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Synergistic Impact of ARSB, TP53, and Maspin Gene Expressions on Survival Outcomes in Colorectal Cancer: A Comprehensive Clinicopathological Analysis

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Abstract: (1) Background: Colorectal cancer (CRC) remains a significant cause of morbidity and mortality worldwide, with its prognosis influenced by genetic and clinicopathological factors. This study investigates the associations between the gene expressions of Arylsulfatase B (ARSB), TP53, and Maspin, alongside traditional clinicopathological features, and their impact on CRC survival outcomes. (2) Methods: 70 consecutive CRC cases were analyzed for ARSB, TP53, and Maspin gene expression using RT-qPCR, and their protein levels were assessed through immunohistochemistry. Clinicopathological parameters—age, gender, tumor localization, macroscopic and microscopic aspects, lymph node ratio, pT stage, and tumor budding—were evaluated for their prognostic significance. Kaplan–Meier survival analysis with Cox proportional hazards regression was used to determine their impact on overall survival. (3) Results: No significant survival differences were observed based on age, gender, tumor localization, and macroscopic aspect. The microscopic aspect and pT stage showed significant associations with survival, with poorer outcomes in G3 and pT3/pT4 stages, respectively. Immunohistochemical positivity for ARSB and Maspin indicated a longer survival, while TP53 protein expression alone did not significantly impact the prognosis. Dual high gene expression (ARSB + TP53, TP53 + Maspin) and triple high gene expression (ARSB + TP53 + Maspin) were significantly associated with better survival outcomes. (4) Conclusions: The combined gene expression profile of ARSB, TP53, and Maspin presents a novel prognostic marker in CRC, offering insights into the molecular dynamics of cancer cells and potential therapeutic targets. These findings emphasize the importance of integrating molecular markers with traditional clinicopathological factors for a more accurate prognostication and personalized treatment approach in CRC.

Keywords: Arylsulfatase B; TP53; Maspin; colorectal cancer

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1. Introduction

The molecular landscape of colorectal cancer (CRC) is a testament to the complexity of cancer biology, showcasing the genetic interactions and expressions that underpin the disease's progression and response to treatment. Central to this landscape are three key markers of this study: Arylsulfatase B (ARSB), TP53, and Maspin, each contributing uniquely to the oncogenic process. ARSB is a lysosomal enzyme involved in the degradation of glycosaminoglycans, molecules pivotal for cell signaling and tissue organization. Studies have shown that ARSB plays a significant role in modulating the tumor microenvironment, influencing CRC aggressiveness and patient prognosis. The decreased expression of ARSB

has been correlated with enhanced tumor growth, invasion, and metastasis [1]. ARSB is proven to play role in CRC progression, suggesting that it could serve as a marker for CRC aggressiveness and a potential therapeutic target [2]. TP53, known for its critical function in cell cycle regulation, apoptosis, and genomic stability, is one of the most extensively studied genes in cancer biology. Mutations in TP53 are prevalent in CRC, leading to a loss of function and contributing to tumor development, progression, and resistance to chemotherapy. The nature and location of TP53 mutations are determinant factors in the clinical outcomes of CRC patients. A comprehensive review discusses the multifaceted roles of TP53 mutations in CRC, underscoring their impact on disease prognosis and treatment strategies [3–5]. Maspin, a serine protease inhibitor with multifaceted roles in cancer biology, is implicated in tumor suppression, apoptosis regulation, and the inhibition of metastasis and angiogenesis. Its expression in CRC has been associated with tumor differentiation, invasion, and patient survival, suggesting its potential utility as a prognostic marker and therapeutic target [6–8]. The investigation of Maspin, TP53, and ARSB in CRC not only provides a deeper understanding of the molecular mechanisms driving the disease, but also highlights the potential of these markers in improving the diagnosis, prognostication, and development of personalized therapeutic strategies.

The aim of this study was to investigate the possible role of Maspin, TP53 and ARSB in CRC progression, and to highlight the prognostic importance of their dual or triple expression.

2. Materials and Methods

2.1. Selection of the Cases

This prospective study was conducted with the approval of the Ethics Committee of Mures County Clinical Emergency Hospital and adhered to the ethical standards of the Declaration of Helsinki. Informed consent was obtained from all participants involved in the study. The cohort consisted of 70 consecutive patients diagnosed with CRC at the Department of Pathology, Mures County Clinical Emergency Hospital. Inclusion criteria were a confirmed diagnosis of CRC, based on histopathological examination, with no history of preoperative chemotherapy or radiotherapy to ensure that the untreated nature of the disease was studied. Patients were randomly selected to encompass a broad spectrum of CRC stages, ensuring a representative sample. The follow-up period ranged from 1 to 33 months, during which patients' clinical outcomes, recurrence, and survival status were tracked. This longitudinal follow-up allowed for the observation of disease progression and response to postoperative treatments, providing valuable insights into the natural history of CRC and the potential prognostic significance of ARSB, TP53, and Maspin gene expression profiles.

2.2. Immunohistochemical Study

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded CRC tissue sections to assess the expression of Maspin, TP53, and ARSB (Table 1). For the detection of tumor budding, Maspin was used as a specific marker, while TP53 and ARSB expression were evaluated to investigate their roles in tumor progression and environment interaction. The immunoreactivity for Maspin, TP53, and ARSB was assessed semiquantitatively based on the intensity and extent of staining in the tumor cells. The evaluation was performed by two independent observers blind to the clinical data, ensuring objective analysis of the staining patterns and intensities (Figure 1).

Table 1. Characteristics of immunohistochemical markers.

Marker	Antibody Type	Clone	Antigen Retrieval	pH
Arylsufatase B	Rabbit polyclonal	Ab 181410 (Abcam)	High pH (Dako)	9
TP53	Mouse monoclonal	Ab-5 (ThermoScientific)	10 mM citrate (Dako)	6
Maspin	Mouse monoclonal	BSB-92 (BioSB)	High pH (Dako)	9

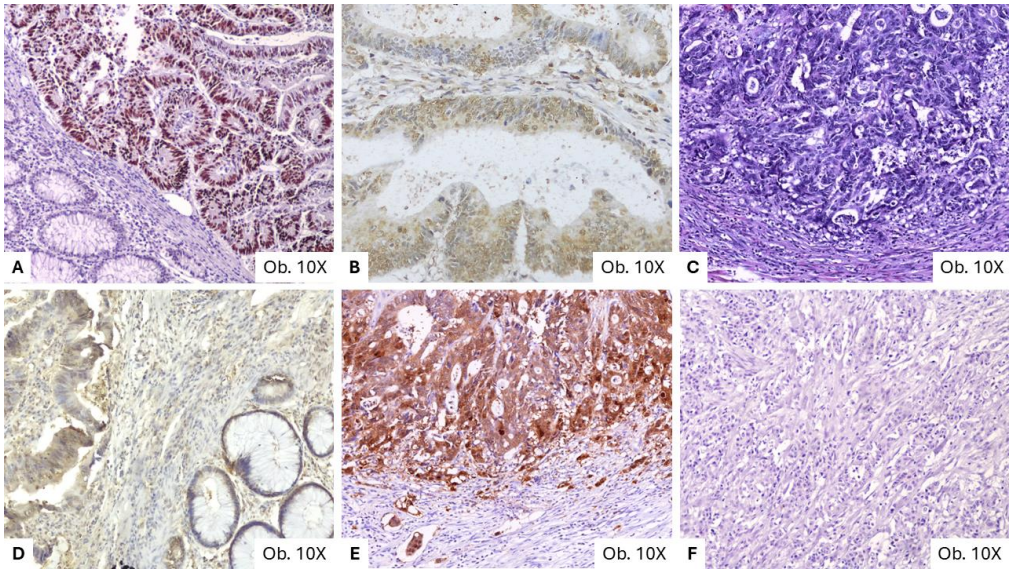

Figure 1. Immunohistochemical staining: (**A**) TP53 positivity over 50%; (**B**) ARSB positivity over 50%; (**C**) TP53 negativity, (**D**) ARSB-negative normal tissue, in addition to positive cancer cells; (**E**) Maspin positivity; (**F**) Maspin negativity.

2.3. Gene Expression Study

Gene expression analyses were carried out on fresh tissue samples harvested during surgical resection from each patient. RNA isolation was performed using Qiagen's (Germany) RNA extraction kit, adhering strictly to the manufacturer's protocols to ensure the integrity and quality of the RNA. The concentration and purity of isolated RNA were assessed using a NanoDrop (Thermo Fisher Scientific, Waltham, MA, USA) spectrophotometer, with only high-quality RNA samples proceeding to the next stage of analysis. For the quantification of ARSB, TP53, and Maspin gene expressions, reverse transcription quantitative PCR (RT-qPCR) was conducted using Qiagen's (Germany) RT-qPCR kit, following the manufacturer's instructions. This approach allowed for the precise quantification of mRNA levels of the target genes, with GAPDH serving as an internal reference gene to normalize the expression data. The relative expression levels of ARSB, TP53, and Maspin were calculated by employing the $2^{-\Delta\Delta Ct}$ method, which facilitates the comparison of gene expression among the patient samples in a relative manner. For the purposes of this study, gene expression levels were categorized based on their relative quantification (RQ) values: an RQ less than 1 indicated low gene expression, while an RQ greater than 1 signified high gene expression. This binary categorization allowed for a straightforward interpretation of the data, facilitating the subsequent statistical analysis to discern the correlation between gene expression levels and various clinical outcomes (Figure 2).

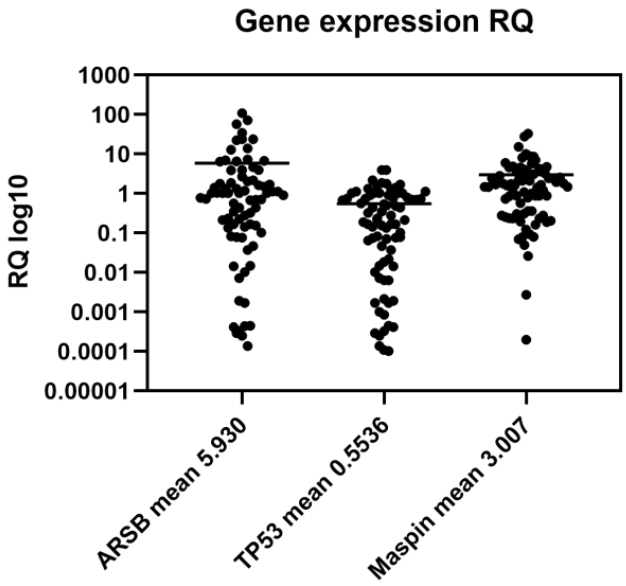

Figure 2. Median gene expression levels after relative quantification.

2.4. Statistical Analysis

Statistical analysis of the gene expression data was conducted using GraphPad Prism software, version 8, employing Chi-square (χ^2) and Fisher's exact tests to evaluate the relationships between gene expression profiles and categorical clinical outcomes, such as the presence or absence of metastasis, tumor staging, and survival rates. These tests were chosen for their suitability in analyzing categorical data, allowing for the assessment of the significance of associations between the gene expression levels and pathological parameters. A p-value of less than 0.05 was considered statistically significant, indicating meaningful association. Survival analysis was conducted to evaluate the impact of ARSB and TP53 gene expression, along with the immunohistochemical expression of Maspin, ARSB, and TP53 proteins, on the overall survival of colorectal cancer patients. Kaplan–Meier survival curves were generated to visually compare the survival rates between patient groups based on high and low expression levels of these markers. Differences in survival rates were statistically assessed using the log-rank (Mantel–Cox) test, which provided insights into the significance of each marker's expression on patient prognosis. Cox proportional hazards regression analysis was employed to adjust for potential confounding variables, such as age, gender, tumor localization, and lymph node ratio, thereby refining the estimation of the hazard ratios for mortality associated with each marker. This methodological approach enabled the identification of prognostic factors that significantly affect the survival outcomes of patients with colorectal cancer, facilitating a deeper understanding of the disease's molecular underpinnings and their implications for patient management.

3. Results

3.1. Gene Expression, Immunohistochemical Markers, and Clinicopathological Features

Significant findings were observed in the expression of ARSB and Maspin genes in relation to various clinicopathological features and their immunohistochemical expression patterns. Notably, both ARSB (p = 0.0462) and Maspin (p = 0.0412) gene expressions were significantly influenced by patient age, indicating a potential age-related impact on their expression levels (Table 2).

Table 2. Correlation between ARSB, TP53, and Maspin gene expression and pathological aspects of colorectal cancer.

Charateristics	Number	ARSB Gene Expression RQ		*p* Value	TP53 Gene Expression RQ		*p* Value	Maspin Gene Expression RQ		*p* Value
		<1	>1		<1	>1		<1	>1	
Age										
≤60 years	17	12	5	0.0462 *[1]	16	1	0.0726 [1]	14	3	0.0412 [1]
>60 years	53	25	33		39	14		29	24	
Gender										
Male	43	21	20	0.5148 [1]	32	11	0.2852 [1]	28	13	0.8560 [1]
Female	27	16	11		23	4		19	8	
Macroscopic aspect										
Vegetant–ulcero-vegetant	27	18	9	0.0164 *[2]	22	5	0.6382 [2]	21	6	0.3514 [2]
Infiltrative–ulcero infiltrative	43	16	27		33	10		29	14	
Microscopic aspect										
G1	16	7	9	0.0018 *[2]	12	4	0.6020 [2]	13	3	0.1451 [2]
G2	20	5	15		14	6		10	10	
G3	34	25	9		27	6		14	10	
Localization										
Proximal	26	12	14	0.3593 [2]	23	3	0.6169 [2]	20	6	0.5818 [2]
Distal	28	15	13		22	6		19	9	
Rectal	16	11	5		13	3		10	6	
LNR										
<0.15	59	31	28	0.4977 [1]	49	10	0.9207 [1]	39	29	0.8615 [1]
≥0.15	11	7	4		9	2		6	5	
pT stage										
≤T2	4	4	0	0.0587 [1]	4	0	0.3488 [1]	4	0	0.2622 [1]
≥T3	66	34	32		54	12		50	16	
Budding										
G1	23	8	15	0.0456 *[1]	19	4	0.3789	7	16	0.0165 *[2]
G2	19	8	11		14	5		7	12	
G3	28	19	9		25	3		19	9	
Maspin IHC										
Positive	38	26	12	0.0097 *[1]	29	9	0.4010 [1]	28	9	<0.0001 [1]
Negative	32	12	20		27	5		8	24	
ARSB IHC										
Positive	47	34	13	0.0026 *[1]	33	14	0.4770 [1]	33	14	0.0309 [1]
Negative	23	8	15		18	5		10	13	
TP53 IHC										
<50%	43	10	34	0.0019 *[1]	15	28	0.0014 *[1]	12	31	0.0005 [1]
>50%	27	16	11		20	7		19	8	

[1] Chi-square (χ^2) test, [2] Fisher's exact test, significant differences are marked with *. G1: well differentiated, G2: moderately differentiated, G3: poorly differentiated.

Further analysis revealed that ARSB gene expression differed significantly with respect to the macroscopic aspect of tumors. Vegetant and ulcero-vegetant tumors exhibited distinct expression profiles compared to infiltrative and ulcero-infiltrative tumors, suggesting that ARSB gene expression may be indicative of the tumor's growth pattern and invasiveness

(p = 0.0164). Additionally, a significant difference in ARSB gene expression was identified across microscopic stages (G1 vs. G2 vs. G3), highlighting its potential role in tumor differentiation and progression, with 35.7% of the cases showing low ARSB gene expression (RQ < 1). In terms of tumor budding, both ARSB (p = 0.0456) and Maspin (p = 0.0165) gene expressions showed significant differences, with consistent results observed across G1, G2, and G3 stages. This finding underscores the potential involvement of these genes in the process of tumor invasion and metastasis. This study also demonstrated significant correlations between the gene expressions of ARSB and Maspin with their respective protein expressions evaluated through immunohistochemistry, as well as with TP53 protein expression (Table 2). These correlations suggest that ARSB and Maspin not only play crucial roles in the molecular landscape of CRC, but also interact with key regulatory pathways implicated in tumor behavior and patient prognosis. These results provide valuable insights into the complex molecular interactions in CRC, highlighting the significance of ARSB and Maspin in CRC and their potential as markers for disease characterization and therapeutic targeting.

3.2. Overall Survival

In assessing the impact of various clinicopathological factors on overall survival in CRC, our analysis revealed no significant differences based on age, gender, tumor localization, or macroscopic aspect of the tumors (Figure 3). These findings suggest that, within the cohort studied, these specific demographic and tumor characteristics do not independently influence the survival outcomes of patients. Despite the variability inherent in patient demographics and tumor presentations, these factors did not correlate with significant variations in survival rates, indicating that other molecular or genetic markers may play more critical roles in determining patient prognosis in colorectal cancer.

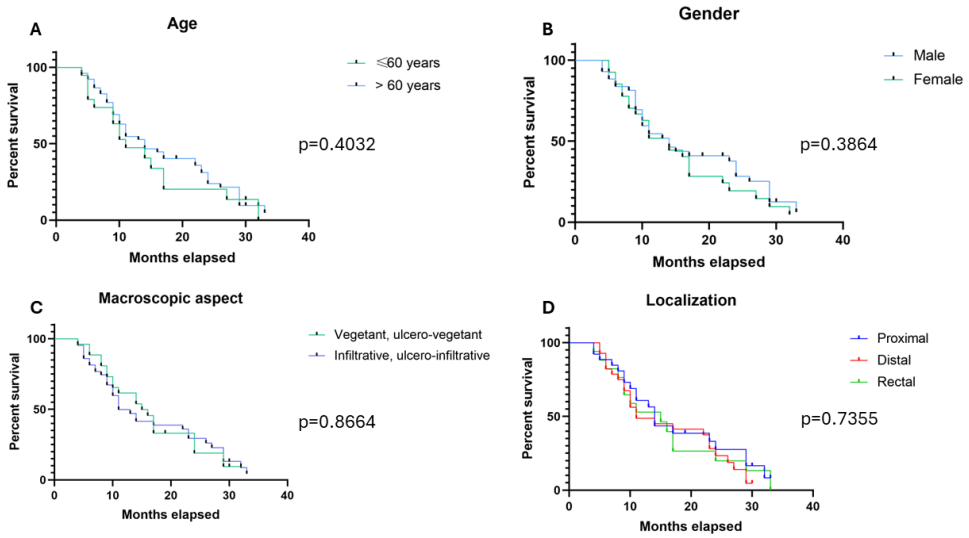

Figure 3. Kaplan–Meier survival curves demonstrating the lack of significant impact of age (**A**), gender (**B**), tumor localization (**D**), and macroscopic aspect (**C**) on overall survival in CRC patients.

The analysis indicated that neither lymph node ratio nor tumor budding significantly impacted survival outcomes. This suggests that these parameters, while indicative of tumor behavior and potential spread, do not alone dictate survival probabilities within the observed cohort. Conversely, significant differences in survival were observed when considering the microscopic aspect and pT stage of the tumors. Patients with tumors classified as G1 and G2 stages experienced better survival outcomes compared to those with G3-stage tumors, highlighting the importance of tumor differentiation as a prognostic indicator. Additionally, cases with a pT stage of less than 2 demonstrated improved survival compared to those with more advanced pT stages (Figure 4).

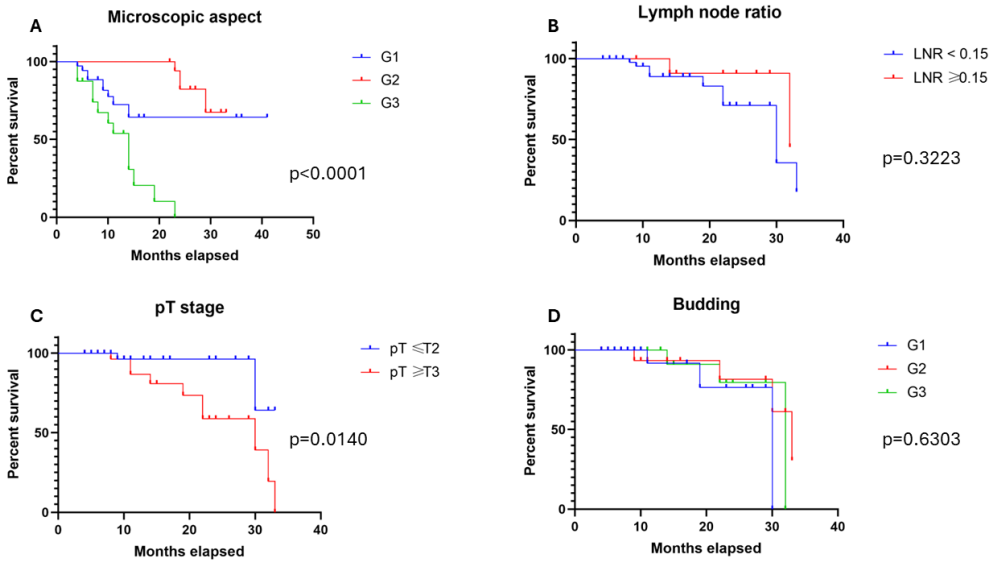

Figure 4. Kaplan–Meier curves highlighting the prognostic significance of microscopic aspect (**A**) and pT stage (**C**), with lymph node ratio (**B**) and budding (**D**) showing no significant impact.

In our comprehensive analysis of immunohistochemical markers and their impact on overall survival, distinct patterns emerged regarding the prognostic significance of ARSB, Maspin, and TP53 protein expressions. Positivity for ARSB, as determined by immunohistochemistry, was associated with better survival outcomes, suggesting its potential role as a protective factor in CRC progression. Similarly, Maspin positivity was linked to improved survival, indicating that its expression might confer a survival advantage, possibly through its effects on tumor suppression and the inhibition of metastasis. However, the immunohistochemical expression of TP53 showed no significant difference in survival (Figure 5).

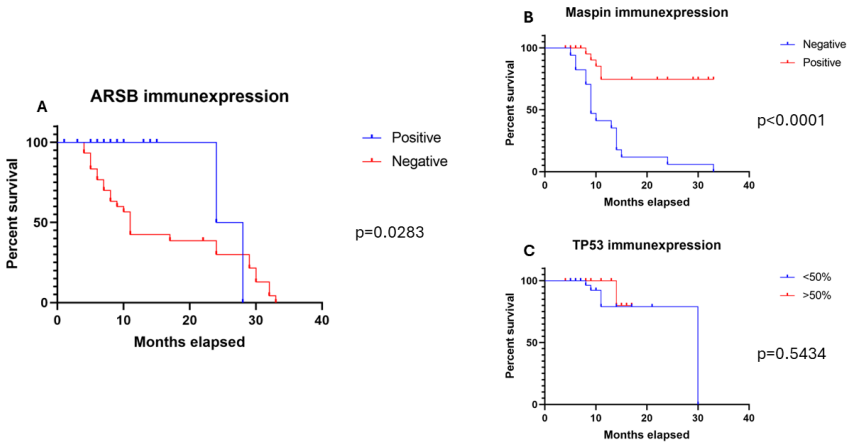

Figure 5. Immunohistochemical analysis of ARSB (**A**) and Maspin (**B**) impact on survival: significant prognostic value contrasted with TP53's (**C**) non-significant influence.

In the exploration of gene expression profiles and their correlation with survival outcomes, our study unveiled noteworthy trends regarding the collective expression of ARSB, TP53, and Maspin. Analysis revealed that patients exhibiting a relative quantification greater than 1 for both ARSB and TP53 genes experienced significantly better survival, suggesting a synergistic effect of these genes in enhancing patient prognosis. Similarly, a combination of TP53 and Maspin genes with RQ > 1 was associated with improved prognostic outcomes, indicating the potential of these markers in predicting favorable survival. Most compellingly, our analysis demonstrated that patients with overexpression (RQ > 1) of all three genes—ARSB, TP53, and Maspin—showed the best survival outcomes,

underscoring the powerful prognostic value of these combined gene expressions in CRC. Conversely, a scenario where all three genes had RQ < 1 was linked to poorer survival, highlighting the critical impact of these genes' underexpression on patient prognosis (Figure 6).

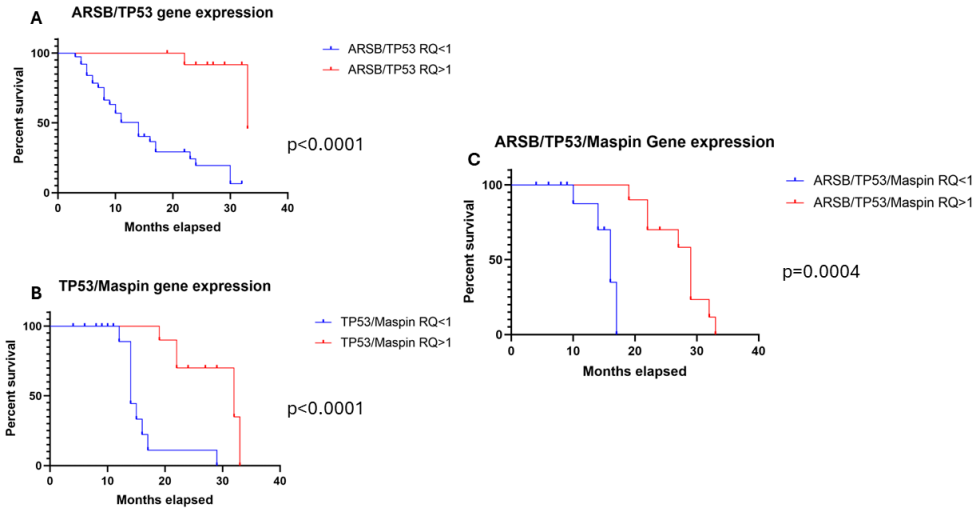

Figure 6. Enhanced survival in linked to dual and triple gene expression elevations: ARSB + TP53 (**A**) and TP53 + Maspin (**B**) combinations, and high ARSB, TP53, and Maspin (**C**) expression synergy.

4. Discussion

This study explores the intricate relationship between clinicopathological features, immunohistochemical expressions, gene expression profiles, and their collective impact on patient survival. This section draws upon the existing literature to contextualize our findings, shedding light on the complex interplay of molecular markers in CRC progression and prognosis.

Our results indicated no significant correlation between TP53 gene expression and a range of clinicopathological features, including age, gender, tumor localization, and macroscopic and microscopic aspects. This lack of association stands in contrast to the significant correlation observed between TP53 gene expression and its immunohistochemical expression, suggesting that while TP53 protein levels might reflect tumor behavior, its gene expression alone does not directly correlate with the traditional clinicopathological indicators of CRC. This finding aligns with research suggesting that TP53 mutations, rather than expression levels, might play a more pivotal role in CRC pathogenesis [9–13].

Significant differences in ARSB gene expression were found related to age, macroscopic aspect, and microscopic aspect, underscoring the gene's potential role in the biological aggressiveness of CRC. Specifically, higher ARSB expression in infiltrative, ulcero-infiltrative tumors, and its decreased expression in G3-stage cases, suggests ARSB's involvement in tumor differentiation and invasion, akin to findings from previous studies [2,14–16]. Moreover, the significant correlation of ARSB expression with tumor budding, and its immunohistochemical expression alongside Maspin and TP53, further emphasizes its intricate role in CRC's molecular landscape, possibly through modulation of the tumor microenvironment [1,2].

Maspin gene expression presented noteworthy associations with age, tumor budding, and immunohistochemical expressions of Maspin, ARSB, and TP53, particularly highlighting its decreased expression in aggressive tumor behaviors (e.g., G3 budding). This pattern indicates Maspin's potential protective role against CRC progression, a notion supported by the literature that links Maspin with tumor suppression and apoptosis [17,18]. The observed discrepancies in Maspin expression relative to ARSB and TP53 immunohistochemistry point to complex regulatory mechanisms influencing CRC dynamics, warranting further investigation into their potential therapeutic implications [1,8,19].

The survival analysis illuminated the prognostic significance of microscopic aspect and pT stage, with poorer outcomes associated with G3 classification and pT > 3 stage, respectively. These findings are consistent with the established understanding that a higher tumor grade and advanced invasion depth are indicative of aggressive disease and worse prognosis [20]. Interestingly, while ARSB and Maspin were negativity correlated with reduced survival, TP53 immunohistochemistry alone did not exhibit a significant survival impact. This divergence underscores the complexity of TP53 role in CRC survival, possibly related to the diverse functional consequences of TP53 mutations [4]. Different expression profiles of TP53 gene highlight the possibility of mutation in the gene itself.

Notably, dual high gene expression (ARSB + TP53 and TP53 + Maspin) and triple high gene expression (ARSB + TP53 + Maspin) were associated with significantly better survival. These results suggest a synergistic effect of these genes in modulating CRC outcomes, a novel insight that could pave the way for multifaceted molecular targeting in CRC therapy [1,2,11,15,21]. The superior survival linked to combined gene overexpression highlights the importance of a comprehensive molecular profiling approach in CRC prognostication and treatment planning.

5. Conclusions

Our study contributes valuable insights into the prognostic landscape of CRC, emphasizing the complex interplay between molecular markers and traditional clinicopathological features. The significant associations between gene expression profiles, particularly in combined analysis, and CRC survival open new avenues for research into targeted therapeutic strategies. Future studies should focus on elucidating the molecular pathways underpinning these relationships, aiming to optimize CRC management through personalized medicine approaches.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Mures County Clinical Emergency Hospital, Targu Mures, Romania.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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