Screening of renal dysfunction among Burkitt lymphoma survivors by novel markers

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\textbf{ABSTRACT}

\textbf{Background:} Burkitt lymphoma (BL) represents the most common pathological type of non-Hodgkin lymphoma in our region. Recently, high success rates have been achieved in BL treatment. Little is known about long-term renal dysfunction in this vulnerable group. In the present study, we tried to detect early chronic kidney diseases (CKD) among BL survivors by using novel screening modalities.

\textbf{Patients and methods:} we investigated 53 children (aged 10 ± 2.8 years, 34 boys) who successfully treated for Burkitt lymphoma, based on LMB96 protocol, as “patient group” and 30 children as control. All eligible participants were subjected to history taking, physical assessment, and routine laboratory investigations including urine analysis, serum creatinine. Estimated glomerular filtration rates using new Schwartz formula (GFR\textsubscript{CKD}) were calculated and chronic kidney disease prevalence was diagnosed accordingly. Also, serum Cystatin-C (Cys-C) and neutrophil-gelatinase-associated Lipocalin (NGAL) were determined as novel markers aiming at early and accurate detection of CKD in BL survivors.

\textbf{Results:} After 18.3 ± 5.2 months of BL cytotoxic therapy completion, almost one fifth of asymptomatic BL survivors showed evidence of subclinical CKD when estimated GFR\textsubscript{CKD} (16.9%), serum Cystatin-C (15%) and serum neutrophil-gelatinase-associated Lipocalin (18.8%) were used for kidney function monitoring. This prevalence was four to fivefolds higher than that detected by routine serum creatinine screening (3.7%). Significant persistent albuminuria was diagnosed at 4/53 (7.5%) of BL survivors and asymptomatic hypertension was reported in 1/53 (1.9%) of them compared to none of the controls. Positive correlation could be displayed between serum Cys-C and serum NGAL. Conversely, negative correlations between both of them and estimated GFR\textsubscript{CKD} were documented.

\textbf{Conclusion:} Novel modalities such new Schwartz formula (GFR\textsubscript{CKD}) estimation, serum Cys-C, and serum NGAL assessment should be incorporated in the routine follow-up screening for CKD among BL survivors for accurate diagnosis of such detrimental morbidity.

\textbf{KEYWORDS}

Pediatrics; Burkitt; long term; renal

\textbf{Introduction}

Burkitt lymphoma (BL) represents the most common pathological type of non-Hodgkin lymphoma in our region \cite{1} and many other areas including Brazil, Kuwait, Saudi Arabia, Germany, and UK \cite{2–5}. Recently, significant improvement in BL treatment outcomes with 5-years overall survival (OS) of 90% and event-free survival of 80.7% have been achieved by our oncology team \cite{1}. As survival has greatly improved, the late effects after BL treatment have increased correspondingly; of particular interest are the late nephrotoxic effects \cite{6}.

Modern treatment protocols have decreased the possibility of acute renal damage, however, late nephrotoxicity manifesting as decreased glomerular filtration rate (GFR), albuminuria, deterioration of the tubular function and/or hypertension should not be ignored \cite{7,8}. Unfortunately, there is no renal function test to date that satisfactorily fulfills all criteria necessary for routine use in pediatric patients \cite{9}. Routine serum creatinine (s.cr) monitoring is widely used as clinical standard for this purpose, but has significant inaccuracies and limitations regarding its diagnostic value \cite{10}. Direct GFR measurement by methods such as inulin clearance or nuclear medicine scintigraphy, is the gold standard for kidney function monitoring \cite{11}, however, they are invasive, expensive, and cumbersome for young patients. Many centers are not able to perform these studies on routine basis \cite{9}.

National kidney foundation (NKF) recommended the use of Schwartz classic formula \cite{12} for estimation of GFR (eGFR\textsubscript{Sch}) in children, but it is not free of disadvantages \cite{13}. New Schwartz formula has been proposed for accurate estimation of GFR in children with mild to moderate renal function impairment (eGFR\textsubscript{CKD}). It utilizes height and gender of the patient as well as creatinine, Cystatin-C (Cys-C), and body urea nitrogen (BUN) level \cite{14}.

The search for kidney function biomarkers has continued for several years, low-molecular-weight
proteins, particularly serum Cys-C and serum neutrophil-gelatinase-associated Lipocalin (NGAL) have been thoroughly investigated in several reports for their diagnostic validity of chronic kidney diseases in pediatric patients. Both of them have been described as sensitive biomarkers that are superior to s.ccr in early diagnosis of CKD in children [7,9,11,15–19].

As little is known about the late renal dysfunction among asymptomatic BL survivors, the aim of this cross-sectional study was to evaluate real frequency of subclinical CKD among such at-risk group by using new screening modalities.

Patients and methods

Patients

This cross-sectional study has been performed at Pediatric Oncology departments of Zagazig University Children Hospital and Tanta National Cancer Institute-Egypt in the period from January 2015 to January 2016. Fifty-three patients who completed chemotherapy treatment for Burkitt lymphoma with LMB96 protocol were our “patient group.” All patients received the following chemotherapy according to LMB 96, vincristine (2 mg/m² IV), prednisone (60 mg/m² oral), cyclophosphamide (250–500 mg/m² IV for 3 days in each course), methotrexate (3000–8000 mg/m² IV), doxorubicin (60 mg/m² IV), cytarabine (50–3000 mg/m² IV), etoposide (200 mg/m² IV), and intrathecal chemotherapy of methotrexate, cytarabine, and hydrocortisone. The demographic, clinical, and laboratory findings of the patients were compared with those of 30 healthy children of comparable age and gender “control group” who are selected from outpatient clinics of participating hospitals. Written consent was taken from parent or guardian of each eligible child before his/her enrollment in the study, the research protocol was approved by Institutional Review Board (IRB) of Faculty of Medicine of corresponding university.

All BL survivors who visited our oncology unit for routine follow-up and screening were involved at our study. They were asymptomatic at the time of interview, any patient who had symptoms suggesting illness or organ dysfunction, and those with known hepatic, renal, metabolic, or cardiovascular dysfunction were excluded from this research and referred for further extensive diagnosis and management by appropriate subspecialty. Patients, who were still on chemotherapy at the interview time, were excluded. Urine analysis was performed at each visit; any one with evidence of urinary tract infection was also excluded.

Method

All participants were subjected to complete history-taking including; age at diagnosis, presenting symptoms, treatment taken, duration of follow-up and any renal complication during or after treatment completion. Physical examination: anthropometric measures and triple measurement of blood pressure were documented for each child and compared with normal range for age, gender, and height [20], urine analysis: fresh-void urine analysis of random diurnal sample and urine dipstick for albuminuria was also performed, if albuminuria was 2+ or more in asymptomatic child, it should be repeated after few weeks to confirm the diagnosis of persistent albuminuria that necessitate referral to nephrologist as recommended by COG LTFU guidelines [21]. Routine investigations: complete blood count, serum electrolytes, liver function test, kidney function test by BUN and s.ccr.

Estimation of GFR

By Schwartz classic formula (eGFR_{Sch}) = \{k \cdot (\text{height (cm)})/(\text{s.ccr (mg/dl)})\}, k is a constant of proportionality [12].

New Schwartz formula for estimated GFR of CKD (eGFR_{CKD}) = (39.1 \cdot (\text{height (m)})/(\text{s.ccr (mg/dl)})^{0.516} \cdot (1.8/(\text{s.Cys-C (mg/dl)})^{0.294} \cdot (30/(\text{BUN (mg/dl)})^{0.169} (1.099 for men, 1 for women) \cdot (\text{height (cm)})/(1.4)^{0.188} [14].

Determination of serum Cystatin-C

By using the Ray Bio Human cystatin C Human Kit: an in vitro enzyme linked immunosorbent assay for quantitative measurement of human Cys-C in serum, plasma, urine, and cell culture supernatants. Cut-off value of abnormal s.Cys-C was ≥0.95 mg/dl [22].

Determination of serum neutrophil-gelatinase-associated Lipocalin

By using the Ray Bio Human Lipocalin-2 ELISA Kit, normal reference range for serum neutrophil-gelatinase-associated Lipocalin (s.NGAL) according to the manufacturer instruction was 295–365 pg/ml.

All previous measures were done once.

Definitions

Elevated blood pressure: systolic and/or diastolic BP that was in the 95th percentile or higher for age, gender, and height on at least three occasions. Survivors who were on regular antihypertension medications were considered hypertensive [23].

High-dose cyclophosphamide or methotrexate: ≥1 g/m²/course [24].

Albuminuria: persistent albuminuria of ≥2++ (100 mg/dl) was chosen as abnormal cut-off value to avoid the overestimation of albuminuria caused by random daytime samples [21].

Decreased GFR: estimated GFR <90 ml/minute/1.73 m² [25].

CKD classification: the National Kidney Foundation’s KDOQI (kidney disease outcomes quality initiative) clinical practice guidelines were used for CKD classifications into mild CKD (GFR 60–89 ml/minute/1.73 m²),
Table 1. Demographic and clinical characteristics of the studied groups.

| Variable                  | Group                        |  p value |
|---------------------------|------------------------------|----------|
|                          | Patients \( n = 53 \)       | Controls \( n = 30 \) |
| Age at diagnosis (Y)      | 6.1 ± 2.8                    | 10.2 ± 2.6 |
| Mean ± SD                 | 0.59 (NS)                    |          |
| Age at interview (Y)      | 10.6 ± 2.8                   | 10.2 ± 2.6 |
| Mean ± SD                 | 0.59 (NS)                    |          |
| Gender                    |                             |          |
| Male (n)                  | 34                           | 19       |
| Female (n)                | 19                           | 11       |
| % of male                 | 0.89 (NS)                    |          |
| Residence                 |                             |          |
| Rural (n)                 | 32                           | 17       |
| Urban (n)                 | 21                           | 13       |
| % of rural                | 0.74 (NS)                    |          |
| Weight (kg)               | 40.2 ± 6.6                   | 43.8 ± 7.2 |
| Mean ± SD                 | 0.48 (NS)                    |          |
| Height (cm)               | 144.3 ± 7.1                  | 145 ± 7.0 |
| Mean ± SD                 | 0.67 (NS)                    |          |
| BMI (kg/m²)               | 18.9 ± 6.7                   | 19.1 ± 5.2 |
| Mean ± SD                 | 0.77 (NS)                    |          |
| Follow-up (months)        | 18.3 ± 5.2                   |          |
| Mean ± SD                 | 0.001                         |          |

*Chi-square.  
t-student test is used for comparison unless specified.  
SD: standard deviation; Y: year; %: percent; n: number; NS: not significant.

moderate CKD (GFR 30–59 ml/minute/1.73 m²), severe CKD (GFR15–29 ml/minute/1.73 m²), and chronic dialysis as kidney failure (GFR <15 ml/minute/1.73 m²) [26].

Results

Our oncology team followed BL survivors for almost 2 years (18.3 ± 5.2 months), their mean age at interview was 10.6 ± 2.8 years (ranged 6–16 years), 64% of them were males (34/53) with male:female ratio was 1.7:1. No statistically significant differences were found between BL survivors and healthy peers as regard to demographic or anthropometric measurements as shown in Table 1. Despite the absence of hypertensive-related symptoms in all enrolled children, one BL survivor had systolic hypertension (1/53 and 1.9%); none of the participants was on regular antihypertensive medications.

On interpreting routine kidney functions, s.cr mean values were statistically significant higher among BL survivors than controls, only two BL survivors (2/53 and 3.7%) had abnormally high (0.1–0.3 mg/dl) s.cr as compared with normal values for their age. Estimated GFR with both Schwartz classic formula (eGFRsch) and new Schwartz formula (eGFRCKD) showed statistically

| Table 2. Renal parameters of the studied groups. |
|-----------------------------------------------|
| Group                                        |
|-----------------------------------------------|
| Variable                       | Patients \( n = 53 \) | Controls \( n = 30 \) |  p value |
|-------------------------------------------|-----------------------|-----------------------|----------|
| sCreatinine (mg/dl)                   | 0.65 ± 0.32           | 0.52 ± 0.15           | <0.001   |
| Mean ± SD                             | 0.4–1.23              | 0.35–0.7              |          |
| Abnormal s.ccr n (%)                  | 2 (3.7)               | 0 (0)                 | *<0.001  |
| eGFRsch (ml/minute/1.73 m²)            | 105.6                 | 186.0                 | **<0.001 |
| Median                                 | 100.5–143.9           | 141.0–193.3           |          |
| IQR                                     | 5 (9.4)               | 0 (0)                 | *<0.001  |
| eGFRckd (ml/minute/1.73 m²)            | 99.7                  | 155.5                 | **<0.001 |
| Median                                 | 66.8–139.0            | 125.2–166.6           |          |
| IQR                                     | 9 (16.9)              | 0 (0)                 | *<0.001  |
| Abnormal GFR <90 ml/minute/1.73 m² n (%)| 1.03                  | 0.71                  | **<0.001 |
| sCystatin-C (mg/dl)                    | 0.85–1.50             | 0.60–0.85             |          |
| Median                                 | 8 (15)                | 0 (0)                 | *<0.001  |
| IQR                                     | 340–640               | 220–306.5             |          |
| Abnormal s.Cys-C n (%)                 | 4 (7.5)               | 0 (0)                 | *<0.001  |
| Albuminuria n (%)                      | 1 (1.9)               | 0 (0)                 | *<0.001  |

*Chi-square test, **Mann–Whitney U test for comparison.  
t-student test is used for comparison unless specified.  
s.ccr: serum creatinine; GFR: glomerular filtration rate; eGFRsch: estimated GFR using Schwartz classic formula; eGFRckd: estimated GFR using new Schwartz formula for chronic renal disease; NGAL: neutrophil-gelatinase-associated lipocalin; Cys-C: Cystatin-C; IQR: interquartile range; n: number; %: percent.
significant lower GFR for BL survivors when compared to healthy children (Figures 1 and 2), 9.4% of them (5/53) had mild CKD with GFR <90 ml/minute/1.73 m², none of them had moderate or severe CKD, all healthy children had GFR >90 ml/minute/1.73 m² when eGFR_{sch} was used. The most important observation in our study was the significantly higher prevalence of mild CKD among BL survivors when new screening modalities as estimated GFR by new Schwartz formula (eGFR_{CKD}) 16.9%, s.Cys-C15%, and s.NGAL 18.8% were used as shown in Figure 3. Median values of s.Cys-C and s.NGAL were significantly higher in BL survivors than comparable healthy peers as shown in Table 2 and displayed by box-plot at Figures 4 and 5. Persistent albuminuria (100 mg/dl, 2++) was observed at four BL survivors (4/53 and 7.5%). Among healthy children, (3/30 and 10%) had 1+ intermittent albuminuria, but none of them had persistent albuminuria of any degree.

On performing Spearman correlation (rho) analysis between renal function monitoring parameters and different clinical variables including age at diagnosis, follow-up duration, and body mass index (BMI), no significant correlation could be detected. Significant positive correlation could be displayed between s.Cys-C and s.NGAL (rho = 0.69 and p < 0.001). Both of them had negative correlation with eGFR, however, s.Cys-C was better correlated than s.NGAL with eGFR_{CKD} as shown in Table 3.

**Discussion**

Cancer and cytotoxic agents are listed among the risk factors for chronic kidney disease (CKD) [27]. In the

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**Figure 1.** Median and IQR of GFR_{sch} among patients and controls.

**Figure 2.** Median and IQR of GFR_{CKD} among patients and controls.
present study, we tested the hypothesis that Burkitt lymphoma survivors may experience late subclinical renal impairment, of variable degrees and types, more frequently than comparable healthy controls. The most striking finding in our work was the significantly high frequency of CKD diagnosis among BL survivors (almost 20%) when new parameters such as estimated GFR<sub>CKD</sub> and measurement of low molecular protein; s.Cyc-C and s.NGAL were used as screening modalities. Meanwhile, the majority of these cases have been missed by using routine methods such as s.cr and eGFR<sub>Sch</sub> for renal function monitoring. Despite the wide use of s.cr as an index of renal function in practice, estimation of s.cr may not automatically imply a sufficient monitoring of renal function [10]. Two BL survivors had s.cr 0.1–0.3 mg/dl above the normal range for their ages, but had concurrent eGFR<sub>Sch</sub> and CKD <90 ml/minute/1.73 m<sup>2</sup>. these findings highlighted the importance of serious consideration of any, even modest, elevation of s.cr, since as much as 50% of renal parenchymal loss must occur before detectable change in s.cr occur [21].

It is well established that none of the eGFR is as reliable as the gold standard clearance measurement such as S<sup>31</sup>Cr-EDTA clearance, but this method is invasive and not suitable for screening purpose. Significantly lower estimated GFRs and higher prevalence of CKD diagnosis were documented among BL survivors when using new Schwartz formula as compared to Schwartz classic one. eGFR<sub>Sch</sub> overestimates creatinine clearance by 12–33 ml/minute/1.73 m<sup>2</sup> compared to direct measurement of GFR, it is also inaccurate in obese or malnourished children and in critically ill children with rapidly changing renal function [28,29]. CKD diagnosis by eGFR<sub>CKD</sub> was several folds more than CKD diagnosis when s.cr-dependent tests were in-use. Stefanowicz and coworkers observed, in their follow-up study of Wilms tumor survivors, that eGFR<sub>CKD</sub> was in closer accordance with the gold standard than eGFR<sub>Sch</sub> [30]. Moreover, new Schwartz formula has been validated by comparing its results with measured lohexol GFR in young children with CKD [14]. Several mechanisms have been proposed as direct or indirect causes for late renal injury after completion of cytotoxic treatment; first, certain chemotherapies have well-documented long-term nephrotoxic effects as ifosfamide and platinum derivatives [8,31], however none of our patients was exposed to such agents. Second, high-dose cyclophosphamide and methotrexate are known for their acute nephrotoxicity but evidence regarding their long-term renal effects is lacking [24]. Recent study by Knijnenburg and his team concluded that the use of high-dose cyclophosphamide had the strongest association with GFR <90 ml/minute/1.73 m<sup>2</sup> but they could not find such association between high-dose methotrexate and any adverse renal outcome [23]. Lastly, the concomitant use of less nephrotoxic cytotoxic agents with other nephrotoxic medications such as aminoglycosides, vancomycin, amphotericin B, diuretics, non-steroid anti-inflammatory, and radio-contrast...
material may provoke persistent chronic renal injury [32,33].

Serum Cystatin-C was significantly higher among BL survivors than healthy peers, dependent on abnormal s.Cys-C, disturbed glomerular filtration were diagnosed at 15% of patient group but not in any healthy child in control group. Cystatin-C has been proved to be superior to s.cr as marker of kidney filtration function as it is not influenced by non-renal factors such as muscle mass, diet, and drugs, and is independent of age, sex, weight, and bilirubin level [15,16,34]. It is a good screening for reduced GFR in children with neoplastic diseases [9,35] and in pediatric kidney, liver, and heart transplant recipients [11,36–39]. Lankisch and colleague documented the diagnostic value of s.Cys-C especially among young (<3 years) cancer survivors, they described s.Cys-C as hopeful accurate modality for renal function monitoring in these at-risk patients [9]. Our finding showed a significant correlation between Cys-C and eGFR by classic and new Schwartz formulas, this correlation could not be detected on comparing Cys-C with clinical variables (age at diagnosis, follow-up duration, body mass index). In accordance with our results, Bradi and coworkers, in their study on children and adolescent who were receiving chemotherapy, found good correlation between Cys-C and Counahan GFR estimate [40]. Lack of correlation between Cys-C and BMI confirmed its independence on non-renal factors, as previously explained, and is considered as an advantage of Cys-C over s.cr as renal function monitoring test [34]. In contrast to our findings, the long duration of follow-

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**Figure 4.** Median and IQR of cystatin among patients and controls.

**Figure 5.** Median and IQR of NGAL among patients and controls.
up since cancer diagnosis represented an important risk factor for lower GFR and higher Cys-C level [23], we thought that the short duration of follow-up in our series might be the cause of lack of such correlation.

In parallel with Cys-C behavior, s.NGAL showed significantly higher values among BL survivors as compared to healthy children. 18.8% of BL survivors had abnormally high s.NGAL values. As observed in our results and reported by others, s.NGAL can be detected earlier than any changes in s.cr [41]. s.NGAL has been described as sensitive and specific marker of acute renal injury as well as CKD [42,43]. Recent study documented s.NGAL as an effective biomarker for detecting early stage renal damage in CKD patients; they also appreciated its role in predicting the underlying CKD severity, progression and prognosis [18]. Significant positive correlation could be displayed between s.Cys-C and s.NGAL; similarly, this correlation was well documented in the aforementioned study [18]. s. Cys-C had closer correlation with eGFR\textsubscript{CKD} than that between s.NGAL and eGFR\textsubscript{CKD}, this is probably due to the effect of associated albuminuria on s.NGAL level [44].

Persistent pathologic albuminuria, another indicator of glomerular function damage, was documented in 7.5% of BL survivors, but in none of the healthy children. Higher incidences of albuminuria among cancer survivors were described by several investigators, it ranged from 11.6 to 16.7% at different reports [23]. The lower incidence among BL survivors may be explained by fact that LMB96 protocol used for our patients does not contain known chronic nephrotoxic agents as ifosfamide or platinum derivatives. Hypertension was documented in only one BL survivors; this patient had the highest s.cr and the lowest eGFR\textsubscript{CKD} in our patients group. These data suggested the underlying renal cause for this elevated BP, as kidney impairment may interfere with salt and water excretion or may lead to increased peripheral vascular resistance through humoral agents [45].

To our surprise, no statistically significant differences could be detected on comparing the anthropometric measurement of BL survivors with healthy children. These findings represent the high body recovery power after the negative impact, of the disease itself, associated illness and medications including the cytotoxic agents, on the physical and the psychologic status of the patient.

The most important strength of this research is the homogeneity of the studied population; that allow accurate estimation of late renal sequels of cytotoxic medications and the disease itself among BL survivors. In conclusion, almost one fifth of BL survivors had mild CKD, novel screening methods such as estimated of GFR\textsubscript{CKD} and measurement of low molecular protein; s.Cyc-C and s.NGAL unmasked this high prevalence.

On the other hand, limitations of the current study included; the small number of patients who are selected from two centers only, lack of comparison of our results with gold standard methods such as inulin clearance or nuclear medicine scintigraphy. Wide scale controlled multicenter study is warranted to support the use of such novel modalities in the routine screening protocols for early detection of renal injury and implementation of kidney protective strategies.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**Ethics approval**

Official permissions were obtained from the scientific ethical committee of the collage “Institutional Review Board” (IRB), directors of the pediatric. Also an informed written consent from patient or their caregivers was taken.

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