



# Investigating the histopathological criteria suggesting Microsatellite instability in patients with colorectal cancer: a systematic review

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## Introduction

Today, cancer is recognized as a major public health problem and colorectal cancer is one of the most common malignancies affecting global health and the economy, especially in industrialized countries. Statistics published by the World Health Organization indicate that colorectal cancer is the third most common cancer worldwide in both sexes combined, the third most common cancer in men, and the second most common cancer in women. Moreover, its incidence has been increasing in most countries over recent decades. In terms of cancer-related mortality, colorectal cancer ranks fourth worldwide in both sexes combined and in men, and third in women, accounting for approximately 694,000 deaths annually. However, statistics reported for Iran are somewhat different: colorectal cancer is the third most common cancer in both sexes combined, the fourth most common cancer in Iranian men, and the second most common cancer in Iranian women. Regarding cancer-related mortality, it ranks fourth in both sexes combined, fifth in Iranian men, and fourth in Iranian women. The highest incidence of colorectal cancer worldwide has been reported in Australia and New Zealand, while the lowest incidence has been observed in West Africa.

## Methods

The 2-year-old male sheep pericardium of the Sanjabi breed was collected from the Kermanshah animal slaughterhouse in Iran. The adipose tissue was detached, and the samples were located in a bottle containing phosphate-buffer. Pericardial tissues were decellularized with different concentrations of ACP (5, 7.5% and 10%) and SDS (1%), as well as the combination of ACP + SDS. Tissue staining, biocompatibility (MTT), hemolysis, blood clotting index (BCI), scanning electron microscopy (SEM), ATR-FTIR spectroscopy, mechanical testing, contact angle, and antibacterial activity were performed.

## Results

This systematic review was designed and conducted with the aim of investigating the histopathological criteria indicative of microsatellite instability in patients with colorectal cancer. All studies that assessed histopathological criteria associated with microsatellite instability in colorectal cancer patients were included. The reviewed studies were limited to those published in Persian or English, regardless of publication date. In this review, all eligible studies were included without any age, gender, or racial restrictions. In this systematic review, conducted to evaluate the histopathological criteria suggestive of microsatellite instability in patients with colorectal cancer, a total of 26 studies with adequate quality scores were included. The selection process of these 26 studies was as follows: initially, 1,551 articles were identified in the primary search. During the screening phase, 994 articles were excluded due to duplication. The remaining articles were then assessed based on their titles and abstracts, and 507 studies were excluded because they were not relevant to the topic. Subsequently, 24 studies were excluded from the meta-analysis due to insufficient data, lack of access to the full text, or inadequate quality. Finally, 26 studies were included in the present meta-analysis.

According to the results presented in Table 1–3, after quality assessment of the articles, 26 studies with acceptable scores were included in the review. A total of 7,808 participants were enrolled across these studies, although gender was not specified in 11 studies. The mean age of the patients in the selected studies was 61.6 years.

The largest sample size was reported in the study by Greenson et al. conducted in the United States (1,649 patients), while the smallest sample size belonged to the cohort study by Jass et al. in Australia (23 patients). The studies were published over a period ranging from 1996 to 2023.

## Results

Regarding the geographical distribution, the highest number of studies was conducted in the United States (8 studies). In terms of histopathological features suggestive of MSI, 16 studies reported the presence of a mucinous histopathological pattern, 16 studies reported increased tumor-infiltrating lymphocytes (TILs), 11 studies reported poor differentiation, 8 studies described a Crohn's-like lymphocytic reaction, 6 studies reported a medullary histopathological pattern, and 5 studies identified signet ring cells. Diagnosing colorectal carcinomas with high levels of DNA microsatellite instability (MSI-H) is crucial due to the therapeutic and prognostic significance associated with MSI, and globally, the assessment of all colorectal tumors for MSI status is generally recommended. According to the revised Bethesda Guidelines, the histological criteria proposed for MSI-H include tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous or signet ring cell differentiation, and a medullary growth pattern. The objective of this systematic study was to determine the distribution of histopathological features indicative of MSI in patients with colorectal cancer. histopathological features suggestive of MSI, with the most common feature being the presence of a mucinous histopathological pattern (reported in 16 studies). At the molecular level, a significant proportion of mucinous carcinomas demonstrate MSI. Mucinous carcinomas are a subtype of colorectal carcinoma characterized by extracellular mucin pools containing tumor cell aggregates. By definition, these mucinous areas must comprise at least 50% of the total tumor mass. Based on the results of the present study, another common histopathological feature among the reviewed studies was the presence of marked tumor-infiltrating lymphocytes (TILs), which was reported in 16 studies.

## Conclusions

The results of this study showed that the presence of a mucinous histopathological pattern, increased tumor-infiltrating lymphocytes (TILs), poor differentiation, Crohn's-like lymphocytic reaction, medullary histopathological pattern, and signet ring cells were the most important criteria defined as histopathological features suggestive of MSI-H. The results of this study showed that the presence of a mucinous histopathological pattern, increased tumor-infiltrating lymphocytes (TILs), poor differentiation, Crohn's-like lymphocytic reaction, medullary histopathological pattern, and signet ring cell features were the most important criteria defined as histopathological features suggestive of MSI-H. The mean age of the patients evaluated in the selected studies was 61.6 years. The largest number of patients was reported in the study by Greenson et al. in the United States (1,649 patients), while the smallest was reported in the cohort study by Jass et al. in Australia (23 patients). The studies were published over the period from 1996 to 2023. In terms of study location, the highest number of studies was conducted in the United States (8 studies). Regarding the histopathological features suggestive of MSI, 16 studies reported the presence of a mucinous histopathological pattern, 16 studies reported increased tumor-infiltrating lymphocytes (TILs), 11 studies reported poor differentiation, 8 studies reported a Crohn's-like lymphocytic reaction, 6 studies reported a medullary histopathological pattern, and 5 studies reported signet ring cell features.