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CLINICAL STUDY

# Correlation of Cystatin-C and radionuclidic measurement method of glomerular filtration rate in patients with lung cancer receiving cisplatin treatment

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**Abstract**

*Objective*: Cisplatin is a chemotherapeutic agent which affects renal functions adversely. The best indicator of renal functions is glomerular filtration rate (GFR) measurement. Cystatin-C appears to be a good alternative to existing methods of measuring GFR. However, it is controversial whether Cystatin-C demonstrates GFR correctly for patients receiving chemotherapy. This study aimed to investigate the correlation between GFR values calculated by Cystatin-C based formulas, radionuclidic method (multiple blood sampling) and blood Cystatin-C values in patients with lung cancer, receiving cisplatin treatment in both pre-treatment and post-treatment periods. *Materials and methods*: Thirty-six patients with lung cancer who were going to receive cisplatin treatment were included in this study. However, the evaluation was performed with 20 patients since 16 of them could not complete the treatment. Blood Cystatin-C values, GFR values calculated via Cystatin-C based formulas, and radionuclidic method were investigated before and after the cisplatin treatment. *Results*: After treatment significant decreases were detected in GFR values, obtained via radionuclidic measuring method. However, there was no significant difference in Cystatin-C values between pre-treatment and post-treatment periods. Also GFR values obtained by Cystatin-C based formulas were not significantly different in pre-treatment and post-treatment periods. There were meaningful correlations between radionuclidic method and Cystatin-C values and Cystatin-C based formulas before treatment. However, all correlations disappeared after the treatment. *Conclusion*: GFR values, calculated by Cystatin-C may not be reliable in following renal functions in patients receiving chemotherapy. When reliable monitoring of the renal functions is necessary radionuclidic method may be preferred in these patients.

**Keywords**

Cystatin-C, cisplatin, glomerular filtration rate, nephrotoxicity, scintigraphy

**History**

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## Introduction

Lung cancer is responsible for 28% of all cancer deaths. The most commonly used and most effective main drug is platinum-group (cisplatin/carboplatin) chemotherapeutics.[1] One of the serious side effects of these drugs is nephrotoxicity.[2] Patients should be closely monitored for nephrotoxicity during and after therapy.

Blood urea value, blood and urine creatinine values, renal plasma blood flow, glomerular filtration rate (GFR), filtration fraction, intra-venous pyelogram (IVP), dynamic and static renal scintigraphy can be used in assessing renal functions. The assessment of GFR is the most reliable and convenient method in routine.

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GFR can be calculated by various biochemical and radionuclidic methods. The gold standard in measuring GFR is the determination of inulin clearance. However, its practical use is very limited since it is invasive, time-consuming, and requires complex and difficult laboratory procedures.[3–6]

Blood creatinine levels can be used for calculating GFR with several formulas practically in clinics. However, blood creatinine levels can be affected by ingestion of meat by diet, slow muscle loss due to chronic illnesses, chronic use of glucocorticoids or malnutrition.[1] Besides, plasma creatinine level does not show increase unless GFR decreases 50% or more.[7] The analysis of creatinine is considered not to be sensitive in detecting mild and moderate changes in GFR.[8] Furthermore, GFR values can be determined by creatinine clearance of a 24-hour urine together with taking blood samples. Missing urine collection of many patients (especially children and the elderly), reduces the sensitivity and reproducibility of the creatinine clearance test significantly.[6] For these reasons, a research on alternative biochemical parameters to the calculation of GFR has been undertaken.

Cystatin-C is a low molecular weight protein.[9] It can be produced from all nucleated cells in the human body. Also it can be freely filtered from renal glomerulus because it has low molecular weight and cannot be connected to proteins.[10,11] It is reabsorbed in proximal renal tubules and is completely metabolized.[12,13] Cystatin-C does not have a significant diurnal rhythm during the day. It is not affected by diet, age, gender or muscle mass.[9,10,12,14,15] It appears to be a good marker of GFR measurement because of its constant production rate, its free filtration from the glomerulus, not being affected by body muscle mass unlike creatinine.

Nevertheless, Cystatin-C has not been exactly studied as a marker of glomerular filtration. In the absence of urinary excretion, variations in the production and urinary clearance of Cystatin-C make it a difficult work to be used as filtration marker.[9] While it was shown in many studies that Cystatin-C can be an ideal endogenous marker in GFR measurement, the accuracy of GFR determinations with Cystatin-C in patients with inflammation along with steroid and chemotherapy treatment is still controversial.[6,10,16] Lin and his colleagues reported that after chemotherapy there was not a statistically significant increase in the urinary Cystatin-C values. They concluded that Cystatin-C could not predict acute kidney injury.[17] As opposed to this, Barnfield and his colleagues reported that Cystatin-C was a much better marker than creatinine in monitoring the renal functions of patients receiving chemotherapy. However, its sensitivity to mild reductions in GFR was still low.[18] Similarly, Bölke and his colleagues declared that GFR calculated by Cystatin-C based formulas demonstrated renal functions better than creatinine clearance in patients receiving chemotherapy.[19] Nevertheless, Aydin and his colleagues emphasized that the Filler formula for Cystatin-C based GFR calculation and serum Cystatin-C values may not demonstrate GFR accurately in their pediatric patient group receiving chemotherapy.[10] It is a controversial issue whether low molecular weighted proteins, such as Cystatin-C and β-trace protein, can demonstrate renal functions accurately in patients receiving chemotherapy.[6]

A strong correlation was found between Cystatin-C, serum creatinine concentration, and creatinine clearance calculated with Counahan formula in children treated with cisplatin, methotrexate, cyclophosphamide and ifosfamide in a study.[20] As opposed to this, in another study authors declared that Cystatin-C might not be a good marker in demonstrating renal functions of in patients, receiving chemotherapy.[10] In this study the correlation between GFR calculated by using Tc99m-DTPA and GFR values calculated from Cystatin-C was found very strong for the group not receiving chemotherapy. However, the correlation was found to be quite weak in the group receiving chemotherapy. Researchers connected this situation to the negative effect on tubular renal function of the chemotherapeutics.[10] Yet studies investigating the correlation between GFR measurements with Cystatin-C and radionuclidic methods in the adult patient group using nephrotoxic chemotherapeutics are very few. Nakai and his colleagues deduced that Cystatin-C is not always a good marker for GFR in a study conducted on a group of 82 cancer and 276 non-cancer patients.[21]

Therefore we aimed to investigate the correlation between GFR values calculated by Cystatin-C based formulas, radionuclidic method and blood Cystatin-C values in patients with lung cancer, receiving cisplatin treatment in both pre-treatment and post-treatment periods.

## Materials and methods

### Patient group

Among the lung cancer patients applying for treatment to the Medical Oncology Clinic, the ones with whom cisplatin over 75 mg/m$^2$ doses were to be used were included prospectively in the study.

The exclusion criteria of the study were determined as being under the age of 18, being pregnant, breastfeeding, having a history of nephrotoxic drugs usage, having a history of renal dysfunction, and having severe ascites, edema, or fluid accumulation in any body region.

A total of 36 patients were included in the study in pre-chemotherapy period. Blood Cystatin-C and GFR measurements were performed in 2 cycles: just before the chemotherapy and as soon as the third course of chemotherapy was finished.

### Determining the levels of blood Cystatin-C

In order to measure Cystatin-C values (Cys-C), 5 ml of blood were drawn from the patients within the same day with radionuclidic GFR measurements. The blood drawn was centrifuged at 3000 rpm for 5 minutes (615 NF, Nuve, Nuve Industry, Ankara, Turkey). Two separate samples of 1 ml of the serum were preserved at −80 °C. Blood Cys-C levels were measured by immunonephelometric method (Beckman Image 800 analyzer, Beckman Coulter, Inc., Brea, CA).

### Cystatin-C based GFR calculations

The GFR values (mL/minute) were calculated separately using the following formulas using Cys-C values:

$$\mathrm{Rule(GFR-CR)};\ (\mathrm{GFR} = 66.8 \times \mathrm{Cystatin-C}^{-1,30}),$$

$$\mathrm{Filler(GFR-CF)};\ (\log(\mathrm{GFR}) = 1.962 + [1.123 \times \log(1/\mathrm{Cystatin-C})],$$

$$\mathrm{Larsson(GFR-CL)};\ (\mathrm{GFR} = 77.24 \times \mathrm{Cystatin-C}^{-1,2623}),$$

$$\mathrm{Hoek(GFR-CH)};\ (\mathrm{GFR} = (80.35 \times 1/\mathrm{Cystatin-C}) - 4.32)^9$$

### Measuring GFR via radionuclidic method

Multiple blood sampling (at the 120th and 240th minutes) were used as radionuclidic method for measuring of GFR (mL/minute).

Patients who were referred nuclear medicine department the day before the examination to measure GFR were suggested poor protein nutrition. They were hydrated orally with 500 ml water half an hour before the examination. The vascular paths of the patients were opened via Intracath and its reliability was checked by injecting a quantity of saline.

Syringes were loaded with 2.5 mCi and 1 mCi Tc-99m DTPA for injecting into patient and for preparing standard solution, respectively. The remaining activity quantities in the syringes were noted after they were measured by the dose calibrator (Atomlab 100, Biodex, Shirley, NY).

At the 120th and 240th minutes after the injection of 2.5 mCi Tc-99m DTPA, 5 ml of blood was taken from the vascular access opened across the extremity where the radiopharmaceutical injection was made into heparinized tubes. After withdrawal of blood, vascular access was washed with 25 IU heparin. The blood was centrifuged at 3000 rpm for 5 minutes. By taking 1 ml from each serum obtained, activity quantities (counts/min) were measured with the gamma counter for a period of 1 minute (Berthold Lb 211, Berthold Technologies GmbH & Co KG., Bad Wildbad, Germany). The obtained values were noted, and the GFR values were calculated using the corresponding formulas.

GFR calculation was performed by the method of multiple blood sampling using the formula [Dln (P1/P2)/ $(T2-T1)]^{([T1lnP2)-(T2lnP1)]/(T2-T1)}$ (D: total amount of injected activity, count per minute; P1: amount of activity at the time of T1, count per minute $X\,ml^{-1}$ ; P2: amount of activity at the time of T2, count per minute $X\,ml^{-1}$; T1: 120 minute; T2: 180 minute.[3] Both Chantler (GFRm1) and Bröchner-Mortensen (GFRm2) methods were used in corrections based on the body surface area.[3,22–26]

### Statistical analysis

SPSS 20.0 package program (IBM Corp., Armonk, NY) was used for statistics in study. Compliance of the variables with the normal distribution was examined using visual (histogram) method and with test of normality (Shapiro–Wilk and Kolmogrov–Smirnov). Because some variables had no normal distribution (Cys-C, GFR-CF) Spearman's correlation analysis was carried out to investigate the correlations among blood Cys-C levels and Cystatin-C based and radionuclidic GFR measurement method before and after treatment with cisplatin. Correlation coefficients (r) were classified as follows for the degrees of meaning: 0.05–0.30; low or insignificant correlation, 0.30–0.40; low moderate correlation, 0.40–0.60; moderate correlation, 0.60–0.70; strong correlation, 0.70–0.75; very strong correlation, and 0.75–1.0; excellent correlation.[27]

Wilcoxon test was carried out to compare the values of all variables both before and after the cisplatin treatment. $P<0.05$ was considered statistically significant in all statistical evaluations.

### Ethical considerations

Our university hospital's scientific and Ethics Committee for human Clinical Research approved this protocol and all patients provided informed consent prior to enrollment into the study.

## Results

Thirty-six lung cancer patients treated with cisplatin were included in the study (4 females, 32 males, mean age of $56.97 \pm 6.56$). Four patients died during chemotherapy and twelve patients did not continue their follow-ups and/or treatment. A total of 20 patients could be evaluated after treatment with cisplatin (3 female, 17 male, mean age of $55.60 \pm 7.493$). Therefore, all statistical evaluations both in pre-treatment and post-treatment periods were made out of 20 patients.

Cys-C and GFR values of each patient calculated via radionuclidic method and Cystatin-C based formulas before and after chemotherapy is shown in Tables 1 and 2.

Comparison of GFR and Cys-C values during pre-treatment and post-treatment periods are presented in Table 3, Figures 1 and 2. A significant decrease was detected in GFR values, obtained via radionuclidic measuring method ($P<0.05$ for all). A slight increase in Cys-C levels after the treatment which is not statistically significant was detected ($P=0.415$). GFR values obtained with Cystatin-C based formulas showed a slight decrease in post-treatment period compared to pre-treatment period, but this reduction was not statistically significant (Table 3). Correlation of GFR measurement methods during pre-treatment and post-treatment periods are shown in Table 4.

### Findings before cisplatin treatment

Significant, moderate, negative correlation was found between blood Cys-C values and GFR values obtained from radionuclidic method (Table 4).

It was found that GFR values that were calculated via all Cystatin-C based formulas showed a statistically significant and excellent positive correlation among them ($r=1{:}00$, $P=0.000$, for all; Table 4).

It was detected that GFR values calculated by radionuclidic method and the ones obtained from Cystatin-C based formulas showed statistically significant, moderate positive correlations (Table 4).

### Findings after cisplatin treatment

There was no significant correlation observed between the blood levels of Cys-C, and radionuclidic method (Table 4). It was found that all GFR values calculated by Cystatin-C based formulas showed significant, excellent positive correlations among them ($r=1{:}00$ for all $P=0.000$) (Table 4).

Statistically significant correlations were not found between GFR values obtained from Cystatin-C based formulas and the ones calculated by radionuclidic method. Degrees of correlation were found out to be low or negligible for all (Table 4).

After treatment significant decreases were detected in GFR values obtained via radionuclidic measuring method. There was a slight increase in Cystatin-C values and a decrease in GFR values obtained by Cystatin-C based formulas. However, there were not statistically significant (Figures 1 and 2; Table 4).

## Discussion

Platinum-based chemotherapy, especially cisplatin plays an important role in treatment of lung cancer. Chemotherapeutics especially cisplatin could cause nephrotoxicity via direct tubular injury through multiple

Table 1. GFR and Cystatin-C values before chemotherapy.

| No | Age | G | GFRm1* | GFRm2* | Cys-C ** | GFR-CR* | GFR-CL* | GFR-CH* | GFR-CF* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 57 | M | 68.59 | 66.49 | 0.86 | 81.26 | 93.43 | 89.11 | 108.53 |
| 2 | 56 | M | 50.27 | 50.01 | 0.92 | 74.44 | 85.81 | 83.01 | 100.61 |
| 3 | 51 | M | 68.18 | 66.13 | 0.83 | 85.10 | 97.72 | 92.48 | 112.94 |
| 4 | 48 | M | 77.29 | 73.98 | 0.95 | 71.40 | 82.40 | 80.25 | 97.05 |
| 5 | 55 | M | 71.80 | 69.28 | 0.90 | 76.60 | 88.22 | 84.95 | 103.13 |
| 6 | 53 | M | 115.44 | 104.40 | 0.87 | 80.05 | 92.08 | 88.03 | 107.13 |
| 7 | 51 | M | 57.01 | 56.18 | 1.11 | 58.32 | 67.70 | 68.06 | 81.48 |
| 8 | 52 | M | 111.02 | 101.08 | 0.94 | 72.39 | 83.51 | 81.15 | 98.21 |
| 9 | 59 | M | 59.95 | 58.83 | 0.94 | 72.39 | 83.51 | 81.15 | 98.21 |
| 10 | 56 | M | 99.56 | 92.23 | 0.93 | 73.4 | 84.64 | 82.07 | 99.40 |
| 11 | 57 | F | 40.61 | 40.94 | 1.21 | 52.13 | 60.72 | 62.08 | 73.96 |
| 12 | 63 | M | 46.36 | 46.37 | 0.91 | 75.51 | 87.00 | 83.97 | 101.85 |
| 13 | 43 | F | 93.27 | 87.22 | 0.87 | 80.05 | 92.08 | 88.03 | 107.13 |
| 14 | 56 | M | 79.56 | 75.91 | 0.81 | 87.85 | 100.77 | 94.87 | 116.08 |
| 15 | 56 | M | 107.12 | 98.11 | 0.73 | 100.56 | 114.91 | 105.74 | 130.46 |
| 16 | 63 | F | 77.12 | 73.84 | 0.78 | 92.26 | 105.69 | 98.69 | 121.10 |
| 17 | 55 | M | 84.15 | 79.76 | 1.13 | 56.98 | 66.19 | 66.78 | 79.87 |
| 18 | 59 | M | 90.78 | 85.20 | 1.04 | 63.47 | 73.50 | 72.93 | 87.67 |
| 19 | 60 | M | 69.74 | 67.49 | 0.99 | 67.67 | 78.22 | 76.84 | 92.66 |
| 20 | 55 | M | 87.68 | 82.67 | 0.94 | 72.39 | 83.51 | 81.15 | 98.21 |
| 21 | 52 | M | 85.36 | 80.76 | 0.72 | 102.38 | 116.93 | 107.27 | 132.49 |
| 22 | 66 | M | 102.25 | 94.34 | 0.84 | 83.79 | 96.25 | 91.33 | 111.43 |
| 23 | 60 | M | 41.61 | 41.89 | 1.00 | 66.8 | 77.24 | 76.03 | 91.62 |
| 24 | 66 | M | 89.81 | 84.41 | 0.61 | 127.01 | 144.15 | 127.40 | 159.61 |
| 25 | 67 | M | 74.16 | 71.32 | 1.29 | 47.97 | 56.00 | 57.96 | 68.83 |
| 26 | 64 | M | 72.47 | 69.86 | 1.05 | 62.69 | 72.62 | 72.20 | 86.73 |
| 27 | 57 | M | 55.65 | 54.95 | 1.19 | 53.28 | 62.01 | 63.20 | 75.36 |
| 28 | 49 | M | 77.19 | 73.90 | 1.16 | 55.07 | 64.04 | 64.94 | 77.55 |
| 29 | 52 | M | 64.4 | 62.80 | 1.13 | 56.98 | 66.19 | 66.78 | 79.87 |
| 30 | 63 | M | 72.02 | 69.47 | 0.88 | 78.87 | 90.76 | 86.98 | 105.76 |
| 31 | 69 | M | 50.52 | 50.23 | 1.96 | 27.85 | 33.03 | 36.67 | 43.03 |
| 32 | 65 | M | 68.41 | 63.16 | 1.09 | 59.72 | 69.27 | 69.39 | 83.17 |
| 33 | 56 | M | 83.8 | 79.46 | 0.92 | 74.44 | 85.81 | 83.01 | 100.61 |
| 34 | 42 | F | 77.38 | 74.06 | 0.90 | 76.60 | 88.2 | 84.95 | 103.13 |
| 35 | 66 | M | 89.81 | 84.41 | 1.31 | 47.02 | 54.93 | 57.01 | 67.65 |
| 36 | 52 | M | 130.98 | 115.63 | 0.86 | 81.26 | 93.43 | 89.11 | 108.53 |

G: sex, No: patient sequence number, GFRm1: Chantler corrected GFR with multiple blood sampling, GFRm2: Brøchner-Mortensen-corrected GFR multiple blood sampling, Cys-C: Cystatin-C, GFR-CR: GFR with Rule formula, GFR-CL: GFR with formula Larsson, GFR-CH: GFR with formula Hoek, GFR-CF: GFR with Filler formula, *ml/min, **mg/L

Table 2. GFR and Cystatin-C values of the patients whose treatment completed after chemotherapy.

| No. | Age | G | GFRm1* | GFRm2* | Cys-C** | GFR-CR* | GFR-CL* | GFR-CH* | GFR-CF* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 57 | E | 68.71 | 66.59 | 0.92 | 74.44 | 85.81 | 83.01 | 100.61 |
| 2 | 56 | E | 38.46 | 38.89 | 0.81 | 87.85 | 100.77 | 94.87 | 116.08 |
| 4 | 48 | E | 76.50 | 73.31 | .87 | 80.05 | 92.08 | 88.03 | 107.13 |
| 5 | 55 | E | 79.37 | 75.75 | 1.04 | 63.47 | 73.5 | 72.93 | 87.67 |
| 7 | 51 | E | 75.36 | 72.34 | 0.90 | 76.6 | 88.22 | 84.95 | 103.13 |
| 8 | 52 | E | 71.25 | 68.80 | 0.96 | 70.44 | 81.32 | 79.37 | 95.92 |
| 13 | 43 | K | 116.73 | 105.36 | 0.83 | 85.10 | 97.72 | 92.48 | 112.94 |
| 14 | 56 | E | 82.84 | 78.66 | 0.87 | 80.05 | 92.08 | 88.03 | 107.13 |
| 16 | 63 | K | 26.53 | 27.26 | 0.82 | 86.46 | 99.22 | 93.66 | 114.49 |
| 17 | 55 | E | 49.93 | 49.69 | 0.90 | 76.60 | 88.22 | 84.95 | 103.13 |
| 20 | 55 | E | 46.20 | 46.22 | 1.76 | 32.03 | 37.83 | 41.33 | 48.56 |
| 21 | 52 | E | 67.23 | 65.29 | 0.95 | 71.40 | 82.40 | 80.25 | 97.05 |
| 22 | 66 | E | 122.32 | 109.45 | 0.89 | 77.72 | 89.48 | 85.96 | 104.43 |
| 23 | 60 | E | 29.21 | 29.91 | 1.27 | 48.95 | 57.12 | 58.94 | 70.05 |
| 24 | 66 | E | 72.25 | 69.67 | 0.58 | 135.61 | 153.62 | 134.21 | 168.91 |
| 28 | 49 | E | 71.77 | 69.25 | 0.97 | 69.49 | 80.26 | 78.51 | 94.81 |
| 31 | 69 | E | 36.85 | 37.34 | 2.08 | 25.78 | 30.64 | 34.30 | 40.25 |
| 32 | 65 | E | 64.81 | 66.33 | 0.84 | 83.79 | 96.25 | 91.33 | 111.43 |
| 34 | 42 | K | 52.37 | 51.94 | 0.74 | 98.80 | 112.95 | 104.26 | 128.48 |
| 36 | 52 | E | 88.91 | 83.68 | 1.30 | 47.49 | 55.46 | 57.48 | 68.24 |

G: sex, No: patient sequence number, GFRm1: Chantler corrected GFR with multiple blood sampling, GFRm2: Brøchner-Mortensen-corrected GFR multiple blood sampling, Cys-C: Cystatin-C, GFR-CR: GFR with Rule formula, GFR-CL: GFR with formula Larsson, GFR-CH: GFR with formula Hoek, GFR-CF: GFR with Filler formula,*ml/min, **mg/L.

mechanisms. The cisplatin concentration in proximal tubular epithelial cells is about 5 times the serum concentration. Conversion of cisplatin to nephrotoxic molecules in the proximal tubule cells is required for cell injury. The proximal tubular dysfunction observed in cisplatin nephrotoxicity precedes alterations in renal hemodynamics. Forty-eight to 72 hours after cisplatin administration, there was impaired proximal and distal tubular reabsorption and increased vascular resistance. Most patients have a reversible decrease in glomerular filtration, but some have an irreversible decrease in glomerular filtration.[28] There are controversies in monitoring renal function in this group of patients.

We aimed to investigate the correlation between GFR values calculated by Cystatin-C based formulas, radionuclidic method and blood Cystatin-C values, in patients receiving cisplatin treatment in pre-treatment and post-treatment periods.

Grönroos and colleagues found a significant correlation between Cystatin-C values and multi blood sampling methods in pediatric patients receiving chemotherapy. As a result of the study, they stated that after treatment, the most accurate method of measuring GFR was radionuclidic measuring method. In addition, they showed that Cystatin-C values were important alternative to the measurement of GFR values.[29]

In a study made in patients with varying degrees of renal failure and healthy volunteers, Trimarchi and his colleagues showed that, in patients whom GFR level is lower than 60 mL/minute, multiple blood sampling method showed the best correlation with Cystatin-C based Hoek formula. ($r = 0.82$, $P < 0.001$). In early stage renal failure patients and healthy population, statistical significance was found to be continuing with declining correlation ($r = 0.60$, $P < 0.001$).[30] In a study Huang and colleagues have made in a heterogeneous group of 42 adult patients, they compared Filler, Grubb, Hoek, Larsson, Le Bricon ve Rule formulas with multiple blood sampling method using Tc-99m DTPA. They found that Cystatin-C based formulas showed a quite good correlation among themselves and that correlation coefficients with radionuclidic method changed between 0.87 and 0.65 (each $P < 0.001$). The best correlation was obtained by Hoek formula.[31] In their study of 28 pediatric patients with spina bifida, by using Tc-99m DTPA, Morgan and colleagues reported the correlation coefficient between Filler formula and blood sampling method as 0.42 ($P = 0.03$).[32] Thomas and colleagues compared the GFR values calculated by Larson, Hoek & Filler formulas with the ones calculated by multiple blood sampling methods in a group of 59 patients of liver transplantation. Correlation coefficients were reported respectively as 0.59, 0.60 and 0.60 (each $P < 0.0001$).[33] In our study, correlation coefficients found between Cystatin-C based GFR and radionuclidic GFR values prior to chemotherapy showed similarities with literature. The correlation degrees between of all Cystatin-C based formulas and radionuclidic method were close. Also, we found that the correlation coefficients were statistically

Table 3. Comparison of the mean GFR and Cystatin-C values during pre-treatment and post-treatment periods.

| | Pretreatment | Post-treatment | *P** |
|---|---|---|---|
| GFRm1* | 79.06 ± 21.19 | 66.88 ± 25.52 | 0.021*** |
| GFRm2* | 74.74 ± 17.76 | 64.28 ± 22.10 | 0.021*** |
| GFR-CR* | 75.22 ± 20.07 | 73.60 ± 23.66 | 0.705 |
| GFR-CL* | 86.59 ± 22.47 | 84.74 ± 26.53 | 0.700 |
| GFR-CH* | 83.15 ± 18.25 | 81.44 ± 21.74 | 0.665 |
| GFR-CF* | 101.09 ± 23.51 | 99.02 ± 27.88 | 0.681 |
| Cys-C** | 0.96 ± 0.27 | 1.01 ± 0.35 | 0.415 |

GFRm1: Chantler corrected GFR with multiple blood sampling, GFRm2: Brøchner-Mortensen-corrected GFR multiple blood sampling, GFR-CR: GFR with Rule formula, GFR-CL: GFR with formula Larsson, GFR-CH: GFR with formula Hoek, GFR-CF: GFR with Filler formula GFR , Cys-C: Cystatin-C, *ml/min, **mg/L, ***$P < 0.05$ is significant.

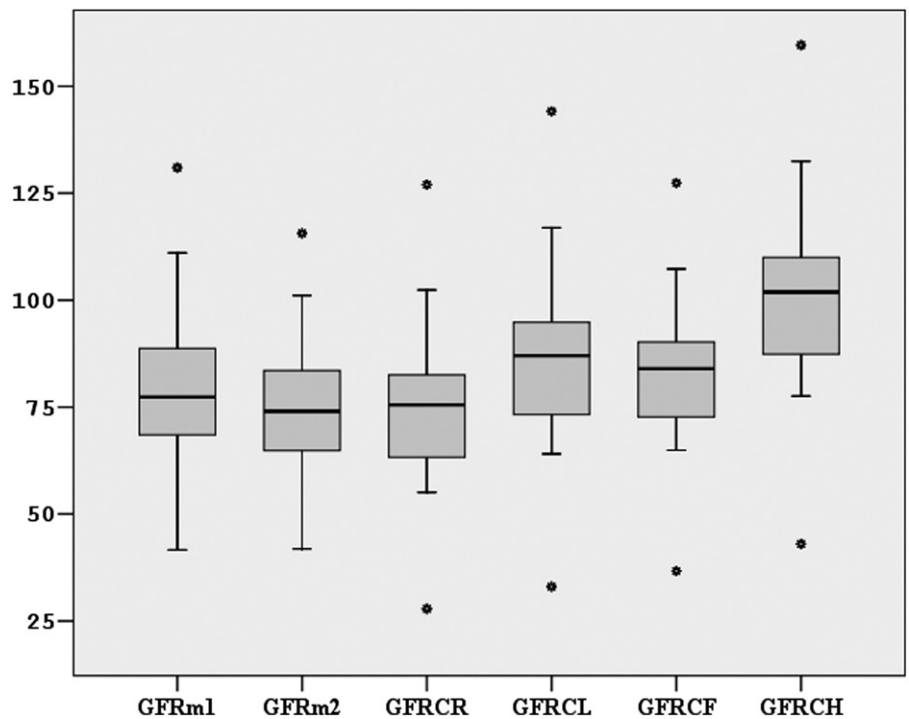



Figure 1. Pre-treatment values of GFR, *Extreme values.

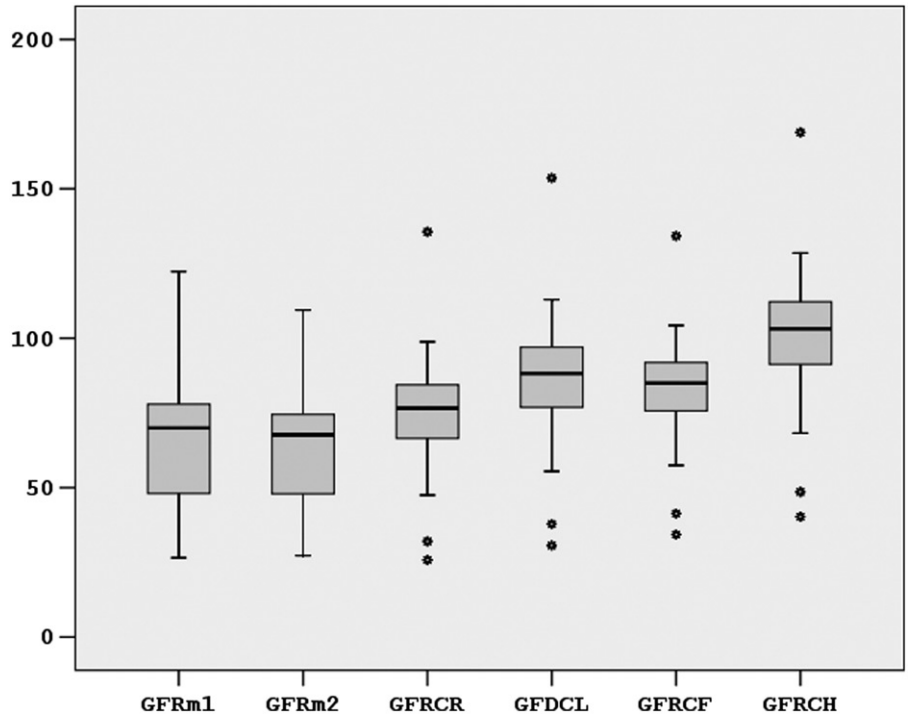



Figure 2. Post-treatment values of GFR, *Extreme values.

Table 4. Correlation of GFR measurement methods during pre-treatment and post-treatment periods.

| | Pre-treatment | | Post-treatment | |
|---|---|---|---|---|
| | *r* | *P* | *r* | *P* |
| GFRm1/GFRm2 | 1.00 | 0.000*** | .99 | 0.000*** |
| GFR-CR/GFR-CL | 1.00 | 0.000*** | 10.00 | 0.000*** |
| GFR-CR/GFR-CH | 1.00 | 0.000*** | 10.00 | 0.000*** |
| GFR-CR/GFR-CF | 1.00 | 0.000*** | 10.00 | 0.000*** |
| GFR-CL/GFR-CH | 1.00 | 0.000*** | 10.00 | 0.000*** |
| GFR-CL/GFR-CF | 1.00 | 0.000*** | 10.00 | 0.000*** |
| GFR-CH/GFR-CF | 1.00 | 0.000*** | 1.00 | 0.000*** |
| GFR-CR/GFRm1 | 0.46 | 0.039*** | 0.07 | 0.757 |
| GFR-CR/GFRm2 | 0.46 | 0.039*** | 0.08 | 0.724 |
| GFR-CL/GFRm1 | 0.46 | 0.041*** | 0.07 | 0.757 |
| GFR-CR/GFRm2 | 0.46 | 0.041*** | 0.08 | 0.724 |
| GFR-CH/GFRm1 | 0.46 | 0.039*** | 0.07 | 0.757 |
| GFR-CH/GFRm2 | 0.46 | 0.039*** | 0.08 | 0.724 |
| GFR-CF/GFRm1 | 0.46 | 0.039*** | 0.07 | 0.757 |
| GFR-CF/GFRm2 | 0.46 | 0.039*** | 0.08 | 0.724 |
| Cysc-C/GFRm1 | −0.46 | 0.039*** | –0.07 | 0.757 |
| Cysc-C/GFRm2 | −0.46 | 0.039*** | –0.08 | 0.724 |

GFRm1: Chantler corrected GFR with multiple blood sampling, GFRm2: Brøchner-Mortensen-corrected GFR multiple blood sampling, GFR-CR: GFR with Rule formula, GFR-CL: GFR with formula Larsson, GFR-CH: GFR with formula Hoek, GFR-CF: GFR with Filler formula GFR, Cys-C: Cystatin-C, $r$ = Spearman correlation coefficient, ***$P < 0.05$ is significant.

significant between the GFR values calculated by radionuclidic method and Cystatin-C values.

In a study of cisplatin-treated ovarian cancer patients, Lubomir and colleagues reported that they could not find any correlation between pre-chemotherapy Cystatin-C levels in the blood, blood creatinine, modification of diet in renal disease (MDRD) and creatinine clearance values. After three cycles of chemotherapy, a weak correlation between blood Cystatin-C, blood creatinine and creatinine clearance was found ($r = -0.03$, $P = 0.03$). But no gold standard for the measurement of GFR was used by the researchers.[34] Similarly, in a study by Nakai and colleagues in a group of 82 cancer and 276 non-cancer patients, they announced that Cystatin-C in cancer patients is always not a good marker for GFR.[21] In the literature, although there are not many available publications that compared Cystatin-C and radionuclidic methods in adult patients receiving chemotherapy; according to those available, whether Cystatin-C evaluates kidney function correctly after chemotherapy or not still remains controversial.

Grönroos MH and colleagues found that there was a statistically significant relationship between radionuclidic GFR measurements and serum Cystatin-C levels in pediatric patients who have received chemotherapy.[29] The results of our study are not compatible with this study.

Aydin and colleagues compared GFR values obtained from multiple blood sampling method with Filler method of Cystatin-C based formula and Cystatin-C values in two distinct pediatric patient groups (receiving and not receiving chemotherapy groups).[10] They found a statistically significant correlation between GFR calculated by radionuclidic method and GFR calculated by serum Cystatin-C values and Filler method in non-chemotherapy group. ($r = -0.78$ and 0.91, respectively, for each $P < 0.05$). In chemotherapy group, though statistically significant, correlation coefficients were reported to be decreasing. In chemotherapy group, correlation coefficients between GFR calculated by radionuclidic method and GFR calculated by serum Cystatin-C values and Filler method were reported as −0.42 and 0.43, respectively (each $P < 0.05$). Urinary β2-microglobulin (β2M), and β-N-acetylglucosaminidase (β-NAG) values were excessively high after chemotherapy compared to the values in pre-chemotherapy. While the change in the value of β-NAG was statistically significant, the change in the value

of β2M was reported not to show statistical significance. Due to statistically significant change in the value of β-NAG, researchers thought the reason of correlation corruption between GFR calculated by radionuclidic method after chemotherapy and GFR calculated from serum Cystatin-C values and Filler method was probably because of chemotherapeutics-induced tubular cell damage and consequent deterioration of the tubular absorption of Cystatin-C and metabolism. In conclusion, they stressed that serum Cystatin-C values and Filler method (Cystatin-C based GFR calculation formula) may not indicate GFR values pediatric patients receiving chemotherapy correctly.[10]

In a recent study, Kos et al. evaluated the correlation of serum Cystatin-C levels with the serum creatinine levels and GFR calculated by Cockcroft–Gault and MDRD formulations in 34 patients who received cisplatin-based chemotherapy.[35] They found a statistically significant linear correlation between the serum levels of Cystatin-C and creatinine prior to the chemotherapy ($r = 0.42$, $P = 0.013$). However, there was no correlation among the level of Cystatin-C subsequent to the cisplatin infusion and serum creatinine level following the third course and MDRD and creatinine clearance–Cockcroft–Gault formulations. Even though the serum Cystatin-C levels were correlated with the serum creatinine levels in their study, it was concluded that it was not an appropriate parameter to predict the potential impairments in the renal function during the chemotherapy.

We found, in pre-treatment period, significant, positive correlation between Cystatin-C based GFR calculation methods and GFR values calculated by radionuclidic calculation method. These correlations deteriorated after treatment with cisplatin. While there were significant differences found between pre-treatment and post-treatment periods of GFR values obtained from radionuclidic method we found no significant difference between values of pre-treatment and post-treatment periods of Cystatin-C. Also GFR values obtained from Cystatin-C-based formulas was not different in pre-treatment and post-treatment periods. These statements could indicate that cisplatin treatment does not influence Cystatin-C and GFR values obtained from Cystatin-C based formulas. Because radionuclidic calculation method of GFR is more sensitive than other methods and it is known as gold standard.

In healthy people, Cystatin-C is excreted by glomerular filtration into primary urine and is then reabsorbed and fully catabolized by the proximal renal tubular cells. Cystatin-C is not normally found in urine in significant amounts, the elevated level of urinary Cystatin-C may indicate dysfunction of tubular cells and tubulointerstitial disease. Serum Cystatin-C performs predominantly as a marker of GFR. However, Cystatin-C in urine is one of the more promising acute kidney injury markers. Urine Cystatin-C reflects renal tubular damage caused by acute tubular necrosis.[36] Chemotherapeutics especially cisplatin could cause renal tubular cell injury and consequently deterioration of the tubular absorption of Cystatin-C and metabolism. Therefore measurement of urine Cystatin-C in these patients could be meaningful. In our study we did not use urine Cystatin-C values as a marker for tubular dysfunction. In the future studies including serum and urine Cystatin-C and GFR measurements could be planned in order to define precisely nephrotoxic effect of chemotherapeutics.

### Limitations of the study

The most important limitation in our study is that, while the initial number of the patients was 36, statistical evaluation was done for only 20 patients who could complete the treatment process.

## Conclusion

In this study we investigated the correlation between GFR values calculated by Cystatin-C-based formulas, radionuclidic method and blood Cystatin-C values in patients with lung cancer, receiving cisplatin treatment in both pre-treatment and post-treatment periods. Before chemotherapy we observed significant correlation between blood Cystatin-C values and GFR values obtained with radionuclidic method. Also GFR values obtained by Cystatin-C-based formulas correlated with GFR values obtained by radionuclidic method significantly. All correlations deteriorated after treatment. This indicates that GFR values that were calculated by Cystatin-C based formulas may not be reliable while monitoring renal functions in patients receiving cisplatin therapy. When reliable monitoring of the renal functions is necessary, radionuclidic methods may be preferred in these patients.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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