# Serum microRNA test to identify individuals with high risk of colorectal cancer: abridged secondary publication

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**KEY MESSAGES**

1. A serum microRNA test is a promising diagnostic biomarker for patients with colorectal cancer.
2. The combination of a serum microRNA test and colonoscopy is more cost-effective than colonoscopy alone.

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## Introduction

Colorectal cancer (CRC) is the most common cancer in Hong Kong. In 2018, 5634 cases of CRC were newly diagnosed, accounting for 16.6% of all new cancer cases. CRC is the second most common cause of cancer-related death. In 2019, there were 2174 deaths from CRC, accounting for 14.6% of all cancer-related deaths.[1] CRC is curable if diagnosed at an early stage. Therefore, screening is particularly important in early detection of CRC.

Several serum miRNAs are promising biomarkers for CRC diagnosis, with individual area under the curve (AUC) values >0.800. We investigated the use of microRNAs (miRNAs) in blood to identify patients with CRC and compared cost-effectiveness between miRNA and conventional strategies for CRC screening.

## Methods

Between 2017 and 2021, serum samples (3 mL each) were collected from patients with CRC and normal individuals at Queen Mary Hospital in Hong Kong. Respectively in the training set (stage 1) and validation set (stage 2), 129 and 200 pairs of normal individuals and patients with CRC were recruited. In the prediction set (stage 3), 105 normal individuals and 155 patients with CRC were recruited to determine the predictive value of miRNA panel (Table).

Serum miRNA was extracted. Total RNA was reverse transcribed to generate 20 µl of genomic DNA-free cDNA. Quantitative polymerase chain reaction (PCR) was performed.

Intergroup comparisons were conducted by *t* tests and Mann-Whitney *U* tests. Statistical

TABLE. Characteristics of normal individuals and patients with colorectal cancer (CRC) in three cohorts

| | Training set | | Validation set | | Prediction set | |
|---|---|---|---|---|---|---|
| | Normal individuals (n=129) | Patients with CRC (n=129) | Normal individuals (n=200) | Patients with CRC (n=200) | Normal individuals (n=105) | Patients with CRC (n=155) |
| No. of men | 40 | 59 | 84 | 135 | 49 | 101 |
| No. of women | 89 | 70 | 116 | 65 | 56 | 54 |
| Age, y* | 58.1±8.23 | 67.5±9.53 | 60.1±11.52 | 67.5±11.88 | 60.1±9.20 | 69.4±12.17 |

* Data are presented as mean ± standard deviation

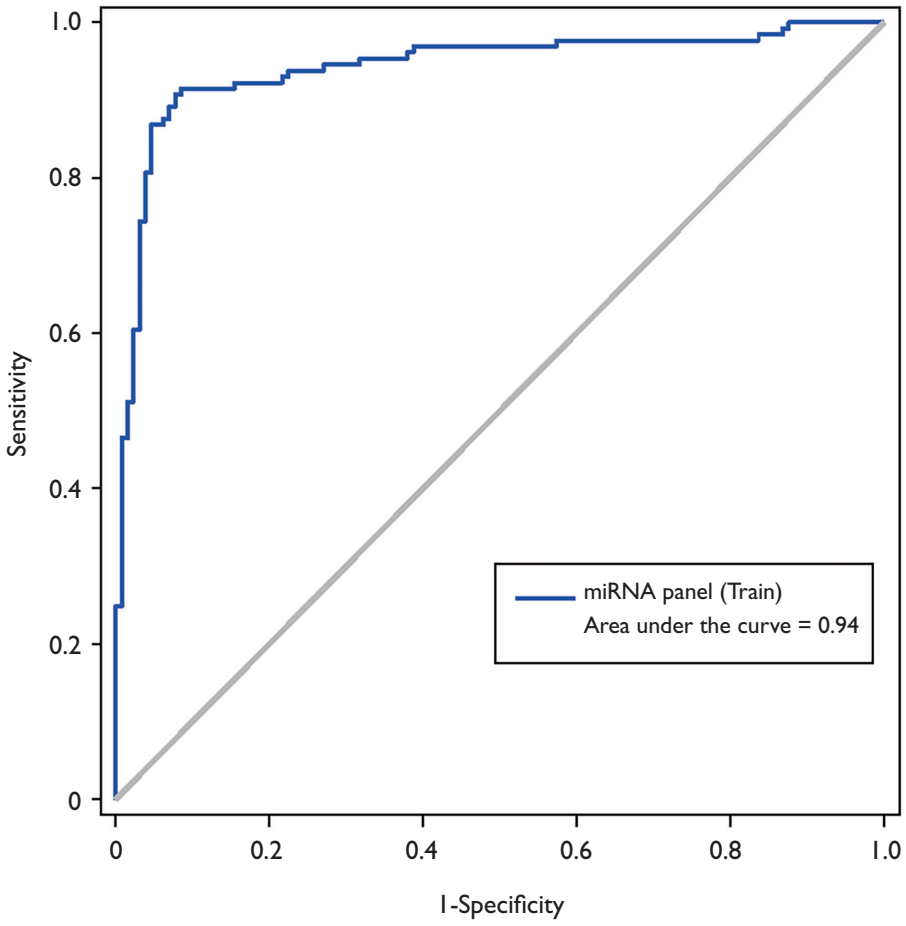


FIG 1. Diagnostic performance of the serum microRNA panel for identifying patients with colorectal cancer in the training set

analyses were conducted using SigmaPlot 10.0 (Systat Software, San Jose [CA], USA). A P value of <0.05 (two-tailed) was considered statistically significant.

We compared the costs of two CRC screening strategies: (1) colonoscopy alone and (2) miRNA panel followed by colonoscopy for miRNA panel–positive patients. The costs of the miRNA test and colonoscopy were determined based on the median costs in the private sector.

## Results

We performed multiple linear regression to identify three miRNA pairs for CRC diagnosis: serum miRNA panel (Training) score = -0.35 + (0.0171 * miR-106b-5p/miR-1246) + (0.217 * miR-106b-5p/miR-16) – (0.133 * miR-106b-5p/miR-21-5p). The AUC of this miRNA panel for CRC diagnosis was 0.94 (P<0.0001, Fig 1).

The AUC of the miRNA panel (Training) for CRC diagnosis in the validation cohort was 0.77 (P<0.0001, Fig 2). The AUC, sensitivity, and specificity were all decreased compared with those values in the training cohort. Hence, we formulated a miRNA panel using data from patients in the validation cohort. The following formula was derived: serum miRNA panel (Validation) score = -0.32 + (0.0471 * miR-106b-5p/miR-1246) + (0.137 * miR-106b-5p/miR-16) + (0.0196 * miR-106b-5p/miR-21-5p). The AUC of this miRNA panel (Validation) for CRC diagnosis was 0.89 (P<0.0001, Fig 2).

We calculated the serum miRNA panel (Validation) score and used a cut-off value of 0.53 for prediction of CRC. Among 155 patients with CRC, 133 patients were correctly identified (sensitivity=85.8%), whereas 85 of 105 normal individuals were correctly identified (specificity=80.95%). The positive and negative predictive values were 86.9% and 79.4%, respectively.

The cost of colonoscopy at 12 private hospitals or medical centres ranged from $4050 to $14 060, and the median cost was $9910 (interquartile range, $8800-$10 610). The cost of the serum miRNA test

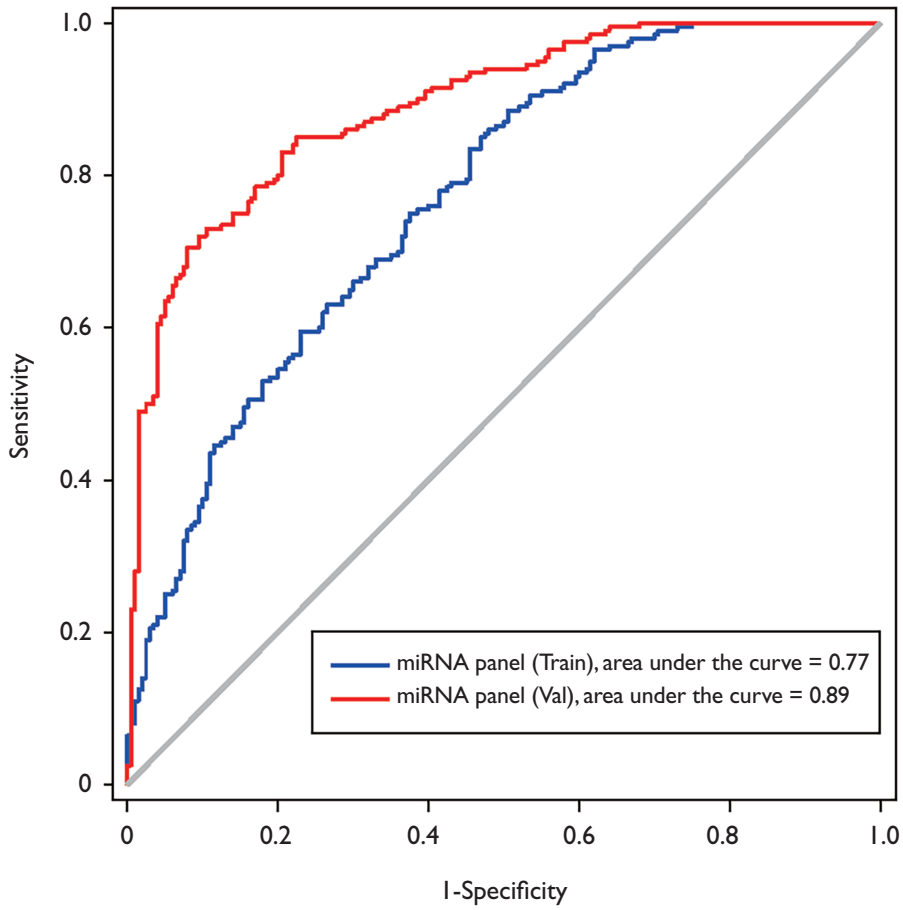


FIG 2. Diagnostic performance of the serum microRNA panel for identifying patients with colorectal cancer in the validation set

was based on the cost of a COVID-19 PCR test, which ranged from $240 to $2110 at 23 private medical centres, and the median cost was $1180 (interquartile range, $950-$1492.5). Between 2017 and 2021, annually on average, 114 patients with CRC and 1975 normal individuals underwent colonoscopy at Queen Mary Hospital.

The estimated CRC detection sensitivity of colonoscopy is 95%.[2] At this sensitivity, the specificity of the serum miRNA test was 52.38%. The cost of the serum miRNA test for all 2089 patients was $2 465 020 (2089 × $1180). Based on the 52.38% specificity of the serum miRNA test, 1094 normal individuals with a normal serum miRNA test result could avoid colonoscopy screening. The savings would be $10 841 540 (1094 × $9910). After subtracting the cost of the serum miRNA test ($10 841 540 – $2 465 020 = $8 376 520), the average cost savings per patient would be $4010 ($8 376 520 / 2089).

## Discussion

The serum miRNA test is a promising diagnostic biomarker for patients with CRC. Moreover, a combination of a serum miRNA test and colonoscopy is more cost-effective than colonoscopy alone. The average cost savings per patient is approximately $4000. From 2017 to 2021, the total number of colonoscopies performed in all public hospitals was around 267 000. Assuming that the proportion of patients with CRC was similar to that in our hospital (52.8%), the number of patients with CRC in all public hospitals was 140 976. Hence, the cost savings using a combination of a serum miRNA test and colonoscopy would have been 564 million dollars.

There were limitations in this study. The samples were collected from patients recruited at a single hospital. Although we validated the findings in three different patient cohorts, the results would be more robust if our serum miRNA panel could perform consistently among patient

samples collected at other hospitals. In addition, the performance of the serum miRNA test in identifying patients with polyps was not evaluated.

## Conclusions

The serum miRNA test is a promising diagnostic biomarker for identifying patients with CRC, with AUC around 0.9. A combination of a serum miRNA test and colonoscopy is more cost-effective than colonoscopy alone.

## Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#04151956). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

### References

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