**评价儿童癌症幸存者肾脏功能障碍的评估**

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**背景：**由于诊断和治疗的改善，儿童癌症的生存率显著提高。尽管如此，儿童癌症幸存者（CCS）仍面临高风险发展晚期并发症，如肾毒性。因此，我们旨在检测早期临床肾脏功能障碍。

**方法：**这项横断面研究在52例儿童癌症幸存者的儿科肿瘤学单位，Menoufiya大学实施。对每个参与者进行实验室评估，包括全血细胞计数，血尿素，血清肌酐，尿蛋白，尿钙，尿酸，以及血清 cystatin C和尿NGAL（UrNGAL）ELISA测定。

**结果：**估计的GFR在23.1%的病例中下降，血清cystatin C, UrNGAL和UrNGAL/Cr升高。尿蛋白/Cr，尿钙/Cr，UACR （p=0.02），UrNGAL和UrNGAL/Cr（P<0.001）在有近端小管功能障碍的患者中显著增加，而无近端小管功能障碍的患者中。有显著差异组两个 cisplatin（P=0.03）和高剂量甲氨蝶呤化疗（p=0.04）。UrNGAL和UrNGAL/Cr的AUCs分别为0.807和0.747。

**结论：**儿童癌症幸存者化疗（如cisplatin和高剂量甲氨蝶呤）中，显著的近端小管功能障碍。

**影响：**
- 检测儿童癌症幸存者化疗后的主要近端小管功能障碍。
- 尿NGAL是检测童年癌症幸存者化疗后近端小管功能障碍的良好预测指标。

**引言：**儿童癌症幸存者的生存率显著提高，作为抗癌症治疗的结果。40%的这些癌症患者遭受生长障碍，神经毒性，心脏功能障碍，肾毒性，荷尔蒙性障碍和第二级癌症等晚期并发症。1 风险因素包括年龄，天然药物毒性，抗癌症治疗（化疗，手术，和放射），和既往的肾损伤。2 最常见的化疗药物中，如顺铂和甲氨蝶呤，是近端小管毒性作用的主要原因。抗癌症治疗对白血病和淋巴瘤的近端小管毒性作用，主要是对造血系统和肠道粘膜的损伤。甲氨蝶呤毒性作用可能由在胎儿性系统和粘膜内甲氨蝶呤的沉淀和其不溶性代谢物（7-OH-MTX和DAMPA）所导致。4

Cystatin-C由于其小尺寸，被过滤器的近端小管吸收和被正常的肾小管和间质的肾小管和间质作用破坏。5

Urine neutrophil gelatinase-associated lipocalin (NGAL) is a protein that was extruded from injured proximal tubular cells into the urine. NGAL is involved in tubular cell injury and repair. Therefore, we aimed to estimate serum cystatin-C for detecting kidney glomerular dysfunction and urine NGAL for detecting kidney tubular dysfunction in survivors of pediatric cancer.

**主题和方法**

**设计**

A cross-sectional study was implemented on fifty-two survivors of pediatric cancer and was evaluated between May 2021 and September 2021. The 25 girls and 27 boys were 4-18 years of age at the time of evaluation; they were recruited from Oncology Unit, Pediatrics Department, Menoufiya University. Prior to blood samples collection, a written informed consent was approved from the Ethics Committee of Faculty of Medicine, Menoufiya University (ID: 24/5/2021.PEDI) was obtained from the guardians of all participants.

The participants were divided into 2 groups: Group I: included 25 patients with kidney tubular dysfunction. Group II: included 27 patients without kidney tubular dysfunction. Sociodemographic information, cancer
type and treatment details, and specific antibacterial and antifungal drugs administered were abstracted from the medical records of each participant who underwent a complete physical examination.

METHODS

Laboratory investigations as complete blood count, serum urea, creatinine, calcium, potassium, sodium, and Cystatin C by ELISA were done. Urinary protein/creatinine ratio, calcium/creatinine ratio and urine uric acid were done through a spot test, and NGAL by ELISA. Serum urea, creatinine, calcium, potassium, sodium were measured on the Beckman Coulter AU680 analyzer (Indianapolis, IN). Cystatin C was measured using the RayBio® Human Cystatin C ELISA Kit supplied by RayBiotech* (Catalog #: ELH-Cystatin C, Raybiotech, Inc., Norcross, Georgia) according to manufacturer’s instructions. Detection Range: 0.3–20 ng/ml, standard curve points: 20, 10, 5, 2.5, 1.25, 0.625, 0.313 and 0 ng/ml, Intra-Assay CV%: <10% and Inter-Assay CV%: <12%. Urine NGAL was analyzed by an NGAL-ELISA kit (Kit 201-12-1720, Sunred Biological Technology Co., Ltd, Shanghai, China). Urinary calcium, uric acid and urinary calcium/creatinine ratio were measured using the Integra 800 device (Pisa, Italy). The estimated glomerular filtration rate (eGFR) was calculated using the modified Schwartz formula for children.7 A normal value of eGFR was ≥90 mL/min/1.73 m² and the decreased value of eGFR was <90 mL/min/1.73 m². Participants were defined to have tubular dysfunction if they had abnormal levels of UProtein/Cr, UrCr/Cr, UACR, and UrNGAL.

Statistical analysis

The primary outcome was the prevalence of tubular and glomerular dysfunction. The secondary outcome was the comparison between patients with and without tubular dysfunction by the tubular markers.

Data were analyzed using IBM SPSS statistics version 20 (SPSS Inc., Chicago, IL). Chi-square test was used to examine the relationship between qualitative variables. Fisher’s exact test was used when the expected cell count of more than 25% of cases was less than 5. For quantitative data, comparison between two groups was done using either student t-test or Mann–Whitney test (non-parametric t-test) as appropriate. Pearson’s correlation coefficient or Spearman-rho method (as appropriate) was used to test correlation between numerical variables. Receiver Operator Characteristic Curve (ROC) is a graphic representation of the relationship between sensitivity and specificity at different cut-off points for UrNGAL and UrNGAL/Cr. A p value <0.05 was considered significant.

RESULTS

Demographic and clinical data of studied survivors

Fifty-two cases were recruited from the oncology unit. They were 25 girls and 27 boys, their ages ranged from 4 to 18 years old. 35 cases (67.3%) were diagnosed acute lymphoblastic leukemia, 9 cases (17.3%) were non-Hodgkin lymphoma, 2 cases (3.8%) were Hodgkin lymphoma, 3 cases (5.8%) were Neuroblastoma and 3

| Demographic and clinical characteristics | Total studied cases (No. = 52) | Mean | Median | SD | Range |
|-----------------------------------------|-------------------------------|------|--------|----|-------|
| Age at diagnosis (years)                | 8.87                          | 8    | 2.68   |    | 3.5–15|
| Age at follow up (years)                | 11.9                          | 11   | 3.6    |    | 4–18  |
| Elapsed time from diagnosis to follow-up (months) | 45.7                          | 50   | 9.8    |    | 10–60 |
| Elapsed time from the end of treatment to follow up (months) | 18.4                          | 12   | 6.4    |    | 4–24  |
| Sex                                     |                               |      |        |    |       |
| Male                                    | 27 (51.9%)                    |      |        |    |       |
| Female                                  | 25 (48.1%)                    |      |        |    |       |
| Distribution of diagnosis               |                               |      |        |    |       |
| Acute lymphoblastic leukemia             | 35 (67.3%)                    |      |        |    |       |
| Neuroblastoma                           | 3 (5.8%)                      |      |        |    |       |
| Hodgkin lymphoma                        | 2 (3.8%)                      |      |        |    |       |
| Non-Hodgkin lymphoma                    | 9 (17.3%)                     |      |        |    |       |
| Wilms tumor                             | 3 (5.8%)                      |      |        |    |       |
| Duration of chemotherapy (months)       | 27.7                          | 34   | 12.5   |    | 6–36  |
| Type of chemotherapy                    |                               |      |        |    |       |
| Cisplatin                               |                               |      |        |    |       |
| Yes                                     | 4 (16.0%)                     | 5    | 18.5%  |    |       |
| No                                      | 21 (84.0%)                    | 22   | 81.0%  |    |       |
| Methotrexate                            |                               |      |        |    |       |
| Yes                                     | 24 (96.0%)                    | 25   | 92.6%  |    |       |
| No                                      | 1 (4.0%)                      | 2    | 7.4%   |    |       |
| Cytarabine                              |                               |      |        |    |       |
| Yes                                     | 19 (76.0%)                    | 22   | 81.5%  |    |       |
| No                                      | 6 (24.0%)                     | 5    | 18.5%  |    |       |
| Cyclophosphamide                        |                               |      |        |    |       |
| Yes                                     | 25 (100%)                     | 25   | 92.6%  |    |       |
| No                                      | 0 (0.0%)                      | 2    | 7.4%   |    |       |

*significant difference <0.05.
cases (5.8%) were Wilms tumor. Duration of chemotherapy ranged from 4 to 24 months. 25 cases (48.1%) had tubular dysfunction and 27 cases (51.9%) had normal tubular function. There was a significant difference in the frequency of treatment with cisplatin and high-dose methotrexate chemotherapy between those with and without tubular dysfunction (Table 1).

Mild anemia was recorded in some cases. Serum electrolytes (Na, K, and Ca), serum urea and creatinine were normal in all patients. eGFR was decreased in 12 cases, and serum Cystatin C was increased in the same 12 cases who had decreased eGFR. The urine calcium/creatinine ratio (UCa/Cr), urine protein/creatinine ratio (Uprotein/Cr) and urine albumin/creatinine ratio were increased in 25 cases (48.1%). In addition, elevated levels of UrNGAL in 30 cases (57.7%) including 5 cases without tubular dysfunction who had a mild increase in UrNGAL and elevated levels of UrNGAL/Cr in all cases (100%) as shown in Table 2.

### Table 2. Laboratory findings of all studied cases.

| Laboratory finding  | Total studied cases (No. = 52) | Mean ± SD           | Median     | SD          | Range          |
|---------------------|--------------------------------|---------------------|------------|-------------|----------------|
| Hb (gm/dl)          | 12.8 ± 1.4 ± 0.10              | 12.8 ± 1.4 ± 0.10   | 12.8       | 1.4         | 10–16          |
| WBCs (x10^9/mm^3)   | 6.3 ± 2.6 ± 0.26               | 6.3 ± 2.6 ± 0.26    | 6.3        | 2.6         | 4–13.7         |
| Platelet (x10^9/mm^3) | 250.7 ± 71.4 ± 5.48         | 250.7 ± 71.4 ± 5.48 | 250.7      | 71.4        | 60–452         |
| Na (mEq/L)          | 135.3 ± 1.5 ± 0.15             | 135.3 ± 1.5 ± 0.15  | 135.3      | 1.5         | 134–139        |
| K (mEq/L)           | 4.1 ± 0.31 ± 0.54              | 4.1 ± 0.31 ± 0.54   | 4.1        | 0.31        | 3.7–5          |
| Ca (mg/dl)          | 9.2 ± 0.54 ± 1.6               | 9.2 ± 0.54 ± 1.6    | 9.2        | 0.54        | 8.5–10.6       |
| Serum urea (mg/dl)  | 22.5 ± 4 ± 1.2                 | 22.5 ± 4 ± 1.2      | 22.5       | 4           | 12–28          |
| Serum creatinine (mg/dl) | 0.79 ± 0.12 ± 0.2           | 0.79 ± 0.12 ± 0.2   | 0.79       | 0.12        | 0.6–1.1        |
| eGFR (mL/min./1.73m^2) | 104.5 ± 17.8 ± 2.5           | 104.5 ± 17.8 ± 2.5  | 104.5      | 17.8        | 75–135 (12 cases <90) |
| Uprotein/Cr         | 0.33 ± 0.09 ± 0.25             | 0.33 ± 0.09 ± 0.25  | 0.33       | 0.09        | 0.12–0.46 (25 cases >0.25) |
| UACR (mg/g)         | 45 ± 17.3 ± 5.4                | 45 ± 17.3 ± 5.4     | 45         | 17.3        | 10–75 (25 cases >30) |
| UCa/Cr              | 0.28 ± 0.12 ± 0.45             | 0.28 ± 0.12 ± 0.45  | 0.28       | 0.12        | 0.15–0.45 (25 cases >0.22) |
| Uric acid in urine, Normal value (250–750 mg/24 h) | 340.8 ± 140.5 ± 6.0 | 340.8 ± 140.5 ± 6.0 | 340.8      | 140.5       | 160–700        |
| Serum cystatin C (mg/L) | 122.6 ± 57.4 ± 8.4            | 122.6 ± 57.4 ± 8.4  | 122.6      | 57.4        | 40–300         |
| UrNGAL (ng/ml)      | 1989.9 ± 1061.3 ± 311.4       | 1989.9 ± 1061.3 ± 311.4 | 1989.9   | 1061        | 3114           |
| UrNGAL/Cr           | 2598.6 ± 1178.1 ± 397.4       | 2598.6 ± 1178.1 ± 397.4 | 2598.6  | 1178        | 3974           |

Hb: Hemoglobin, WBCs: white blood cells, Na: sodium, K: potassium, Ca: calcium, eGFR: estimated glomerular filtration rate, UACR: urinary albumin creatinine ratio, NGAL: neutrophil gelatinase-associated lipocalin.

### Table 3. Comparison between cases with tubular dysfunction and those without tubular dysfunction regarding urinary markers.

| Parameters                  | Total cases (No. = 52) | Test of significance | P value |
|-----------------------------|------------------------|----------------------|---------|
|                            | With tubular dysfunction (No. = 25) | Without tubular dysfunction (No. = 27) | t-test | 0.02 |
| Uprotein/Cr Median (range) | 0.35 (0.25–0.46)       | 0.13 (0.09–0.22)     | _______ | <0.001** |
| Normal value up to 0.2 mg/mg |                        |                      | _______ | <0.001** |
| UCa/Cr Median (range)      | 0.31 (0.28–0.45)       | 0.16 (0.12–0.22)     | _______ | <0.001** |
| Normal value up to 0.22 mg/mg |                    |                      | _______ | <0.001** |
| UACR (mg/g) Normal value 2–30 mg/g | 43.87 ± 17.98 | 31.93 ± 14.57       | t-test = 3.22 | 0.02 |
| UrNGAL (ng/ml) Normal value 0.2–132 | 2249.3 ± 497.4 | 174.9 ± 33.91       | t-test = 4.19 | <0.001** |
| Mean ± SD                  | 2990.9 ± 747.4         | 223.5 ± 51.76        | t-test = 4.21 | <0.001** |

*significant difference.
DISCUSSION

The reported prevalence of kidney dysfunction varied from 0 to 84%. This wide range may be related to variations in the definition of abnormal kidney function and cohort factors, including the type of malignancy, chemotherapeutic agents, radiation therapy, and supportive drug use.8–10

The present study revealed tubular dysfunction among childhood cancer survivors. We evaluated patients by eGFR, proteinuria, albuminuria and urinary markers for tubular dysfunction. We found low eGFR in 12 cases (23.1%), proteinuria, microalbuminuria and elevated UCa/Cr, UrNGAL and UrNGAL/Cr as well as elevated serum Cystatin C. In addition, there was a significant difference between

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**Table 4.** Correlation between serum Cystatin C, UrNGAL, UrNGAL/Cr and other parameters.

| Parameters                  | Serum Cystatin C | UrNGAL (ng/ml) | UrNGAL/Cr |
|-----------------------------|------------------|----------------|-----------|
|                             | r     | P value | r     | P value | r     | P value |
| Age (years)                 | −0.052 | 0.13   | −0.300 | 0.03   | −0.217 | 0.12   |
| Duration of chemotherapy (months) | 0.046   | 0.14    | 0.087  | 0.54    | 0.146  | 0.30    |
| Na (mEq/L)                  | −0.147 | 0.42   | −0.127 | 0.37   | −0.189 | 0.18   |
| K (mEq/L)                   | 0.242  | 0.62    | 0.020  | 0.89    | −0.066 | 0.64    |
| Ca (mg/dl)                  | 0.065  | 0.53    | −0.055 | 0.69    | 0.199  | 0.16    |
| Serum urea (mg/dl)          | 0.313  | 0.03    | 0.307  | 0.001** | 0.504  | <0.001**|
| Serum creatinine (mg/dl)    | 0.521  | <0.001**| 0.423  | 0.003** | 0.494  | <0.001**|
| eGFR (mL/min./1.73m²)       | −0.518 | <0.001** | −0.289 | 0.04    | 0.189  | 0.18    |
| Uprotein/Cr                 | 0.114  | 0.24    | 0.431  | 0.001** | 0.408  | 0.003*  |
| UACR (mg/g)                 | 0.054  | 0.66    | 0.472  | <0.001**| 0.381  | 0.005   |
| UCa/Cr                      | 0.882  | 0.71    | 0.312  | 0.02    | 0.333  | 0.01    |
| Uric acid in urine          | 0.212  | 0.16    | 0.335  | 0.01    | 0.306  | 0.03    |

*significant difference.

**Table 5.** ROC curve of UrNGAL and UrNGAL/Cr for detection of Kidney tubular dysfunction.

| Parameter | AUC    | Cutoff point | Sensitivity | Specificity | PPV    | NPV    | Accuracy |
|-----------|--------|--------------|-------------|-------------|--------|--------|----------|
| UrNGAL    | 0.807  | 1964.7       | 84%         | 70.4%       | 72.4%  | 82.6%  | 76.9%    |
| UrNGAL/Cr | 0.747  | 2182         | 84%         | 40.7%       | 56.8%  | 73.3%  | 61.5%    |

AUC area under the curve, PPV positive predictive value, NPV negative predictive value.
patients with tubular dysfunction and those without tubular dysfunction regarding cisplatin and methotrexate chemotherapy. Erdem et al.\textsuperscript{11} showed that low GFR was detected in 32% of all survivors mainly who received nephrotoxic drugs including amino-glycosides, vancomycin or amphotericin B. Certain studies revealed that cisplatin, high-dose methotrexate, and nephrotropic drugs taken during febrile neutropenia were associated with low eGFR.\textsuperscript{12-14}

A Cumulative dose of high-dose MTX, in the range of 1000–33,000 mg/m\textsuperscript{2} with a combination of calcium leucovorin, is associated with acute kidney injury (AKI) in 0–12.4% with an overall incidence of 1.8%.\textsuperscript{15}

The current study revealed 36.5% of cases had proteinuria and 28.8% of cases had microalbuminuria. Also; Oberlin et al.\textsuperscript{16} illustrated that proteinuria in 24-h urine collection was detected in 11.3% of survivors and Knijnenburg et al.\textsuperscript{17} detected albuminuria in 14.5% and decrease eGFR in 62 survivors (4.2%) of all 1442 survivors who were treated with chemotherapeutic.

The current study showed elevated levels of UrNGAL, UrNGAL/Cr and serum Cystatin. Mehdibadi et al.\textsuperscript{18} reported an abnormal albuminuria in 14.5% and decrease eGFR in 62 survivors (4.2%) of all 1442 survivors mainly who received nephrotoxic drugs including amino-glycoside, vancomycin or amphotericin B. Certain studies revealed that cisplatin, high-dose methotrexate, and nephrotoxic drugs taken during febrile neutropenia were associated with low eGFR.\textsuperscript{12-14}

Cystatin C had an increased diagnostic accuracy for decreased GFR and hematological malignancies as it is less dependent on muscle mass and hematological malignancies as it is less dependent on muscle mass and hematological malignancies as it is less dependent on muscle mass and hematological malignancies as it is less dependent on muscle mass and hematological malignancies as it is less dependent on muscle mass and hematological malignancies as it is less dependent on muscle mass and hematological malignancies as it is less dependent on muscle mass. Serum Cystatin C had an increased diagnostic accuracy for decreased GFR when compared to serum creatinine.\textsuperscript{19}

Limitation of the study
Small sample size and a small number of cases receiving ifosfamide and cisplatin.

CONCLUSION
There was a significant tubular dysfunction among childhood cancer survivors receiving chemotherapy as cisplatin and high-dose methotrexate. So, early detection of subclinical kidney dysfunction is very important for early intervention to prevent long-term complications such as chronic kidney disease.

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AUTHOR CONTRIBUTIONS
A.M., H.A., S.E., F.Z., H.A., M.E.: took part in database design, data collection, and writing, reporting of search and reviewed the manuscript.

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COMPETING INTERESTS
The authors declare no competing interests.
ETHICAL APPROVAL
The Institutional Review Board (IRB) of the Menoufia Faculty of Medicine approved the study (ID: 24/5/2021.PEDI). Research work was performed in accordance with the Declaration of Helsinki.

INFORMED CONSENT
Informed consent was obtained from all individual participants included in the study or their legally authorized representatives ROC curve of UrNGAL and, UrNGAL/Cr for detection of kidney tubular dysfunction.

ADDITIONAL INFORMATION
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