Evaluation of Basal Renal Function in Treatment-naïve Patients with Malignancy and Comparison with Age Matched Healthy Control

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Abstract

There is a paucity of data regarding the prevalence of renal insufficiency in patients with malignancy at baseline before initiation of therapy. The published studies based on patient with prior exposure to cytotoxic therapy have reported a high prevalence of renal impairment. However, these studies have utilized creatinine-based glomerular filtration rate (GFR) prediction equations to assess the level of renal function. These equations are known to have some serious limitations in reliably predicting GFR. The aim of the study was to accurately document the state of renal function in treatment-naïve cancer patients and compare them against age-matched healthy controls using a reference "creatinine independent" GFR measurement technique. Age-matched comparison of GFR of 1,373 treatment-naïve cancer patients and 1,089 healthy controls were done retrospectively. There was no difference in GFR between cancer and healthy group when analyzed under various age groups, though the overall mean GFR in healthy controls was significantly higher compared to cancer group (80.14 ± 17.63 mL vs 74.43 ± 20.84, $P \leq 0.01$), whereas the mean age in control arm was significantly lower compared to cancer group (44.24 ± 17.63 years vs. 50.70 ± 20.84 years, $P \leq 0.01$). Treatment-naïve cancer patients have identical renal function to their healthy age-matched peers. Malignancy *per se* does not directly lead to the decline in filtration capacity of the kidneys.

Keywords: Glomerular filtration rate, healthy control, malignancy, renal function

Introduction

There is a paucity of data regarding the prevalence of renal insufficiency in patients with malignancy at baseline before initiation of therapy. The patients with chronic renal failure are known to have higher incidence of malignancy but the issue of whether cancer patients have higher prevalence of renal insufficiency has not been adequately addressed so far.[1,2] In three separate recent studies recruiting more than 7,000 patients, very high prevalence rates (27.1–57%) of renal insufficiency in patients with malignancy have been reported, but whether this high prevalence rate of renal insufficiency is induced by cancer or secondarily due to therapy has not been adequately clarified.[3-5] Glomerular filtration rate (GFR) is considered the best parameter of renal function. However, in all the abovementioned studies GFR values were obtained by one of the simplified creatinine-based GFR prediction equations rather than the standard GFR measurement technique. Limitations of creatinine-based GFR prediction equations in accurately predicting the level of GFR has been well documented in literature.

In order to document the actual state of renal function in patients with malignancy and to document the prevalence rate of renal insufficiency in cancer patients, results needs to be compared with age-matched healthy controls drawn from same racial population. The aim of this study was to document the actual prevalence rate of renal insufficiency among cancer patients at baseline, before the initiation of cytotoxic therapy by

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directly measuring instead of estimating GFR by a valid creatinine independent measurement technique, and to compare the level of renal function with age-matched healthy controls drawn from the same racial population.

Materials and Methods

Records of cancer patients who underwent the GFR measurement study in the Department of Nuclear Medicine of our institution between February 2007 and August 2013 were retrospectively analyzed for the purpose of the study. Voluntary kidney donors who underwent the GFR measurement during the same period formed the control group. Only those patients who were ≥18 years and have histologically proven malignancy and were not exposed to any prior chemotherapy were included in the study arm. The patients with the following disorders were excluded from the study: Hypertension; diabetes; primary renal parenchymal disorders; multiple myeloma; and malignancies that can cause mechanical obstruction to urine flow and thus can secondarily affect renal function like cervical cancer, prostate cancer, and urinary bladder cancer. The patients with malignancies that directly damages renal parenchyma such as renal primary and secondaries to kidneys were also excluded.

A kidney donor was considered healthy and was included in the data analysis when the following conditions were satisfied: Age ≥18 years, normotensive (systolic blood pressure of <140 mmHg, and diastolic blood pressure of <90 mmHg), body mass index between 18.5 kg/m^2 and 24.9 kg/m^2, serum creatinine <123.7 μmol/L (<1.4 mg%), blood urea nitrogen <7 mmol/L (<20 mg/dL), normal urine microscopic and biochemical analysis, normal split renal function (45–55%) on isotope renal scan, hemoglobin 7.4–11.2 mmol/L (12–18 g/dL), serum calcium 2.2–2.6 mmol/L (9–10.5 mg%), serum sodium 130–149 mEq/L, serum potassium 3.5–5 mEq/L, total plasma protein 6.6–8.7 gm% (66–87 gm/L), serum albumin 3.5–5.5 gm% (35–55 gm/L), uric acid 150–480 mmol/L (2.5–8 mg%), serum liver enzyme level (aspartate aminotransferase and alanine aminotransferase) <50 international unit, normal ultrasound study of abdomen, fasting blood sugar <7 mmol/L (<126 mg%), and absence of any clinical history suggesting renal impairment.

Participant preparation
On the day of the study, all the subjects were asked to report after overnight fasting. All participants were advised to avoid high protein diet on the previous day and a gap of 7 days was kept between any contrast study and GFR measurement.

They were given oral hydration with 5 mL/kg of plain water 30 min before the study started. Freshly prepared MBq (megabecquerel) Tc99m-diethyl-triamine-penta-acetic acid (DTPA) was administered intravenously and GFR was obtained from calculating plasma clearance of Tc99m-DTPA by obtaining two venous blood samples at 60 min and 180 min after injection using the modified Russell's algorithm.[6] All the DTPA formulations used were certified by the manufacturer (Board of Radiation and Isotope Technology, Government of India) to have less than 1% plasma protein binding and to yield minimum 99% radiochemical purity. After every preparation of Tc99m-DTPA, instant thin layer chromatography (ITLC) was performed to check the percentage of DTPA molecule labeled with Tc99m. Any preparation with less than 98% labeling of DTPA was discarded.

Statistical analysis
Differences in GFR between various age groups of the cancer patients and healthy control arms were assessed by the unpaired *t*-test and results expressed in mean and two standard deviations. The level of significance was set at the conventional value of *P* < 0.05.

Results

In the cancer group, records of 1,632 patients were evaluated, out of which 259 patients were excluded as they did not meet the inclusion criteria or met one or more of the exclusion criteria. The final analysis included a total of 1,373 cancer patients and 1,089 healthy controls. For the purpose of the study, all the subjects were divided into various age groups and age matched comparison between cancer and control arms were made [Table 1].

The mean age of the cancer patients was 50.70 ± 20.84 years and that of healthy control group was 44.24 ± 17.63 years. The mean GFR was 74.43 ± 20.84 mL/min in cancer group and 80.14 ± 17.63 mL/min in control group [Figure 1]. There was significant difference in mean GFR in between the two groups (*P* < 0.01). However, when analyzed

Table 1: Number and percentage distribution of subjects in various age groups in both study and control arm

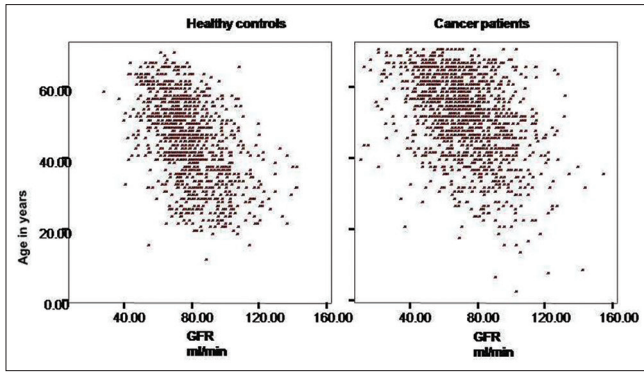| Age group	Number of subject in cancer group and (%) of total arm	Number of subject in control group and (%) of total arm
≤20 years	17 (1.2)	16 (1.4)
21-30 years	61 (4.4)	153 (14.0)
31-40 years	185 (13.4)	233 (21.3)
41-50 years	337 (24.5)	319 (29.2)
51-60 years	464 (33.7)	277 (25.4)
>60 years	309 (22.5)	91 (8.3)

Figure 1: Distribution of GFR in (*X*-axis) in relation to age (*Y*-axis) in a scatter plot
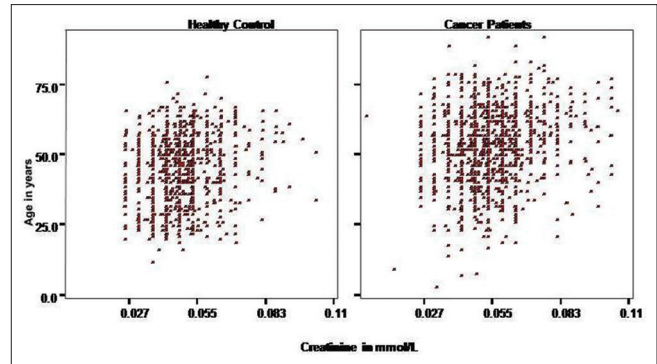

Figure 2: Distribution of serum creatinine level (*X*-axis) in relation to age (*Y*-axis) in a scatter plot

under various age groups there was no difference in GFR between the cancer and healthy groups [Table 2].

The mean serum creatinine level of the cancer group was 0.056 ± 0.013 mmol/L (1.01 ± 0.25 mg/dL) and that of the healthy control group was 0.051 ± 0.012 mmol/L (0.919 ± 0.218 mg/dL) [Figure 2]. There was significant difference in mean creatinine in between the two groups ($P = 0.01$). Age group wise breakup of mean creatinine values are presented in Table 3. There was significant difference in creatinine levels between cancer and healthy group in most of the age groups when analyzed under various age groups.

Discussion

In this study, we observed that the treatment-naïve cancer patients have similar GFR level as their age-matched healthy counterparts. Though the overall mean GFR was lower in the cancer group compared to the control group, but since mean age was higher in cancer group this phenomenon probably reflects a physiological age associated decline in renal function. Physiological decline in GFR is accepted around 0.7–1 mL/year and this could easily explain the lower GFR in the cancer group with higher mean age.[4,5]

GFR is considered the most reliable parameter of renal function. Unfortunately, it cannot be accessed directly as it would require micropuncture of all the Bowman's capsules. Because such a procedure on humans is impractical, GFR is measured indirectly by using glomerular filtration markers such as inulin, EDTA, iothalamate, or DTPA. These substances are not metabolized in the body and are excreted only through glomerular filtration, and clearance of these substances from blood reflects the filtration capacity of kidney.[7] This method of GFR assessment is referred as "measurement techniques" and is considered as reference procedures against which other GFR assessment tools such as GFR prediction equations are evaluated.[8]

Table 2: Age group wise comparison of GFR in cancer patients and in healthy controls

Age group	GFR in cancer group	GFR in control group	Significance
≤20 years	98.76±23.43	94.93±14.13	0.577
21-30 years	89.95±18.50	93.40±16.82	0.189
31-40 years	84.96±21.95	87.66±17.88	0.167
41-50 years	78.63±19.81	79.15±15.07	0.710
51-60 years	71.10±16.88	71.65±13.26	0.644
>60 years	64.15±20.13	65.26±12.21	0.617

GFR: Glomerular filtration rate

Table 3: Age wise breakup of creatinine level in the cancer group and healthy control group

Age group	Serum creatinine in cancer group millimol/L	Serum creatinine in control group milimol/L	Significance
≤20 years	0.050±0.015	0.048±0.012	0.73
21-30 years	0.051±0.011	0.047±0.010	0.02
31-40 years	0.052±0.013	0.050±0.011	0.10
41-50 years	0.055±0.013	0.050±0.011	0.02
51-60 years	0.056±0.014	0.052±0.013	0.01
>60 years	0.059±0.015	0.055±0.011	0.02

Measurement techniques of GFR assessment though are most accurate and reliable but they do suffer from the drawbacks of being time-consuming, relatively costly and invasive as it requires multiple blood samples. To circumvent these limitations, GFR prediction equation based on creatinine value has been proposed.[9] However, when compared to reference measurement procedures all the prediction equations perform suboptimally for routine clinical use. There is consensus in literature not to use GFR prediction equation when critical decision based on renal function are to be taken such as nephrectomy or suitability for renal transplantation.[10]

Many indigenous substances has been evaluated concentration of which may be used as a surrogate marker for level of GFR, such as urea, creatinine, and cystatin-c. Out of these the use of creatinine has gained

widespread clinical acceptance. The use serum creatinine level of as an index of GFR rests on three important assumptions: (a) Creatinine is an ideal filtration marker whose clearance approximates GFR; (b) creatinine excretion rate is constant among individuals and over time; and (c) measurement of serum creatinine is accurate and reproducible across clinical laboratories.[11,12] Although the serum creatinine concentration can provide a rough index of the level of GFR, none of these assumptions is strictly true, and numerous factors can lead to errors in estimation of the level of GFR from the serum creatinine concentration alone. Creatinine is freely filtered by the glomerulus, but is also secreted by the proximal tubule. Hence, the amount of creatinine excreted in the urine is the composite of both the filtered and secreted creatinine. Factors other than the level of GFR can also influence creatinine secretion.[13,14] Creatinine secretion is inhibited by some commonly used medications and the traditional assay for measurement of creatinine, the alkaline picrate method detects noncreatinine chromogens in serum (approximately 0.2 mg/dL), as well as creatinine.[15]

A review of literature did not reveal any similar study where GFR was measured in treatment-naïve cancer patients by a creatinine independent measurement technique and compared with normal controls age for age; hence no direct comparison could be made. In a partly similar study, Martin *et al.* measured GFR by ^{51}Cr-EDTA clearance and estimated GFR by Cockcroft-Gault equation in 123 cancer patients, 55 of whom had received previous chemotherapy.[16] They reported 18% lower GFR in previously treated patient compared to untreated patients when compared age for age. Vincent *et al.* estimated GFR by creatinine based equation in 4,684 cancer patients regardless of previous or ongoing treatment and reported a prevalence of renal impairment in 57.4% patients by cockroft-gault method and in 52.9% patients by MDRD equation.[4] Janus *et al.* evaluated renal function in a cohort of 1,218 patients among them, 302 were chemotherapy naïve. They reported 14.6% chemotherapy naïve patients to have estimated GFR <60 mL/min using the modified the MDRD equation.[5]

Malignancy can cause renal impairment by both direct and indirect mechanism. An example of direct renal injury is renal cell carcinoma where cancer cell directly destroys functioning renal parenchyma. An indirect example of renal injury is prostatic or ureteric cancer which causes renal outflow obstruction and parenchyma is destroyed secondary to obstruction. In multiple myeloma, toxic immunoglobulin molecules are precipitated in renal tubules and this leads to tubular atrophy. Many of the commonly used drugs to treat malignancy have well documented renal toxicity.[17]

Patients suffering from the above type of cancers and patients who have received nephrotoxic chemotherapy in the past can be expected to have lower GFR compared to normal controls. In this present study, we have excluded patients from urological and hematological malignancies and taken only treatment-naïve patients so that true level of GFR in malignancy can be ascertained.

Conclusion

Treatment-naïve cancer patients have identical renal function to their healthy age-matched peers. Malignancy *per se* directly does not lead to any decline in the filtration capacity of the kidneys.

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