

INPLASY PROTOCOL

To cite: Dansero et al.
Investigating the role of
circulating miRNAs as
biomarkers in colorectal
cancer: an epidemiological
systematic review. Inplasy
protocol 202290002. doi:
10.37766/inplasy2022.9.0002

Received: 01 September 2022

Published: 01 September 2022

Corresponding author:
Carlotta Sacerdote

carlotta.sacerdote@cpo.it

Author Affiliation:
Città della Salute e della
Scienza University-Hospital.

Support: Italian Ministry of
Health.

**Review Stage at time of this
submission:** Completed but
not published.

Conflicts of interest:
None declared.

Investigating the role of circulating miRNAs as biomarkers in colorectal cancer: an epidemiological systematic review

Dansero, L¹; Sacerdote, C².

Review question / Objective: What is the potential role of microRNAs as biomarkers of colorectal cancer.

Eligibility criteria: Studies were considered eligible for the systematic review if they met the following criteria: 1) study patients have been diagnosed with CRC; 2) healthy individuals were used as controls; 3) biological samples were plasma or serum or blood; 4) results included any of AUC, sensitivity, and specificity and/or fold change values. Studies were excluded if they were: 1) reviews, meta-analyses, conference abstracts, letters; 2) animals or cells experiments; 3) studies that investigated prognosis, survival, or metastatic cancers only; 4) studies that investigated toxicity or therapy efficacy; 5) studies with insufficient data; 6) studies not published in English language.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 September 2022 and was last updated on 01 September 2022 (registration number INPLASY202290002).

INTRODUCTION

Review question / Objective: What is the potential role of microRNAs as biomarkers of colorectal cancer.

Rationale: In this study, we aimed to review the relevant existing literature to identify

published studies reporting the use of plasma, serum, or blood-based circulating miRNA as biomarkers for diagnosis of CRC. Identifying a preclinical biomarker of disease, such a miRNA or a panel of miRNAs, that overlaps a marker of exposure (such as obesity or inflammation) would strengthen causal links

between these exposures and the disease in a meet-in-the-middle approach.

Condition being studied: We want to study the circulating miRNAs as biomarkers in colorectal cancer patients.

METHODS

Search strategy: Databases: PubMed and EMBASE Restrictions: English language, peer reviewed articles Search keywords: excluding “cells” and “tissue”. “miRNA or microRNA”, “colon or colorectal cancer”, “circulating or exosomal” with restrictions to “humans”.

Participant or population: Population Inclusion criteria: Adult men and women (>18 y).

Intervention: In this review we will assess how useful circulating miRNAs as biomarkers for diagnosis and early detection of colorectal cancer.

Comparator: The included studies should have a control group of healthy men and women.

Study designs to be included: Inclusion: Observational studies (case-control and cohort studies).

Eligibility criteria: Studies were considered eligible for the systematic review if they met the following criteria: 1) study patients have been diagnosed with CRC; 2) healthy individuals were used as controls; 3) biological samples were plasma or serum or blood; 4) results included any of AUC, sensitivity, and specificity and/or fold change values. Studies were excluded if they were: 1) reviews, meta-analyses, conference abstracts, letters; 2) animals or cells experiments; 3) studies that investigated prognosis, survival, or metastatic cancers only; 4) studies that investigated toxicity or therapy efficacy; 5) studies with insufficient data; 6) studies not published in English language.

Information sources: PubMed and EMBASE.

Main outcome(s): The main outcomes are sensitivity, specificity and other parameters (such as true negative, false negative, true positive, false positive, AUC).

Additional outcome(s): Additional outcomes are: diagnostic odds ratio and fold change.

Data management: We screened the abstracts extracted from the bibliographic databases to exclude duplicates, metanalysis, review, expert opinion, etc... Once full texts were selected, references were screened to search for other relevant studies. According to inclusion criteria, data were extracted by two independent authors. Disagreements were solved through involvement of a third author. Extracted data form included: first author's name and reference, country, sample size, biological sample (plasma, serum, or blood), miRNA, cut-off value, AUC value (95% CI), sensitivity (95% CI), specificity (95% CI), fold change (95% CI), p-value, median relative expression (s.d.), miRNA source (candidate or discovery if found in a screening phase), and expression (up or down-regulation). Diagnostic performance data were extracted or calculated for the studies included in the meta-analysis (FP, FN, TP, TN).

Quality assessment / Risk of bias analysis: Included studies were evaluated according to the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) checklist to assess the risk of bias and applicability of studies of diagnostic accuracy.

Strategy of data synthesis: By utilizing the diagnostic performance data (TP, TN, FP, FN) pooled sensitivity, specificity has been calculated for single microRNA by considering the reported thresholds of the studies using appropriate statistical methods.

Subgroup analysis: Biological sample type (plasma vs serum), reference miRNA used for normalization, and method for choosing the studied miRNA (literature vs discovery) were used as covariates in the meta-regression. Statistically significant

heterogeneity was found for sample type, indicating that studies using plasma samples had a smaller heterogeneity than studies using serum sample. However, both groups have a small sample, with studies with plasma and five with serum samples (one study was excluded as indicated generally blood).

Sensitivity analysis: No sensitivity analysis.

Language restriction: English.

Country(ies) involved: Italy.

Keywords: microRNA; colorectal cancer; circulating; biomarker.

Contributions of each author:

Author 1 - Carlotta Sacerdote - Conceptualization, methodology, investigation, data curation, original draft preparation, review and editing and funding acquisition.

Email: carlotta.sacerdote@cpo.it

Author 2 - Lucia Dansero - Formal analysis, methodology, investigation, data curation, original draft preparation.

Email: lucia.dansero@unito.it