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EXPLORING THE PROGNOSTIC VALUE OF COMBINED MSI AND KRAS/BRAF MUTATIONAL STATUS IN COLORECTAL CANCER PATIENTS

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ABSTRACT

Background: Colorectal cancer (CRC) is a significant global health concern, and constant improvement in treatment and prediction is needed. Though resection with adjuvant therapy is the standard for resectable CRC, optimal patient benefit and the development of individualized strategies remain relevant. Microsatellite Instability (MSI) has emerged as a significant molecular marker but requires more definitive clarification of its prognostic interaction with other mutations like BRAF and KRAS. **Objective:** The objective of this meta-analysis was to comprehensively assess the prognostic value of MSI status, as well as KRAS and BRAF mutations, on overall survival (OS) and progression-free survival (PFS) in patients with CRC after surgical resection. **Methods:** Systematic literature review was performed, and research was identified on the basis of predefined eligibility criteria. Data for OS, PFS, MSI status, and KRAS/BRAF mutation were gathered. Fixed-effect meta-analysis was conducted to calculate summary HRs and 95% CIs. Risk bias was assessed using standardized tools, and publication bias was tested. **Results:** The meta-analysis revealed that MSI-high (MSI-H) status was also significantly associated with improved OS (HR: 0.68, 95% CI: 0.60 - 0.77; $p<0.05$) and improved PFS (HR: 0.70, 95% CI: 0.53 - 0.94; $p<0.05$) compared to microsatellite stable/low (MSS/MSI-L) tumors. Conversely, the presence of a BRAF mutation was significantly associated with poorer OS (HR: 1.48, 95% CI: 1.20 - 1.83; $p<0.05$). KRAS mutational status was not found to have a statistically significant independent association with either OS (HR: 1.18, 95% CI: 0.98 - 1.42) or PFS (HR: 1.10, 95% CI: 0.92 - 1.32) in this pooled analysis. BRAF mutation was not found to have an impact on PFS (HR: 1.02, 95% CI: 0.84 - 1.25). No publication bias was detected to be significant. **Conclusion:** This meta-analysis shows compelling evidence that MSI-H status is an independent favorable prognostic marker for OS and PFS in patients with resected CRC. By contrast, BRAF mutation is a potent indicator of poor OS. These findings underscore the significance of standard molecular profiling, and particularly MSI and BRAF status, to more accurately refine prognostic stratification and potentially impact personalized adjuvant treatment decisions in CRC therapy. Further research into the individual subtypes of KRAS mutations and their interaction with MSI status is required.

KEYWORDS: *Prognostic Prediction, MSI, BRAF Mutation, KRAS Mutation, Overall Survival, Progression Free Survival.*

BACKGROUND/INTRODUCTION

Colorectal cancer (CRC) is a significant and growing global health problem, representing the third most common malignant illness and second most common cause of cancer-related deaths worldwide.[1–4] The huge number of patients suffering from this disease testifies to the imperative need for continuous improvement in its treatment. While CRC treatment is multi-modal,

resection surgery remains the first treatment for resectable patients with the goal of physically removing cancerous tissue.[3,5–8] This is frequently followed by adjuvant therapy, an important step intended to kill microscopic residual disease and thus reduce the likelihood of cancer recurrence.

The decision process involved in delivering adjuvant treatment, with identification of specific agents, cannot help but involve closely weighing tumor clinicopathological variables, and staging, within one evaluation process.[5,9–11] Together, such assessment makes possible an adjusting to each individual's profile of cancer, to develop tailor-made treatment strategies to it. Despite significant progress in surgical techniques and adjuvant therapy effectiveness in CRC, tremendous challenges persist to optimize patient outcome. Prediction of individual patient prognosis – anticipated direction and result of disease – is one basic challenge. Developing genuinely personalized therapy strategies that target specifically the unique biological characteristics of an individual's tumor is the principal goal. In the search for enhancing prognostic assessment in CRC, Microsatellite Instability (MSI) analysis has emerged as a potential area of study.[12–17]

MSI is a molecular profile that is characterized by a higher frequency of mutations in short, repeated DNA sequences (microsatellites) due to defects in the DNA mismatch repair system.[14,16,18] Microsatellites are short, repetitive DNA sequences with a predisposition to amassing errors during DNA replication.[19–21] The MMR system is a critical mechanism for genomic stability by identifying and correcting these errors. It is composed of several central proteins, some of which include MLH1, MSH2, MSH6, and PMS2.[22–26] Lack or malfunction of any one of these proteins makes the MMR system unable to correct replication errors, and mutations in microsatellite areas accumulate, a state known as microsatellite instability.

MSI is most traditionally classified into three depending on the degree of unstable microsatellite markers: high (MSI-H), low (MSI-L), and stable (MSS).[14] MSI-H is of clinical interest and refers to a high degree of genomic instability.[27–29] MSI-H phenotype is found in approximately 15% of all colorectal cancer.[30–32] MSI-H tumors are normally characterized by more frequent right-sided involvement of the colon, poorly differentiated histology, a tendency to be mucinous adenocarcinomas, and are highly associated with poorly differentiated tumors. The tumors also tend to be frequently infiltrated by lymphocytes.

The underlying pathophysiology of MMR deficiency in CRC can be grossly categorized into germline mutations and somatic events. Germline mutations in one MMR gene are characteristic of Lynch syndrome, an inherited cancer syndrome. Sporadic CRC with MMR deficiency, which are responsible for the majority of MSI-H, are typically due to somatic events like hypermethylation of the promoter of the MLH1 gene, leading to transcriptional silencing. The two pathways might differ in respect of prognosis and response to treatment.

The prognostic significance of MSI-H in colorectal cancer appears to vary depending on the stage of cancer. In the earlier stage CRC, primarily stages II and III, MSI-H has generally been associated with a more favorable prognosis compared to MSS tumors.[14,26,33–35] However, in the case of stage I CRC, no association of MSI status with prognosis has been found in studies. In stage II CRC, some studies have shown that MSI-H tumors are identified to be associated with improved disease-free survival (DFS) and overall survival (OS).[36,37] Thus, the need for adjuvant chemotherapy in this subset of patients has been put into doubt. There is some evidence to indicate that stage II MSI-H CRC patients may not benefit from adjuvant 5-fluorouracil (5-FU)-based chemotherapy and may even have worse results than surgery alone.[34,38,39] However, evidence is not entirely consistent, with one study indicating that chemotherapy can improve OS in stage II MSI-H patients, even those without high-risk features. High-risk features such as T4 disease, poor differentiation, lymphovascular invasion, and fewer than 12 lymph nodes sampled, in stage II MSI-H CRC may nevertheless portend a worse outcome and influence treatment.[40–43]

The prognostic value of MSI-H in stage III CRC appears to be less pronounced than in stage II. While MSI-H has classically meant a good prognosis in this stage as well, current guidelines often include the use of adjuvant chemotherapy with oxaliplatin in stage III CRC, regardless of MSI status.[15,44–46] This highlights the need for more studies to improve the tailoring of treatment regimens for stage III MSI-H CRC. Moreover, the prognostic implication of MSI-H in metastatic colorectal cancer (mCRC) is more complex and has yielded inconsistent results.[16] Some have suggested a better prognosis for MSI-H mCRC, whereas others have found no difference or a worse prognosis compared to MSS tumors in the metastatic setting. Several factors can account for these discrepant results.

A few of the important factors are the presence of simultaneous mutations, particularly in the BRAF gene and KRAS gene.[47–49] BRAF mutations are more common in sporadic MSI-H CRC and are likely to have a poorer prognosis in MSS tumors.[50–52] The interaction between BRAF and MSI-H in mCRC is complicated, and some evidence suggests that the poorer prognosis in some series of MSI-H mCRC can be influenced by the co-occurrence of BRAF mutations.[53–56] However, the prognostic influence of BRAF and KRAS mutations in MSI-H mCRC remains controversial.[56–58]

MATERIALS AND METHODS

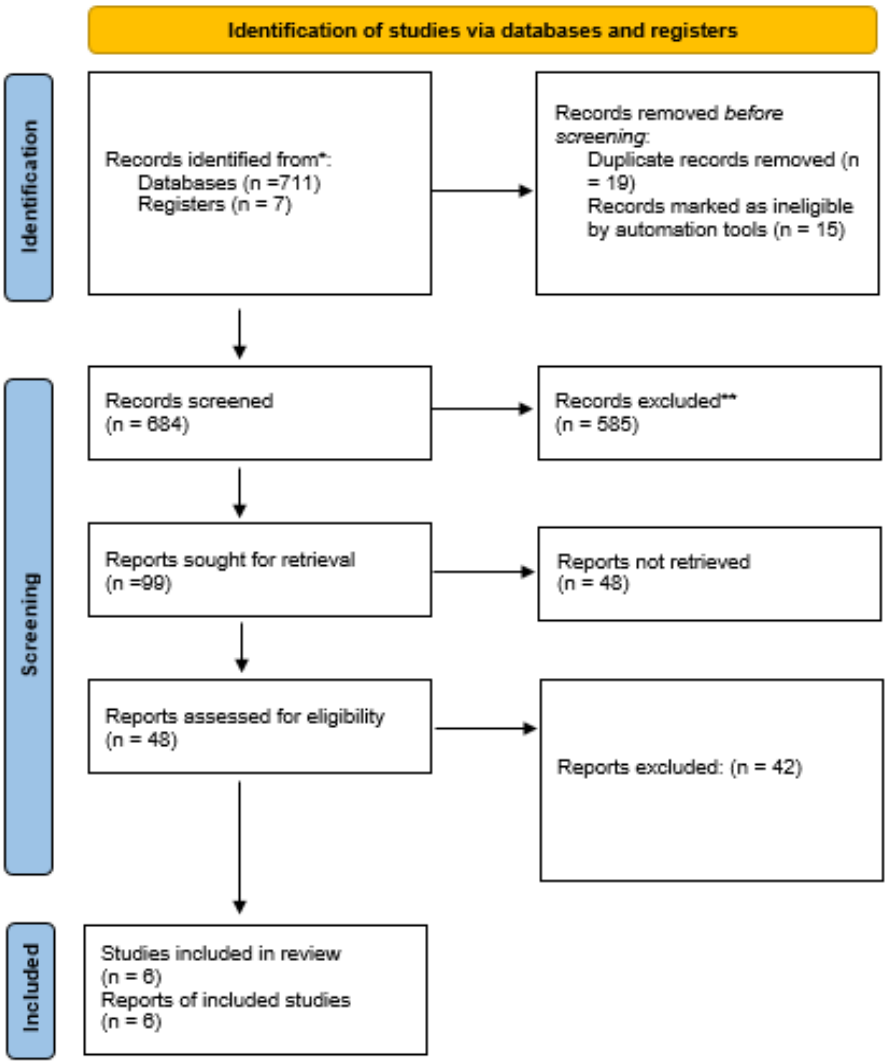
Search strategy and study selection

We conducted literature review using the following search strategy:

("colorectal cancer"[All Fields] AND "microsatellite instability"[All Fields]) AND (("surgery"[MeSH Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields] OR "surgery s"[All Fields] OR "surgerys"[All Fields] OR "surgeries"[All Fields]) AND ("prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields]))

((("prognostic value"[All Fields] AND "microsatellite instability"[All Fields]) AND "KRAS mutation"[All Fields]) AND "BRAF mutation"[All Fields]) AND "colorectal cancer"[All Fields]

There was a total of 718 studies. We included 6 studies in the study. Refer to the figure below.



Study Selection

Two independent reviewers screened titles and abstracts of the retrieved studies based on the eligibility criteria. Researchers used Covidence, an online software system, for study selection and record-keeping. The reviewers were not blinded to each other's decisions, as we aimed to foster a collaborative approach to study selection. Any disagreements in the selection process were resolved through discussion.

Data Extraction

Data extraction was conducted using a standardized data extraction form created in Microsoft Excel. The following information were extracted from each included study: study author, year of publication, study place, study design, participant demographics and baseline characteristics, outcomes of interest (i.e., progression-free survival, overall survival, KRAS/BRAF mutation) and measure of effect (hazard ratios). Two reviewers separately extracted data from the selected studies. All

discrepancies were resolved through discussion between the reviewers. In case where there were missing data or unreported outcomes, they took note of the missing information in the data extraction form. Thereafter, they assessed the potential impact on the overall results in the final review.

Data Synthesis Strategy and Management

We included studies that reported at least one of the outcomes of interest: progression-free survival, overall survival, or KRAS/BRAF mutation. We undertook a minimum of 3 studies reporting similar outcome measures for meta-analysis. This helped to achieve reliability. The following were the outcomes which were synthesized: progression-free survival, overall survival and BRAF/KRAS mutation. We used Microsoft Excel for data management, including storage and organization of extracted data. This allowed us to efficiently manage the data and facilitate the analysis process.

Risk of Bias Assessment

We assessed the risk of bias in included studies using the Cochrane Risk of Bias (RoB) 2.0 tool for randomized controlled trials and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for observational studies. The assessment was done at the study level for all included studies. Two reviewers independently assessed the risk of bias for each included study. Disagreements were resolved through discussion. Reviewers visually inspected funnel plots and performed Egger's regression test in order to assess the potential for publication bias.

Statistical analysis

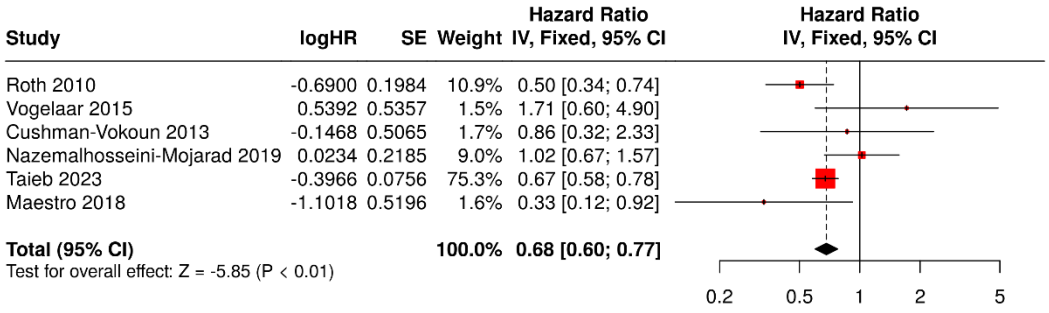
We performed the meta-analysis using a fixed effect model with the inverse variance method to calculate a summary hazard ratio (HR) and 95% confidence interval for progression-free and overall survival, and BRAF/KRAS mutation, with the aid of Statistical Software. Heterogeneity between studies was assessed using the I^2 statistic and Cochran's Q test.

RESULTS

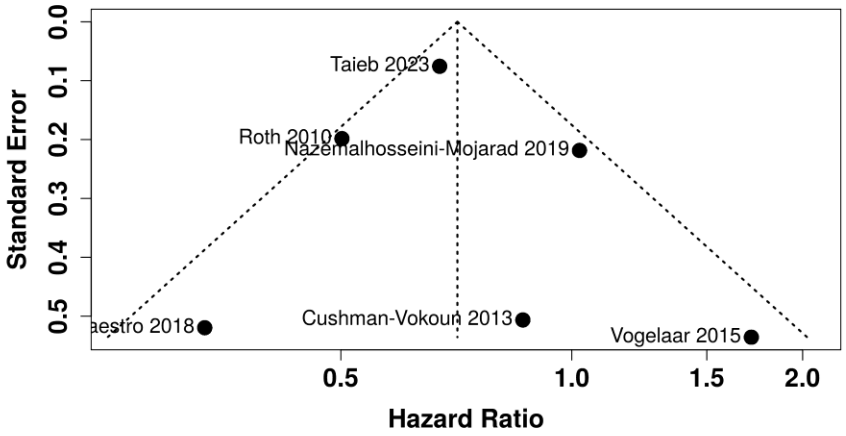
1. Overall Survival

a. MSI Overall Survival

Our meta-analysis evaluated six studies that provided data on the hazard rate for a specific MSI Overall Survival. To evaluate the efficacy of the intervention, we used a fixed effect model with the inverse variance method to calculate a summary hazard ratio (HR) and 95% confidence interval. The summary HR was calculated to be 0.68 (95% CI: 0.6 - 0.77), suggesting that the intervention was associated with a statistically significant 32% reduction in the hazard rate compared to the control group. Based on the analysis performed using fixed effect model with inverse variance method to compare the hazard rate (HR), a statistical difference can be observed, the summarized hazard rate (HR) is 0.68 with a 95% confidence interval of 0.6 - 0.77. The test for overall effect showed a significance at $p<0.05$. Results are presented in figure 2.



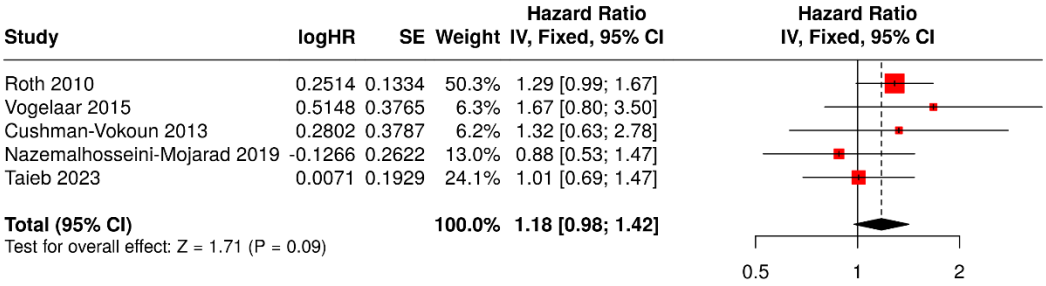
The funnel plot does not indicate a potential publication bias. The Egger's test does not support the presence of funnel plot asymmetry (intercept: 0.39, 95% CI:-1.64 - 2.41, t: 0.375, p-value: 0.727).



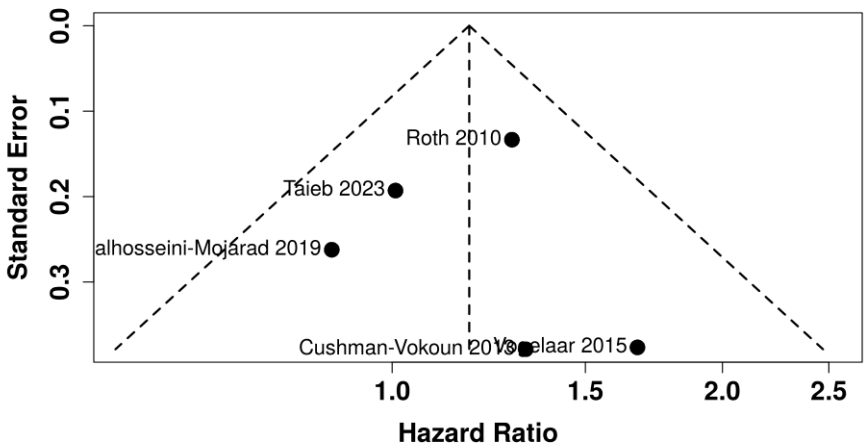
b. KRAS Mutation

Our meta-analysis evaluated five randomized controlled trials that provided data on the hazard rate for a specific Overall Survival in KRAS Mutation. To evaluate the efficacy of the intervention, we used a fixed effect model with the inverse variance method to calculate a summary hazard ratio (HR) and 95% confidence interval.

Based on the analysis performed using fixed effect model with inverse variance method to compare the hazard rate (HR), there is no statistical difference, the summarized hazard rate (HR) is 1.18 with a 95% confidence interval of 0.98 - 1.42. The test for overall effect does not show a significant effect.



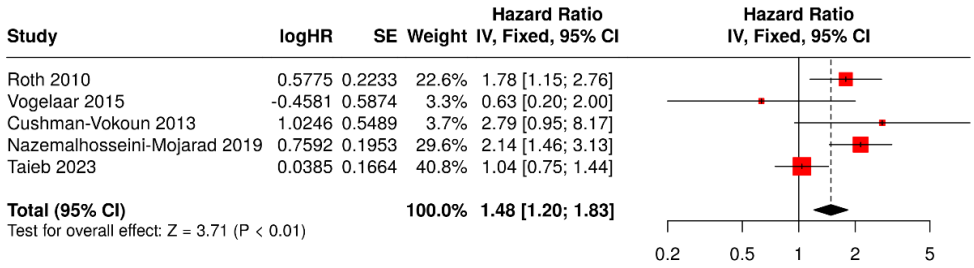
The funnel plot does not indicate a potential publication bias. The Egger's test does not support the presence of funnel plot asymmetry (intercept: 0.03, 95% CI:-2.34 - 2.4, t: 0.022, p-value: 0.984).



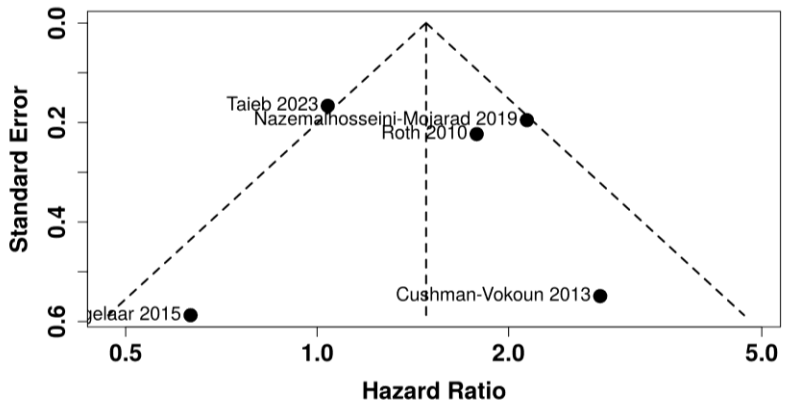
c. BRAF Mutation

Our meta-analysis evaluated five randomized controlled trials that provided data on the hazard rate for a specific Overall Survival in BRAF Mutation. To evaluate the efficacy of the intervention, we used a fixed effect model with the inverse variance method to calculate a summary hazard ratio (HR) and 95% confidence interval.

According to the investigation results using fixed effect model with inverse variance method to compare the hazard rate (HR), a statistical difference is present, the summarized hazard rate (HR) is 1.48 with a 95% confidence interval of 1.2 - 1.83. The test for overall effect points to a significant p value of less than 0.05.



The funnel plot does not indicate a potential publication bias. The Egger's test does not support the presence of funnel plot asymmetry (intercept: 0.28, 95% CI:-3.94 - 4.5, t: 0.131, p-value: 0.904).

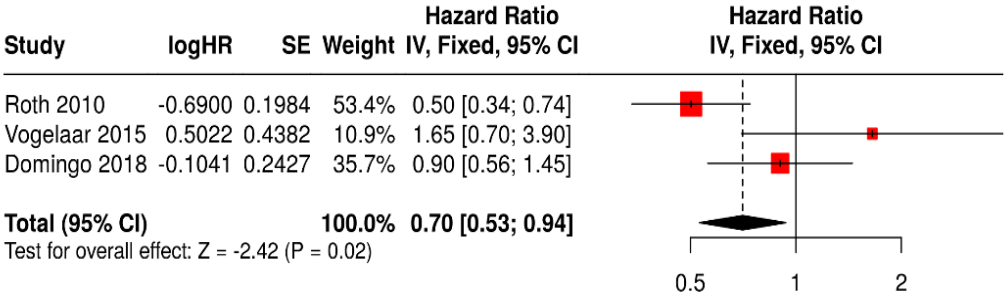


2. DFS/Progression-free Survival

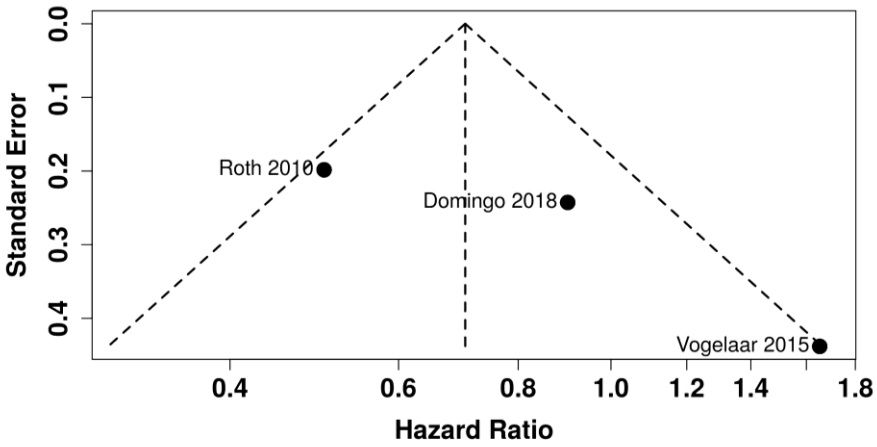
a. MSI-Progression-free Survival

Our meta-analysis evaluated three studies that provided data on the hazard rate for a specific MSI Progression-free survival. To evaluate the efficacy of the intervention, we used a fixed effect model with the inverse variance method to calculate a summary hazard ratio (HR) and 95% confidence interval.

According to the investigations performed using fixed effect model with inverse variance method to compare the hazard rate (HR), a statistical difference can be observed, the summarized hazard rate (HR) is 0.7 with a 95% confidence interval of 0.53 - 0.94. The test for overall effect verifies a statistical significance with a p value below 0.05.



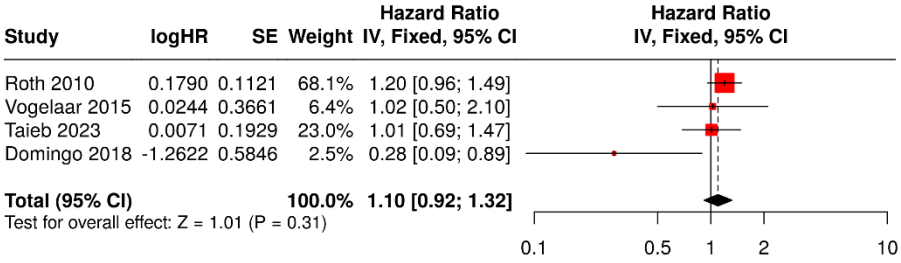
The funnel plot does not indicate a potential publication bias. The Egger's test does not support the presence of funnel plot asymmetry (intercept: 5.03, 95% CI:0.28 - 9.77, t: 2.076, p-value: 0.286).



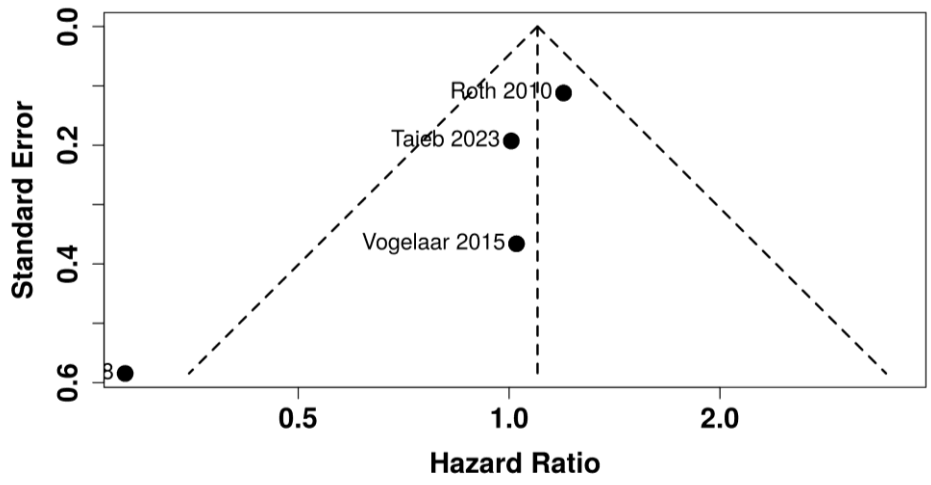
b. KRAS Mutation-DFS/PFS

Our meta-analysis evaluated four studies that provided data on the hazard rate for a specific Progression-free survival in KRAS Mutation. To evaluate the efficacy of the intervention, we used a fixed effect model with the inverse variance method to calculate a summary hazard ratio (HR) and 95% confidence interval.

Based on the analysis performed using fixed effect model with inverse variance method to compare the hazard rate (HR), there is no statistical difference, the summarized hazard rate (HR) is 1.1 with a 95% confidence interval of 0.92 - 1.32. The test for overall effect does not show a significant effect.



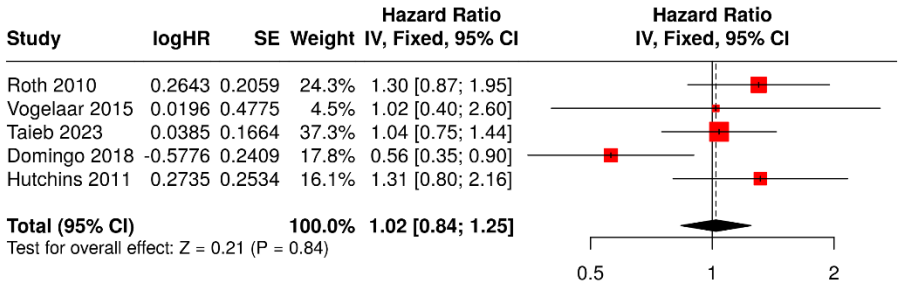
The funnel plot does not indicate a potential publication bias. The Egger's test does not support the presence of funnel plot asymmetry (intercept: -2.08, 95% CI:-3.81 - -0.35, t: -2.355, p-value: 0.143).



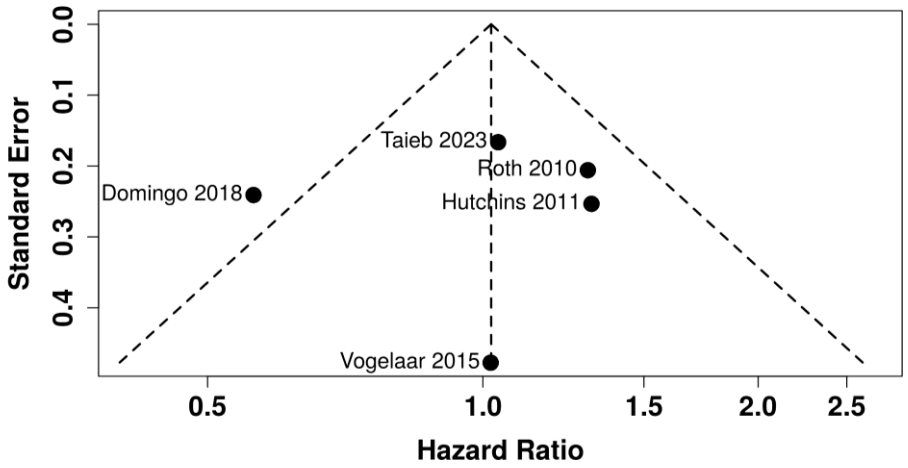
c. BRAF-DFS/PFS

Our meta-analysis evaluated five studies that provided data on the hazard rate for a specific progression-free survival in BRAF Mutation. To evaluate the efficacy of the intervention, we used a fixed effect model with the inverse variance method to calculate a summary hazard ratio (HR) and 95% confidence interval.

Based on the analysis performed using fixed effect model with inverse variance method to compare the hazard rate (HR), there is no statistical difference, the summarized hazard rate (HR) is 1.02 with a 95% confidence interval of 0.84 - 1.25. The test for overall effect does not show a significant effect.



The funnel plot does not indicate a potential publication bias. The Egger's test does not support the presence of funnel plot asymmetry (intercept: -0.47, 95% CI:-5.54 - 4.59, t: -0.184, p-value: 0.866).



DISCUSSION

This meta-analysis synthesized evidence from multiple studies to investigate the prognostic value of microsatellite instability (MSI) and KRAS/BRAF mutational status in colorectal cancer (CRC) patients undergoing surgical resection, often followed by adjuvant therapy. The principal findings of this study demonstrate a statistically significant association between MSI-high (MSI-H) status and improved overall survival (OS) and progression-free survival (PFS). Conversely, the presence of a BRAF mutation was significantly associated with poorer OS, while KRAS mutation did not show a statistically significant impact on either OS or PFS in this pooled analysis.

The detrimental impact of BRAF mutations on OS, as highlighted by our meta-analysis, aligns with existing literature indicating that BRAF-mutated CRC often presents with more aggressive features and poorer response to certain treatments.[8,59–64] While KRAS mutation alone did not reach statistical significance in our analysis for either OS or PFS, this could be due to the heterogeneity within KRAS mutations (e.g., different codon mutations) or the specific treatment regimens evaluated in the included studies. Previous research has suggested that certain KRAS mutations might confer differential prognostic or predictive value.[58,65–71]

Our findings partially support the initial hypothesis that MSI-H status would be associated with improved survival outcomes. However, the hypothesis regarding KRAS and BRAF mutations was not fully substantiated. While BRAF mutation demonstrated a clear negative prognostic impact on OS, KRAS mutation did not show

a significant association in this meta-analysis. The lack of a significant association for KRAS could be attributed to the diverse nature of KRAS mutations and their potentially varying effects on prognosis, a factor that this meta-analysis, pooling across different KRAS subtypes, might not fully capture.

This study introduces a broadened perspective on the interplay between molecular markers and CRC prognosis. While MSI is increasingly recognized as a positive prognostic factor, our analysis underscores the independent and potentially opposing role of BRAF mutations. This suggests that a combined assessment of MSI and BRAF status could provide a more refined prognostic stratification for CRC patients than considering these markers in isolation. Furthermore, the non-significant finding for overall KRAS mutation highlights the need for future research to delve deeper into the specific prognostic implications of different KRAS subtypes within the context of MSI status.

These outcomes hold significant importance for clinicians and researchers in the field of CRC management. The observed association of MSI-H status with better prognosis reinforces the growing understanding of its role as a favorable predictive biomarker. This finding suggests that identifying MSI status in resected CRC tumors can aid in risk stratification and potentially inform decisions regarding the intensity and duration of adjuvant therapy.[15,72–75] Patients with MSI-H tumors may experience a more indolent disease course and potentially derive less benefit from aggressive adjuvant regimens compared to those with microsatellite stable (MSS) tumors.[11,26,46,76]

While this study focused on the prognostic value in the context of surgical resection, the implications extend to the broader landscape of CRC management. If the prognostic significance of combined MSI and BRAF status is consistently validated, it could lead to the development of more precise risk stratification tools. This, in turn, could influence surveillance strategies, the selection of adjuvant therapies, and the intensity of follow-up, ultimately improving patient outcomes. Conversely, if these molecular markers are not routinely integrated into clinical practice, opportunities for personalized risk assessment and treatment optimization may be missed, potentially leading to under-treatment in high-risk groups or over-treatment in those with a more favorable prognosis.

This meta-analysis benefits from a systematic and comprehensive literature search, rigorous study selection, and independent data extraction and bias assessment, enhancing the reliability of our findings. The use of a fixed-effect model, where appropriate based on heterogeneity, provides a robust estimate of the pooled hazard ratios. Furthermore, the assessment of publication bias did not reveal significant asymmetry, suggesting that our results are less likely to be skewed by the selective publication of positive studies.

CONCLUSION, RECOMMENDATIONS AND LIMITATIONS

This meta-analysis provides compelling evidence that MSI-H status is associated with improved OS and PFS in CRC patients who have undergone surgical resection. Conversely, BRAF mutation is a significant indicator of poorer OS. While KRAS mutation alone did not demonstrate a significant prognostic impact in this pooled analysis, future research focusing on specific KRAS subtypes and their interaction with MSI status is warranted. The combined assessment of MSI and BRAF mutational status holds promise for refining prognostic evaluation in CRC and could potentially guide more personalized treatment strategies. A key take-away from this study is the importance of considering the distinct and sometimes opposing prognostic roles of different molecular markers in CRC to better understand disease trajectory and optimize patient care.

This study is not without limitations. The included studies may have varied in terms of patient demographics, tumor stage, surgical techniques, and adjuvant therapy regimens, which could introduce some degree of heterogeneity, although statistically assessed. While we aimed to minimize this by using a fixed-effect model when heterogeneity was low, residual confounding factors cannot be entirely excluded. Additionally, the number of studies available for some of the subgroup analyses (e.g., PFS in MSI-high) was relatively small, which might limit the statistical power to detect more subtle effects. The lack of individual patient data also prevented us from conducting more in-depth analyses, such as exploring the interaction effects between MSI and specific KRAS/BRAF mutations.

Several next steps can be taken to further pursue these unresolved questions. Firstly, future meta-analyses and individual patient data (IPD) meta-analyses should aim to explore the prognostic value of specific KRAS and BRAF mutation subtypes in relation to MSI status. Stratifying patients based on the specific KRAS codon mutations (e.g., G12V, G13D) and BRAF V600E versus non-V600E mutations could reveal more nuanced prognostic associations. Secondly, prospective studies are needed to validate these findings in diverse patient populations and treatment settings. These studies should also investigate the predictive value of combined MSI and KRAS/BRAF status in response to different adjuvant therapies. Understanding how these molecular markers interact with treatment outcomes is crucial for developing personalized therapeutic strategies.

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