# Serum Cystatin C Levels in Gastric Cancer Patients: Scientific Letter

## *MİDE KANSERİNİN SERUM SİSTATİN C DÜZEYLERİNE OLAN ETKİSİ*

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## Abstract

Elevated activities of cysteine proteinases in cancers are attributed to impaired regulation by the endogenous cysteine proteinase inhibitors (cystatins). Cystatin C is suggested to be a reliable marker of glomerular filtration rate (GFR). The purpose of this study was to evaluate whether cystatin C concentration was influenced by gastric malignancy, which is a common cancer type and the availability of this parameter safely for screening renal dysfunction in these patients. Since there is inadequate information on the clinical significance of cystatin C expression in human gastric cancers, we studied the differences in levels of serum cystatin C in this type of cancer and also evaluated them with respect to cancer stages. The levels of cystatin C in patients with gastric adenocancer were similar to those in the control group. Similarly, the values of serum creatinine and GFR in the patients were comparable to those of the controls. Serum creatinine values in controls and in patients did not show a statistically significant difference 0.8 ± 0.16 and 0.9 ± 0.35 respectively (p> 0.05). Serum cystatin C values in controls and patients were 0.74 ± 0.32 and 0.72 ± 0.6 respectively, which was also not different statistically (p> 0.05). When the patients were evaluated with respect to the stages of the cancer, the cystatin C values did not differ significantly. The mean ± SD levels of the patients in low and advanced stages were 0.79 ± 0.51 and 0.69 ± 0.64 respectively (p> 0.05). Our study clearly demonstrates that serum cystatin C has valuable potential for the detection and monitoring of GFR and may be safely used in gastric cancer patients.

**Key Words:** Stomach neoplasms; cystatin C; glomerular filtration rate

## Özet

Kanserlerde sistein proteinazların artmış aktiviteleri, endojen sistein proteinaz inhibitörlerinin (sistatinler) bozulmuş regülasyonuna bağlı olduğu düşünülmektedir. Sistatin C glomerüler filtrasyon hızının (GFR) güvenilir bir belirteci olarak kabul edilir. Bu çalışmanın amacı sık görülen bir kanser olan gastrik malignitede sistatin C konsantrasyonunun değişimini ve bu hastalarda renal disfonksiyonu belirlemede kullanılabilirliğini değerlendirmekdir. İnsan gastric kanserlerinde sistatin C ekspresyonunun klinik önemi hakkında yeterli bilgi bulunmamasından dolayı, biz bu kanser tipinde serum sistatin C seviyelerindeki değişimi izledik ve kanserin evrelerine göre değerlendirdik. Gastrik adenokanser hastalarında sistatin C düzeyleri kontrol grubuyla benzerlik gösterdi. Aynı şekilde hastaların serum kreatinin ve GFR'ı değerleri kontrollerle uylumluydu. Kontrollerde ve hastalarda serum kreatinin düzeyleri anlamlı bir değişiklik 0.8 ± 0.16 ve 0.9 ± 0.35 göstermedi (p> 0.05). Kontroller ve hastalardaki serum sistatin C düzeyleri 0.74 ± 0.32 ve 0.72 ± 0.6 arasında istatistiksel bir fark yoktu (p> 0.05). Hastalar kanserin evrelerine göre değerlendirildiğinde, sistatin C seviyelerinde anlamlı bir fark bulunmadı. Hastaların ortalama ± SS değerleri erken ve geç evrede 0.79 ± 0.51 ile 0.69 ± 0.64 olarak bulundu (p> 0.05). Bizim çalışmamız sistatin C'nin gastrik kanserli hastalarda GFR'nin belirlenmesinde ve takibinde değerli olduğunu ve güvenilir bir şekilde kullanılabileceğini gösterdi.

**Anahtar Kelimeler:** Gastrik kanserler; sistatin C; glamerüler filtrasyon hızı

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The GFR reflects the best information about renal function and cystatin C has been suggested as a new and promising marker for estimating GFR both in healthy subjects and patients with renal dysfunction.[1] Although the suggestions on the superiority of cystatin C as a screening test for early renal dysfunction and monitoring its progression in cancer patients are present, there are still insufficient data on the influence of malignancy on this marker.[2] Previous studies involving only a few kind of malignancies are not adequate to draw defi-nitive conclusions for cystatin C in malignancy.

In cancer patients renal function must be determined to evaluate the effect of cancer on renal

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**Table 1.** Mean ± SD cystatin C and creatinine levels in patients and control groups.

| | Patients (n=39) | Controls (n=40) | p value |
|---|---|---|---|
| Serum creatinine (μmol/L) | 79.6 ± 30.9 | 70.7 ± 14.1 | p> 0.05 |
| Creatinine clearance (ml/min/1.73 $m^2$) | 98.65 ± 56.8 | 91.2 ± 26.4 | p> 0.05 |
| Serum cystatin C (mg/L) | 0.72 ± 0.6 | 0.74 ± 0.32 | p> 0.05 |

tubules. Therefore, it may be useful to detect small changes in renal function as soon as possible. The aim of our study was to highlight the value of serum cystatin C among patients with gastric cancer.

In this study, a total of 39 patients (19 males and 20 females) with gastric cancer and 40 healthy volunteers as controls (28 males and 12 females) were investigated. The mean age of the patients and the controls were 56.89 ± 3.4 and 51.4 ± 6.0 years respectively. All cases were selected among cancer patients who received neither chemotherapeutic nor radiotherapy. Thus all were at the stage of initial diagnosis. Informed consents from patients were obtained before inclusion in the study, according to Helsinki Declaration.

Serum samples were used for both cystatin C and creatinine assays. For creatinine clearance (CrCl) 24-hours urine was collected. Serum and urine creatinine levels were measured with the Jaffe method (Beckman Reagent) by Cx7 analyzer (Beckman). Serum cystatin C assay was performed by the latex particle enhanced turbidimetric immunoassay (DAKO) on the Cx7 analyzer (Beckman). CrCI was calculated using the standard formula: [CrCl= Urine creatinine concentration (μmol/L) × urine volume measured from 24 hour collection (ml/24hour)/serum creatinine (μmol/L) × 1440].

Differences between the patients and the controls were compared with paired-t test. All statistical analysis were performed using the SPSS 11.0 program.

Statistical analysis revealed that the values of creatinine, cystatin C and GFR in the patient group were not different from those of the controls. There was no significant difference in serum creatinine levels between the patients (79.6 ± 30.9 μmol/L) and the controls (70.7 ± 14.1 μmol/L) (p>0.05). Serum cystatin C values in the controls and the patients were 0.74 ± 0.32 and 0.72 ± 0.6 mg/L. Similar to creatinine, there was no significant difference between these values (p> 0.05). The mean value of GFR estimated as 24-hours CrCl was 98.65 ± 56.8 ml/min/1.73 $m^2$ and this result was within the reference range (71-151 ml/min/1.73 $m^2$) (Table 1).

**Table 2.** The comparison of mean ± SD cystatin C levels in patients with gastric cancer according to the stages and the controls.

| | Cystatin C (mg/L) | p |
|---|---|---|
| Patients with early stage (n= 11) | 0.79 ± 0.51 | p> 0.05 |
| Patients with advanced stage (n= 28) | 0.69 ± 0.64 | p> 0.05 |
| Control group (n= 40) | 0.74 ± 0.32 | p> 0.05 |

When the patients were evaluated with respect to the stages, the mean ± SD levels of cystatin C were 0.79 ± 0.51 mg/L and 0.69 ± 0.64 mg/L in early and advanced stages and there was no significant difference between them (p> 0.05) (Table 2).

In this study, we showed that the serum concentration of cystatin C was not significantly changed in gastric cancer patients in all stages. In these patients lack of CrCl clearance means no or minimal changes in GFR.

Increasing evidence emphasized that overexpression of cysteine proteinases played an active role in some of the malignancies such as gastric cancer.[3] Proteinases are known to be involved in carcinogenesis and various substrates are now available to measure the activity of such enzymes.[4] Some authors propose that an imbalance between proteinases and cystatins, associated with metastatic tumor cell phenotype, may facilitate tumor

cell invasion and methastasis.[5] We have recently reported that the serum concentration of cystatin C was significantly higher in patients with leukemia.[6] Kos et al showed in malignancy that there was an enhancement in mRNA and protein of cysteine proteinases but moderately enhanced or unchanged levels of cystatin C in the serum of such patients.[7]

Cystatin C mRNA shown in gastric tissue by Northern Blot analysis suggested that it was synthesised in gastric tissue.[8] In an immunohistochemical study, while many neuroendocrine cells showed strong cystatin C immunoreactivity throughout the gastrointestinal tract, non-endocrine epithelial cells of the gastrointestinal mucosa did not. Furthermore, most of the adenocarcinomas from these sites showed weak cystatin C immunoreactivity.[9]

In the literature, cystein proteinases cathepsins B and L are suggested to play a role in the process of cancer invasion and the progression of precancerous changes into gastric cancer but there is no report evaluating the levels of cysteine proteinase inhibitor cystatin C in such patients.[10] This study on gastric cancer clearly shows that the levels of cystatin C were not changed in any gastric tumor sample when compared with healthy controls.

## REFERENCES


1. Arias IM, Pobes A, Banos M. Cystatin C. New marker of renal function. Nefrologia 2005;25:217-20.
2. Stabuc B, Vrhovec L, Stabuc-Silih M, Cizej TE. Improved prediction of decreased creatinine clearance by serum cystatin C: use in cancer patients before and during chemotherapy. Clin Chem 2000;46:193-7.
3. Ebert MP, Kruger S, Fogeron ML, Lamer S, Chen J, Pross M, et al. Overexpression of cathepsin B in gastric cancer identified by proteome analysis. Proteomics 2005;5:1693-704.
4. Bongers V, Konings CH, Grijpma AM, Steen I, Braakhuis BJ, Snow GB. Serum proteinase activities in head and neck squamous cell carcinoma patients. Anticancer Res 1995;15(6B):2763-6.
5. Kos J, Stabuc B, Cimerman N, Brunner N. Serum cystatin C, a new marker of glomerular filtration rate, is increased during malignant progression. Clin Chem 1998;44:2556-7.
6. Demirtas S, Akan O, Can M, Elmali E, Akan H. Cystatin C can be affected by nonrenal factors: a preliminary study on leukemia. Clin Biochem 2006;39:115-8.
7. Kos J, Lah TT. Cysteine proteinases and their endogenous inhibitors: target proteins for prognosis, diagnosis and therapy in cancer (review). Oncol Rep 1998;5:1349-61.
8. Rubio CA. Five types of pyloric cells in the antral mucosa of the stomach. Pathol Res Pract 1992;188:157-61
9. Lignelid H, Jacobsson B. Cystatin C in the human pancreas and gut: an immunohistochemical study of normal and neoplastic tissues. Virchows Arch A Pathol Anat Histopathol 1992;421:491-5.
10. Saleh Y, Siewinski M, Kielan W, Ziolkowski P, Grybos M, Rybka J. Regulation of cathepsin B and L expression in vitro in gastric cancer tissues by egg cystatin. J Exp Ther Oncol 2003;3:319-24.