p53 Mutations' Prognostic Significance in Metastatic Colorectal Cancer: A Comprehensive Study and Meta-Analysis

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Abstract

One of the genes that is most frequently altered in colorectal cancer (CRC) is P53. The goal of the current investigation was to establish a reliable estimate of the prognostic significance of *p53* mutations in individuals with metastatic CRC. The Preferred Reporting Item for Systematic Reviews and Meta-Analysis 2020 standards were followed for conducting this meta-analysis. PubMed and Google Scholar were used to look up studies written in English and published in the previous 10 years. the presence of Hazard Ratios (HRs) with 95% Confidence Intervals (CIs), and 1) relationship with overall survival as the final selection criteria. Using the Newcastle-Ottawa Scale and the QUIPS instrument, the articles were assessed for quality and bias risk. The Hartung-Knapp-Sidik-Jonkman method was used to do the meta-analysis, and the findings were presented in traditional Forest plots. Statistics like I2 and Tau2 were used to gauge study heterogeneity. The *p53* mutation's connection to clinic-pathological factors was investigated using the 2 test

Keywords: *p53* prognosis; Mutations; Metastatic colorectal cancer; Meta-analysis

Introduction

A significant portion of cancer-related fatalities globally are caused by metastatic Colorectal Cancer (CRC). A projected 1.8 million new cases and 862,000 fatalities from metastatic CRC were reported in 2018.The overall survival rate for metastatic CRC remains low, with a 5-year survival rate of less than 10%, in spite of advancements in systemic treatment options such chemotherapy, targeted therapy, and immunotherapy. The emergence of resistance limits the effect of treatments on overall survival, stressing the demand for novel therapeutic approches and tactics. It's interesting how recent developments in the genetic understanding of metastatic CRC have improved our comprehension of the disease's underlying mechanisms. The development of molecularly stratified trials has been prompted by the finding of various genetic variants associated with a poor prognosis and resistance to therapy as a result of these advancements.One of these mutations that occurs most frequently in metastatic CRC is p53. It is situated on chromosome 17's short arm, sometimes referred to as the "guardian of the genome," and it is important for both physiologic and pathological disorders, including cancer.When *p53* is working properly, it serves as a transcription factor to activate downstream target genes that encourage cell growth arrest, DNA repair, or programmed cell death. *p53* functions primarily as a tumour suppressor by causing cell death in response to DNA damage. Loss of Function (LOF) and Gain of Function (GOF) are two outcomes of *p53* gene mutations. The most prevalent kind of *p53* mutations in cancer, called LOF mutations, prevent the *p53* protein from acting as a tumour suppressor. On the other hand, GOF mutations give the p53 protein new oncogenic capabilities, which increases the risk of cancer growth and development. These mutations are linked to more aggressive cancer phenotypes and activate *p53* in the absence of DNA damage. This meta-analysis followed the principles of the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) 2020 criteria and was reported with the PROSPERO registry. The following search terms were used to find a total of 140 studies: "metastatic colorectal cancer" OR "metastatic colorectal tumour" OR "metastatic colorectal carcinoma" AND "p53" OR "tp53" AND "prognosis" OR "survival"". Despite the known role of *p53* in cancer, the specific prognostic relationship between *p53* and metastatic CRC is not well understood. In order to provide a strong and higher level of evidence on its potential clinical role in an evolutionary context where molecular assessments are increasingly gaining space in patient management, the current study was conducted to pool the data on the prognostic value of *p53* mutations in metastatic CRC patients. The Hartung-Knapp-Sidik-Jonkman technique was utilised to conduct this meta-analysis, but due to the heterogeneity seen across the studies, a random-effects model was adopted. In a nutshell, a fixed-effects model presupposes that the true effect size is constant throughout all studies that are integrated and that any reported variations in effect sizes among studies are the result of random error. Contrarily, a random-effects model presupposes that the true effect size varies among studies and that the observed variations in effect sizes are caused by both random error and genuine variations in effect sizes. The summary effect is the weighted average of the effects reported in the many research. The random-effects model assumes that the genuine effects vary between studies. It is the preferable model when heterogeneity is present because it seeks to provide a more cautious estimate of the pooled HR. Results of the meta-analysis are shown in traditional Forest plots, along with HRs, 95% CIs, and a final pooled HR. The I2 and Tau2 statistics were used to quantify the degree of heterogeneity (difference between studies). The first determines the percentage of observed variation that is attributable to genuine differences rather than random variation. I2 is calculated using the equation I2 = 100% x (Q - DF)/Q, where Q stands for the degrees of freedom and DF for the Cochran's heterogeneity statistic. To guarantee that I2 falls between 0% and 100%, negative I2 values are set to zero. No observable heterogeneity is indicated by a value of 0%, while increasing heterogeneity is indicated by higher values. Tau2 was used in addition to I2 to determine how heterogeneous the studies in our meta-analysis were. It is a measurement of the variation between research that accounts for the size of the various investigations. Tau2 calculates the absolute amount of the between-study variation as opposed to I2, which offers a relative measure of heterogeneity. Tau2 is particularly helpful when studies have different sample sizes and effect estimations, whereas I2 is frequently used to measure heterogeneity in meta-analyses. It is important to note, nonetheless, that the chosen studies showed significant heterogeneity that might have an impact on the consistency and dependability of the *p53* prognostic function in the metastatic clinical scenario of CRC. One drawback is that the methods and scope of *p53* sequencing varied, which may have resulted in a large underestimating of *p53* changes. One study was the only one to distinguish between the prognostic impact of LOF and GOF mutations, which may have consequences for the assessment of prognosis. In reality, both kinds of modifications have the potential to cause cancer-related occurrences in theory however they might have different effects on how the prognosis develops. A significant drawback given the genetic dynamism of cancer is the fact that information regarding the analysed tissue (whether primary or metastatic) is frequently elusive. Consequently, the wild-type gene in primary tissue can change into a mutant version in the metastatic progeny, and the inverse phenomena known as "regressive trajectories" is also conceivable. Another drawback is the surprising lack of prospective investigations on the prognostic significance of *p53* in metastatic CRC in the literature. Finally, there was a wide range in the study sample sizes. The retrospective nature of the investigations and the varied sample size could both introduce unidentified and uncontrollable biases that could potentially affect the outcomes.

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