SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Complex analysis of acute kidney injury in childhood hemato-oncological diseases

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DOCTORAL SCHOOL OF LAKI KÁLMÁN

DEBRECEN, 2023.

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The PhD Defense takes place at the Lecture Hall of Urology Department, Faculty of Medicine, University of Debrecen
2023.02.02 13.00

Background and objectives of the doctoral thesis

Hemato-oncology patients are classified as high-risk patients for acute kidney failure, which occurs approx.1.5–2.5 times more often in this risk group than in the average population. The 1-year cumulative incidence of acute kidney injury (AKI) is high (52%) in the pediatric hemato-oncology patients, and nearly half of AKI episodes occur within two weeks of diagnosis with a median onset on the ninth day after diagnosis. Eventually, roughly 26% of childhood cancer survivors experience renal dysfunction at least once during treatment.

Tumor lysis syndrome (TLS) is one of the most serious emergencies in onco-hematology patients, and the incidence of TLS increasing in parallel with the development of more effective chemotherapy treatments. Tumor lysis syndrome is characterized by hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia based on the Cairo–Bishop criteria. Clinical tumor lysis syndrome is known to be associated with high morbidity and mortality rate, because the progression of TLS can lead to severe organ damage, including kidney damage, seizures, cardiac arrhythmias, pulmonary edema or

even death. Acute kidney injury is one of the most common complications of TLS and its presence is an important predictor of both short- and long-term mortality.

The acute kidney failure has been proven to increase the risk of chronic kidney disease (CKD) (even after complete recovery of kidney function) according to follow-up studies. Nearly half of patients, who had acute kidney failure show later signs of chronic kidney disease. In long-term haemato-oncology survivors (follow-up >5 years) severe kidney disease (CKD grade ≥ 3) was quite rare, occurring only in less than 1% of them according to current clinical investigations. But a lot of them suffers from hipertonia, proteinuria or some kind of tubular dysorders. The slight or medium CKD (stadium 2, 3) occur by 3-30% of patients.

According to literature data, episodes of acute renal injury is underdiagnosed in hemato-oncology patient group due to the reduced serum creatinine level associated with reduced muscle mass. However, the incidence of latent and asymptomatic appearance of acute renal failure seems to be increased, in parallel with higher nephrotoxic exposure of patients. Consequently, early detection and prevention of acute kidney failure is of great importance for choosing an adequate

with optimal timing. it is obvious, that elimination of potential nephrotoxic drug exposutre is essential for adequate therapeutic management. Additionally, ensuring the appropriate volume status (avoidance of excication and diuretic drugs) is also essential.

Previous studies of the exact pathophysiology of acute kidney injury indicated the dominant role of the tubular function: where the initial damage supposed to cause functional changes in the tubular cells, that later followed by substantial morphological changes. Utilizing measurements of dynamic changes of tubular biomarkers enabled us recognize earlier acute kidney episodes more effectively (days before serum creatinine level rises), and not only morbidity data improved significantly but the management of these patients became more accurate compared to previous traditional approach based on single serum creatinine measurements alone.

The analysis of several urinal signal molecules (for example NGAL, KIM-1, NAG) opened a new era in the diagnosis and management of AKI of which such non-invasive tests represented an easily performed pre-screening method for detecting acute renal failure.

Not only the diagnosis, but also the definition of acute renal failure broadened with the appearance of the significance of tubular markers.
The following subgroups were identified:
• hemodynamic form (biomarker negative and serum creatinine positive): prerenal/hemodynamic kidney involvement
• subclinical form (biomarker positive and serum creatinine negative): in this phase, only functional changes of tubular cells have occurred with the causing tubular cell metabolic disorders.
• clinical form: true manifestation of AKI with morphological differences

Our research plan, as retrospective data analysis, was designed for comprehensive examination of hemato-oncology risk groups, highlighting the role of tubular functions using two methods:

I: The guideline for risk assessment ("Biomarker Guided Risk Assessment Guideline" proposed by the American Association for Clinical Chemistry (AACC)) based on the use of urine

biomarkers defining new subgroups and enabling earlier recognition of kidney involvement.
The occurance of these episodes may precede the episode of clinically significant kidney failure of which is already accompanied by morphological changes.

Accordingly, we investigated the frequency and nature of the occurrence of acute renal failure using conventional and tubular marker.

We chose the N-acetyl-β-D-glucosaminidase (NAG), which usefulness as an indicator of the functional state of the renal tubules was described more than 40 years ago. This enzyme originates from the lysosomes of the proximal tubular epithelial cells, an increase in its level in the urine usually indicates kidney disease due to damage to tubular cells in parallel to kidney damage. NAG has a relatively high molecular weight, so it is not filtered through the glomeruli and is rapidly metabolized in the liver. As highlighted in previous publications, it is excellent for tracking and/or monitoring kidney function after chemotherapy treatment. However, some limitations have also been raised and later confirmed in the literature, such as the fact that NAG is often being elevated in chronic kidney patients, it is not specific and it has been found

that its level can also be elevated in other forms of active kidney disease, as well as in the case of renal involvement without clinically significant AKI, which appears with numerous tubular injuries its level increases (rheumatoid arthritis inflammation, reduced glucose tolerance, hyperthyroidism, diabetes mellitus, nephrotic syndrome, urinary tract infection, perinatal asphyxia, heavy metal poisoning, several urological malformations.

33 children suffering from cancer with appropriate selection criteria was performed in our retrospective analysis with a total of 367 uNAG measurements. In our study, we included patients who underwent a serial uNAG test (at least 5 samples/patient) in order to ensure accurate patient follow-up, and who attended the Hemato-oncology Department or the Outpatient Clinic of the Children's Clinic of the University of Debrecen, during the availability of the NAG laboratory test (2009-2019). Kidney function was determined on the basis of cystatin-C and creatinine-based GFR, as well as the relative increase of the NAG index (NAGRI).

In addition to clinical (according to pRIFLE criteria) and subclinical AKI episodes (according to Biomarker-guided risk assessment), we also examined the occurrence of chronic kidney

damage, and if necessary, the patient was followed up even after NAG was no longer available, in addition to analyzing the serum creatinine level. We examined the ratio of tubular / tubuloglomerular damage and also analyzed the regeneration time.

II: We analyzed one of the most serious onco-hematological emergencies - tumor lysis syndrome - from the perspective of acute kidney failure in a group of patients with leukemia and lymphoma, supplementing it with one of the most difficult decisions, the dilemma of the need for dialysis treatment.

Based on the current treatment recommendations, both the Hungarian Children's Oncology Group (HPOG) and the "British Hematology Standards Committee" tumor lysis syndrome treatment guidelines, patients can be classified into different tumor lysis syndrome risk groups. In "low-risk" patients, the guideline recommends aggressive hydration in addition to the use of allopurinol, in the case of "medium" and "high" risk patients, one of the main elements of conservative treatment is the use of recombinant urate oxidase (Rasburicase®), which is able to effectively remove the uric acid, since for a long time changes in uric acid homeostasis were

considered the most important causal factor in the pathomechanism of tumor lysis syndrome.

However, Rasburicase treatment is still controversial with regard to the development of renal failure. Based on several studies, according to the statistical modeling used, acute renal failure did not decrease significantly with rasburicase treatment. Although its early application may mitigate further kidney damage, especially in mild cases, where regeneration is also faster with its application, it seemingly did not significantly affect the outcome of severe acute kidney failure.

In severe cases, treatment should be combined with renal replacement therapy, while there is no consensus on the modality and timing of renal replacement therapy. Early renal replacement therapy has a proven renal protective effect, although the difference in outcome between early and late initiation was not significant in terms of long-term renal survival.

During the retrospective study of tumor lysis syndrome, in children with leukemia and lymphoma treated between 2006 and 2016 in four Hungarian pediatric uniclinic were examined. After appropriate selection process (due to incomplete documentation and different etiological reasons behind the

laboratory abnormalities found), a total of 31 pediatric patients with tumor lysis syndrome, defined according to the Cairo-Bishop criteria system, were included in our study. Patients were also grouped according to the "traditional" tumor lysis syndrome criteria, such as laboratory or clinically significant tumor lysis syndrome, and in nephrological point of view, as defined according to pRIFLE criteria, such as mild (pRIFLE: 0, R, I) and severe (pRIFLE: F) acute renal failure subgroups. We focus was on the incidence and characteristics of acute renal failure. Our goal was to select the best-performing traditional biomarker that can predict the development of severe kidney failure.

New scientific results of the thesis

I. Based on the AACC guideline, we identified 60 renal episodes in a total of 26 patients, detecting 18/60 clinical and 12/60 subclinical renal episodes. In 27/60 episodes, only NAG values increased without therapeutic consequences, likely due to low urinary creatinine level associated with higher fluid intake based on chemotherapy treatment recommendations.

We observed 3 "silent" episodes of AKI in two patients, during which an increase in early AKI markers was observed parallel to the decrease in creatinine level.

Based on the ROC analysis for the occurrence of acute renal failure, NAGRI significantly indicated the presence of acute renal failure, its sensitivity and specificity being higher than creatinine-based GFR changes. However, serial NAG measurements are recommended in order to reduce the large number of false positive NAG results, the causes of which are the elevated blood pressure associated with hematological treatments.

During the analysis of regeneration, tubular function impairment resolved faster, while tubuloglomerular impairment resolved slower.

Chronic tubuloglomerular injury occurred in 5 patients, following these patients with extended follow-up time, we detected the development of CKD2 in 1 patient.

By using biomarker-driven risk assessment, 1.5 times more clinical and subclinical AKI episodes were identified than when using creatinine level measurement alone, and we also identified a low percentage of „silent" acute renal failure.

II. Several parameters (laboratory parameters, patient-specific data) were analyzed between the subgroups in our tumor lysis syndrome -related examination. Significant differences were found by the changes in the parameters of phosphate homeostasis, respectively of urea level.

It is known from the literature that the development of tumor lysis syndrome is often preceded by hypophosphatemia and that an increase in the peak serum phosphate level is a good predictor of the development of acute renal failure associated with tumor lysis syndrome in adults.

Although the etiological background of the preceding hypo- and consequent hyperphosphatemia can be varied, the first cause may be an increased urinary phosphate excretion, which than can increase not only the development of acute renal

failure but the risk of nephrocalcinosis. Evidently its causal role has been suggested behind renal failure cases associated with severe tumor lysis syndrome.

Detailed 24-hour urinalysis data from eight patients indicated only transiently increased phosphate excretion, parallel to elevated serum phosphate levels and the development of kidney failure.

The age-specific normal phosphate ranges show significant differences in childhood, which we used in our analysis.

Hypophosphatemia was also common in our study before the occurance of tumor lysis syndrome (19/31 cases), while hyperphosphatemia was observed in the period after TLS (26/31 cases). In the observed hyperphosphatemic phase desintegration of tubular function and progression of kidney involvement plays a clear role. Beyond many variables such as peak of phosphate level before and after the onset of tumor lysis syndrome, we identified the change in the daily serum phosphate leve las an important factor in TLS progression. We analysed that the peaks of the serum phosphate level show only a moderate increase in the subgroups without renal replacement therapy.

The limit value of the daily serum phosphate level increase before acute renal failure was 0.32 mmol/l according to the ROC analysis in case of severe renal involvement (pRIFLe: F), which was the most significant discriminator for severe AKI.

Summary

Our data clearly demonstrate that the accurate assessment of actual kidney function requires a more advanced method, than a single creatinine measurement or creatinine-based GFR calculation, especially in the high-risk patient group. The early recognition of acute renal failure is difficult, special in the high-risk population, such as the hemato-oncology patients. Next to the use of alert and early warning systems, the measurement of tubular markers can help.

Complementing the routine renal panel with a urinary tubular marker (such as NAG) can improve the detection of acute renal failure and, based on the "AACC guid**e**line", can also help clarify the etiological causes of acute renal failure.

The analysis of childhood tumor lysis syndrome showed the frequency of acute nephrological complications and the

importance of phosphate kinetics. The most predictive parameter for severe kidney involvement was the daily change in serum phosphate, which can help to select those patients at risk, where renal replacement therapy may be necessary, and may encourage its earlier initiation.

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Registry number: DEENK/230/2023.PL
Subject: PhD Publication List

Candidate: Erika Biró
Doctoral School: Kálmán Laki Doctoral School

List of publications related to the dissertation

1. **Biró, E.**, Erdélyi, D., Varga, P., Sinkó, M., Bartyik, K., Kovács, G., Ottóffy, G., Vincze, F., Szegedi, I., Kiss, C., Szabó, T.: Daily serum phosphate increase as early and reliable indicator of kidney injury in children with leukemia and lymphoma developing tumor lysis syndrome. *Pediatr. Nephrol. [Epub ahead of print]*, 2023.
   DOI: http://dx.doi.org/10.1007/s00467-023-05923-z
   IF: 3.651 (2021)

2. **Biró, E.**, Szegedi, I., Kiss, C., Oláh, A., Dockrell, M. E. C., Price, R. G., Szabó, T.: The role of urinary N-acetyl-[béta]-D-glucosaminidase in early detection of acute kidney injury among pediatric patients with neoplastic disorders in a retrospective study. *BMC Pediatr.* 22 (1), 1-8, 2022.
   DOI: http://dx.doi.org/10.1186/s12887-022-03416-w
   IF: 2.567 (2021)

3. **Biró, E.**, Szikszay, E., Orosz, P., Bigida, L., Balla, G., Szabó, T.: Acute interstitial nephritis in T-cell leukemia in a pediatric patient.
   Pediatr. Int. 58 (9), 940-942, 2016.
   DOI: http://dx.doi.org/10.1111/ped.13029
   IF: 0.822

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List of other publications

4. Varga, P., Balajthy, A., **Biró, E.**, Bíró, B., Reiger, Z., Szikszay, E., Mogyorósy, G., Káposzta, R., Szabó, T.: Multicolored MIS-C, a single-centre cohort study.
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DOI: http://dx.doi.org/10.1186/s12887-023-03997-0
IF: 2.567 (2021)

5. **Biró, E.**, Szabó, T.: Dialíziskezelés szerepe a sürgősséget igénylő örökletes újszülöttkori anyagcserezavarok komplex kezelésében.
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6. Orosz, P., Durányik, M., **Biró, E.**, Körhegyi, I., Balogh, I., Szabó, T.: Question of Prophylactic Anticoagulation in Steroid Sensitive Nephrotic Syndrome: rare Complication in Pediatrics.
J. Pediatr. & Child Health Care. 2 (1), 1-3, 2017.
IF: 1.449

Total IF of journals (all publications): 11,056
Total IF of journals (publications related to the dissertation): 7,04

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

08 June, 2023

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