Editorial Commentary

Long-term kidney function of childhood cancer survivors—who needs to be monitored?

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Kidney failure among childhood is a serious health condition that, although relatively rare, has a profound impact on affected children's health and quality of life. The incidence is approximately 15 per million in the pediatric population, which equates to a small but significant number of children globally (1). In general, pediatric population, kidney failure results from conditions such as congenital anomalies of the kidney and urinary tract, glomerulonephritis, or complication from serious medical condition such as prematurity or malignancy. Kidney failure negatively impacts growth, cognitive development, and overall wellbeing, necessitating comprehensive medical interventions like dialysis or transplantation, underscoring the need for early detection and management strategies (2).

During the last five decades, the treatment of children and adolescents affected by cancer has achieved dramatic improvements with subsequent high survival rates, from 5-year survival of 25% in the mid-1960s to 85% nowadays; 0.2% of general population is deemed childhood cancer survivors (3). As the survival rate increases, there has been a lot of interest in their long-term quality of life, and extensive research has been conducted on their adverse long-term complications such as cardiovascular, endocrinological or renal disease (4). Among them, kidney damage can occur due to direct infiltration of tumors in the kidney and urinary tract, usage of nephrotoxic agents such as chemotherapeutics, targeted agents such as antiangiogenesis drugs and antimicrobials, abdominal radiation, nephrectomy, and systemic reactions such as sepsis (5). These can result in acute kidney injury (AKI) as well as have detrimental effects on long-term kidney function, which could be a cause of kidney failure in childhood cancer survivors; 35-year cumulative incidence of kidney failure among childhood cancer survivors was 1.7%, which was significantly higher in matched sibling of 0.2% (5-8). Kidney failure among cancer survivors can significantly impact their quality of life due to the need for lifelong dialysis or kidney transplantation, and it can also lead to a various health complication, such as cardiovascular disease and growth failure. Furthermore, it is crucial to take into account the potential risk of malignancy recurrence due to post-transplant immunosuppression when considering kidney transplantation. Several risk factors can increase the likelihood of developing kidney failure among childhood cancer survivors; these include exposure to nephrotoxic chemotherapy, radiation to the kidney area, and pre-existing kidney disease. Additionally, individuals with a history of tumors in the renal region, such as Wilms tumor, may have an elevated risk of kidney failure (6,8). However, it is currently unknown precisely which patients among

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childhood cancer survivors are at a higher risk for these complications, and therefore, which patients should be closely monitored for kidney function.

In a recent issue of the *Journal of Clinical Oncology*, Wu *et al.* developed a simple prediction model applicable during and after the treatment of childhood cancer using the largest cohorts of long-term survivors of childhood cancer known as Childhood Cancer Survivor Study (CCSS) (9). Through this model, they were able to calculate risk scores and perform risk stratification. The authors utilized information from the self-report in the US National Cancer Institute-funded CCSS to identify exposures and information from the Organ Procurement and Transplantation Network and the National Death Index to identify outcomes. According to the developed model with information easily accessible at the 5-year mark following cancer diagnosis, including race/ethnicity, age at diagnosis, exposure to ifosfamide, platinum-based antineoplastics or anthracycline, nephrectomy, abdominal radiation, genitourinary anomalies, and hypertension within 5 years of diagnosis, the cancer survivors were divided into three groups according to their long-term kidney failure risk. Among the entire cohort, it was demonstrated that the high-risk group, comprising approximately 2–3% of the cohort, had a cumulative incidence of kidney failure exceeding 5% by the age of 40. Furthermore, they provided an online risk calculator to facilitate the easy identification of individuals at higher risk in clinical practice (10). This tool assists in identifying those individuals who are at a higher risk of developing kidney failure.

One particularly noteworthy finding was that hypertension within 5 years of diagnosis conferred the highest risk score; hypertension within 5 years of diagnosis showed a risk score twice as high as that of nephrectomy, which is generally considered a major risk factor. This suggests that hypertension during treatment should not be simply attributed to transient phenomenon due to medications used in patients with hematologic malignancies or undergoing stem cell transplantation, such as corticosteroids and calcineurin inhibitors. Instead, it indicates that hypertension itself is a significant risk factor for kidney failure and requires close monitoring and follow-up. Furthermore, hypertension is a modifiable risk factor. Therefore, regular blood pressure monitoring and timely treatment may be particularly crucial, although the causal relationship has not been established. Effective management and control of hypertension could potentially attenuate the risk of renal failure in childhood cancer survivors, paralleling strategies applied in the broader pediatric population with chronic kidney disease (11). Moreover, unlike chemotherapeutics such as ifosfamide or platinum-based antineoplastics, which are well-known for their effect on AKI and subsequent chronic kidney disease through tubular injury, anthracyclines like adriamycin are not generally known to cause AKI. However, rodent models show that anthracyclines cause glomerular injury similar to focal segmental glomerulosclerosis and gradually lead to kidney failure (12,13). As a result, they may receive less attention during acute-phase treatment compared to other drugs. However, as demonstrated in the study, they confer a risk for long-term kidney failure. Therefore, after the appropriate treatment for pediatric cancer patients is completed, a review of the use of these agents and an assessment of whether kidney function is well-maintained should be conducted.

The authors themselves acknowledged the limitations of relying on self-reported data from cancer survivor cohorts, which prevented the inclusion of readily available physiologic laboratory-based information such as blood pressure, estimated glomerular filtration rate (eGFR), hyperuricemia, and proteinuria at the time of treatment completion in the prediction model. It is important to note that this study only included survivors who had reached the 5-year mark, which introduces a potential selection bias. Additionally, well-known risks for kidney failure, such as a history of AKI and tumor lysis syndrome, were not taken into account in this study (6). Furthermore, since the population under investigation was recruited and treated prior to the year 2000, the treatment methods and outcomes may differ from those employed today. However, it is remarkable that using only dichotomous variables, such as those included in the model, allows for robust risk stratification and the identification of patients who require intensive monitoring and follow-up. In this regard, this paper can help healthcare providers in determining which patients require closer and more frequent kidney function monitoring and follow-up, allowing for proactive management and interventions to mitigate the risks associated with kidney dysfunction, such as the strict blood pressure management, in childhood cancer survivors (*Table 1*).

How is kidney function monitoring conducted for childhood cancer survivors in actual clinical practice? According to the well-known Children's Oncology Group (COG) guidelines, for patients who received ifosfamide, platinum-based antineoplastics, or abdominal radiation, it is recommended to monitor blood pressure yearly and perform laboratory tests as a baseline for long-term follow-

Table 1 Suggested monitoring strategy of childhood cancer survivor, retrieved from the simple model developed by Wu *et al.* (9)

Kidney failure risk factors	Score
Black, non-Hispanic	1
Age at diagnosis <10 years	1
Nephrectomy	2
Chemotherapeutics usage	
Ifosfamide	2
Platinum	1
Anthracycline	1
Abdominal radiation	1
Genitourinary anomalies	2
Hypertension within 5 years	4

Score ≥6: high risk for kidney failure; close monitoring of blood pressure, eGFR, and proteinuria is recommended. eGFR, estimated glomerular filtration rate.

up and when clinically indicated (14-16). For patients who underwent hematopoietic stem cell transplantation (HSCT) or nephrectomy, the guidelines recommend yearly blood pressure and laboratory tests including eGFR monitoring, although we advocate for more frequent monitoring, at least for blood pressure and urinalysis (17). However, it is important to note that clinical practices may vary among different hospitals. In our hospital, for all pediatric cancer survivors, we perform blood pressure measurement, creatinine- and cystatin C-based eGFR, and urinalysis assessments once a year. If hypertension, abnormal results in urinalysis including proteinuria or a decrease in eGFR is observed, we refer the patient to a pediatric nephrologist. At the very least, for patients classified as high-risk based on the risk calculation, regular monitoring of creatinine levels and urinalysis and prompt referral to pediatric nephrologist can help detect the progression of chronic kidney disease at an early stage (*Table 1*).

Considering the advancements in cancer immunotherapy and targeted therapy, there is a growing trend towards reducing the use of cytotoxic chemotherapy in the treatment of pediatric cancer patients to minimize potential long-term adverse effects associated with traditional chemotherapy. Moreover, efforts should be made to optimize the management of modifiable risk factors such as blood pressure control and proteinuria reduction, aiming to delay the progression of kidney failure as much as possible.

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