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PhD THESIS

ACUTE KIDNEY INJURY IN THE PEDIATRIC POPULATION – INCIDENCE AND OUTCOMES

– A B S T R A C T –

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GENERAL PART

1. EPIDEMIOLOGY

"If you look for perfection, you'll never be content." Leo Tolstoy

AKI is a complex disorder characterised by a rapid (hours to days) decrease of renal excretory function, with accumulation of waste products or decreased urine output, or both. It is the clinical manifestation of several disorders that can affect the kidney acutely.

AKI has become an area of intense focus over the last two decades since a consensus definition has emerged. Having a uniform standard for AKI definition and classification enhanced researchers to provide comprehensive evidence-based recommendations using a grading system for current practice.

There has never been a time that humankind had not suffered from AKI. The 18th century provided the first organ-based classification of 'ischuria renalis', inflammation, and nephritis. It wasn't until the 20th century that the clinical course and pathology of acute renal failure (ARF) were reported, with postwar progress that demonstrated the reversibility and now the available treatment of ARF.

Mounting evidence suggests that a continuum of kidney injury exists before clinical manifestations and biological alterations are documented. Thus, in the face of epidemiologic transition, the term ARF proved to be insufficient. This is why, in 2004, the ADQI group developed a new grading system, based on serum creatinine level and urine output, under the acronym RIFLE. The first three grades are used for AKI grading while the last two rather define the outcome of the duration of loss of kidney function. This further led to a pediatric-modified RIFLE (pRIFLE) criteria to assess AKI incidence and AKI course that suited small children with or without underlying chronic diseases.

In 2007, the Acute kidney Injury Network (AKIN) endorsed the RIFLE criteria with a small modification to include small serum creatinine changes over a 48-hour period. RIFLE/AKIN criteria provided a uniform definition of AKI being analogous to the Kidney Disease Outcomes Quality Initiative (KDOQI). The rising evidence of AKI outcomes in the face of a non-steady state serum creatinine provided strong rationale for use of both RIFLE and AKIN criteria.

Further, in time, in 2012, the first AKI guideline was published by KDIGO to provide comprehensive evidence-based recommendations based on a grading system. The new and improved AKI definition gathered under the three staging classification both RIFLE and AKIN, giving a uniform criteria for the first time. Notably, the benefit of the harmonised KDIGO definition is immense as it is the only definition that contains both adult and pediatric criteria.

2. AWARENESS

Epidemiological studies underline the dramatic rise in the incidence of AKI. This brought an imperative need for AKI awareness among physicians who fail to recognize AKI or have insufficient data regarding AKI management. Moreover, the diverse heath care providers that encounter patients with AKI overrun the reduced numbers of nephrologists. The shortage of pediatric nephrologists across the globe has limited AKI recognition, thus failing to implement simple and inexpensive measures. Worldwide, collaborative efforts urge the need to raise awareness of AKI globally.

The low awareness rates of AKI represent a global health problem. Although AKI awareness is indisputable low in pediatric patients, mitigating for awareness is the gold standard in preventing this devastating complication. The landscape of pediatric AKI is continuing to change, however AKI is mostly encountered in different settings and dependent of the underlying disease. There are several risk factors known to increase the risk of AKI: prematurity, mechanical ventilation, use of inotropes, nephrotoxic medications, sepsis, cardiac surgery and so on. Several strategies have already been implemented in the pediatric field such as the use of AKI electronic alerts.

3. RISK ASSESSMENT

Risk assessment of AKI is required in all admitted patients, especially in the intensive care unit. The kidney can tolerate renal insults without suffering functional or structural changes. However, acute changes that alter the kidney function often indicate the underlying systemic disease. AKI increases in the presence of several known renal insults as previously stated in the AKI KDIGO guideline. Risk assessment should be performed in all admitted patients. Understanding the individual risk factors may help physicians to stratify and manage patients according to their exposures and susceptibilities in order to reduce the risk of AKI. Given the pleiotropic factors that determine personal susceptibilities and the interaction with several known types of exposures during hospitalization, with an increased risk of AKI occurrence and progression to CKD, risk assessment should be integrated from the emergency department along with appropriate serum biochemistry. Nonetheless, AKI occurrence is heterogonous in the pediatric population with a wide individual variability.
As AKI occurrence is a secondary response to a systemic disease or external intervention one should asses the management and treatment to further reduce renal injury.

4. AKI DEFFINITION, CAUSES AND DURATION

AKI is defined by a sudden decrease in the ability of the kidneys function along with a reduction in glomerular filtration rate (GFR), defined by a reduction in urine output or an increase in serum creatinine (SCr), or a combination of both. Clinically, changes in SCr and urine output are surrogates for GFR changes. However, there is a broad consensus that currently the wide accepted AKI definition in both children and adults is the KDIGO criteria. The KDIGO criteria comprise both the RIFLE and AKIN definition as we previously described. AKI is defined by an increase in SCr by more than 0.3mg/dl within 48 hours, or a 1.5 times increase in SCr from baseline within the prior 7 days, or urine volume less than 0.5ml/kg/h for at least 6 hours.

After injury has occurred, the next step is identifying the cause of AKI. This is of upmost importance in clinical settings. However, there are some difficulties in identifying the causes of AKI in patients with community-acquired AKI. The causes of AKI can be simplified in clinical settings in prerenal, renal and postrenal causes.

The prerenal cause of AKI should be considered in selected causes of decreased renal perfusion such as: dehydration or volume depletion, anaemia, sepsis, critical illness, burns and so on. This requires volume status evaluation and resuscitation before any other medical intervention. Acute infectious diseases can be further evaluated and treated with complete or partial resolution of AKI. Commonly, patients whom develop prerenal AKI have multiple triggers that input renal injury. Besides the decrease in urine output and/or a rise in SCr, attention should be focused on fluid management during hospitalization. Neonates and children in ICU settings are at high risk of fluid overload [66-68]. Nevertheless, the renal outcomes can be shifted by the severity of the underlying disease spectrum. Critically ill children and neonates are exposed to nephrotoxic medication, mechanical ventilation and longer hospital stay that further increase the risk of nosocomial infections, need for medical devices and the associated complications. Patients with prerenal AKI should always be managed according to the cause of their disease, and thus it is important to determine the cause whenever possible. Albeit, renal hypoperfusion and systemic vasodilation are the main causes for developing AKI, once kidney injury is present it associates worse outcomes.

The intrinsic cause of AKI is represented by injuries in the renal structure and function such as acute glomerulonephritis, tubule-interstitial nephritis, acute tubular necrosis, vasculitis, and thrombotic microangiopathy. As opposed to prerenal AKI, where often the cause of AKI does not dictate specific therapy, the syndrome of intrinsic AKI in specific kidney diseases, has an available treatment. It is important to mention that in some cases, prerenal AKI evolves towards renal AKI through the extension of kidney injury in time and/or by the severity of AKI. This will be addressed later in the continuum of kidney injury in children. As opposed to prerenal AKI, intrinsic AKI associated worse renal outcomes.

The postrenal cause of AKI is secondary to obstruction in the urine flow. In children, AKI usually occurs when obstruction is below or at the level of the bladder as seen in posterior urethral valves in boys, urethral stricture, neurogenic bladder, and complete labial adhesions in girls. Above the bladder, the blockage must me bilateral to cause AKI, but it can also be unilateral in children with a single kidney or post-kidney transplant. The main frequent causes of urinary retention are kidney stones, urethral strictures and medication-related. It is axiomatic to say that acute urinary retention should be screened at bedside

using abdominal echography. Finally, in-hospital patients who benefit from diuresis monitoring and develop new on-set AKI, an occluded urinary catheter must be excluded first. Unfortunately, several factors may falsely indicate oliguria, for instance kinking of the urinary catheter.

The different thresholds for AKI duration and functional recovery discriminates transient-AKI (T-AKI) from persistent-AKI (P-AKI). However, the distinction between short-term AKI and P-AKI is not delineated in children, albeit several studies underline the link between T-AKI and P-AKI in children. Rapid reversal of kidney injury corresponds to the disappearance of the raised SCr and low urine output according to KDIGO AKI criteria.

T-AKI is defined by early renal recovery, over the course of 48 hours. Transient kidney injury is fairly common in children with prerenal AKI where rapid resolution of the AKI episode is described when volume status is addressed. Various phenotypes of recovery after T-AKI have been identified, each correlated with different long-term outcomes. Firstly, early sustained recovery, when correct treatment has been applied without any other injury noted throughout medical monitoring. Secondly, relapse-AKI and recovery, when another AKI episode is identified during hospitalization followed by complete renal recovery. Thirdly, relapse-AKI with evidence of persistent decreased renal function with or without markers of kidney damage. The consensus report of the ADQI Acute kidney disease and renal recovery, recommends an arbitrary 48 hour time period when referring to relapse-AKI. Nevertheless, after sustained recovery, new investigations are imposed when a second AKI episode has occurred.

P-AKI is considered to have a late recovery as it is represented by a prolonged AKI episode, lasting over 48 hours. Persistent kidney injury duration may generate renal remodelling (e.g. tubule-interstitial inflammation and fibrosis) dependent of the AKI cause and AKI severity. As well as in T-AKI, the persistence of AKI in time can follow several trajectories such as: injury resolution in the first 7 days, progression to acute kidney disease (AKD) when AKI duration is over 7 days, progression to CKD when more than 3 months of renal damage is identified, or kidney failure that requires RRT. As opposed to T-AKI, the self-repair mechanism in P-AKI can be altered by the underlying disease severity, the external aggressors, and the kidney health status prior to the AKI episode.

5. AKD

The term AKD was first introduced in the 2012 KDIGO AKI guideline followed by the 2016 Consensus report of ADQI definition, staging and strategies for the management of affected patients. The continuum of AKI-AKD-CKD is an intricate relationship between the initial injury to persistent renal injury

AKD was defined as AKI stage 1 or greater based on the KDIGO AKI criteria with a duration of more than 7 days and under 90 days after an AKI initiating event. AKD is a heterogeneous syndrome that is frequently encountered in the clinical settings with an increased mortality risk and incidental CKD. However, the data is scarce in children. Certainly, when compared to adults, the epidemiologic traits of AKD and the impact on health are not readily available. This is why, we performed a retrospective study on a mixed population of children (critically ill and non-critically ill) from birth until 18 years old, to assess the continuum of AKI on AKD development and worse renal outcomes.

The incidence of AKD in children is between 6.35% and 42.3% respectively. These wide ranges in AKD incidences are linked to a specific population in most cases. The highest incidence of 42.3% reported by Deng et al. was reported in a smaller cohort, after excluding the neonates, while LoBasso reported the lowest AKD incidence (6.3%) in children who underwent cardio-pulmonary by-pass. However, we found that almost 1 out of 3 admitted patients develop AKD during hospitalization. Nevertheless, AKD is a result of persistence of kidney injury, and attention should focus on medical intervention and the underlying disease treatment.

Current data from adults recognizes AKD as an independent risk factor for CKD development. However, several large studies investigated the link of novel biomarkers after an AKI episode with an increased incidence of CKD independent of SCr. In children, the data are scarce. Patel reported AKD to be a superior risk factor for new-onset CKD in children after non-kidney solid transplantation. In the follow-up renal assessment of injury long-term after AKI (FRAIL-AKI) study in children with cardiac surgery using cardio-pulmonary bypass, patients with postoperative AKI had elevated urinary biomarkers 7 years after the AKI episode without functional evidence of CKD. However, the Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) study in children following cardiac surgery found no association between preoperative biomarkers and CKD after 5 years of follow-up. However, the TRIBE-AKI study reported a high prevalence of CKD and arterial hypertension at 5 years after cardiac surgery, without the biomarkers measurements at follow-up.

Certainly, there is a lack of data in both adults and children regarding some biomarkers evolution in patients with AKI and AKD, mostly due to high costs and reduced accessibility. Nevertheless, the use of kinetic estimated GFR, as recommended by the ADQI consensus could represent an alternative approach in evaluating GFR in patients with AKD. Our study proved kinetic modelling of estimated GFR to be a predictor for AKD and worse renal outcomes.

SPECIAL PART

1. ACUTE KIDNEY INJURY IN CHILDREN: INCIDENCE, AWARENESS AND OUTCOME

In our study, children aged less than 1 month – 49.5% – represented the most numerous age group. Our incidence is 2.5 times greater than that reported by Sutherland (19%). Neonatal patients presented the highest awareness rate, and patients aged between 3 and 12 years had the lowest AKI awareness. The incidence of CA-AKI of 38.8% was similar to that in the existing published data (38.8%), but the awareness rate was slightly greater among patients with IH-AKI (29%). The diagnosis of CA-AKI, as well as the staging of AKI, is challenging for pediatric doctors. Proper management of modifiable risk factors together with careful risk assessment can lead to rapid AKI identification, thus improving short- and long-term prognosis. To our knowledge, no other study has evaluated differences in AKI awareness between community-acquired and in-hospital AKI patients.

According to previously published data from AKI-EPI, Baby-Ninja, AWARE, AWAKEN and many other regional studies, the prolongation of increased serum creatinine and the severity of AKI are associated with worse outcomes. The incidence of AKD in our cohort was 17.8%, and AKI was recognized by physicians in half of these patients. In adult settings, AKD is associated with increased morbidity and mortality. On the other hand, the pediatric population has a high capacity for kidney function improvement even with full renal recovery.

Prerenal AKI is the main cause of AKI. Most pediatric studies have reported the most prevalent cause of AKI. Our cohort presented a wide spectrum of diseases. Almost one-third of the patients in our cohort presented with acute tubule-interstitial disease, and the need for mechanical ventilation, critical illness and sepsis generated secondary prerenal AKI in more than 50% of the patients. Volume depletion or dehydration is the main cause of AKI. On the other hand, the presence of dehydration becomes an important indicator of repeated serum creatinine measurements. As expected, AKI severity was correlated with the severity of underlying disease. The presence of exposures such as trauma, hypovolemic shock, critical illness, sepsis and mechanical ventilation increased AKI awareness. In addition, the correct diagnosis of AKI was made in children who were hypovolemic, preterm or had chronic diseases such as CKD, neoplasia or heart failure. One should keep in mind that the failure to correctly diagnose AKI is most likely related to the small baseline creatinine values in children associated with wide normal laboratory ranges.

The presence of personal susceptibilities associated with different types of exposure in admitted patients may increase the risk of developing AKI; thus, repeated serum creatinine measurements are mandatory. Many studies have focused on already known vulnerable categories from the adult population but have not evaluated the impact of personal exposures and susceptibilities in children at risk of developing AKI.

After adjusting the risk assessment, we identified a high prevalence of specific exposures and susceptibilities in children with AKI. Sepsis, mechanical ventilation and nephrotoxic drugs were the most prevalent exposures. The most commonly encountered susceptibilities were dehydration or volume depletion, anaemia and prematurity. As

previously mentioned, only creatinine follow-up can increase the number of patients diagnosed with AKI, increasing AKI awareness. Hence, the renal angina index (RAI) has shown improved accuracy for predicting severe AKI in critically ill patients and young adults, and the first step remains the diagnosis of AKI.

Currently, AKI is recognized as a syndrome that is secondary to treatments or other systemic diseases and is associated with increased mortality. To identify the cause of renal injury, AKI must first be identified. In community acquired AKI you can do that with the use of an algorithmically approach. Our overall mortality rate was low, but the presence of AKI increased it by more than 79 times. Our mortality risk of AKI was significantly greater than that reported by Meena in a recent meta-analysis (4.6 times). Our results regarding the mortality rate among AKI patients (11.6%) are similar to those reported by the meta-analysis from 2023 (11%) and the one presented by Susantiaphong in 2012. The relative risk of mortality in our cohort was most likely lower than that identified in the present study. The reasons are poor AKI screening among patients, a reduced number of creatinine measurements and a lack of urine output. Nevertheless, AKI awareness increased mortality by 39%, especially in the context of a higher incidence of severe AKI in the AKI-free group.

Exposure to hypovolemic shock, sepsis, the need for mechanical ventilation or critical illness increased mortality, similar to previously published data. Only some susceptibilities, such as neoplasia and heart failure, seemed to influence mortality in our cohort.

The progression towards AKI increases costs and prolongs hospitalization. For instance, in our study, AKI patients had a 4-fold longer hospital stay than non-AKI patients. In addition, patients for whom physicians were aware of AKI had longer hospital stays because of more severe AKI events. If the physician is not aware of AKI in a patient with several susceptibilities, then he or she is at a high risk of being exposed to renal insults.

Lamaire emphasized the important increase in AKI incidence in the 2016 Epidemiology of Acute Kidney Injury in China. He mitigated the imperative need for studies identifying the real incidence and outcomes of AKI in addition to a rise in awareness of AKI among physicians. Insufficient awareness of AKI leads to poor management and, ultimately, to worse outcomes and increased costs. The most beneficial impact would be in the implementation of simple, inexpensive measures from the beginning. We cannot agree more with Lamaire and believe that this is the endpoint of our study. Although more than a decade have passed since the AKI-KDIGO guidelines were established, AKI is still underdiagnosed in adults and children. The need for AKI awareness, proper management and appropriate long-term follow-up was expressed in the Consensus-Based Recommendations on Priority Activities to Address Acute Kidney Injury In Children from 2022.

2. OUTCOMES OF ACUTE KIDNEY INJURY CONTINUUM IN CHILDREN

In our study, the incidence of AKI in our study was 1.64%, which is higher than that reported by Sutherland in children in the USA (0.39%) but lower than that reported in the most recent meta-analysis (26%). Surely, the results are related to the retrospective and single-centre nature of the study.

One of the studies that evaluated the outcomes of AKI duration using the T-AKI, P-AKI and AKD classifications was by Nagata in 2021 in adults. In the present study, the

incidence of T-AKI was 19%, which was much lower than that of AKD and P-AKI (40% each). One should consider that adults are prone to a longer AKI duration as a result of the coexistence of multiple comorbidities. On the other hand, children present a greater renal reserve and greater renal recovery capacity. As seen in our cohort, P-AKI had the highest incidence (43%), followed by AKD (29%) and T-AKI (28%). Most of the reported incidences of AKD among children are heterogeneous and scarce. For instance, the lowest reported AKD incidence was by LoBasso, at 6.3%, in children with cardiopulmonary bypass, and the highest was by Deng, at 42.3%, in hospitalized children (excluding neonates).

T-AKI patients from our cohort were older and presented higher creatinine and urea levels than AKD and P-AKI patients. The major risk factor for developing T-AKI is a prerenal state with reduced renal perfusion. AKI causes the rapid reversal of AKI. Compared to children, adults present long-term aggressors such as cardiovascular disease, arterial hypertension or diabetes mellitus. In the face of these differences, children present a greater renal reserve and thus a greater renal recovery capacity. If early renal recovery is not present, the incidence of stage 2 or 3 AKI increases, most likely because of the underlying disease severity. Several risk factors present on day 1 of AKI could predict AKI duration. The risk factors are younger age; higher baseline and maximum serum creatinine levels; higher urea and inflammatory marker levels; lower serum protein, thrombocyte and haemoglobin levels; and younger age. Increased levels of proinflammatory cytokines, hypoxia and decreased renal perfusion are a consequence of prolonged prerenal injury, which leads to intrinsic renal damage. Patients with P-AKI presented a greater incidence of proinflammatory states (hypoxia, systemic inflammatory response syndrome, septic shock or sepsis) with a longer reversal time than hypovolemic patients. Multiple factors influence progression towards AKD. Our cohort revealed that patients with AKD presented with more severe underlying disease. In this clinical status, there is a greater chance of exposure to external renal aggressors such as nephrotoxic medication, which contributes to the pathological renal injury continuum.

The mortality in our AKI cohort was 13.1%, similar to that in the meta-analysis by Meena from 2023 (11%). The lowest mortality rate was associated with P-AKI (9.8%), followed by T-AKI (14.6%) and AKD (16.4%). The patients with T-AKI had unexpectedly high mortality, probably as a result of the underlying disease severity. Because of the retrospective nature of the study, we were unable to correctly identify the beginning of AKI, only the first day of recorded AKI, especially in patients with CA-AKI. This could mean that some patients with T-AKI are actually already in a state of P-AKI or even AKD. To overcome this issue, there is an imperative need for future prospective studies to more accurately assess the impact of AKI duration on mortality risk in children. For example, LoBasso reported different mortality rates regarding AKI duration. He reported a much greater mortality rate for P-AKI (25.5%) than for T-AKI (8.9%) in children who underwent cardiopulmonary bypass surgery. His study is the only one that stratified AKI mortality risk according to AKI duration in pediatric patients. One should not overcome the fact that LoBasso's cohort was in a specific subgroup of children, in antithesis with ours that comprise a broader spectrum of pathologies. AKI remains an independent risk factor for mortality, even though it is a syndrome that occurs in response to multiple injury mechanisms. The underlying disease severity is reflected in AKI severity and duration.

Recently, the academic world has focused on AKD as the missing link between AKI and CKD. Data on this subject in children are scarce. The continuum of AKI to AKD is associated with increased morbidity and mortality.

The need for renal replacement therapy in our cohort was low—1.1%, and most of these patients were in the AKD group. To date, mortality in AKD children varies from 10% to 32%. Due to a prolongation of AKI, AKD is more likely to be associated with intrinsic renal damage, either as a result of multiple renal aggressors or due to a prolongation of prerenal AKI. Children who develop AKD require longer treatment for the underlying disease, so they are prone to longer exposure to nephrotoxic agents. This could lead to a possible progression towards tubular or interstitial damage. While T-AKI is a functional AKI with rapid recovery, the prolongation of AKI over time may evolve with renal remodelling (for instance, tubulointerstitial fibrosis and inflammation). This evolution explains our results that AKD is an independent risk factor for new-onset CKD. Our cohort revealed that AKI cause, not AKI severity, influenced the progression towards CKD. Only one other study in the pediatric field identified AKD as a risk factor for progression towards CKD, but the study included a specific group of patients who underwent nonrenal transplants. A study of adults revealed that 15 to almost 40$ of patients with AKD progress to CKD. In our cohort, only 4% of the patients progressed to CKD, with an incidence of 8% in patients with AKD. According to our analysis, the presence of AKD increased the risk of new-onset CKD by 5-fold, similar to the findings of the most recent meta-analysis on adults. In adults, the risk of incident CKD is high due to the high incidence of CKD risk factors such as cardiovascular disease, arterial hypertension or diabetes mellitus. In children, incident CKD is a result of nephron loss, which is in some cases directly linked to AKI duration. These results suggest that AKD is an independent risk factor for new-onset CKD even in pediatric patients. Our analysis also showed that multiple AKI episodes did not influence the risk of CKD development. Notably, we did not evaluate the impact of other possible risk factors for CKD, such as post-AKI proteinuria, nephroto.in exposure or chronic underlying disease.

With this study, we wanted to show that the AKI-AKD-CKD continuum of renal injury is associated with high morbidity and mortality. The limitations of our study include, in addition to its single-centre and retrospective nature, the lack of urine output for AKI diagnosis. In addition, we could not evaluate covariates such as the presence of chronic disease, post-AKI proteinuria or exposure to nephrotoxins in patients with new-onset CKD. The relatively large number of patients in the pediatric field and the new insights represent the strong points in AKI duration, AKD development and progression to CKD in pediatric patients of all ages. We are aware that future prospective studies are needed to validate our results.

This study is the first to evaluate the real impact of AKI duration on mortality and CKD development in a pediatric population. As we stated in the discussion, the data regarding AKI duration in children are scarce, and most of the studies evaluated only specific subgroups of children (cardio-pulmonary bypass, non-renal transplants). In this study, we showed that an AKI duration longer than 7 days not only increases mortality but also seems to be the single independent risk factor for new-onset CKD.

3. KINETIC-ESTIMATED GLOMERULAR FILTRATION RATE IN PREDICTING PAEDIATRIC ACUTE KIDNEY DISEASE

To our knowledge, our study is the first to use the kGFR to predict AKD in children. Thus far, the kGFR has been shown to be useful for predicting AKI with high specificity and sensitivity in patients at high risk of developing AKI. To be used as an AKI predictor, the kGFR was calculated before AKI occurrence. Due to the retrospective nature of this study, we had the possibility of calculating the kGFR in the first 24 hours of AKI development as well as in the 24 hours prior to AKD occurrence. In the kGFR formula, we used the patient's baseline serum creatinine. We adjusted the kGFR for children by estimating the total body water using Morgenstern et al.'s recalculation of Mellits and Cheek's formula. In this way, we were able to eliminate a potential source of bias because the creatinine distribution volume is close to the water distribution volume. Compared to adults, even small changes in the volume status of children can lead to changes in the serum creatinine level. To further use an even more appropriate kGFR formula for children, we replaced the correction factor of 1.5 mg/dl from Chen's formula with the estimation of the maximum increase in the serum creatinine level in 24 hours adjusted for each individual distribution volume.

We found that more than a quarter of AKI patients progress to AKD; thus, AKD prediction is important. AKD occurrence is a sum of underlying disease severity and medical intervention. KDIGO guidelines from 2012 and the 2017 ADQI Consensus Report mentioned AKD as a prolongation of AKI with an impact on mortality and morbidity. The cause of AKD can be either renal injury resolution or progression towards CKD. Given the high incidence of AKD in Aki patients, there is an urgent need for inexpensive and reliable tools for AKD prediction.

Patients who progressed to AKD presented higher levels of serum creatinine on days 1–7 of AKI and were younger. This was mirrored by lower kGFRs in AKD patients during the AKI episode than in non-AKD patients. We identified that half of our cohort presented a kGFR lower than 60 ml/min/1.73 sm, as reflected by AKI severity and duration. These data are consistent with previously published data. A reduced kGFR reflects the severity of AKD. Given that more than 70% of children with AKI who had a kGFR1 below 60 ml/min/1.73 sm progressed to AKD, the utility of the kGFR calculation on the first day of identified AKI should be emphasized. The progression of AKI is influenced by medical intervention (need for mechanical ventilation, fluid overload, nephrotoxic medication or fluid resuscitation). These interventions lead, in most cases, to full renal recovery. Nevertheless, more than 1 in for children from our cohort presented a prolongation of AKI to more than 7 days with a contribution to kidney injury. The kGFR calculated on day 2 after AKI was shown to independently influence progression towards AKD. As expected, the kGFR calculated on day 7 after AKI better predicted AKD occurrence. KGFR2 was identified as an independent predictor of AKD. For instance, a child with a kGFR1 less than 15 ml/min/1.73 sm has a 28-fold greater risk of progression to AKD. In the face of this high risk, kGFR2 could be used to predict AKD and MAKE30. In the face of prolonged renal injury, kGFR2 is a better predictor of MAKE30 and AKD. The transition from AKI to AKD is reflected in the high number of patients in the AKD group who presented a kGFR1 less than 60 ml/min/1.73 sm. For kGFR2, the risk of AKD and MAKE30 starts at stage 3, while for kGFR1, it starts only in stage 5. In the face of these results, we mitigate the need for repeated kinetic glomerular filtration rate

measurements. Careful monitoring should be performed for patients with a kGFR less than 15 ml/min/1.73 sm after one day of AKI and less than 60 ml/min/1.73 sm on the 7th day of AKI.

The kGFR has been shown to be useful for predicting AKI. For example, Dewitte et al. showed that kGFR was superior to neutrophil gelatinase-associated lipocalin (NGAL), a product between urine insulin-like growth factor-binding protein 7 and tissue inhibitor of metalloproteinase-2, in predicting AKI. In addition, Hekmat et al. showed that the kGFR better predicted AKI than other creatinine-based formulas. [264] Additionally, he found a strong correlation between NGAL and the kGFR. [264] In clinical practice, it is difficult to use expensive biomarkers, and in the face of limitations, the kGFR has become a cheap and reliable tool.

The available published articles failed to identify a relationship between the kGFR and 30-day mortality. Dewitte presented good precision models for MAKEs30 based on the kGFR in intensive care units. Our results also suggest a connection between kGFR and MAKE30. KGFR2 was more effective than kGFR1 in predicting MAKE30, thus reiterating the need for repeated kGFR measurements. The evolution of AKI is multidirectional towards full renal recovery, prolongation for up to 90 days, progression to CKD or, in the worst-case scenario, death. In patients who do not recover renal function during hospitalization, the kGFR2 (calculated on day 7 after AKI) value can be a predictor of AKD occurrence, mortality, renal replacement therapy necessity or even AKD at 30 days.

The KRFGR1 model had a fair ability to predict MAKE30 (AUC=0.7), while the KGFR2 model had a good ability to predict MAKE30 (AUC=0.82). The AUC of Dewitte's model for MAKE30 prediction was similar to that of our model (0.81).

In the face of a rising serum creatinine level that meets the criteria for AKI, the kinetic glomerular filtration rate can predict AKI outcomes (AKD and MAKE30). The clinical usefulness of the kGFR is important, regardless of whether it is calculated over the course of an AKI event or even in patients without AKI but at high risk (for instance, in intensive care unit (ICU) settings).

The limitations of our study include its retrospective design, single-centre nature and lack of urine output criteria for AKI diagnosis and classification. The high number of AKI patients, both those who were not critically ill and those who were critically ill, including those in neonatal settings, represents strong points. Our study is the first to use the kinetic glomerular filtration rate formula for baseline serum creatinine in children. We were able to perform this analysis due to the possibility of identifying the baseline serum creatinine level in the electronic data system. Another strong point is the estimation of the maximum creatinine production in 24 hours of no renal function with Morgenstern's formula adjustment in Mellits and Cheek's formula. The most important point was the use of the kGFR in predicting AKD and MAKE30.

The kGFR has already been shown to be useful for predicting AKI development. We believe that it can be used as a complementary tool in AKI patients for a better estimate of the outcome. We believe that prospective studies in children can confirm our results. We adjusted for the use of the kGFR in pediatric intensive care units (ICUs) to stratify the risk of AKI in patients with or without AKI.

Even in the pediatric population, there is a high incidence of AKD. This increases the need for inexpensive and reliable methods for AKD prediction. With our study, we showed that the use of a relatively simple formula, in the context of AKI, could offer some tools to physicians. kGFR calculation requires two consecutive creatinine measurements within 24

hours and the estimation of total body water with already known methods. The value of the kGFR in AKI patients was shown to be a good predictor of AKI outcomes. Values below 15 ml/min/1.3 sm increase AKD development and MAKE30 at any moment during the calculation. Multiple evaluations of the kGFR on different days after AKI onset predict even better AKI outcomes.

With this simple tool implemented in day-to-day practice, not only in intensive care units, we believe that physicians could better evaluate AKI patients and improve management in certain cases.

4. PROGNOSTIC VALUE OF SERUM CREATININE DYNAMICS IN NEONATES

In the face of the development of a standardized neonatal AKI definition, advances have been made in evaluating AKI in new-borns. There are still limitations in using SC changes in the first week of life due to unstable renal function and the use of urine output criteria for AKI. The transfer of SC from the mother and gestational age influence the rate of SC decline, and a reduced decline in the first 7 days after birth is associated with worse outcomes (a need for diuretics and inotropes, prolonged mechanical ventilation, and longer hospitalization). Even though there are high-quality evidence of AKI outcomes in neonates, there is no consensus regarding the real kidney function estimated by SC. Nevertheless, SC remains the least expensive and easiest method for evaluating kidney function. Some studies suggest that newborns who fail to reach a specified SC by day 7 present longer hospital stays, higher mortality and greater risk of AKI development after the first week of life. Less is known about the impact of SC dynamics on neonatal AKI development.

Therefore, we retrospectively evaluated all neonates who underwent SC measurement in the first 24 hours. We further evaluated only patients with a known SC trend in the first 7 days of life who were born after 32 weeks of gestation. The cohort consisted of 939 patients. The majority of the patients presented a decrease in the natural SC in the first 7 days of life (79.2%). [Most of the patients in our cohort required NICU admission, which may influence SC dynamics in the first week of life. The overall AKI incidence was similar to that in previously published data (26.2%), but the distribution differed significantly depending on the SC trend. This trend also influenced the timeframe of AKI occurrence. The day 1 SC was similar between the two groups (AT and DT), but all the other SC measurements (from day 2 until day 28) were greater in the AT group. These differences reflected AKI occurrence; the AT group presented an AKI incidence of 66.2%, and 81.4% of AKI patients were in the first week of life. We identified the following risk factors for SC AT: renal or cardiac malformations, lower serum protein levels and higher urea levels. These children have poorer outcomes based on biological and clinical assessments that mirror the underlying disease severity. Kidney impairment, even translated into a small increase in creatinine, is a consequence of multiple risk factors that independently influence patient outcomes.

An AT translates to a greater risk of developing AKI in the first week of life. However, in the adjusted models, SC AT decreased the risk of AKI development after the first 7 days. New-borns with renal or cardiac malformations presented a greater risk of AT SC. Cardiac

malformations are a risk factor for overall AKI development, but renal malformations increase AKI occurrence only after the first week of life.

A total of 82% of new-borns required NICU admission, with a greater risk of overall AKI and AKI after the first week. In addition to experiencing peri and intrapartum events, patients admitted to the NICU are exposed to high-risk medical interventions, such as nosocomial infections, the use of inotropes or/and nephrotoxic medications, and mechanical ventilation. Longer hospitalization was associated with more severe underlying disease in NICU patients, regardless of the trend in the creatinine level.

Neonatal mortality has decreased in recent decades. AKI is recognized as an independent risk factor for mortality worldwide. A crude analysis revealed that AKI increased mortality by 1150%. Even after adjustment for several confounding factors, AKI remained an independent risk factor for mortality. The crude analysis showed that an AT SC increased mortality by 400%, and after adjustments, it increased mortality by 92%. In addition to traditional risk factors such as AKI, nephrotoxic exposure, mechanical ventilation, cardiac malformations, kidney impairment, and unnecessary injury, reflected by a small increase in SC volume, are associated with worse outcomes. AKI and kidney impairment influence survival, and both sides are the same. The physiology of the neonatal kidney is still poorly understood, especially in new-borns who did not reach the theoretical landmark of renal development – weeks 34 to 36 of gestation. The ascending SC trend in an immature kidney could be a red flag for clinicians at the bedside to evaluate kidney function repeatedly and to identify aggressors early. We propose the use of the SC trend in clinical practice, especially in NICU settings, as a complementary tool to the current neonatal AKI definition.

The highlight of our study is the analysis of the subgroup of patients without AKI. The AT of SC increased mortality independently. This confirms that kidney impairment can evolve towards AKI or can switch towards a decline in SC that can progress to AKI or continue the decline towards nadir. Our results encourage repeated SC measurements in neonates who do not have a normal SC after birth. To validate our results, there is an imperative need for prospective multicentre studies on the impact of SC dynamics in the first week of life.

Prematurity is a recognized risk factor for CKD development in adulthood. Nevertheless, there is a lack of evidence regarding neonatal AKI as a risk factor for CKD. The progression to CKD is linked to a reduced nephron number, especially in the absence of underlying renal disease (genetic disorders, urinary tract malformations, congenital kidney, etc.). In our cohort, less than 40% of the patients had a follow-up after 3 months. The CKD incidence was low (3.7%). Crude analysis revealed that SC AT increased the risk of CKD by 800%. On the other hand, in the adjusted model, only AKI increased the risk of CKD by 10.2 times. Our results should be interpreted carefully due to the reduced number of events (14 out of 376). The progression to CKD is linked to many factors in addition to AKI. There are several common factors for CKD and AKI development, such as cardiac malformations, renal malformations and prematurity. Attention should be given to patients at risk with closer follow-up for early intervention.

SC is a marker of delayed kidney function (48-72 hours). It reflects function and not injury and is dependent on muscle mass. In neonates, reaching the SC nadir requires a longer time. In the face of all these statements, careful interpretation of SC dynamics is necessary. Our results show that if the creatinine level increases in the first week of life, the time to reach the nadir increases.

There are several limitations of our study, including its retrospective, single-centre nature, lack of urine output for AKI diagnosis and reduced follow-up of SC later in life. The strengths are the high number of patients, the evaluation of SC values in the first week of life followed at days 14 and 28 and the evaluation of CKD development. To our knowledge, this is the first study to evaluate the impact of SC trends in the first 7 days of life on AKI development, mortality and CKD.

The correct evaluation of kidney function is difficult in neonates due to the non-steady state of serum creatinine. The natural decline in creatinine after birth is disrupted by several factors. In this study, we showed that even a small increase in SC, less than 0.3 mg/dl, without fulfilling the AKI definition, increased mortality. A rise in creatinine during the first 7 days of life is associated with worse outcomes. This increase seems to be associated with CKD development, but only due to the progression towards AKI in the first phase. Cardiac malformations, NICU admission, and worse biological parameters at birth increase the risk of a rise in SC as well as increased mortality.

FINAL CONCLUSIONS

AKI incidence in paediatric settings varies in different regions of the world due to several factors. Our first study highlighted the real incidence of AKI in Romania. Our results suggest that the incidence is approximately 1.65% in mixed paediatric patients. In neonates, the real AKI incidence could be greater.

AKI remains an important risk factor for mortality. AKI awareness leads to increased mortality, most likely due to AKI severity. On the other hand, in the presence of several susceptibilities and certain exposures, AKI awareness increases for the same reasons. AKI remains an important global issue, and to improve AKI treatment, physicians must be aware of this issue. With the first study, we aimed to mitigate existing guidelines for real-life medicine.

The second study from this thesis is the first to evaluate the real impact of AKI duration on mortality and CKD development in a pediatric population. The data regarding AKI duration in children are scarce, and most of the studies evaluated only specific subgroups of children (cardio-pulmonary bypass, non-renal transplants). In this study, we showed that an AKI duration longer than 7 days not only increases mortality but also seems to be the single independent risk factor for new-onset CKD. In all the AKI duration groups, mortality was directly linked to the underlying disease severity. Mortality was greater in patients with lower serum protein levels, lower thrombocyte counts, lower haemoglobin levels or higher procalcitonin levels. Each of these factors was an independent predictor of mortality. With respect to renal injury, microvasculature alterations and acute tubular necrosis increase mortality. As the duration of AKI increases, the chance of renal structure remodelling increases. Renal injury can evolve either with full renal recovery or with renal fibrosis and loss of nephrons. The loss of nephrons could translate to CKD. In the end, we wanted to highlight the importance of AKI in the development of renal health in children. The clinician's duty is to identify AKI early, treat its causes and avoid additional renal external aggression. Although we did not evaluate the impact of nephrotoxic medication on CKD incidence, the use of possible nephrotoxic agents should be limited, especially in patients with AKI.

Even in the pediatric population, there is a high incidence of AKD. This increases the need for inexpensive and reliable methods for AKD prediction. With our third study, we showed that the use of a relatively simple formula, in the context of AKI, could offer some tools to physicians. KGFR calculation requires two consecutive creatinine measurements within 24 hours and the estimation of total body water with already known methods. The value of the kGFR in AKI patients was shown to be a good predictor of AKI outcomes. Values below 15 ml/min/1.73sm increase AKD development and MAKE30 at any moment during the calculation. Multiple evaluations of the kGFR on different days after AKI onset predict even better AKI outcomes. With this simple tool implemented in day-to-day practice, not only in intensive care units, we believe that physicians could better evaluate AKI patients and improve management in certain cases. The correct evaluation of kidney function is difficult in neonates due to the non-steady state of serum creatinine. The natural decline in creatinine after birth is disrupted by several factors. In the fourth study, we showed that even a small increase in SC, less than 0.3 mg/dl, without fulfilling the AKI definition, increased mortality. A rise in creatinine during the first 7 days of life is associated with worse outcomes.

This increase seems to be associated with CKD development, but only due to the progression towards AKI in the first phase. Cardiac malformations, NICU admission, and worse biological parameters at birth increase the risk of a rise in SC as well as increased mortality.

The global burden of AKI remains high in both adult and pediatric settings. Current guidelines adopted under the same umbrella both children and adults, however it seems that regardless of the AKI criteria fulfilment, any increase in serum creatinine portends worse outcomes. With this thesis, we found AKI to be prevalent in children and neonates, whom are at high risk of progressing towards AKD during hospitalization, with increased hospital stay and mortality. The rate of progression to new-onset CKD is high after an AKD episode. These results emphasize the need for physicians to be aware of patients at risk for developing AKI in order to reduce AKI incidence, severity and duration.