Clinical Research

Correlation Between Renal Function and Kidney Computed Tomography Histogram Analysis; A Radiomics Study

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ABSTRACT

Objective: In this study we aimed to investigate correlation between computed tomography (CT) histogram analysis of kidney parenchyma and renal functional status.

Material and Method: Renal parenchyma CT densities were measured by using a region of interest (ROI) from both cortex and medulla, who had a non-contrast CT of abdomen (120 kV) and serum creatinine level in the same day in a cohort of 225 patients (115 female, 110 male). Serum creatinine levels were within normal limits in 186 and high in 39 of patients. ROI histogram data was analyzed by using Matlab® program which calculated the median, mean, maxiumum, minimum, standard deviation, variance, entropy, size % L, size % U, size % M, kurtosis, skewness and uniformity values.

Results: Age and gender were significantly different among the groups (age p <0.001, gender p =0.002). Significant correlations was noted between serum creatinine level and kidney medulla mean (r=-0.22, p <0.001), maximum (r =-0,16, p <0.05), median (r =-0.17, p <0.001), size % L (r =-0.14, p <0.05) and entropy (r =-0.13, p <0.05) values as well as size %U (r =-0.14, p <0.05), size %M (r =0.14, p <0.05) density from kidney cortex.

There was significant difference among patients with normal and high creatinine levels in terms of median (p =0.011), mean (p =0.004), size %M (p =0.032), and uniformity (p =0.045) values from kidney medulla as well as entropy (p =0.036) value from cortex.

Conclusion: There is a negative correlation between serum creatinine levels and renal parenchyma CT densities particulary from medulla. Decreased renal function should be predicted by calculating the histogram analysis of kidney from cortex or medulla in a non-enhanced abdomen CT.

Keywords: *Texture Analysis, Chronic Renal Failure.*

ÖZ

Böbrek Fonksiyonu ile Böbrek Bilgisayarlı Tomografi Histogram Analizi Arasındaki Korelasyon

Amaç: Bu çalışmada böbrek parankiminin bilgisayarlı tomografi (BT) histogram analizi ile böbrek fonksiyon durumu arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Böbrek parankim BT yoğunlukları, aynı gün içinde kontrastsız abdomen BT'si (120 kV) ve serum kreatinin düzeyi olan toplam 225 hastada (115 kadın, 110 erkek) hem korteks hem de medulladan bir ilgi alanı (ROI) kullanılarak ölçüldü. Serum kreatinin düzeyleri hastaların 186'sında normal, 39'unda yüksekti. ROI histogram verileri, medyan, ortalama, maksimum, minimum, standart sapma, varyans, entropi, boyut % L, boyut % U, boyut % M, basıklık, çarpıklık ve tekdüzelik değerlerini hesaplayan Matlab® programı kullanılarak analiz edildi.

Bulgular: Yaş ve cinsiyet gruplar arasında farklılık göstermekteydi. (yaş p <0.001, cinsiyet p=0.002). Serum kreatinin düzeyi ile böbrek medulla ortalaması ((r =-0.22, p <0.001),), medyan (r =-0.17, p <0.001), maksimum (r =-0,16, p <0.05), boyut % L (r =-0.14, p =0.05) ve entropi ((r =-0.13, p <0.05) ayrıca böbrek korteksinden alınan , boyut %U (r =-0.14, p <0.05) boyut %M (r =0.14, p <0.05) değerlerinde anlamlı korelasyon kaydedildi.Kreatinin düzeyi normal ve yüksek olan gruplar arasında böbrek medullasından median (p =0.011), ortalama (p =0,004), size %M (p =0.032) ve uniformity (p =0.045) değerleri yanı sıra korteksten entropi (p=0.036) değeri.açısından anlamlı fark vardı.

Sonuç: Serum kreatinin düzeyleri ile özellikle medulladan renal parankim BT yoğunlukları arasında negatif bir korelasyon vardır. Kontrastsız batın BT'de azalmış böbrek fonksiyonu, korteks veya medulladan alınan histogram analizi değerleriyle ile tahmin edilebilir gözükmektedir.

Anahtar Sözcükler: *Doku Analizi, Kronik Böbrek Yetmezliği, Bilgisayarlı Tomografi Histogram Analizi.*

Bu makale atıfta nasıl kullanılır: Kılıç A, Özçetin M. Böbrek Fonksiyonu ile Böbrek Bilgisayarlı Tomografi Histogram Analizi Arasındaki Korelasyon. Fırat Tıp Dergisi 2024; 29(3): 165-169.

How to cite this article: Kilic A, Ozcetin M. Correlation Between Renal Function and Kidney Computed Tomography Histogram Analysis; A Radiomics Study. Firat Med J 2024; 29(3): 165-169.

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Chronic kidney disease (CKD), represents deterioration in kidney function and structure during course of many diseases. As a global public health problem, patients with kidney failure have risk of, cardiovascular complications, premature death as well as low quality of life. Staging of disease severity is based on glomerular filtration rate (GFR), is commonly estimated by serum creatinine levels in adults by Cockcroft-Gault equation (1). Serum biomarkers have limitations as they represent estimated GFR for a patient not a single kidney. Reliable prediction of decrease in kidney function thus remains difficult, in routine practice (2)

Texture analysis (TA) is offering new approach and gaining new diagnostic information upon conventional techniques. CT, MRG or sintigraphy derived data have been further analyzed by statistical-based techniques in

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Geliş Tarihi/Received: 22.11.2023 Kabul Tarihi/Accepted: 09.02.2024

terms of variation of pixel intensity. Distribution or relationship of gray level of pixels in an area of interest let an objective assessment and interpretation and may give idea about microenvironment of the tissue. From histogram of pixel intensity in a ROI, mean intensity, threshold, entropy (irregularity), standard deviation, skewness (asymmetry) and kurtosis (peakedness /flatness of pixel histogram) values are extracted. As showing tumor heterogeneity TA have been mostly studied in oncology for discrimination of benign-malign or aggressive- less aggressive lesions and for prediction outcome or response) (3-7). Other than that non-oncologic studies (liver fibrosis, lung fibrosis,) have shown promising results by using texture analysis (8-10).

By the way cross-sectional imaging has been used mostly for kidney volume measurement and DWI measuring ADC levels from renal parenchyma in order to quantify kidney functional capacity (11).

This study was designed by forecasting that the collimated X-ray beam may reflect changes in the attenuation value of the renal parenchyma via the histogram properties of the area of interest before visible features. By using radiomics; knowing that sclerosis of renal parenchyma cells which is major histopathologic finding in CHD; we had postulated that CT TA may extract lower entropy and more uniformity values in correlation with renal functional status.

In this study we aimed to investigate correlation between CT texture analysis of kidney parenchyma and renal functional status by using histogram properties.

MATERIAL AND METHOD

Patient selection

Medical records from January 2017 through June 2018 was searched to select adult patients (>18 years-old) whom had a non-contrast CT of abdomen and serum creatinine level within 24 hours in a tertiary care unit. Patients with a diagnosis of acute renal failure, kidney trauma, single kidney, AD polycystic renal disease, kidney atrophy, cystic or solid kidney mass, staghorn stone, D-J catheter, hydronephrosis, hemodialysis, kidney transplantation were not included. A total of 225 (115 female,110 male) patients met inclusion criteria.

Radiological studies

Non- contrast upper abdomen CT of the patients were acquired from a 320 row-multidedector CT scanner (Aquilion ONE, Canon Medical Systems, Otawara, Japan). Scan parameters were as follows; tube voltage; 120 kvp, tube current; (mA) R229, eff mAs 133, thickness 3 mm, reconstruction thickness, 1.5 mm; pitch, 0.984:1; and gantry rotation time, 0.35s, matrix, 512 × 512.

Image measurements were done blindly by C.M. K on workstation equipped with 27 inch iMac computer (Apple Inc. Cupertino, 88 California, US; OsiriX V.4.9 imaging software Pixmeo, Switzerland). Renal parenchyma CT densities (Hounsfield Unit) were measured by using region of interest (ROI) placed manually on mid portion of cortex and medulla soft tissue reconstruction kernel. Figure 1 is showing the placement of ROI.

Local ethics committee approval was obtained. Informed consent had been obtained just before CT examination from each patient.

Data analysis

Kidney parenchyma CT densities (Hounsfield Units) were measured from mid portion of one (left) kidney by using ROI (area 60 mm2) manually on soft tissue window preset (Figure 1).

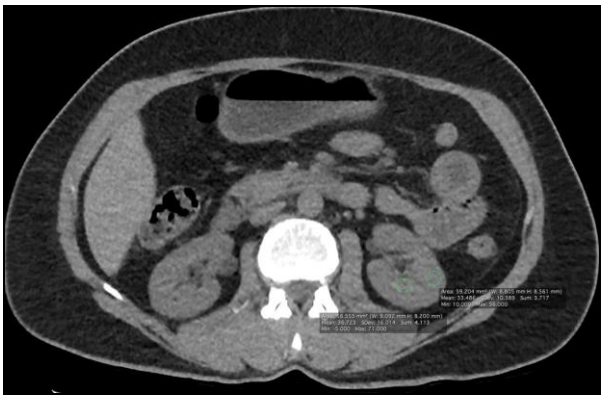

Figure 1. *Placement of region of interest in cortex and medulla separately is shown.*

Data from kidney cortex (near to capsule) and medulla (near to pyramis) were recorded separately. The gray level intensity values (HU) of each pixel within the ROI were transferred via XML (eXtensible Markum Language) file to MATLAB (MATrix LABoratory, Mathworks Inc, Natick, USA) version 2009b software. After the transformation of the individual grey level intensity pixel intensity to histograms. The data from each kidney was averaged. We have used statistical based 13 texture analysis parameters (Table 1).

Table 1. *Texture analysis features used in this study. SD (standart deviation).*

Texture Analysis Features
mean
maximun,
minimum,
median
standart deviation
entropy(irregularity)
uniformity (inhomogeneity),
variance
size %L percentage of pixels under -1 standart deviation (SD)
size %M , percentage of pixels between -1 and +1 SD
size %U (percentage of pixels over +1 SD
skewness (asymmetry of the histogram),
kurtosis(peakedness or flatness of histogram)

First order statistics included mean, maximum, minimum, median intensity and entropy(irregularity), uniformity (inhomogeneity), Second order statistics consisted variance and percentage of pixels under -1 stand-

ard deviation (SD) (size %L), percentage of pixels between -1 and +1 SD (size %M), percentage of pixels over +1 SD (size %U). Skewness (asymmetry of the histogram), and kurtosis (peakedness or flatness of histogram) were accepted third and fourth order.
Using first-order pixel intensity distribution was quantified. Second-order statistics, were applied to define the spatial relationship between pairs of pixels.

Statistical analysis

All data were analyzed with statistical program SPSS 22.0 (IBM SPSS for Windows version 22, IBM Corporation, Armonk, USA). The distribution of data was examined using the Shapiro-Wilk test. Pearson correlation was used in order to analyze correlation within variables. The Mann-Whitney U test was used to compare the groups in the variables that did not show normal distribution. The p <0.05 was accepted statistically significant. The area under the ROC curve (AUC) results were considered excellent for AUC values between 0.9-1, good for AUC values between0.8-0.9, fair for AUC values between 0.7-0.8, poor for AUC values between 0.6-0.7 and failed for AUC values between 0.5-0.6 (10).

RESULTS

Serum creatinine level was within normal limits in 186 patients (mean creatinine level was 0,70 mg/dl) and high in 39 (mean creatinine level was 2.96 mg/dl). of patients., Mean age was 61.7 years in the pathologic (high creatinine level) group as well as 42.0 years in control group.
Age and gender were significantly different among the groups (age p =<0.001, gender p =0.002).
Significant correlations were noted between serum creatinine level and kidney medulla mean (r =-0.22, p =0.001), maximum (r =-0,16, p =0.05), median (r =-0.174, p =0.001), size % L (r =-0.14, p=0.05) and entropy (r =-0.13, p=0.05) values as well as size %U (r =-0.14, p =0.05), size %M (r =0.14, p=0.05) density from kidney cortex (Figure 2).

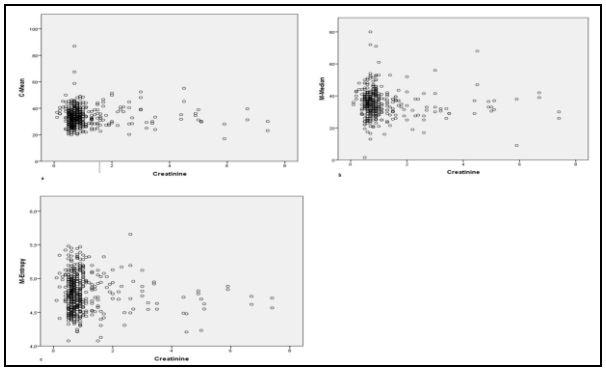

Figure 2. *Plot graphs are showing the correlation between mean (a), median (b) and entrophy ©values and serum creatinine levels with a level mean (r =-0.22, p =0.001), median (r =-0.174, p =0.001) and entrophy (r =-0.13, p =0.05).*

From 13 texture features 7 of them differed significantly among groups. Significant differences among patients with normal and high creatinine levels in terms of median (p =0.011), mean (p =0.004), size %M (p =0.032), and uniformity (p =0.045) values from kidney medulla as well as entropy (p=0.036) value from cortex (Table 2).

Table 2. *Texture analysis features those differed between patients with normal serum kreatinin levels (Group 1) and high kreatinin levels(Group 2).*

Texture Analysis features	Region	p	Group 1 (normal creatinine levels)	Group2 (high creatinine levels)	AUC
entropy	cortex	0.036*	4.81	4.71	0.580
uniformity	medulla	0.045*	0.30	0.32	0.549
mean	medulla	0.004*	36.5	32.5	0.607
median	medulla	0.011*	16.08	17.6	0.563
maximum	medulla	0.047*	69.1	63.8	0.562
%L size	medulla	0.014*	16.08	17.6	0.562
%M size	medulla	0.032*	67.6	65.4	0.569

*(%L size- percentage of pixels over +1 standart deviation) (%M size=percentage of pixels between -1 and +1 standart deviation) Roc Curve: α:0.05; *Statistically significant.*

DISCUSSION

Early diagnosis of CKD by imaging is crucial as there is not apparent clinical sign or finding in early stages (1). CT TA can have the potential in the evaluation of renal function before biochemical or anatomical changes occur. The expectations about texture analysis in our study is to put forth the microstructural differences quantitatively, in patients with chronic renal disease by using non enhanced CT images before human eye perceives. In this manner by using statistical based technique (by MATLAB), via placing ROI on cortex and medulla of the kidney; CT histogram method which extract 13 texture features, a total of 7 results managed to discriminate patients with high creatinine levels from the normal ones with a sensitivity from %70 to %52,4 and specifity from %56,4 to %50.0 And the features including kidney medulla mean maximum (r =-0,16, p =0.05), median , size % Land entropy values as well as size %U, size %M density from kidney cortex showed significant correlations with creatinine levels.
Kidneys possess high blood flow for water transport function. GFR which decreases during the development of chronic renal failure, is the result of glomerular loss and fibrosis histopathologically. In this process, structural deterioration that occurs is insidious; typically, kidneys with reduced size with thin parenchyma are seen in end-stage renal disease patients, while there is no CT finding indicating decreased GFR in the early period. This study was designed by predicting that the attenuation value of the collimated X-ray beam in the area of interest can reflect histopathological changes before visible changes, thanks to histogram features. To the best of our knowledge, this is the first study that

investigated CT histogram analysis to reveal such a relationship.

Previously, via DWI which detects the free Brownian motion of water molecules within a voxel of targeted tissue; relationship between DWI, eGFR and ADC values was examined (11). Although low eGFR patients tended to show with low ADC values, no significant correlation was found. However, in another study comparing the ADC values according to the stages, the ADC values were found to be significantly higher in stage 3, 4, 5 compared to the normal population (12).

In a comprehensive texture analysis study conducted according to the stages of liver fibrosis in the literature, whom had studied texture-based analysis on contrast-enhanced CT images suggested that texture features might have the potential to reveal liver fibrosis non-invasively (10). They also used MATLAB program like we did and found out 7 histogram features which were able to discriminate groups of hepatic fibrosis stages. Of these, fibrosis scores; the most correlated finding was median and the highest AUC value showed 'poor 'ROC curve results. In our study, similar to this study, when the group with normal creatinine levels was compared with the group with high creatinine levels; the highest AUC value is 'mean' value from the medulla. And this value corresponded to the range of poor ROC curve results (Table 2).

Previously, for ADC measurements of kidneys made from DWIs, where molecular diffusion was calculated for this purpose, ROI was placed at the corticomedullary junction to include the cortex and medulla from the middle part of the kidneys (11). In this study, we placed two separate ROI in the cortex and medulla although, there were some who predicted that this is not certain (13) Although the borders of the cortex and medulla are not clear, a circular ROI (60 mm^2) with a diameter of 5 mm and the closest (at least 2 mm distance) to the sinus was placed in the cortex closest to the capsule (at least 2 mm away) to increase the hit rate.

As a matter of fact, histogram values taken from the medulla showed more correlation with creatinine values than those taken from the cortex (total 5 values in the medulla) (mean, median, maximum, size %L and entropy); and 2 values in the cortex (size %U, and size %M). Besides this; a total of 4 distinct features from the medulla and only 1 feature of the cortex differed between the normal and reduced renal functions group. This difference overlaps with the classical knowledge that microstructural changes occur primarily in the medulla.

In this study, texture analysis was performed with a statistical based method; and images are quantified with standard markers (Table 1). The distribution of the gray color level of the pixels in the ROI or their relationship to each other has turned into quantitative figures.

In some of the studies in the literature (3, 10, 14), it is seen that before CT histogram measurement filtration applications were used to reduce the exposure to photon noise at the beginning; by using spatial scale factor at different levels, for example (0 mm no filtrasyon, 2 mm fine texture scale, 3, 4 and 5 mm medium scale and 6 mm coarse texture scale (on the Laplacian of Gaussian spatial bandpass scale filter to produce images of different spatial scales) were used (15). Before histogram analysis we did not apply filtration because the number of pixels in the ROI drawn semi-quantitatively was almost standard, has smaller number of pixels than the others and the CT examinations in current study were without contrast. If we had used filtration; it probably would not have much of an effect for the reasons we mentioned above.

Histogram analysis is a post processing method; which produces diverse spectrum of texture features related to vendors (TEXRAD, MATLAB etc) but not standard. In this study we have used MAtlab program dealing with 13 features related to histogram features. For instance, Daginawala et al (10) in their study investigating the early diagnosis and staging of liver fibrosis, a total of 41 features including One gray level co-occurrence, 6 gray level run length, 1 Laws level, 4 gray level gradient matrix I have been investigated, 12 of which were histograms (mean median, SD, range etc.). Studies examining the relationship between tumor heterogeneity such as colorectal cancer, esophageal cancer, prognosis or response to treatment was activated gray level co-occurrence matrix dealing with 5 features (3-5).

The 'entropy' value is mostly a data corresponding to spatial heterogeneity in lesions with malignant potential and the mean value of the medulla and the serum creatine level are negatively correlated. In addition, a significant difference in terms of 'uniformity' values in the group with normal and abnormal creatinine levels were detected; It can be thought that as a result of sclerosis and fibrosis, the kidneys turn into a more uniform structure.

Generally, decrease in density of renal pixels is observed during chronic renal failure. And negative correlation with creatinine levels and mean, maximum and median % L size values; support this knowledge statistically.

Being a retrospective study, low number of patients with high serum creatinine levels; not correlated with histopathology findings, placement of ROI s manually (cortex and medulla discrimination may not be done on each patient) were limitations of this study. Intra or inter observer agreement was not tested. Serum creatinine levels may also affected by other conditions including dehydration, edema, infection and drugs those were not further interested. Data extracted from these type of studies may be helpful in a patient who has undergone non-contrast abdominal CT imaging for any reason, elevated serum creatinine can be predicted before visible changes begin.

Conclusion

There were no previous studies that examined the correlation of renal functions with CT histogram analysis. A one-to-one comparison could not be made since this

study was not found in the similar literature. However, the obtained data may be referred by future studies.
The changes in pixel level that occur before size or contour abnormalities develop in the kidneys of the patient group we included; may reflect early microscopic changes. There is a negative correlation between serum creatinine levels and renal parenchyma CT densities particularly from medulla. Decreased renal function should be predicted by calculating the histogram analysis of kidney from cortex or medulla in a non-enhanced abdomen CT threshold values can be determined by comprehensive CT TA studies supporting ours.

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