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The Cancer Control Challenge:
Better Understanding It to Better Face It

MMP FAMILY GENE EXPRESSION PROFILES AND THEIR CLINICOPATHOLOGICAL ASSOCIATIONS IN GASTRIC CANCER PATIENTS FROM PARÁ, BRAZIL

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Introduction: Gastric cancer is the fifth most common type of cancer worldwide, while in the state of Pará, it is the second most frequent. Factors contributing to this high incidence include late diagnosis and tumor heterogeneity. Genes from the matrix metalloproteinase (MMP) family also play a role in the development and progression of gastric cancer, particularly in the modulation of the extracellular matrix (ECM). **Objectives:** we aimed to investigate the expression profile of genes from the MMP family and their association with clinicopathological factors in gastric cancer patients from the state of Pará. **Methods:** For this purpose, samples from patients treated at a reference oncology center in the state of Pará were used. A total of 88 samples were analyzed: 34 paired samples of tumor and adjacent tissue, 15 tumor-only samples, and 5 non-tumor adjacent tissues (CAAE 10272913.8.0000.0017). Total RNA was extracted using TRIzol® and its integrity was evaluated with the 2200 TapeStation System (Agilent Technologies). RNA sequencing was conducted on the Illumina NextSeq platform (USA). Sequencing reads were converted to FASTQ format using Reporter software and subsequently mapped to the hg38 reference genome (GENCODE) using the Salmon tool. Differential gene expression analysis was performed with the DESeq2 package, considering genes with a [Log2(Fold-Change)] greater than two and a p-value < 0.05 as differentially expressed. For the survival analysis, deaths occurring within 30 days after surgery (n = 5) were excluded to reduce the impact of confounding factors on survival outcomes. The Survminer v0.4.9 package was used to dichotomize hub gene expression levels. Survival curves with statistically significant differences ($p < 0.05$) were assessed using the log-rank test in the Survival package v3.2-13. **Results:** Of the 24 MMP family genes, six (MMP2, MMP7, MMP9, MMP10, MMP12, and MMP14) were found to be overexpressed in the analyzed samples. For the analysis of clinicopathological characteristics, only differentially expressed MMPs were considered. No significant differences in MMP gene expression were observed between intestinal-type and diffuse-type tumors. Patients who did not undergo adjuvant therapy showed higher expression of MMP12 (adjusted $p = 0.049$) compared to those who received

neoadjuvant therapy. Additionally, patients without *H. pylori* infection exhibited higher expression of the MMP7 gene (adjusted p = 0.04) compared to those with *H. pylori* presence. No significant differences in MMP gene expression were observed across different disease stages. Moreover, high expression of MMP14 (p = 0.021) was potentially associated with poorer patient survival. **Conclusion:** This study highlights significant alterations in six genes from the MMP family among patients with gastric cancer (GC). Moreover, a notable association was found between the presence of *H. pylori* in GC tissues and increased expression of MMP7, as well as between high MMP14 expression and reduced patient survival. These expression changes may play a critical role in tumor progression and metastasis. However, more comprehensive studies are necessary. The heterogeneity of GC requires a larger sample size to thoroughly understand the impact of altered MMP gene expression on patient prognosis.

Keywords: MMPs; Gastric Cancer; RNA-seq.