Original Article

A prospective cohort study of TIMP1 as prognostic biomarker in gastric and colon cancer

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Background: Tissue inhibitor metalloproteinase 1 (TIMP1) inhibits proteins which has proteolytic activity, but in cancer it contributes for tumoral invasion and metastization. The authors investigated the expression of TIMP1 in different digestive cancer types. The aim of this study was to test TIMP1 as a serum marker since in clinical practice there is a lack of biomarkers to monitor the response to treatments or to detect early relapses.

Methods: It was performed a prospective study with recently diagnosed patients with gastrointestinal cancers. Patients with esophageal, gastric, colon, rectal, hepatocarcinoma, and cholangiocarcinoma at any stage, that did not perform any type of treatment, were included. Enzyme-linked immunosorbent assays and chemiluminescence were used to quantify levels of TIMP1. The differences of the Kaplan-Meier survival curves were tested for statistical significance with the log rank test, and the 95% confidence intervals were calculated. Multivariate analysis was done using the COX proportional hazard model and a forward stepwise method. Statistical analyses were done using the IBM SPSS Statistics version 26.0. P value inferior to 0.05 was considered significant.

Results: A total of 190 patients were recruited: 54.7% males, median age of 68 years old, 57.9% with colorectal cancer followed by esophagogastric disease with 22.6%. TIMP1 level were increased in 29.5%. In colon cancer, patients with higher levels of TIMP1 are associated with worse progression free survival (PFS) (P=0.007) and overall survival (OS) (P=0.036). No relationship was seen with Rat sarcoma virus (RAS), B-raf (BRAF) and Microsatellite instability status (MSI). In gastric cancer, patients with higher levels of TIMP1 are associated with worse OS (P=0.020), with no difference in PFS.

Conclusions: Higher TIMP1 levels in gastric and colon cancer patients are associated with worse prognosis. Further studies are needed: higher number of patients and sequential measurements of TIMP1 during patient treatments.

Keywords: Digestive cancers; tissue inhibitor metalloproteinase 1 (TIMP1); metalloproteinases; biomarkers; prognosis

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Introduction

Tissue inhibitor metalloproteinase 1 (TIMP1) is a protein encoded by chromosome Xp11.3-p11.23 and belongs to the Tissue Inhibitor of Metalloproteinases family which include four identified members (TIMP1, TIMP2, TIMP3, and TIMP4) (1). This protein contributes to the inhibition of matrix metalloproteinases with proteolytic activity, which are responsible for tumoral invasion and metastization (such as collagenases) (2). On the other hand, TIMP1 also stimulates cell growth and have anti-apoptotic functions (3). These two functions are apparently contradictory. The explanation for these is the aberrant glycosylation of TIMP1 and the altered level of TIMP1 in cancer (4). Cancer cells have the capacity of upregulate the N-acetylglucosaminyltransferase V, which transforms the TIMP1 in an aberrant glycoprotein. As result, the collagenases are not inhibited and start the degradation of basal membrane and interstitial matrix, physical barriers to the spread of cancer cells (5).

Different studies demonstrated that the aberrant expression of TIMP1 is increased in several types of cancer, such as melanoma (6), breast cancer (7), thyroid (8), and digestive cancer. In colon cancer, the upregulation of TIMP1 in cancer tissues, compared with normal tissue (9), was considered an independent prognostic factor for disease free survival (10). In combination with carcinoembryonic antigen (CEA), it was validated for colorectal cancer detection, but its sensibility and specificity were not sufficiently high to be considered a good tool for population screening (11). In rectal cancer, some studies concluded that TIMP1 could differentiate early-stage cancers from healthy patients, with its elevation meaning disease progression (12,13). In gastric cancer, the patients' follow-up is made by endoscopy, an expensive and invasive procedure. Some studies showed an elevation of TIMP1 in gastric cancer patients, and its association with recurrent disease (14,15). Also in esophageal cancer, it showed upregulation of TIMP1 and its association with worst prognosis and progression (16,17).

The existing prognostic biomarkers for digestive cancer have low sensitivity and specificity for the diagnosis, to monitoring an eventual progression and to access prognosis. In clinical practice, clinicians combine multiple biomarkers to improve the accuracy. The carbohydrate antigen (CA) 72.4 in gastric cancer was found to be significantly associated with prognostic risk factors (18). CA19.9 is the most commonly tumor marker associated with pancreatic ductal adenocarcinoma (19). New biomarkers are arising due to the need for better elements to monitor cancer behavior, however, they imply a more invasive method, for example, a tissue biopsy. Sox2 expression is correlated with poor outcomes in patients with digestive tract cancers (20). MMP14 expression was associated with advanced tumor stage in colon cancer (21). Loss of KLF4 expression is correlated with a worse outcome (22). CD166 expression indicate advanced T category and N-positive status in colorectal cancer (23).

There is an exceptional need for reliable, minimally invasive, highly sensitive biomarkers for early diagnosis, to monitor response to treatment and to evaluate early relapses.

The present study was conducted to investigate the expression of TIMP1 in different digestive cancer types and clarify the correlation between the TIMP1 expression and clinicopathological parameters, overall survival (OS) and progression free survival (PFS). The aim of this study was to test TIMP-1 as a serum marker. We present the following article in accordance with REMARK reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-22-69/rc).

Methods

Patient information and clinical specimens

A prospective study with patients diagnosed during the year of 2018 with digestive cancer were conducted. Inclusion criteria were patients with esophageal, gastric, colon, rectal, hepatocarcinoma, and cholangiocarcinoma at any stage, that did not perform any type of treatment (surgery, chemotherapy and radiotherapy) that signed the informed consent. Exclusion criteria were patients that have made some kind of treatment, patients with incomplete information, and patients that did not sign the informed consent. All the information was collected from the clinical record of the patient.

This study was approved by the Institutional Research Ethics Committee of the Portuguese Oncology Institute of Coimbra. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Enzyme-linked immunosorbent assays (ELISA) and chemiluminescence (CLIA)

The study material consisted of serum samples obtained from the blood of the patients collected prior to the treatment. Blood serum was stored at –80 ℃ immediately

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Table 1 Characteristics of the sample

Tumor	Total, n (%)	Sex, n (%)	Age, n (%)	TNM stage, n (%)				CEA, n (%)	TIMP1, n (%)
		Male	≥65 years	I	II	III	IV	≥5 ng/mL	≥342 ng/mL
Esophagus	16 (100%)	13 (81%)	12 (75%)	1 (6.2%)	2 (12.5%)	3 (18.8%)	10 (62.5%)	–	7 (44%)
Gastric	27 (100%)	11 (41%)	15 (56%)	2 (7.4%)	4 (14.8%)	12 (44.4%)	9 (33.3%)	5 (18.5%)	5 (18.5%)
Colon	73 (100%)	40 (55%)	47 (65%)	1 (1.4%)	19 (26%)	23 (31.5%)	29 (39.7%)	42 (57.5%)	20 (27.4%)
Rectum	37 (100%)	18 (49%)	18 (49%)	1 (2.7%)	2 (5.4%)	21 (56.8%)	13 (35.1%)	24 (64.9%)	18 (48.6%)
Pancreas	24 (100%)	15 (62.5%)	17 (70.8%)	2 (8.3%)	1 (4.2%)	1 (4.2%)	19 (79.2%)	16 (66.7%)	8 (33.3%)
Cholangiocarcinoma	7 (100%)	3 (42.9%)	6 (85.7%)	0	2 (28.6%)	0	5 (71.4%)	3 (42.9%)	3 (42.9%)
Hepatocarcinoma	6 (100%)	4 (66.7%)	5 (83.3%)	1 (16.7%)	0	2 (33.3%)	3 (50%)	-	2 (33.3%)

CEA, carcinoembryonic antigen; n, absolute number; TIMP1, tissue inhibitor metalloproteinase 1; TNM, tumor node metastasis.

after centrifugation until the assay was performed. ELISA and CLIA were used to quantify levels of TIMP1. Specimens, standards and reagents were prepared according to the ELISA manufacturer's instructions. The ADVIA Centaur XP TIMP1 assay (Siemens Healthineers®) was used with two monoclonal antibodies and were adopted the manufacturer's cutoff values.

Statistical analysis

Because the distributions of our variables showed no normal distributions (Shapiro-Wilk test), all studied groups were characterized by median values and as an interquartile range.

The differences of the Kaplan-Meier survival curves were tested for statistical significance with the log rank test, and the 95% confidence intervals were calculated. Multivariate analysis was done using the COX proportional hazard model and a forward stepwise method was used to bring variables into the model to identify independent predictors of survival: age at diagnosis, gender, cancer type (esophagus, gastric, colon, rectum, pancreatic, cholangiocarcinoma, hepatocarcinoma), cT, cN, cM, stage, CEA, CA19.9, TIMP1.

Further statistical analyses were done using the IBM SPSS Statistics version 26.0. A significant difference was declared if the p value from a two-tailed test was less than 0.05.

Results

A total of 190 patients were recruited. The clinicopathological features are described in *Table 1*. The median age at diagnosis were 68 years old (range, 25–93), 120 patients (63%) had more than 65 years old, 104 were males (54.7%), and 86 were females (45.3%). Colorectal cancer was present in 110 patients (57.9%), followed by esophagogastric disease with 43 patients (22.6%), and hepato-bilio-pancreatic disease with 37 patients (19.5%). Adenocarcinoma (87.4%) and stage IV disease (45.8%) were more prevalent. At diagnosis, 51% of the patients had CEA level increased and 29.5% had TIMP1 level increased. Patients with colorectal cancer had their mutational status determined: 60% were Rat sarcoma virus (RAS) mutated, 2.5% were B-raf (BRAF) mutated, and 92% were Microsatellite instability (MSI) low. Patients were accompanied for 2 years, during this period 82 patients (43.2%) had progressed, and 77 patients (40.5%) died.

Studying the different types of cancer, the main results were: TIMP1 level were significantly different (P=0.016) between male and female in rectal cancer (*Table 2*); no differences exist between older and younger patients (*Table 3*); there are a significantly difference (P=0.041) in TIMP1 levels between stages in gastric cancer (*Table 4*) and there is no difference between CEA levels (*Table 5*).

In colon cancer, patients with higher levels of TIMP1 are associated with worse PFS (P=0.007), and OS (P=0.036) (*Figure 1*). The hazard ratio for death was 2.89 (95% CI: 1.013–8.267); P=0.047 and for progression was 3.15 (95% CI: 1.100–9.020); P=0.033. No relationship was seen with RAS, BRAF and MSI status. In gastric cancer, patients with higher levels of TIMP1 are associated with worse OS (P=0.020), with no difference in PFS (*Figure 2*). The hazard ratio for death was 0.21 (95% CI: 0.05–0.90); P=0.036) and for progression was 0.3 (95% CI: 0.089–1.35); P=0.128.

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Table 2 Relationship between sex and TIMP1

Tumor	Male		Female		P[a]
	n	TIMP1, ng/mL	n	TIMP1, ng/mL	
Esophagus	13	250.60; 161.80	3	270.30	0.946
Gastric	11	250.70; 110.50	16	238.85; 94.05	0.730
Colon	40	270.75; 192.20	33	234.90; 118.80	0.103
Rectum	18	332.75; 413.50	19	241,10; 88,90	0.016
Pancreas	15	296.00; 240.30	9	232.20; 143.00	0.222
Cholangiocarcinoma	3	525.30	4	218.85; 421.48	0.157
Hepatocarcinoma	4	332.35; 213.01	2	254.75	0.264

Data are shown as median; IQR1-IQR3. [a], Mann-Whitney U-test or Kruskal-Wallis test. IQR1-IQR3, interquartile range; n, absolute number; TIMP1, tissue inhibitor metalloproteinase 1.

Table 3 Relationship between age and TIMP1

Tumor	Age <65 years old		Age ≥65 years old		P[a]
	n	TIMP1, ng/mL	n	TIMP1, ng/mL	
Esophagus	4	334.75; 731.52	12	260.45; 157.30	0.716
Gastric	12	230.70; 82.18	15	259.60; 399.30	0.157
Colon	26	270.75; 186.48	47	247.40; 146.80	0.240
Rectum	19	256.40; 110.10	18	327.45; 429.53	0.121
Pancreas	7	291.30; 396.00	17	232.20; 178.35	0.153
Cholangiocarcinoma	1	203.00	6	419.70; 708.18	0.134
Hepatocarcinoma	1	249.20	5	318.7; 226.65	0.480

Data are shown as median; IQR1-IQR3. [a], Mann-Whitney U-test or Kruskal-Wallis test. IQR1-IQR3, interquartile range; n, absolute number; TIMP1, tissue inhibitor metalloproteinase 1.

Table 4 Relationship between stage and TIMP1

Tumor	Stage I		Stage II		Stage III		Stage IV		P[a]
	n	TIMP1, ng/mL	n	TIMP1, ng/mL	n	TIMP1, ng/mL	n	TIMP1, ng/mL	
Esophagus	1	250.60	2	289.00	3	432.20	10	240.10; 145.45	0.280
Gastric	2	220.30	4	172.00; 65.48	12	263.20; 177.50	9	234.40; 320.05	0.041
Colon	1	261.00	19	254.10; 71.90	23	234.90; 152.70	29	275.10; 212.25	0.587
Rectum	1	213.20	2	275.15	21	280.30; 135.40	13	290.00; 446.70	0.296
Pancreas	2	237.25	1	291.30	1	210.60	19	277.00; 244.90	0.700
Cholangiocarcinoma	–	–	2	826.60	–	–	5	314.10; 423.20	0.998
Hepatocarcinoma	1	249.20	–	–	2	435.60	3	254.75	0.223

Data are shown as median; IQR1-IQR3. [a], Mann-Whitney U-test or Kruskal-Wallis test. IQR1-IQR3, interquartile range; n, absolute number; TIMP1, tissue inhibitor metalloproteinase 1.

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Table 5 Relationship between CEA level and TIMP1

Tumor	CEA <5 ng/mL		CEA ≥5 ng/mL		P[a]
	n	TIMP1, ng/mL	n	TIMP1, ng/mL	
Gastric	22	238.85; 111.47	5	250.70; 302.35	0.574
Colon	31	237.70; 92.80	42	261.30; 183.60	0.253
Rectum	13	275.80; 112.00	24	295.00; 431.92	0.127
Pancreas	8	284.15; 231.55	16	260.25; 184.70	0.806
Cholangiocarcinoma	4	218.85; 421.48	3	525.30	0.157

Data are shown as median; IQR1-IQR3. [a], Mann-Whitney U-test or Kruskal-Wallis test. IQR1-IQR3, interquartile range; CEA, carcinoembryonic antigen; n, absolute number; TIMP1, tissue inhibitor metalloproteinase 1.

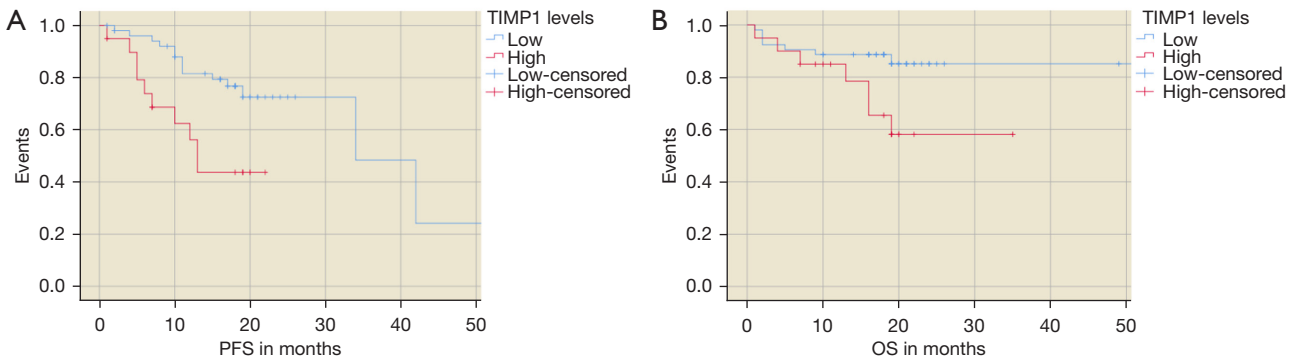

Figure 1 Kaplan-Meier curve in colon cancer for: (A) progression-free survival (PFS) (P=0.007) and (B) overall survival (OS) (P=0.036) according to tissue inhibitor metalloproteinase 1 (TIMP1) level.

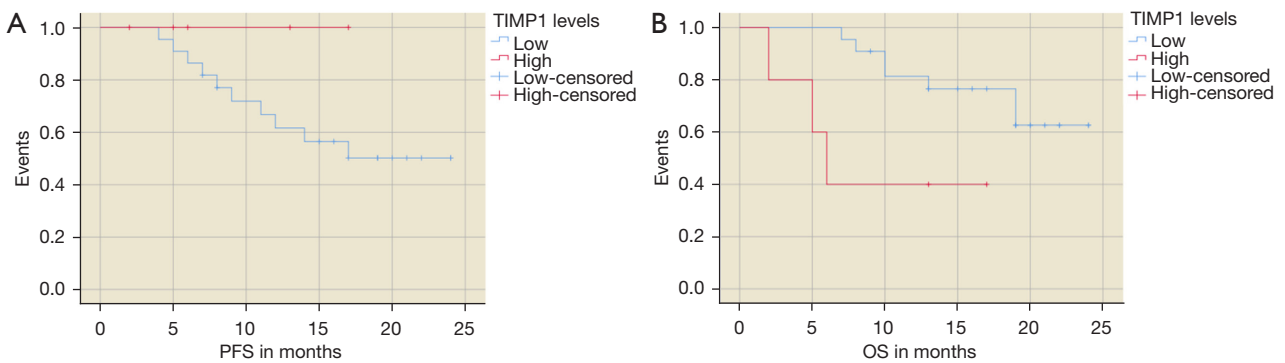

Figure 2 Kaplan-Meier curve in gastric cancer for: (A) progression-free survival (PFS) (P=0.242) and (B) overall survival (OS) (P=0.020) according to according to tissue inhibitor metalloproteinase 1 (TIMP1) level.

Discussion

Gastrointestinal (GI) tumors are extremely prevalent worldwide, ones with better prognosis than others. In 2018, GI cancers accounted for 26% of the total cancer incidence and 35% of all cancer-related deaths (24). It was estimated 4.8 million new cases and 3.4 million deaths due to GI cancer (24). The majority of new cases are emerging in Asia (63%), followed by Europe (26%) and North America (23%). Incidence is greater in developing countries, where

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there are fewer health care resources to diagnose GI cancers. Colorectal cancer and pancreatic cancer are more prevalent in Western countries and liver, esophageal and gastric cancers are more common in Asia (25). These data demonstrate the importance of GI cancers to public health. Due to this burden, the ideal will be the disposal of serum biomarkers to help physicians to diagnose and monitor GI cancer.

The extracellular matrix contains multiple structural proteins such collagen, laminin, and fibronectin, that provides the microenvironment for cancer to grow (26). Matrix metalloproteinases (MMP) are proteolytic enzymes that break basement membranes and components of extracellular matrix. On the other hand, MMP activity is controlled by endogenous inhibitors such TIMP1 (27). Different studies reported different activities of TIMP1: (I) TIMP1 inhibits the proteolytic activity of MMP by the formation of noncovalent 1:1 complexes that are resistant to denaturation and degradation (1), and this balance between deposition and degradation is essential in maintaining the homeostasis; (II) TIMP1 promotes cell proliferation; (III) participate in angiogenesis regulation; (IV) inhibit apoptosis (28).

Malignant cancer is composed not only by neoplastic cells, but also a microenvironment that permits that malignant cells survive, renew, and grow (stromal cells, fibroblast, cytokines) (29). Degradation of the extracellular matrix is mandatory for cancer to invade structures and metastasize, being TIMP1 of extreme importance for these achievements. With these data, it is easy to understand how TIMP1 affects cancer patient's prognosis.

This molecule is stored in granules of platelets and leucocytes and is released due to cellular fragmentation when cells are recruited. As so, TIMP1 could be measured in blood samples or body fluids. CEA is still the only biomarker recommended in GI cancers, but it has some limitations. A persistently high value of CEA might suggest recurrent or metastatic disease, but, in some patients, CEA level could rise without recurrence or they could present a normal CEA with disseminated disease (30). On the other hand, CEA could rise for other reasons like pancreatitis, some medications, smoking or liver cirrhosis (31). Therefore, additional biomarkers are needed.

Our study showed that higher levels of TIMP1 are associated with shorter time until progression in gastric and colon cancer. Additionally, elevated levels of TIMP1 are associated with shorter overall survival in colon cancer. There is some evidence that TIMP1 exerts different effects on tumor progression in various cancers. In prostate cancer, high levels of TIMP1 are associated with biochemical recurrence (32). It is a predictor of disease recurrence in lung cancer (33). In triple negative breast cancer it is highly expressed and associated with poor prognosis (34). Concerning GI cancers, TIMP1 was overexpressed in esophageal cancer and was correlated with clinicopathologic features, like tumor size (16). In hepatocarcinoma, TIMP1 is abnormally upregulated in 76% of the cases and associated with lower OS. TIMP1 was considered an efficacious predictive factor for hepatocarcinoma outcome after surgery (35,36). In colorectal cancer, TIMP1 predicts the prognosis and is associated with OS (37,10). In patients with colorectal liver metastasis, the invasion front has high expression of stromal TIMP1, which is associated with poor progression free survival (38).

High TIMP1 level is a poor prognostic factor of disease recurrence in gastric cancer (14). Data for pancreatic cancer is more contradictory. Some data showed that TIMP1 overexpression reduced cancer growth and metastization (39), but other showed TIMP1 expression increased susceptibility to pancreatic cancer (40). A recent study proved that miR-6745-TIMP1 axis participates in gastric cancer tumorigenesis and could be a potential therapeutic target for progression prevention (41).

Our study has a limitation since we do not have serial measurements of TIMP1 during patient treatments. This was intentional, to avoid increasing the cost of the study. Since the results showed statistical significance for gastric and colon cancer, the next step will be the sequential measurement of TIMP1 in these two types of cancer during treatments and in follow-up period. This way the authors will verify if elevation in TIMP1 level will correlate with recurrence. On the other hand, some types of cancer had a low representativity which could constitute a bias. The authors will continue recruiting.

Conclusions

Higher levels of TIMP1 predict lower OS in colon and gastric cancer and lower PFS in colon cancer. TIMP1 could be used to discriminate patients with worse outcome. The next step will be the sequential measurements of TIMP1 levels during treatment.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-22-69/rc

Data Sharing Statement: Available at https://cco.amegroups.com/article/view/10.21037/cco-22-69/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-22-69/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Research Ethics Committee of the Portuguese Oncology Institute of Coimbra and informed consent was taken from all individual participants. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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