test when more than 20% of cells had an expected frequency of less than five. The strength of association was expressed as odds ratios and prevalence ratios with 95% confidence intervals calculated using the Woolf method. The effect size for 2×2 tables was expressed as the phi coefficient. The trend in prevalence across ordered age categories was tested using the Cochran–Armitage test for trend with linear score weighting.

The age distribution between the positive and negative result groups was compared using the Mann–Whitney test as the primary analysis, supplemented by Welch's t-test as a parametric comparator and Levene's test to assess equality of variances. Effect sizes were expressed as Cohen's *d* and bias-corrected Hedges' *g*. The discriminative ability of age for a positive result was evaluated using receiver operating characteristic curve analysis, with calculation of the area under the curve and its 95% confidence interval using the Hanley–McNeil method.

Multivariable analysis was performed using binary logistic regression with a positive result as the outcome variable and age and sex as predictors. Model adequacy was assessed using the likelihood ratio test, McFadden's pseudo- $R^2$ , the Akaike information criterion, and the Hosmer–Lemeshow goodness-of-fit test based on deciles of predicted probability. As a complementary analysis free from functional-form assumptions, age-stratified odds ratios were calculated using the Mantel–Haenszel method with Robins–Breslow–Greenland standard errors, and the interaction between sex and age group was tested using a product term in the logistic model.

Heterogeneity in prevalence across villages/urban wards was evaluated using an overall chi-square test, a permutation test with 20,000 iterations to overcome the limitations of asymptotic approximation in tables with small expected frequencies, and Cochran's *Q* statistic and the  $I^2$  index calculated on the logit scale with Haldane–Anscombe continuity correction. The fit of the

distribution of positive cases across villages to a homogeneous binomial distribution was assessed using a chi-square goodness-of-fit test and the variance-to-mean ratio.

The precision of the prevalence estimate was expressed as the half-width of the 95% confidence interval and mapped against various sample sizes. Post-hoc statistical power for the between-sex comparison was calculated using Cohen's h effect size for proportions. In addition, a scenario analysis was performed that translated the number of positive results into the projected number of lesions expected to be detected at confirmatory colonoscopy, using three levels of positive predictive value derived from the global literature: a low positive predictive value scenario reflecting community-based settings in low- and middle-income countries, an intermediate scenario, and a high scenario reflecting well-established organized programs. The number needed to screen was calculated as the reciprocal of the detection rate.<sup>20,21,36</sup>

### **Research Ethics**

This study constitutes an analysis of data from a public health service program conducted within the framework of the primary health center's core duties and functions. All participants received a verbal explanation of the purpose, procedures, benefits, and limitations of the examination before consenting to participate. Data confidentiality was maintained through removal of personal identifiers from the analytical database. All participants with positive results received counseling and referral in accordance with service standards at no additional cost, in line with the principle that screening can be ethically justified only when a follow-up pathway is available.

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## **RESULTS**

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### **Characteristics of Screening Participants**

A total of 181 participants from twelve villages and one urban ward in the catchment area of Tomoni Primary Health Center submitted adequate stool specimens and underwent fecal occult blood testing. Twelve areas contributed fifteen participants each, whereas Lestari Village contributed only one participant; its contribution to the area-stratified analysis was therefore limited. Age data were available for 166 participants (91.7%) and sex data for 180 participants (99.4%). Missing age data were concentrated in Bangun Karya Village (14 participants) and Lestari Village (1 participant), reflecting limitations in administrative record-keeping in the field

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than a pattern of missingness related to the test outcome. The complete participant characteristics are presented in Table 2.

**Table 2. Demographic characteristics of fecal occult blood screening participants (N = 181)**

| Characteristic                     | Value            | Percentage / distribution |
|------------------------------------|------------------|---------------------------|
| <b>Number of participants</b>      | <b>181</b>       | <b>100.0%</b>             |
| Age (years), n with available data | 166              | 91.7% of all participants |
| Mean $\pm$ standard deviation      | 63.7 $\pm$ 7.0   | —                         |
| Median (interquartile range)       | 63.0 (60.0–68.0) | —                         |
| Range (minimum–maximum)            | 46–83            | —                         |
| Skewness coefficient               | 0.164            | Approximately symmetrical |
| Shapiro–Wilk normality test        | W = 0.985        | p = 0.081                 |
| <b>Age group (n = 166)</b>         |                  |                           |
| <50 years                          | 4                | 2.4%                      |
| 50–59 years                        | 34               | 20.5%                     |
| 60–69 years                        | 96               | 57.8%                     |
| 70–79 years                        | 28               | 16.9%                     |
| $\geq 80$ years                    | 4                | 2.4%                      |
| $\geq 50$ years (screening target) | 162              | 97.6%                     |
| $\geq 60$ years                    | 128              | 77.1%                     |
| <b>Sex (n = 180)</b>               |                  |                           |
| Male                               | 91               | 50.6%                     |
| Female                             | 89               | 49.4%                     |
| Male : female ratio                | 1.02 : 1         | —                         |
| Age of men (mean $\pm$ SD)         | 63.9 $\pm$ 6.4   | n = 89                    |
| Age of women (mean $\pm$ SD)       | 63.4 $\pm$ 7.6   | n = 77; p = 0.429         |
| <b>Area of origin</b>              |                  |                           |

|                                |    |                              |
|--------------------------------|----|------------------------------|
| Number of villages/urban wards | 13 | 12 villages and 1 urban ward |
| Participants per area (mode)   | 15 | 12 of 13 areas               |
| <b>Missing data</b>            |    |                              |
| Age                            | 15 | 8.3%                         |
| Sex                            | 1  | 0.6%                         |
| Test result                    | 0  | 0.0%                         |

Note: SD = standard deviation. Age was compared between men and women using the Mann–Whitney test. Percentages for age groups were calculated relative to the 166 participants with available age data.

The mean age of participants was 63.7 years with a standard deviation of 7.0 years, a median of 63.0 years, and an interquartile range of 60.0 to 68.0 years. Participant age ranged from 46 to 83 years. The Shapiro–Wilk test did not reject the hypothesis of normality ( $W = 0.985$ ;  $p = 0.081$ ), and a skewness coefficient of 0.164 confirmed an approximately symmetrical distribution; thus, parametric and non-parametric analyzes could be applied equivalently. A total of 162 participants (97.6% of those with age data) were aged 50 years or older and 128 participants (77.1%) were aged 60 years or older, indicating that mobilization through Posbindu PTM and Posyandu Lansia successfully reached the screening target age group as recommended by the Asia-Pacific consensus. The age distribution of participants is shown in Figure 3, panel A.<sup>17</sup>

The sex composition of participants was nearly balanced, with 91 men (50.6%) and 89 women (49.4%), yielding a ratio of 1.02 to 1. This balance is a noteworthy finding, since Posbindu PTM activities in Indonesia have historically been dominated by female participants, with proportions reaching 80% to 86% in previous multiprovincial studies. The age distribution did not differ significantly between men ( $63.9 \pm 6.4$  years) and women ( $63.4 \pm 7.6$  years) ( $p = 0.429$ ); therefore, the between-sex comparison of prevalence was not threatened by imbalanced age confounding.<sup>24,25</sup>

### Prevalence of Positive Fecal Occult Blood Test Results

Of the 181 participants tested, 30 had positive results and 151 had negative results, yielding a prevalence of positive fecal occult blood test results of 16.57%, or 16.6% when rounded. The 95% confidence interval estimated using the Wilson score method as the primary estimator was 11.86% to 22.67%. The Wald normal approximation method yielded an interval of 11.17% to 21.98%, whereas the Clopper–Pearson exact method yielded an interval of 11.47% to 22.81%. The concordance of these three methods indicates that the estimate is robust and independent of the choice of computational approach. The prevalence estimate and all its confidence intervals are presented in Table 3 and visualized in Figure 2.

**Table 3. Prevalence of positive fecal occult blood test results with 95% confidence intervals according to various estimation methods (N = 181)**

| Parameter                                 | Estimate     | Lower limit<br>of 95% CI | Upper limit<br>of 95% CI | Interval<br>width |
|-------------------------------------------|--------------|--------------------------|--------------------------|-------------------|
| Number of positive results                | 30           | —                        | —                        | —                 |
| Number of negative results                | 151          | —                        | —                        | —                 |
| <b>Prevalence of positive results (%)</b> | <b>16.57</b> |                          |                          |                   |
| Wilson score method (primary)             | 16.57        | 11.86                    | 22.67                    | 10.81             |
| Wald method (normal approximation)        | 16.57        | 11.17                    | 21.98                    | 10.81             |
| Clopper–Pearson exact method              | 16.57        | 11.47                    | 22.81                    | 11.34             |
| Cluster design effect–corrected           | 16.57        | 11.16                    | 21.99                    | 10.83             |
| Half-width of 95% CI (percentage points)  | ± 5.41       | —                        | —                        | —                 |
| Inter-village intraclass                  | –0.050       | —                        | —                        | Assumed           |

| correlation coefficient                       |      |   |   | to be zero |
|-----------------------------------------------|------|---|---|------------|
| Design effect                                 | 1.00 | — | — | —          |
| Effective sample size                         | 180  | — | — | —          |
| Number needed to screen per 1 positive result | 6.03 | — | — | —          |

Note: CI = confidence interval. The intraclass correlation coefficient was calculated using the analysis of variance method and had a small negative value, which in practical terms indicates the absence of positive within-cluster correlation; this value was truncated at zero in the design effect calculation.

**Figure 2. Prevalence of positive fecal occult blood test results (N = 181)**

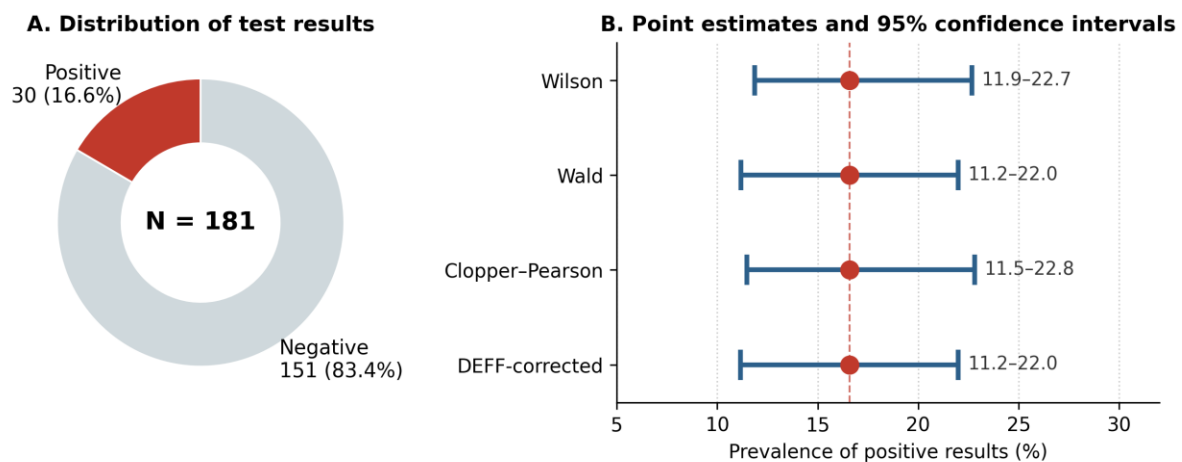


Figure 2. Prevalence of positive fecal occult blood test results among 181 screening participants. Panel A shows the distribution of test results. Panel B compares the point estimates and 95% confidence intervals calculated using the Wilson score method, the Wald normal approximation, the Clopper–Pearson exact method, and the cluster design effect correction. All four approaches yielded nearly identical intervals, indicating the robustness of the estimate.

The inter-village intraclass correlation coefficient was  $-0.050$ , a small negative value, which in practical terms means that within-village variation in results was not smaller than between-village variation and that there was no meaningful positive clustering. Consequently, the design

effect was 1.00 and the effective sample size was practically equivalent to the nominal sample size, namely 180. The design effect–corrected confidence interval (11.16% to 21.99%) did not differ substantially from the Wilson interval; hence, village-based recruitment did not introduce any inflation of uncertainty requiring correction. The precision achieved for the estimate was  $\pm 5.41$  percentage points.

From an operational perspective, a prevalence of 16.57% means that approximately six individuals need to be screened to obtain one positive result requiring further evaluation. This figure has direct implications for workload planning of referral services, as elaborated further in the scenario analysis subsection.

### Association between Age and Positive Test Results

Analysis of age as a continuous variable showed no difference between the positive and negative result groups. Participants with positive results had a mean age of  $63.6 \pm 7.6$  years with a median of 62.5 years (interquartile range 60.0–67.3), whereas participants with negative results had a mean age of  $63.7 \pm 6.9$  years with a median of 63.0 years (interquartile range 60.0–68.0). The Mann–Whitney test found no significant difference ( $U = 1,910.5$ ;  $p = 0.928$ ), nor did Welch's t-test as a parametric comparator ( $t = -0.061$ ; degrees of freedom 36.5;  $p = 0.951$ ). Levene's test confirmed equality of variances between groups ( $p = 0.750$ ). The calculated effect sizes were negligible, with a Cohen's  $d$  of  $-0.014$  and a bias-corrected Hedges'  $g$  of  $-0.014$ , well below the threshold for a small effect. The comparison of age distribution by test result is presented in Figure 3, panel B, and summarized in Table 4.

**Table 4. Comparison of age distribution between the positive and negative result groups (n = 166)**

| Age parameter                         | Positive result<br>(n = 28) | Negative<br>result (n =<br>138) | Statistical test                  | p value |
|---------------------------------------|-----------------------------|---------------------------------|-----------------------------------|---------|
| Mean $\pm$ standard deviation (years) | $63.6 \pm 7.6$              | $63.7 \pm 6.9$                  | Welch's $t = -0.061$<br>(df 36.5) | 0.951   |

|                              |                  |                  |                            |       |
|------------------------------|------------------|------------------|----------------------------|-------|
| Median (interquartile range) | 62.5 (60.0–67.3) | 63.0 (60.0–68.0) | Mann–Whitney U = 1,910.5   | 0.928 |
| Equality of variances        | —                | —                | Levene                     | 0.750 |
| Cohen's d                    | —                | —                | –0.014                     | —     |
| Hedges' g (bias-corrected)   | —                | —                | –0.014                     | —     |
| Area under the ROC curve     | —                | —                | 0.494 (95% CI 0.377–0.612) | 0.926 |

Note: df = degrees of freedom; ROC = receiver operating characteristic. The area under the curve of 0.494 is statistically indistinguishable from 0.500, which represents discriminative ability equivalent to random guessing.

**Figure 3. Age characteristics of screening participants**

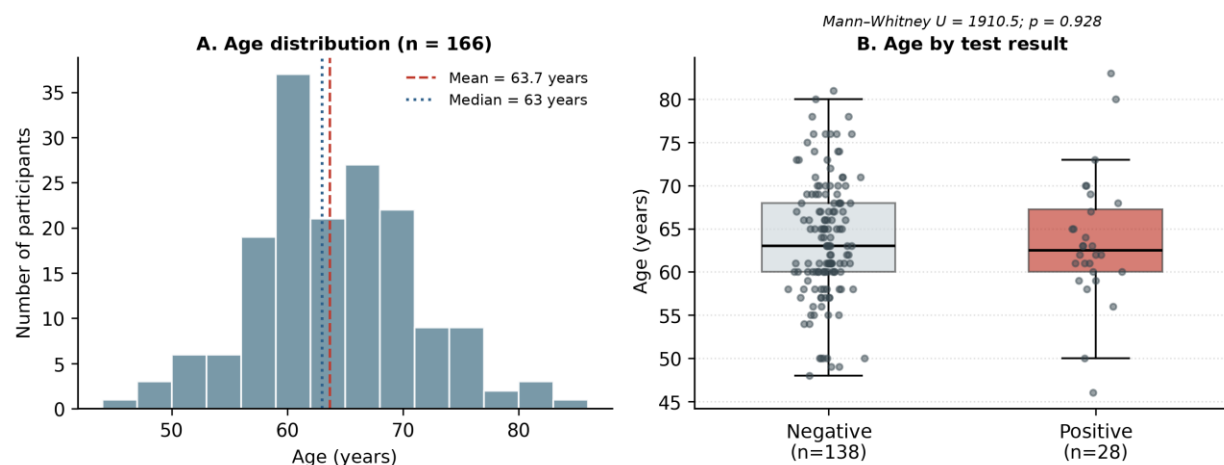


Figure 3. Age characteristics of screening participants. Panel A shows a histogram of the age distribution among the 166 participants with available age data, with markers for the mean and median. Panel B compares the age distribution between the negative and positive result groups with superimposed individual data points; there was no significant difference between the two groups.

Analysis of age as a categorical variable revealed a non-monotonic pattern. The prevalence of positive results was 25.0% in the age group below 50 years (1 of 4 participants), 14.7% in the

50–59-year group (5 of 34), 17.7% in the 60–69-year group (17 of 96), 10.7% in the 70–79-year group (3 of 28), and 50.0% in the group aged 80 years and older (2 of 4). The chi-square test found no significant difference across age groups ( $\chi^2 = 4.238$ ; degrees of freedom 4;  $p = 0.375$ ). It should be noted that 50% of cells in the contingency table had an expected frequency of less than five, particularly in the extreme age groups comprising only four participants each; the asymptotic  $p$  value should therefore be interpreted with caution. The apparently high prevalence in the age groups below 50 years and 80 years and older is entirely an artifact of the very small sample sizes, as reflected by the very wide confidence intervals of 4.6% to 69.9% and 15.0% to 85.0%, respectively.

**Table 5. Prevalence of positive fecal occult blood test results by age group (n = 166)**

| Age group (years)      | Number of participants | Positive results | Prevalence (%) | 95% Wilson CI (%)  |
|------------------------|------------------------|------------------|----------------|--------------------|
| <50                    | 4                      | 1                | 25.00          | 4.56–69.94         |
| 50–59                  | 34                     | 5                | 14.71          | 6.45–30.13         |
| 60–69                  | 96                     | 17               | 17.71          | 11.36–26.54        |
| 70–79                  | 28                     | 3                | 10.71          | 3.71–27.20         |
| $\geq 80$              | 4                      | 2                | 50.00          | 15.00–85.00        |
| <b>Total</b>           | <b>166</b>             | <b>28</b>        | <b>16.87</b>   | <b>11.94–23.30</b> |
| <b>Dichotomization</b> |                        |                  |                |                    |
| <60                    | 38                     | 6                | 15.79          | 7.44–30.42         |
| $\geq 60$              | 128                    | 22               | 17.19          | 11.63–24.65        |

Note: Chi-square test across the five age groups  $\chi^2 = 4.238$ ; degrees of freedom 4;  $p = 0.375$ , with 50% of cells having an expected frequency of less than five. Cochran–Armitage test for trend  $Z = 0.279$ ;  $p = 0.780$ . The dichotomous comparison of  $\geq 60$  years versus  $< 60$  years yielded an odds ratio of 1.11 (95% CI 0.41–2.97); Fisher's exact test  $p = 1.000$ .

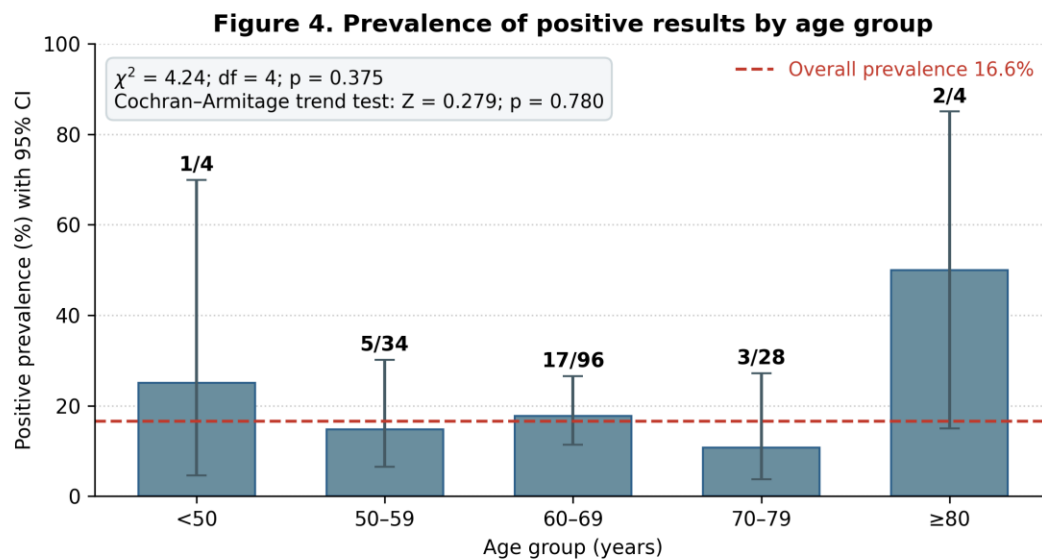


Figure 4. Prevalence of positive fecal occult blood test results by age group with 95% Wilson confidence intervals. The numbers above each bar indicate the number of positive results relative to the number of participants in that group. The horizontal dashed line indicates the overall prevalence. The very wide confidence intervals in the extreme age groups reflect the very small sample sizes in these two groups.

The Cochran–Armitage test for trend with linear score weighting found no directional trend in prevalence across ordered age groups ( $Z = 0.279$ ;  $p = 0.780$ ). Dichotomous analysis using a cut-off of 60 years likewise found no significant difference: the prevalence in participants aged 60 years and older was 17.19% (95% CI 11.63–24.65) compared with 15.79% (95% CI 7.44–30.42) in those younger than 60 years, with an odds ratio of 1.11 (95% CI 0.41–2.97) and Fisher's exact test  $p = 1.000$ . Receiver operating characteristic curve analysis confirmed the absence of discriminative ability of age for a positive result, with an area under the curve of 0.494 (95% CI 0.377–0.612;  $p = 0.926$ ), statistically indistinguishable from 0.500. The curve is presented in Figure 9.

### Association between Sex and Positive Test Results

The prevalence of positive results in men was 21.98% (20 of 91 participants; 95% Wilson CI 14.70–31.52), nearly twice that in women at 11.24% (10 of 89 participants; 95% Wilson CI 6.22–19.46). The absolute difference in prevalence was 10.74 percentage points. Pearson's chi-

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square test without continuity correction yielded  $\chi^2 = 3.738$  with  $p = 0.053$ , whereas with Yates' continuity correction it yielded  $\chi^2 = 3.005$  with  $p = 0.083$ . Fisher's exact test yielded  $p = 0.071$ . All three approaches lay at the threshold of conventional significance, indicating an association that was consistent in direction but did not reach statistical significance in the crude analysis. The minimum expected frequency in the contingency table was 14.8; hence, the assumptions of the chi-square test were fulfilled. Details of the analysis are presented in Table 6.

**Table 6. Distribution of fecal occult blood test results by sex and measures of association (n = 180)**

| Parameter                          | Male        | Female     | Measure of association (95% CI)    | p value |
|------------------------------------|-------------|------------|------------------------------------|---------|
| Number of participants             | 91          | 89         | —                                  | —       |
| Positive results, n                | 20          | 10         | —                                  | —       |
| Negative results, n                | 71          | 79         | —                                  | —       |
| Prevalence of positive results (%) | 21.98       | 11.24      | Difference 10.74 percentage points | —       |
| 95% Wilson CI of prevalence (%)    | 14.70–31.52 | 6.22–19.46 | —                                  | —       |
| <b>Pearson's chi-square test</b>   |             |            | $\chi^2 = 3.738$ (df 1)            | 0.053   |
| <b>Yates-corrected chi-square</b>  |             |            | $\chi^2 = 3.005$ (df 1)            | 0.083   |
| <b>Fisher's exact test</b>         |             |            | —                                  | 0.071   |
| <b>Odds ratio</b>                  |             |            | 2.23 (0.98–5.07)                   | 0.071   |
| <b>Prevalence ratio</b>            |             |            | 1.96 (0.97–3.94)                   | —       |
| <b>Phi coefficient</b>             |             |            | 0.144                              | —       |
| <b>Post-hoc statistical power</b>  |             |            | Cohen's h = 0.292; power = 50.0%   | —       |

Note: df = degrees of freedom. The minimum expected frequency of 14.8 fulfilled the assumptions of the chi-square test. One participant with invalid sex data was excluded from this analysis.

**Figure 5. Prevalence of positive results by sex and age stratum**

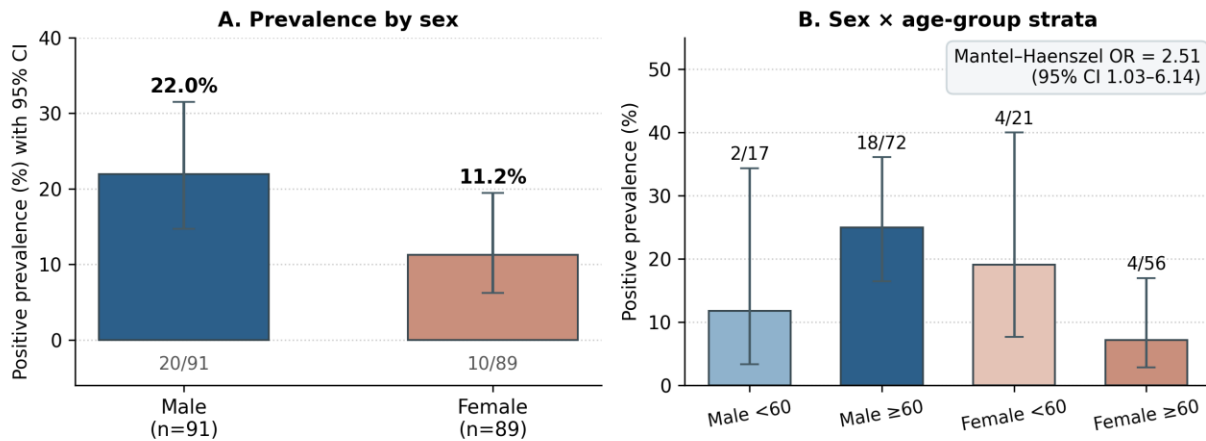


Figure 5. Prevalence of positive fecal occult blood test results by sex and age stratum. Panel A shows the comparison of prevalence between men and women with 95% Wilson confidence intervals. Panel B shows prevalence in four combined sex and age-group strata, demonstrating that the between-sex difference was most pronounced in the group aged 60 years and older.

The odds ratio for a positive result in men compared with women was 2.23 with a 95% confidence interval of 0.98 to 5.07, whereas the prevalence ratio was 1.96 with a 95% confidence interval of 0.97 to 3.94. A phi coefficient of 0.144 indicates a weak-to-moderate strength of association for categorical data. Post-hoc statistical power analysis revealed that, with a Cohen's h effect size of 0.292 and approximately 90 participants per group, this study had only 50.0% power to detect a difference of the magnitude observed. Approximately 184 participants per sex group, or 368 participants in total, would be required to achieve 80% power. This finding underscores that a p value lying just at the threshold of significance reflects the limited sample size rather than the absence of a true effect.

Analysis stratified by age group provided a clearer picture. In the stratum aged 60 years and older, the prevalence of positive results in men reached 25.00% (18 of 72 participants) compared

with only 7.14% (4 of 56 participants) in women, a difference of 17.86 percentage points. Conversely, in the stratum younger than 60 years this pattern was reversed, with a prevalence of 11.76% in men (2 of 17) and 19.05% in women (4 of 21), although both strata comprised small numbers of participants. The age-stratified Mantel–Haenszel pooled odds ratio was 2.51 with a 95% confidence interval of 1.03 to 6.14, which reached statistical significance. The test for interaction between sex and age group yielded an interaction odds ratio of 7.65 with  $p = 0.065$ ; thus, significant effect modification could not be concluded, although there was a directional indication. Details of the stratified analysis are presented in Table 7.

**Table 7. Prevalence of positive results by combined sex and age-group strata with Mantel–Haenszel analysis (n = 166)**

| Stratum                                | Number of participants | Positive results | Prevalence (%) | 95% Wilson CI (%) |
|----------------------------------------|------------------------|------------------|----------------|-------------------|
| Male, <60 years                        | 17                     | 2                | 11.76          | 3.29–34.34        |
| Male, ≥60 years                        | 72                     | 18               | 25.00          | 16.44–36.09       |
| Female, <60 years                      | 21                     | 4                | 19.05          | 7.67–40.00        |
| Female, ≥60 years                      | 56                     | 4                | 7.14           | 2.81–16.98        |
| <b>Odds ratio, &lt;60-year stratum</b> |                        |                  | <b>0.57</b>    | —                 |
| <b>Odds ratio, ≥60-year stratum</b>    |                        |                  | <b>4.33</b>    | —                 |
| <b>Mantel–Haenszel odds ratio</b>      |                        |                  | <b>2.51</b>    | <b>1.03–6.14</b>  |
| <b>Interaction term odds ratio</b>     |                        |                  | <b>7.65</b>    | $p = 0.065$       |

Note: The Mantel–Haenszel odds ratio was calculated with Robins–Breslow–Greenland standard errors. The interaction term was tested through the product of the sex and age-group variables in the binary logistic regression model. Confidence intervals for the separate strata are not displayed owing to instability arising from small cell frequencies.

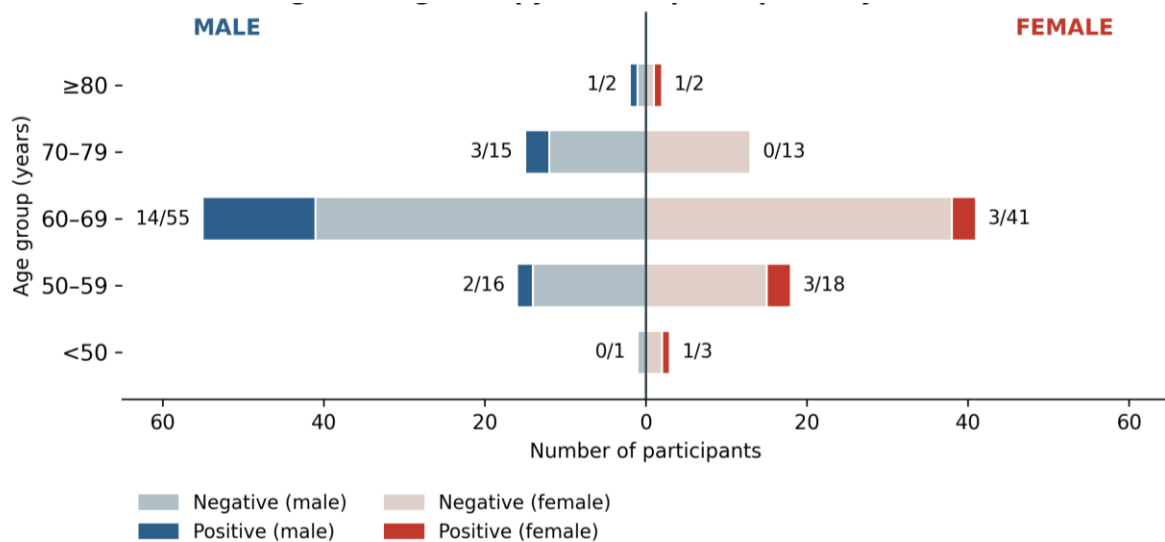


Figure 6. Age–sex pyramid of screening participants, color-coded by test result. The numbers on each bar indicate the number of positive results relative to the number of participants in that stratum. The concentration of positive results among men aged 60 to 69 years is prominent compared with women in the same age group.

### Geographical Variation in the Prevalence of Positive Results across Villages and Urban Wards

The prevalence of positive results ranged from 6.67% in Ujung Baru Village to 26.67% in Bangun Jaya Village, with Lestari Village having only one participant and no positive results. Twelve of the thirteen areas (92.3%) had at least one positive result, indicating that the findings were not concentrated in one or two particular areas but were evenly distributed throughout the primary health center's catchment area. Details of prevalence by area are presented in Table 8 and visualized as a forest plot in Figure 7.

**Table 8. Prevalence of positive fecal occult blood test results by village and urban ward (N = 181)**

| Village / Urban ward | Number of participants | Positive results | Negative results | Prevalence (%) | 95% Wilson CI (%)  |
|----------------------|------------------------|------------------|------------------|----------------|--------------------|
| Bangun Jaya          | 15                     | 4                | 11               | 26.67          | 10.90–51.95        |
| Beringin Jaya        | 15                     | 3                | 12               | 20.00          | 7.05–45.19         |
| Kalpataru            | 15                     | 3                | 12               | 20.00          | 7.05–45.19         |
| Mandiri              | 15                     | 3                | 12               | 20.00          | 7.05–45.19         |
| Mulyasri             | 15                     | 3                | 12               | 20.00          | 7.05–45.19         |
| Tadulako             | 15                     | 3                | 12               | 20.00          | 7.05–45.19         |
| Bangun Karya         | 15                     | 2                | 13               | 13.33          | 3.74–37.88         |
| Bayondo              | 15                     | 2                | 13               | 13.33          | 3.74–37.88         |
| Rantemario           | 15                     | 2                | 13               | 13.33          | 3.74–37.88         |
| Sumber Alam          | 15                     | 2                | 13               | 13.33          | 3.74–37.88         |
| Tomoni Urban Ward    | 15                     | 2                | 13               | 13.33          | 3.74–37.88         |
| Ujung Baru           | 15                     | 1                | 14               | 6.67           | 1.19–29.82         |
| Lestari              | 1                      | 0                | 1                | 0.00           | 0.00–79.35         |
| <b>Total</b>         | <b>181</b>             | <b>30</b>        | <b>151</b>       | <b>16.57</b>   | <b>11.86–22.67</b> |

Note: Chi-square test across areas  $\chi^2 = 3.575$ ; degrees of freedom 12;  $p = 0.990$ , with 53.8% of cells having an expected frequency of less than five; the permutation test with 20,000 iterations yielded  $p = 0.993$ . The heterogeneity test across the twelve areas with five or more participants yielded Cochran's  $Q = 2.77$ ; degrees of freedom 11;  $p = 0.993$ ;  $I^2 = 0.0\%$ . The variance-to-mean ratio of the number of positive cases per area was 0.255.

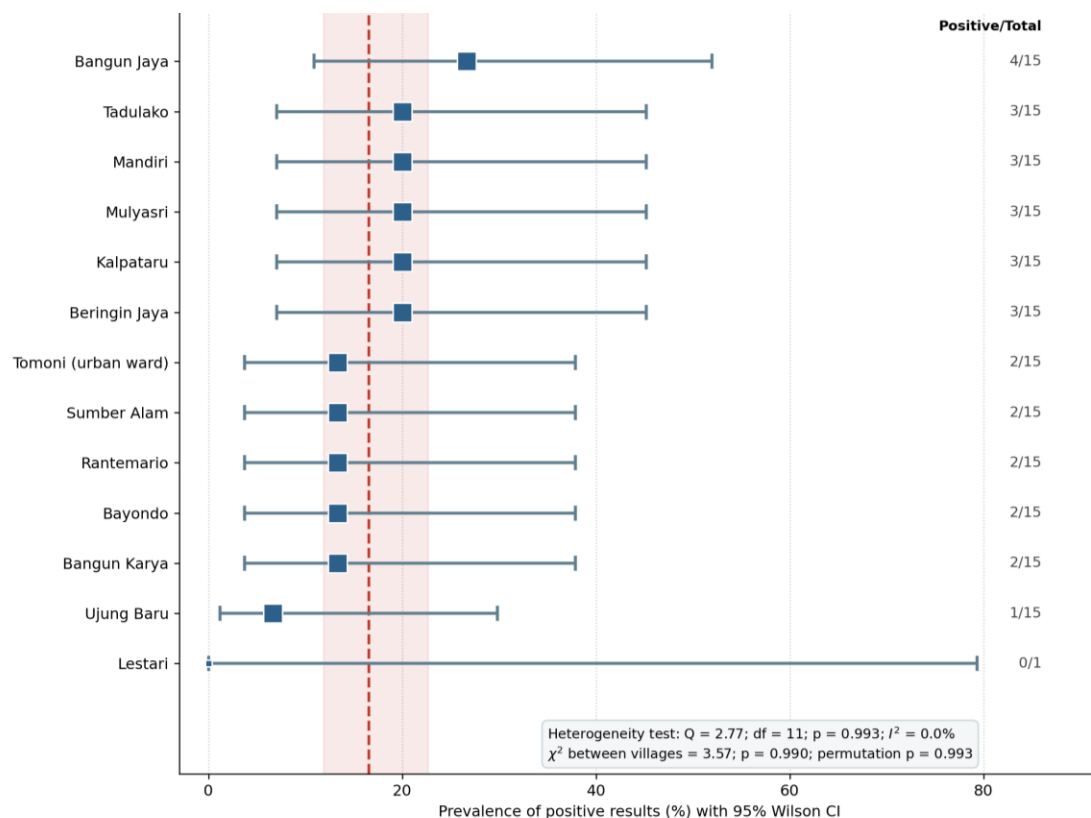


Figure 7. Forest plot of the prevalence of positive fecal occult blood test results by village and urban ward. Marker size is proportional to the number of participants. The vertical dashed line indicates the overall prevalence and the shaded band indicates the overall 95% confidence interval. All area-specific confidence intervals overlap with the overall estimate.

The chi-square test across areas found no significant difference ( $\chi^2 = 3.575$ ; degrees of freedom 12;  $p = 0.990$ ). Given that 53.8% of cells had an expected frequency of less than five, rendering the asymptotic approximation unreliable, a permutation test with 20,000 iterations was performed, which yielded  $p = 0.993$  and confirmed the same conclusion. Heterogeneity analysis across the twelve areas with five or more participants yielded a Cochran's Q statistic of 2.77 with 11 degrees of freedom and  $p = 0.993$ , and an  $I^2$  index of 0.0%, indicating that all between-area variation in prevalence could be fully explained by sampling error without requiring a between-area variance component. The goodness-of-fit test against a homogeneous binomial distribution yielded

$\chi^2 = 2.80$  with 11 degrees of freedom and  $p = 0.993$ , whereas the variance-to-mean ratio of the number of positive cases per area was 0.255, far below unity, indicating an underdispersed distribution rather than clustering.

The convergence of five different analytical approaches on the same conclusion provides high confidence that the prevalence of positive results is homogeneous across the entire catchment area of Tomoni Primary Health Center. The practical implication is that selective geographical targeting is not required when expanding the program, and screening resources can be allocated in proportion to the target population size in each village.

### **Multivariable Analysis of Determinants of Positive Results**

Binary logistic regression modeling was performed on the 166 participants with complete age and sex data. In this subset, the prevalence of positive results was 16.87% (95% CI 11.94–23.30), practically identical to the estimate in the full population, confirming that incomplete covariate data did not introduce meaningful selection bias into the prevalence estimate. The prevalence in men in this subset was 22.47% (20 of 89) and in women 10.39% (8 of 77).

The model incorporating age and sex simultaneously identified male sex as the sole independent predictor of a positive result, with a  $\beta$  coefficient of 0.919 (standard error 0.452), corresponding to an adjusted odds ratio of 2.51 (95% CI 1.03–6.08;  $p = 0.042$ ). Age made no predictive contribution, with a  $\beta$  coefficient of  $-0.004$  (standard error 0.031), an odds ratio of 1.00 per year (95% CI 0.94–1.06;  $p = 0.886$ ), and an odds ratio of 0.98 per five years (95% CI 0.72–1.33). The likelihood ratio test for the overall model yielded  $\chi^2 = 4.47$  with 2 degrees of freedom and  $p = 0.107$ , indicating that the model as a whole did not reach significance, although one of its predictors was significant. A McFadden pseudo- $R^2$  of 0.0296 indicates that the two demographic variables explained only a small proportion of the variation in the outcome, as is typical of models containing only demographic variables without clinical and behavioral variables. The Hosmer–Lemeshow goodness-of-fit test did not reject model fit ( $\chi^2 = 7.36$ ; degrees of freedom 8;  $p = 0.498$ ).

**Table 9. Binary logistic regression model of determinants of positive fecal occult blood test results (n = 166)**

| Variable                       | $\beta$<br>coefficient | Standard<br>error | Odds<br>ratio | 95% CI    | p value |
|--------------------------------|------------------------|-------------------|---------------|-----------|---------|
| <b>Univariable model</b>       |                        |                   |               |           |         |
| Male sex (reference: female)   | 0.916                  | 0.451             | 2.50          | 1.03–6.06 | 0.042   |
| Age (per 1 year)               | −0.002                 | 0.030             | 1.00          | 0.94–1.06 | 0.947   |
| <b>Multivariable model</b>     |                        |                   |               |           |         |
| Constant                       | −1.872                 | 1.996             | —             | —         | 0.348   |
| Male sex (reference: female)   | 0.919                  | 0.452             | 2.51          | 1.03–6.08 | 0.042   |
| Age (per 1 year)               | −0.004                 | 0.031             | 1.00          | 0.94–1.06 | 0.886   |
| Age (per 5 years)              | −0.022                 | 0.155             | 0.98          | 0.72–1.33 | 0.886   |
| <b>Model performance</b>       |                        |                   |               |           |         |
| Likelihood ratio test          | $\chi^2 = 4.47$        | df = 2            | —             | —         | 0.107   |
| McFadden pseudo-R <sup>2</sup> | 0.0296                 | —                 | —             | —         | —       |
| Akaike information criterion   | 152.2                  | —                 | —             | —         | —       |
| Hosmer–Lemeshow test           | $\chi^2 = 7.36$        | df = 8            | —             | —         | 0.498   |

Note: df = degrees of freedom. The odds ratio per five years was calculated by exponential transformation of five times the age coefficient. The Hosmer–Lemeshow test was computed based on deciles of predicted probability.

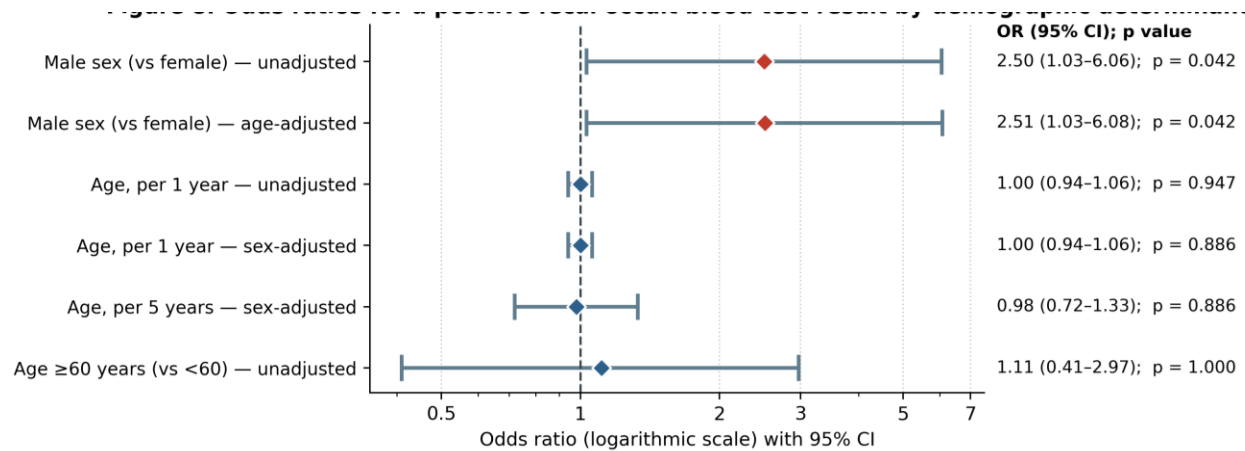


Figure 8. Forest plot of odds ratios for a positive fecal occult blood test result by demographic determinant on a logarithmic scale. Red markers indicate estimates whose intervals do not cross unity. Male sex was the only determinant to reach statistical significance, both before and after adjustment for age.

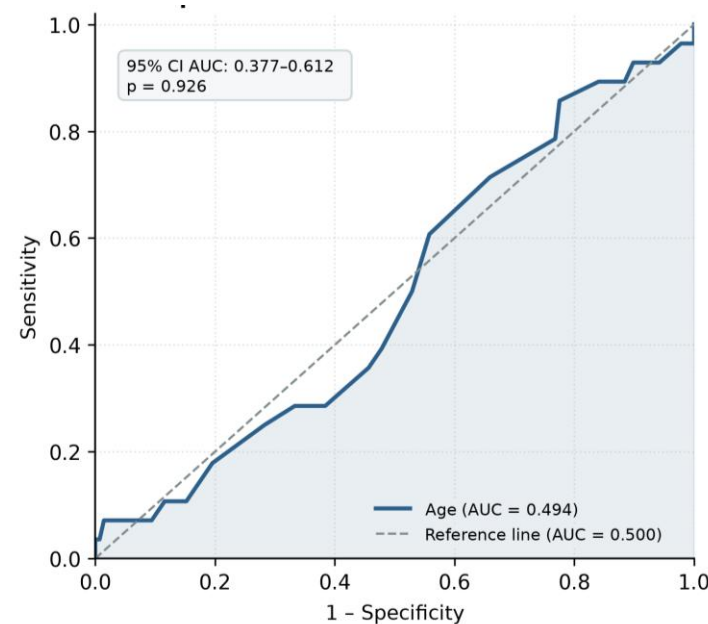


Figure 9. Receiver operating characteristic curve for age as a predictor of a positive fecal occult blood test result. The curve almost coincides with the diagonal reference line, with an area under the curve of 0.494, statistically indistinguishable from 0.500.

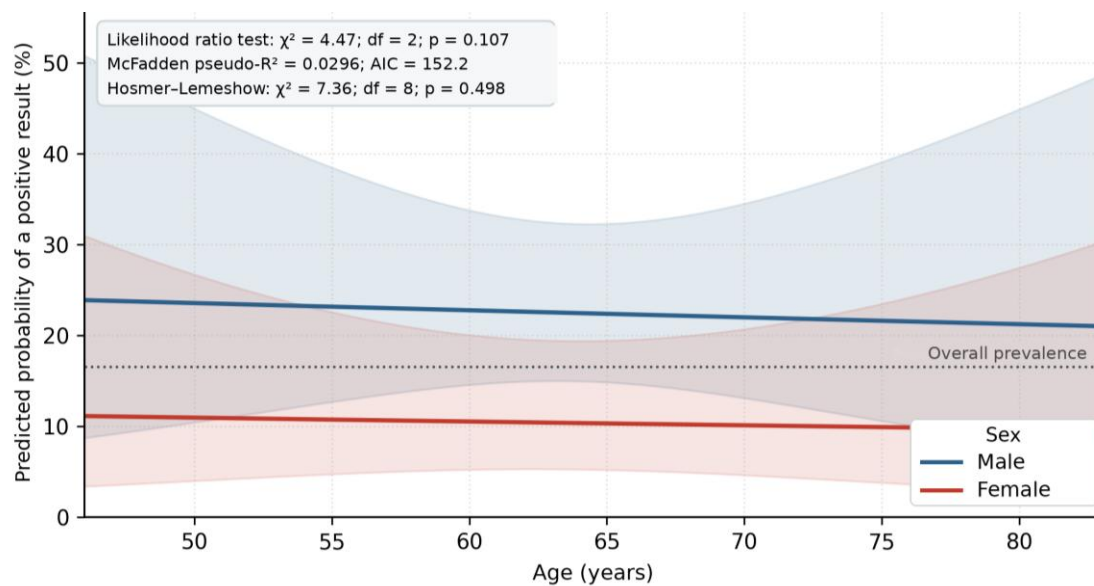


Figure 10. Predicted probability of a positive fecal occult blood test result by age and sex based on the binary logistic regression model, with 95% confidence interval bands. The curve for men lies consistently above that for women across the entire age range, whereas the slopes of both curves are practically flat, reflecting the absence of an age effect.

### Sensitivity Analysis and Robustness of Findings

A series of sensitivity analyzes was performed to test the robustness of the main findings to different analytical decisions. The prevalence estimates in the full population (16.57%) and in the complete-case subset (16.87%) differed by only 0.30 percentage points, with almost perfectly overlapping confidence intervals; hence, the handling of missing data did not affect the conclusions. Confidence interval estimation using four different approaches yielded limits differing by less than one percentage point. The association between sex and a positive result was consistent across five analytical approaches, namely the chi-square test, Fisher's exact test, univariable logistic regression, multivariable logistic regression, and stratified Mantel–Haenszel analysis. The absence of an association between age and a positive result was consistent across six approaches, namely the Mann–Whitney test, Welch's t-test, the chi-square test across groups, the Cochran–Armitage test for trend, receiver operating characteristic curve analysis, and logistic regression. A summary of all sensitivity analyzes is presented in Table 10.

**Table 10. Summary of sensitivity analyzes of the main findings**

| Aspect tested              | Alternative approach                | Result                                   | Conclusion                |
|----------------------------|-------------------------------------|------------------------------------------|---------------------------|
| Prevalence estimate        | Full population (N = 181)           | 16.57% (11.86–22.67)                     | Consistent                |
|                            | Complete-case subset (n = 166)      | 16.87% (11.94–23.30)                     | Consistent                |
| Confidence interval method | Wilson, Wald, Clopper–Pearson, DEFF | Difference in limits <1 percentage point | Robust                    |
| Village cluster effect     | Design effect correction            | DEFF = 1.00; effective n = 180           | No effect                 |
| Sex association            | Uncorrected chi-square              | p = 0.053                                | Threshold of significance |
|                            | Yates-corrected chi-square          | p = 0.083                                | Threshold of significance |
|                            | Fisher's exact test                 | p = 0.071                                | Threshold of significance |
|                            | Age-adjusted logistic regression    | OR 2.51 (1.03–6.08); p = 0.042           | Significant               |
|                            | Stratified Mantel–Haenszel          | OR 2.51 (1.03–6.14)                      | Significant               |
| Age association            | Mann–Whitney                        | p = 0.928                                | Not significant           |
|                            | Welch's t-test                      | p = 0.951                                | Not significant           |
|                            | Chi-square across five age groups   | p = 0.375                                | Not significant           |
|                            | Cochran–Armitage trend              | p = 0.780                                | Not significant           |
|                            | Area under the ROC                  | 0.494 (0.377–0.612)                      | Not significant           |

|                             |                                     |                                  |                |
|-----------------------------|-------------------------------------|----------------------------------|----------------|
|                             | curve                               |                                  |                |
| Inter-village heterogeneity | Asymptotic chi-square               | p = 0.990                        | Homogeneous    |
|                             | Permutation test, 20,000 iterations | p = 0.993                        | Homogeneous    |
|                             | Cochran's Q and I <sup>2</sup>      | p = 0.993; I <sup>2</sup> = 0.0% | Homogeneous    |
|                             | Variance-to-mean ratio              | 0.255                            | Underdispersed |

Note: DEFF = design effect; OR = odds ratio; ROC = receiver operating characteristic.

### Scenario Analysis of Downstream Diagnostic Burden

The thirty positive results identified require colonoscopic confirmation. Because endoscopic confirmation had not yet been performed at the time this study was prepared, projected colonoscopy yields were calculated through a scenario analysis using three levels of positive predictive value derived from the global literature. The low positive predictive value scenario adopted figures from a community-based study in low- and middle-income countries, namely 1.1% for invasive carcinoma and 7.0% for advanced adenoma. The intermediate scenario adopted intermediate values commonly reported by established screening programs, namely 3.5% for carcinoma and 15.0% for advanced neoplasia. The high scenario adopted the first-round figures of a large organized program, namely 5.1% for carcinoma and 20.4% for high-risk precursors. The projected results are presented in Table 11 and Figure 11.<sup>21,36</sup>

**Table 11. Projected confirmatory colonoscopy yield and diagnostic burden according to three positive predictive value scenarios**

| Parameter                                            | Low scenario | Intermediate scenario | High scenario |
|------------------------------------------------------|--------------|-----------------------|---------------|
| Positive predictive value for carcinoma (%)          | 1.1          | 3.5                   | 5.1           |
| Positive predictive value for advanced neoplasia (%) | 7.0          | 15.0                  | 20.4          |

|                                                            |      |      |      |
|------------------------------------------------------------|------|------|------|
| Estimated number of colorectal carcinomas detected         | 0.33 | 1.05 | 1.53 |
| Estimated number of advanced neoplasias detected           | 2.10 | 4.50 | 6.12 |
| Carcinoma detection rate per 1,000 participants            | 1.82 | 5.80 | 8.45 |
| Number needed to screen per 1 carcinoma                    | 548  | 172  | 118  |
| Number of colonoscopies required                           | 30   | 30   | 30   |
| Proportion of colonoscopies without advanced neoplasia (%) | 93.0 | 85.0 | 79.6 |

Note: Projections were calculated by multiplying the observed number of positive results (n = 30) by the reference positive predictive values. These figures are literature-based projections rather than direct observations and should therefore be interpreted as planning estimates, not as diagnostic findings of this study.

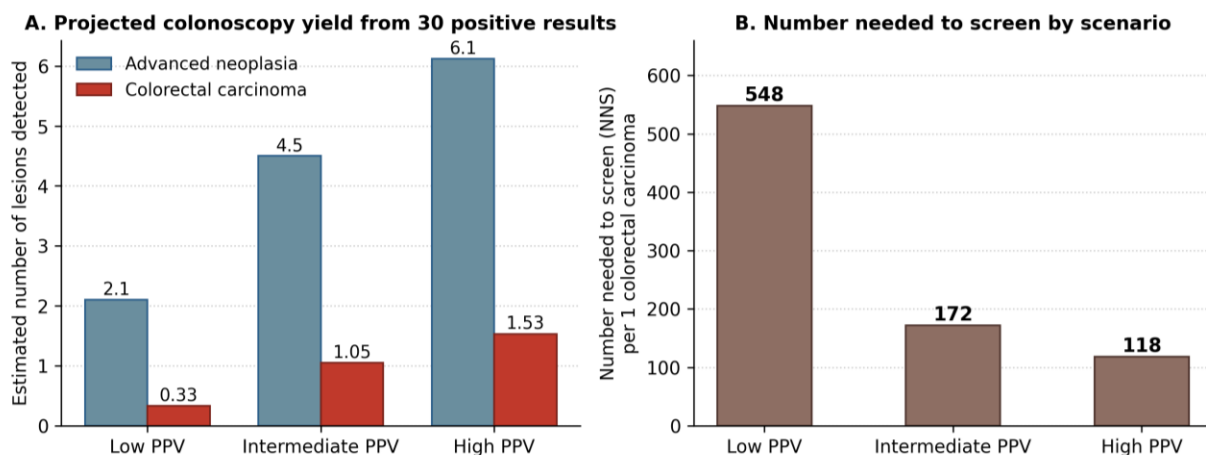


Figure 11. Scenario analysis of the diagnostic burden and expected yield from thirty positive results. Panel A shows the estimated numbers of advanced neoplasias and colorectal carcinomas expected

to be detected under three positive predictive value scenarios. Panel B shows the number needed to screen to detect one colorectal carcinoma under each scenario.

The wide range of projections, namely 0.33 to 1.53 carcinomas and 2.10 to 6.12 advanced neoplasias, reflects substantial uncertainty regarding the positive predictive value applicable to this population. Nevertheless, all scenarios converge on the same operational implication: a capacity of thirty confirmatory colonoscopies is required to complete one screening cycle for 181 participants, of which 79.6% to 93.0% are expected not to reveal advanced neoplasia. This ratio of colonoscopies to findings is a central consideration in program planning in settings with limited endoscopic capacity.

The precision and statistical power analyzes provide guidance for the design of further studies. With 181 participants, the precision achieved for the prevalence estimate was  $\pm 5.41$  percentage points. Achieving a precision of  $\pm 3.0$  percentage points at a prevalence of approximately 16.6% would require approximately 590 participants. Detecting a between-sex difference in prevalence of the magnitude observed in this study with 80% power would require approximately 184 participants per group, or 368 participants in total.

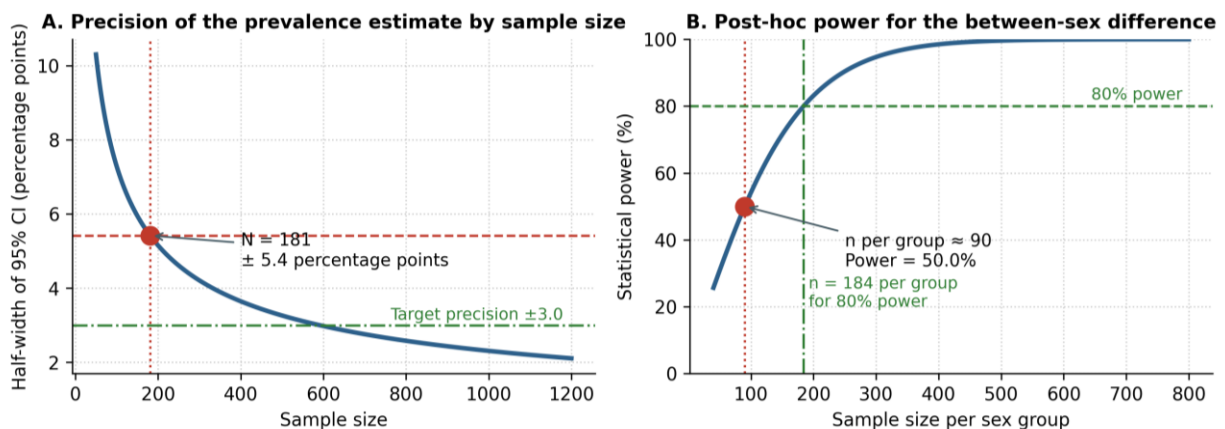


Figure 12. Precision of the estimate and statistical power of the study. Panel A shows the relationship between sample size and the half-width of the 95% confidence interval for a prevalence of 16.6%, with a marker indicating the position of the present study. Panel B shows the statistical

power curve for the between-sex comparison of prevalence, demonstrating that the power achieved in this study was only 50.0%.

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## DISCUSSION

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### Principal Findings

This study found that the prevalence of positive fecal occult blood test results in a community-based colorectal carcinoma screening program in the catchment area of Tomoni Primary Health Center was 16.57% (95% CI 11.86–22.67). This figure is well above the positivity rates reported by almost all organized screening programs in high-income countries. Male sex was the sole independent determinant of a positive result, with an adjusted odds ratio of 2.51, whereas age showed no association whatsoever with the test outcome, whether analyzed as a continuous, categorical, dichotomous, or ordered variable. Prevalence was homogeneous across the entire catchment area, with no evidence of geographical clustering. These three findings are discussed in turn in relation to the available literature.

### Positivity Rate in the Context of the Global Literature

A global systematic review and meta-analysis encompassing 93 studies with nearly 90 million person-tests reported a pooled fecal immunochemical test positivity rate of 7.28%, with an invalid test rate of 1.08% and a carcinoma detection rate of 0.28%. The positivity rate in the present study, 16.57%, is 2.3 times this pooled rate, and the lower limit of its confidence interval (11.86%) still lies above the global reference rate. A detailed comparison with various programs and studies is presented in Table 12.<sup>20</sup>

**Table 12. Comparison of fecal occult blood test positivity rates in the present study with selected literature**

| Source / setting                                        | Type of test       | Population                 | Positivity rate (%) |
|---------------------------------------------------------|--------------------|----------------------------|---------------------|
| Present study (Tomoni Primary Health Center, Indonesia) | Fecal occult blood | 181 community participants | 16.57               |

|                                                                   |                                   |                          |                |
|-------------------------------------------------------------------|-----------------------------------|--------------------------|----------------|
| Global meta-analysis of 93 studies                                | Fecal immunochemical              | ≈90 million person-tests | 7.28           |
| Netherlands, first round, threshold 10 µg Hb/g                    | Fecal immunochemical              | 10,008 invitees          | M 10.7; F 6.3  |
| Netherlands, randomized trial of two brands, threshold 10 µg Hb/g | Fecal immunochemical              | 19,291 participants      | 7.9 and 6.5    |
| Netherlands, randomized comparison                                | Guaiac vs immunochemical          | 20,623 participants      | 2.4 vs 5.5     |
| England, national pilot, threshold 20 µg Hb/g                     | Fecal immunochemical              | 40,930 invitees          | 7.8 (5.7–11.1) |
| Basque Country, Spain, threshold 20 µg Hb/g                       | Fecal immunochemical              | 444,582 invitees         | M 8.3; F 4.8   |
| Finland, sex-specific thresholds                                  | Fecal immunochemical              | 27,728 invitees          | M 2.8; F 2.4   |
| United States, five test brands                                   | Fecal immunochemical              | 3,761 participants       | 3.9–16.4       |
| China, qualitative–quantitative comparison                        | Fecal immunochemical              | 5,841 participants       | 12.86 vs 5.87  |
| Nigeria, community-based                                          | Qualitative immunochemical        | 2,109 participants       | 21.0           |
| Shanghai, China, community-based                                  | Occult blood + risk questionnaire | 809,528 participants     | 22.2           |
| Established program, first biennial round                         | Fecal immunochemical              | 2.81 million individuals | 5.8            |

Note: M = male; F = female; Hb = hemoglobin. The positivity rate in the Shanghai program encompasses combined fecal occult blood and risk assessment questionnaire screening and is therefore not fully comparable with stool-only screening.

There are at least five complementary explanations for the high positivity rate observed. The first, and probably the dominant, explanation is the characteristics of the test device used. The evidence on this point is compelling. A randomized comparison of five immunochemical test brands in 3,761 participants in the United States found a fourfold variation in positivity rates, from 3.9% to 16.4%, with sensitivity for advanced colorectal neoplasia ranging from 10.1% to 36.7% and specificity from 85.5% to 96.6%; the authors concluded that, although grouped as a single class, the various immunochemical tests cannot be regarded as interchangeable. A community-based study in China of 5,841 participants who underwent both types of test concurrently found a positivity rate of 12.86% for the qualitative test compared with 5.87% for the quantitative test at the conventional threshold, with a positive predictive value for carcinoma only half as high (3.20% versus 6.12%). Because qualitative rapid test devices are the most commonly available modality in primary health center laboratories in Indonesia, a positivity rate of 16.57% falls within the range that can be anticipated for this class of device.<sup>32,33</sup>

The second explanation relates to the age structure of participants, which was considerably older than that of organized program populations in general. The mean age of participants in this study was 63.7 years, with 77.1% aged 60 years or older, whereas European screening programs generally invite individuals aged 50 to 74 years, with a mean age of approximately 61 years and a much larger proportion of younger participants. The national pilot in England demonstrated a clear age gradient in positivity rates, ranging from 5.7% in women aged 59 to 64 years to 11.1% in men aged 70 to 75 years. An analysis of risk factors for false-positive results in the German program likewise found that age 65 years or older was associated with increased odds of a positive result, with an odds ratio of 1.27 (95% CI 1.01–1.59). Thus, the concentration of participants in older age groups structurally raises the aggregate positivity rate, although this is not reflected as an age gradient within the present study itself owing to the narrow age range of participants.<sup>35,45</sup>

The third explanation concerns the high prevalence of non-neoplastic gastrointestinal conditions that may cause occult bleeding in this population. A prospective analysis of 604,495 women participating in the English screening program found that fecal occult blood test positivity was associated not only with colorectal neoplasia but also with diverticular disease, inflammatory bowel disease, hemorrhoids, esophagitis, peptic ulcer, anemia, and other hematological disorders, with relative risks ranging from 2 to 5 for upper gastrointestinal and hematological abnormalities and 26.3 for inflammatory bowel disease. A classic study comparing bidirectional endoscopy in 248 patients with positive occult blood results found upper gastrointestinal lesions in a substantial proportion. In tropical settings with a high prevalence of *Helicobacter pylori* infection and peptic ulcer disease, the contribution of non-colorectal bleeding sources to positivity may be even greater; a study in Taiwan found that the *Helicobacter pylori* stool antigen test had a sensitivity of 52.5% for upper gastrointestinal lesions among participants with a negative immunochemical result, with a community positive predictive value of 31.9%. A systematic review of gastroscopy following a positive result with a normal colonoscopy, although not recommending routine upper endoscopy, noted a high proportion of abnormal findings in the form of gastric polyps and gastritis.<sup>48,49,50,51</sup>

The fourth explanation relates to participant factors that increase the likelihood of a positive result in the absence of neoplasia. A meta-analysis of 14 studies with 54,499 participants found that the use of non-steroidal anti-inflammatory drugs increased the risk of a false-positive result, with a relative risk of 1.16 (95% CI 1.06–1.27). An analysis in the German screening program of 4,656 participants with a normal colonoscopy found that apparently false-positive results were associated with male sex, age 65 years or older, a body mass index of 30 kg/m<sup>2</sup> or higher, current smoking, aspirin use, and other non-neoplastic findings at colonoscopy. A Dutch screening cohort study likewise found that men, smokers, and regular users of non-steroidal anti-inflammatory drugs had lower test specificity. Data on these variables were not collected in the present study, which constitutes one of its principal limitations.<sup>45,46,47</sup>

The fifth, and most clinically relevant, explanation is the possibility that a proportion of the positive results genuinely reflects an undetected burden of colorectal neoplasia in a population that has never previously undergone screening. The first-round phenomenon is a highly consistent

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finding in the screening literature. An analysis of seven rounds of a biennial screening program involving 2.81 million individuals found that the first round yielded the highest positivity rate (5.8% among all invitees), the highest positive predictive values for carcinoma (5.1%) and for high-risk precursors (20.4%), and the highest carcinoma detection rate (2.65 per 1,000 participants), which subsequently declined and stabilized at a much lower level after the third round. Because the Tomoni population had never been exposed to an organized screening program, the observed positivity rate reflects the cumulative prevalence of lesions accumulated over decades rather than incidence over a two-year interval.<sup>36</sup>

Comparison with the most socioeconomically comparable settings reinforces this interpretation. A population-based cross-sectional study of 2,109 average-risk participants in three Nigerian states reported a positivity rate of 21%, with regional variation from 11% to 28%; among positive participants who underwent colonoscopy, the positive predictive value was only 1.1% (95% CI 0.3–3.3) for invasive carcinoma and 7.0% (95% CI 4.5–10.8) for advanced adenoma. The authors concluded that, although stool-based screening was feasible and highly acceptable, the low positive predictive value together with the endoscopic burden of investigating false-positive results may render this modality an inappropriate screening tool in that setting. A community-based program in Shanghai combining fecal occult blood testing with a risk questionnaire yielded a positivity rate of 22.2%, with a carcinoma detection rate of 201.35 per 100,000 participants. The rate in the present study lies between those of European programs and those of these two community settings.<sup>21,23</sup>

### **Differences in Positivity by Sex**

The finding that men had a prevalence of positive results almost twice that of women is consistent with one of the most robust findings in the colorectal carcinoma screening literature. A prospective cohort study of 10,008 average-risk participants in the Netherlands found a positivity rate of 10.7% in men compared with 6.3% in women at a threshold of 10 µg Hb/g feces ( $p < 0.001$ ), with advanced neoplasia detection rates of 4.4% versus 2.2% and false-positive rates of 6.3% versus 4.1%. The Basque screening program of 444,582 invitees reported a positivity rate of 8.3% in men compared with 4.8% in women, with advanced neoplasia detection rates of 44.0 versus 15.9 per

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thousand. A colonoscopy-controlled study of German screening program participants found that, at every cut-off of the quantitative test and for all qualitative and guaiac tests, sensitivity and positive predictive value were substantially higher and specificity lower in men than in women, with a prevalence of advanced colorectal neoplasia of 13.5% in men versus 7.5% in women.<sup>37,38,39</sup>

An evaluation of nine immunochemical test brands in a colonoscopy-controlled setting found that pooled sensitivity was consistently lower and specificity higher in women (25.7% versus 34.6% for sensitivity, and 96.2% versus 90.8% for specificity), such that a negative result is less reliable for ruling out advanced neoplasia in men. An analysis of the Kaiser Permanente program involving 640,859 participants found a higher programmatic sensitivity in men than in women (77.0% versus 70.6%;  $p = 0.011$ ). A meta-analysis of 46 studies with 2.4 million participants specifically examining the influence of sex, age, and positivity threshold concluded that further research is needed to establish specific thresholds for each sex and age subgroup.<sup>40,41,42</sup>

Several programs have translated this evidence into operational policy. The Finnish screening program, relaunched in 2019, applies sex-specific thresholds of 70  $\mu\text{g}$  Hb/g feces for men and 25  $\mu\text{g}$  Hb/g feces for women, and has succeeded in narrowing the gap in diagnostic performance between the sexes, with positivity rates of 2.8% in men and 2.4% in women. A recent microsimulation analysis of age- and sex-tailored threshold strategies found that such approaches are potentially cost-effective compared with uniform screening, although the additional health benefit is likely to be small, approximately one additional quality-adjusted life-year per thousand individuals. The findings of the present study add to the evidence that sex-based disparities also apply to the Indonesian population, making sex-based stratification a relevant consideration in the design of a national program.<sup>43,44</sup>

An important nuance should be noted. A meta-analysis of risk factors for erroneous test results found that male sex was, in fact, associated with a lower risk of false-positive results (relative risk 0.84; 95% CI 0.74–0.94) but a considerably higher risk of false-negative results (relative risk 1.83; 95% CI 1.53–2.19). This combination of findings implies that the higher positivity in men does not merely reflect impaired specificity but predominantly reflects a genuinely higher prevalence of neoplasia. Accordingly, the findings of this study should be interpreted as a

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clinically meaningful epidemiological signal rather than merely a test artifact, and they support the specific targeting of outreach efforts towards older men. Participation considerations also support the choice of a stool-based modality in this setting, given that the COLONPREV randomized controlled trial involving 53,302 participants found substantially higher participation in stool-based screening than in colonoscopy (34.2% versus 24.6%;  $p < 0.001$ ), with an equivalent number of carcinomas detected at initial screening. This is consistent with an Asia Cohort Consortium analysis of more than 619,000 Asian participants, which found that the association between body mass index and colorectal carcinoma risk was stronger in men, and with a review of the sexually dimorphic nature of colorectal carcinoma highlighting differences in pathophysiology, tumor location, and screening participation between the sexes.<sup>46,64,69</sup>

### **Absence of an Association between Age and Positive Results**

The absence of an association between age and positive results in this study, consistent across six different analytical approaches, appears at first glance to contradict the well-established knowledge that colorectal carcinoma risk increases sharply with age. The most plausible explanation is range restriction in age. A total of 97.6% of participants were aged 50 years or older and 77.1% were aged 60 years or older, with an interquartile range spanning only eight years (60 to 68 years). Within such a narrow age range lying entirely within the high-risk group, the discriminative ability of age is mathematically suppressed, as reflected by an area under the curve of 0.494. This range restriction phenomenon is a structural limitation inherent in the study design, not evidence that age is unrelated to colorectal carcinoma risk.

The second explanation is that a meta-analysis of risk factors for erroneous test results found no systematic effect of age on either false positivity or false negativity of immunochemical tests. In other words, the age gradient in positivity rates observed in population screening programs reflects differences in the underlying prevalence of neoplasia rather than differences in the behavior of the test itself. In a population lying entirely within at-risk age groups and never previously exposed to screening, differences in prevalence between age decades may be relatively small compared with the absolute difference between previously screened and never-screened groups.<sup>46</sup>

The third explanation is limited statistical power. The age groups below 50 years and 80 years and older each comprised only four participants, with confidence intervals spanning more than 60 percentage points. Even the largest age group, 60 to 69 years with 96 participants, yielded only 17 positive cases. In such a configuration, even a moderate age gradient would go undetected. Therefore, the finding of no association with age in this study should be read as absence of evidence rather than evidence of absence.

The practical implication of this finding is, in fact, constructive. Because age provides no additional discriminative information within the age range already captured by the program, participant targeting within the group aged 50 years and older need not be further narrowed on the basis of age. The Asia-Pacific Colorectal Screening score, which combines age, sex, family history, and smoking status, remains a more appropriate instrument for risk stratification than age alone, and its validation in the Indonesian population is an urgent research priority. A risk-stratified screening approach using age, sex, and prior screening history has been proposed as a realistic first step towards more targeted screening.<sup>30,65</sup>

### **Geographical Homogeneity and Its Implications**

The homogeneity of prevalence across the twelve villages and one urban ward, confirmed by five independent analytical approaches with an  $I^2$  of 0.0% and a variance-to-mean ratio of 0.255, has two implications. The methodological implication is that village-cluster-based recruitment did not generate intraclass correlation requiring correction; conventional confidence interval estimates therefore remain valid, and future studies may use standard sample size calculations without design effect inflation. The programmatic implication is that the positivity burden is evenly distributed throughout the catchment area, so that selective geographical targeting is unnecessary and screening resources can be allocated in proportion to the size of the target population.

This homogeneity contrasts with the findings of the Nigerian study, which reported wide variation in positivity rates across states, namely 11% in Lagos, 20% in Osun, and 28% in Kwara. These differences probably reflect far greater heterogeneity in socioeconomic status, dietary patterns, and background gastrointestinal disease at the inter-state scale than at the inter-village

scale within a single primary health center catchment area with relatively uniform agroecological and social characteristics.<sup>21</sup>

### **Empowerment of Posbindu PTM and Posyandu Lansia as Mobilization Channels**

A finding worth highlighting from an implementation perspective is the achievement of a nearly balanced sex composition, namely 50.6% men and 49.4% women. This contrasts sharply with the participant profile of Posbindu PTM reported in multiprovincial studies in Indonesia. A mixed-methods evaluation of 114,581 visits by 54,224 participants at 475 Posbindu sites found that approximately 80% of attendees were women, and its authors explicitly highlighted the suboptimal coverage of men and young adults as a missed opportunity. A satisfaction survey of 1,263 participants in Central Java, East Java, and North Sumatra found that 86.4% of respondents were women. Another implementation study in Yogyakarta likewise found that men and the elderly were the groups most frequently missed by Posbindu screening.<sup>24,25</sup>

The success of this study in reaching men in equal proportion carries particular strategic value, given that it is precisely men who have a twofold prevalence of positive results and a higher risk of colorectal carcinoma. A presumed contributing factor is the combination of two platforms, namely Posbindu PTM, which targets the productive-age population, and Posyandu Lansia, which targets the elderly, such that their age and sex coverage are complementary. This experience supports the recommendation that improved access to non-communicable disease screening can be achieved through integration into existing community-based activities.<sup>25</sup>

The evidence for the effectiveness of empowering community cadres to increase cancer screening is robust. Three Community Guide systematic reviews encompassing 76 studies found that interventions engaging community health workers increased colorectal carcinoma screening by a median of 10.5 percentage points (interquartile range 4.5–17.5), and that their effectiveness was independent of race, ethnicity, income, or insurance status. A systematic review of sixteen randomized controlled trials in low- and middle-income countries likewise concluded that programs utilizing community health workers are potentially effective for the primary prevention of non-communicable diseases. A scoping review of colorectal carcinoma screening implementation in low- and middle-income countries found that face-to-face recruitment strategies, either alone or in

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combination, achieved coverage above 65% in ten of fifteen studies, and that interventions combining education with screening achieved similar coverage in three of four studies.<sup>22,28,29</sup>

### **A Critical Challenge: Continuity of the Referral Chain**

The finding that most determines program success is not the positivity rate but the proportion of positive participants who actually undergo confirmatory colonoscopy. It is at this point that the literature issues its strongest warning. The community-based program in Shanghai, which achieved 97.7% completion of initial screening, succeeded in bringing only 39.8% of positive participants to colonoscopy, with the proportion declining with increasing age and lower educational attainment. An analysis of the Korean National Cancer Screening Program involving 214,131 individuals with positive results found one-year follow-up adherence of only 56.5%, with older age as a strong predictor of non-adherence; participants aged 80 years or older had substantially lower odds of adherence than those aged 50 to 59 years.<sup>23,68</sup>

In the Indonesian context, the warning signal is even clearer. A cross-sectional analysis of 277 adults identified as having hypertension and/or elevated glucose at Posbindu screening in Aceh Besar found that only 42.2% completed follow-up at the primary health center, with older age and female sex as predictors of better adherence, whereas being employed and unmarried were associated with lower adherence. If follow-up for conditions manageable at the primary health center reaches only 42.2%, follow-up in the form of colonoscopy—which requires referral to district or provincial facilities, bowel preparation, sedation, transportation costs, and waiting time—is potentially far lower still.<sup>27</sup>

The consequences of failed follow-up are serious and measurable. A prospective cohort analysis of 318,096 individuals invited to screening in Stockholm-Gotland found that participants with positive results who did not undergo colonoscopy had a colorectal carcinoma incidence 4.21 times that of the general population (95% CI 3.24–5.48), whereas participants with negative colonoscopy findings had a lower incidence (standardized incidence ratio 0.52; 95% CI 0.39–0.68). A cohort study of 265,881 Dutch participants showed that repeated positivity is a strong predictor of future advanced neoplasia. Furthermore, fecal occult blood positivity is associated with an increased risk of death not only from colorectal carcinoma (hazard ratio 7.79; 95% CI 6.13–9.89) but also

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from various other causes (hazard ratio 1.58; 95% CI 1.45–1.73); a positive result should therefore be regarded as a marker of overall health risk rather than solely a marker of colorectal risk.<sup>52,58,72</sup>

Regarding the timeframe for follow-up, the evidence indicates that moderate delays are tolerable but prolonged delays are harmful. An analysis of 70,124 Kaiser Permanente participants found that, compared with colonoscopy within 8 to 30 days, there was no difference in risk up to the ninth month, but carcinoma risk increased at intervals of 10 to 12 months (odds ratio 1.48; 95% CI 1.05–2.08) and more than 12 months (odds ratio 2.25; 95% CI 1.89–2.68), with the risk of advanced-stage disease reaching an odds ratio of 3.22 at intervals exceeding 12 months. An analysis of 204,733 United States veterans found an increased risk beginning at intervals of 13 to 15 months. A systematic review concluded that colonoscopy should not be delayed beyond nine months. Conversely, a French national cohort study of 374,113 individuals with 86.6% adherence found no increased risk up to 24 months, and its authors argued that ensuring colonoscopy adherence is more important than rigid adherence to time intervals. For the Indonesian setting, with its limited endoscopic capacity, this message is both reassuring and clarifying of priorities: what matters most is ensuring that colonoscopy is performed, not meeting a deadline of a few weeks.<sup>54,55,56,57</sup>

Interventions proven to improve follow-up have been well identified. A systematic review of 23 studies found moderate-strength evidence supporting patient navigators as well as reminders and performance feedback for healthcare providers. A randomized controlled trial in primary care facilities found that centralized telephone-based patient navigation increased one-year colonoscopy completion from 38.7% to 69.0% ( $p = 0.006$ ), with a mean reduction in time to colonoscopy of 80.4 days. A pragmatic randomized controlled trial across twelve service sites found that centralized outreach increased screening completion from 9.7% to 30.0% and improved the detection of advanced colorectal neoplasia. Organized outreach has also proven cost-effective, at a cost of 9,200 United States dollars per quality-adjusted life-year gained. The Posbindu and Posyandu Lansia cadre-based outreach model, which has been shown in this study to mobilize participants, could naturally be extended to serve as referral navigators.<sup>59,60,61,62</sup>

The Nigerian experience offers a relevant alternative model. An early detection program combining a six-month community awareness campaign with patient navigation succeeded in

increasing awareness of colorectal carcinoma from 16.8% to 96.9% and achieved colonoscopy completion of 73.0% among protocol-compliant participants, with advanced adenomas detected in 11% and carcinoma in 3.4% of those who underwent colonoscopy. The combination of community engagement and patient navigation appears to be the most promising formula for resource-limited settings.<sup>63</sup>

### **Implications for Policy and Practice**

The Asia-Pacific consensus explicitly states that in resource-limited countries, fecal occult blood testing is the first choice for colorectal carcinoma screening, and that screening should be a national health priority in most Asian countries. The third consensus reaffirms the central role of stool-based screening while emphasizing the importance of program quality assurance. An analysis of 58 organized screening programs in 22 countries found that programs operating for more than five years were associated with reduced mortality, and that this reduction was not significant for immunochemical programs operating for less than five years. This message is important for Indonesian program planners: the benefits of screening are cumulative and require long-term commitment rather than one-off activities. The American College of Gastroenterology guideline likewise emphasizes that optimizing screening requires achieving high adherence rates, quality monitoring, and elimination of barriers across the entire care continuum, from non-invasive testing to diagnostic colonoscopy.<sup>17,18,66,67</sup>

The findings of this study support several concrete operational decisions. First, a positivity rate of 16.57% means that extending the program to the entire target population of the catchment area will generate a substantial colonoscopy demand, approximately 166 referrals per thousand participants screened. Referral endoscopy capacity must be secured before expansion, since screening without an adequate follow-up pathway cannot be justified either ethically or in terms of cost-effectiveness. Second, if the test device used is a quantitative immunochemical test, upward adjustment of the positivity threshold could substantially reduce the colonoscopy burden at the cost of a moderate loss of sensitivity. A Norwegian analysis showed that increasing the threshold from 15 to 47 µg Hb/g feces reduced the number of colonoscopies to 49.3% while retaining detection of 75.9% of carcinomas; however, a further increase to 150 µg Hb/g feces reduced carcinoma

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detection to 56.2% and shifted the stage distribution unfavorably. Third, the use of quantitative rather than qualitative testing could potentially halve colonoscopy demand, as demonstrated in the Chinese community study.<sup>33,71</sup>

These three technical recommendations must be placed within a realistic framework of resource constraints. In Indonesian primary health center settings, quantitative immunochemical testing with automated reading is generally not yet available, and its device costs far exceed those of qualitative rapid test devices. Therefore, the most realistic short-term strategy is not replacement of the modality but strengthening of the post-screening phase: documentation of factors that may cause false-positive results, screening for upper gastrointestinal symptoms, and prioritization of referral based on the combination of a positive result with clinical risk factors.

### **Strengths of the Study**

This study has several strengths. First, the data were obtained directly from a community population through existing primary care platforms rather than from a referral hospital population; the prevalence estimate therefore better represents the burden in the general population and is less subject to referral selection bias. Second, comprehensive geographical coverage encompassing all twelve villages and one urban ward in the catchment area enabled a thorough examination of geographical heterogeneity. Third, there were no missing data for the outcome variable; hence, the primary prevalence estimate was not threatened by attrition bias. Fourth, the analytical approach applied goes well beyond conventional prevalence reporting, with triangulation of interval estimation methods, cluster design effect correction, permutation testing to overcome the limitations of asymptotic approximation, quantification of heterogeneity, multivariable modeling with calibration assessment, and explicit sensitivity and statistical power analyses. Fifth, this study documents the feasibility of empowering Posbindu PTM and Posyandu Lansia for oncological screening, a replicable implementation contribution.

### **Directions for Future Research**

The most urgent priority for future research is a prospective cohort study following all participants with positive results through to confirmatory colonoscopy, so that the positive predictive value, the advanced neoplasia detection rate, and the number needed to screen can be

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measured directly in the Indonesian population. Such a study could simultaneously measure the proportion completing colonoscopy, the mean time to colonoscopy, and the barriers faced by participants, which are the most decisive program performance indicators.

The second agenda item is the expanded collection of clinical and behavioral variables to enable the development of more informative risk prediction models, together with validation of the Asia-Pacific Colorectal Screening score in the Indonesian population. The third is a study with an adequate sample size, namely at least 590 participants to achieve a precision of  $\pm 3.0$  percentage points or 368 participants to detect a between-sex difference with 80% power. The fourth is a head-to-head comparison of the qualitative test devices commonly used in primary health centers with quantitative test devices, accompanied by a cost-effectiveness analysis in the Indonesian setting. The fifth is an intervention trial to improve colonoscopy completion, for example through cadre-based patient navigation, given the strong evidence for the effectiveness of this approach in other settings. The sixth is monitoring of program continuity in subsequent screening rounds to observe whether the positivity rate declines, as documented in established programs, while building program resilience against service disruptions, in light of the Asia-Pacific experience showing that prolonged interruption of screening reduces the effectiveness of mortality reduction by 6%.<sup>30,36,59,60,70</sup>

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## CONCLUSIONS AND RECOMMENDATIONS

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### Conclusions

The prevalence of positive fecal occult blood test results in a community-based colorectal carcinoma screening program in the catchment area of Tomoni Primary Health Center was 16.57% (95% CI 11.86–22.67), approximately 2.3 times the pooled positivity rate of global screening programs. Operationally, this finding means that one in every six participants screened requires further diagnostic evaluation.

Male sex was the sole independent determinant of a positive result. A prevalence of 21.98% in men compared with 11.24% in women yielded a crude odds ratio of 2.23 (95% CI 0.98–5.07), which reached statistical significance after adjustment for age (odds ratio 2.51; 95% CI 1.03–6.08;  $p = 0.042$ ) and in the Mantel–Haenszel stratified analysis (odds ratio 2.51; 95% CI 1.03–6.14). The

most pronounced difference was found in the group aged 60 years and older, namely 25.00% in men compared with 7.14% in women.

Age was not associated with a positive test result across all analytical approaches applied, with an area under the receiver operating characteristic curve of 0.494 (95% CI 0.377–0.612). This finding is most likely a consequence of restriction of the participants' age range, 97.6% of whom were aged 50 years or older, and should be read as absence of evidence rather than evidence of absence of an association.

The prevalence of positive results was homogeneous across all twelve villages and one urban ward, with an  $I^2$  index of 0.0% and convergence of conclusions across five independent analytical approaches; there is thus no basis for selective geographical targeting. The empowerment of Posbindu PTM and Posyandu Lansia proved feasible as a channel for mobilizing participants for oncological screening and succeeded in achieving a nearly balanced sex composition, an achievement that contrasts with the predominance of female participants commonly reported in Posbindu activities in Indonesia.

## **Recommendations**

### **Recommendations for Primary Care Providers**

First, all participants with positive results must be guaranteed access to colonoscopic evaluation, and the screening program should not be expanded before a secure referral pathway has been established. Second, the role of Posbindu PTM and Posyandu Lansia cadres, which has proven effective in mobilization, should be expanded to include referral navigation, encompassing assistance with scheduling, periodic reminders, explanation of bowel preparation, and tracing of participants who have not yet undergone further examination. Third, the recording system should be strengthened through standardized documentation of the brand and detection threshold of the test device, the dates of specimen collection and examination, history of hemorrhoids and gastrointestinal disease, use of non-steroidal anti-inflammatory drugs and anticoagulants, smoking status, body mass index, and family history of colorectal carcinoma. Fourth, participants with positive results whose colonoscopy reveals no colorectal abnormality should be evaluated for possible upper gastrointestinal sources of bleeding, particularly in populations with a high

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prevalence of *Helicobacter pylori* infection. Fifth, post-screening counseling must emphasize that a positive result is not a diagnosis of malignancy, and that a negative result does not entirely exclude disease, so that periodic screening remains necessary.<sup>50,51</sup>

### **Recommendations for Policymakers**

First, colonoscopy capacity at the district level should be mapped and strengthened in proportion to the projected referral burden arising from program expansion, approximately 166 referrals per thousand participants screened. Second, the integration of colorectal carcinoma screening into the service packages of Posbindu PTM and Posyandu Lansia should be considered as formal policy, with adequate provision of logistics, cadre training, and financing. Third, the choice of test modality should be evaluated on an evidence basis, taking into account that quantitative immunochemical testing could potentially halve colonoscopy demand compared with qualitative testing; the difference in device costs should therefore be weighed against the savings in endoscopy costs. Fourth, dedicated outreach for older men should be designed, given that this group has a twofold prevalence of positive results and has historically been the least reached by Posbindu activities. Fifth, program commitment should be long term, given the evidence that mortality reduction is achieved only in programs operating for more than five years.<sup>33,67</sup>

### **Recommendations for Future Research**

Future research should take the form of a prospective cohort with colonoscopic confirmation as the gold standard, a sample size of at least 590 participants for adequate precision, comprehensive collection of clinical and behavioral variables, full documentation of test device characteristics, and measurement of program performance indicators, namely the proportion completing colonoscopy and time to colonoscopy. Validation of the Asia-Pacific Colorectal Screening score in the Indonesian population and trials of cadre-based patient navigation interventions are the two agenda items with the greatest potential for direct practical impact.<sup>30,60</sup>

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**Data availability.** The anonymized dataset underlying the findings of this study is available from the corresponding author upon reasonable request.

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