# THE FREQUENCY OF SEVERITY OF ACUTE KIDNEY INJURY IN ASPHYXIA NEOTORUM

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KEYWORDS

AKI, Chi Square, Birth Weight, Gender, Severity, Consecutive Sampling

ABSTRACT

This research designs to check the actuate kidney disease in newborn babies. For conducting this research new born babies of Children Hospital Lahore are considered as target population. A sample of 201 children is selected with the help of consecutive sampling. Analysis consists of the frequency and pie graph are used for demographic analysis. Chi square test is used for checking the relationship of birth weight and severity of AKI (Acute Kidney Injury) by controlling the gender. Results shows that 31.8% baby patients are not suffering from AKI, 33.8% baby patients are suffering from the Stage-I(Mild), AKI, 16.9% baby patients are suffering from the Stage-II(Moderate) AKI and 17.4% baby patients are suffering from the Stage-III(Severe) AKI. Overall, 68.2 % patients are suffering from AKI. All the p values are significant. Thus, our hypothesis about the relationship of gender and the severity of the AKI, about the severity of AKI are accepted respectively.

## INTRODUCTION

As per existing research studies, AKI-Acute Kidney Injury (previously renowned as acute renal failure) has been witnessed and founded in 8% to 24% of preterm neonates who has been admitted to neonatal intensive care units. Latterly, Bellomo, Kellum and Ronco (2004) said that in the current era only the RIFLE System is being used to diagnose AKI and due to that there is an increasing trends of AKI intensity such as risk, injury, failure, and loss and in the close, end stage kidney disease. Further, this system was modernized with certain inputs from Acute kidney injury network (Gavriatopoulou, Terpos, Kastritis & Dimopoulos 2016; Mehta, Kellum & Shah, 2007). On the beginning stage sign of AKI possibility consist of 50'% rise in creatinine of serum ("or ≥ 0.3 mg/dl" under the period of 48 hours), and/or a urine output is less than 0.5mg/kg/hr within six hours (Bellomo et al., 2012; Mehta et al., 2007; Nation, Li, Cars, Couet, Dudley, Kaye & Tsuji 2015), which indicates that there is identifiable reduced GFR.

To define categorically AKI within particular neonatal populated environment although it wasn't created. The reasons for the "AKI in the preterm neonates are specifically pre-renal in source or origin, happen due to the renal perfusion like hypotension, hypoxia and sepsis (Cataldi, Leone, Moretti, Zanardo, Attardo, Benini & Cuzzolin, 2005)". Such conditions also become reason for such inflammatory procedures, secondly apoptotic, and in the last necrotic presence in the kidney's ("Morizane, Lam, Freedman, Kishi, Valerius, & Bonventre 2015"). Particularly, acute kidney injury is a major reason for the long-lasting chronic renal diseases particularly in the preterm neonates (Petäjä, Vaara, Liuhanen, Ylinen, Mildh, Nisula & Pettilä, 2017). There is a study, which was conducted by Cataldi et al. (2005) within the 172 preterm neonates and it was founded that the AKI happen due to administration of drugs related to neonatal and maternal ("non-steroidal anti-inflammatory drugs) and antibiotics, particularly ceftazidime"), such the decreased Apgar score, and such type patent ductusarteriosus.

But surprisingly age gestational don't have any impact over AKI, although heavy quantity of identified AKI patients 79% weighted<"1.5 kg at birth" ("Cataldi et al., 2005"). Also, Cuzzolin, Cataldi, Leone, Moretti, Martano and Benini (2005) conducted the study over 281 preterm neonates and as a result there were founded multiple risk factors for AKI. These factors were consisting on the administration of maternal like NSAID, Decreased "Apgar Score, respiratory distress syndrome, neonatal drug administration (antibiotics and NSAID'S) and multiple clinical interventions (intubation at birth, catheterization, and phototherapy and mechanical ventilation"). There was much more importance given to the early identification and cure of AKI but in recent times such concentration to unhide biomarkers of such novel urinary and its occurrence of latest biomarker provides an assistance to identify rapid decline in renal functioning ahead to cellular like injury (Bellomo et al., 2012) and identified that as much as time taken to diagnose and curing of AKI always become major reason for more renal injury. This study is being conducted at Children Hospital Lahore to check AKI in neonates.

The current study is designed to check AKI in the neonates of Children Hospital Lahore. In this regard, following are the objectives of this research study.

1. The objective of current study is to check the frequency of acute kidney injury in asphyxia neonatorum.
2. To check the relationship of birth weight and severity of AKI (Acute Kidney Injury) by controlling the gender.

## LITERATURE REVIEW

### Acute Kidney Injury

It will be measured in terms of lab investigation. It is further categorized as Stage-I (Mild), Stage-II (Moderate) and Stage-III (Severe). According to (KDIGO, 2012)[84], the following are the criteria of these three stages.

| "Stage | Serum creatinine | Urine output |
|---|---|---|
| 1 (Mild) | "1.5–1.9 times baseline OR X0.3 mg/dl (X26.5 mmol/l) increase" | <0.5 ml/kg/h for 6–12 hours |
| 2 (Moderate) | "2.0–2.9 times baseline" | "<0.5 ml/kg/h- X12 hours" |
| 3 (Severe) | "3.0 times baseline OR Increase in serum creatinine to X4.0 mg/dl (X353.6 mmol/l) OR Initiation of renal replacement therapy OR, In patients o18 years, decrease in eGFR to o35 ml/min per 1.73 m2" | "<0.3 ml/kg/h for X24 hours OR Anuria for X12 hours" |

### Asphyxia Neonatorum

It is measured in terms of Apgar score, if Apgar score is ≤ 3 at five minutes according to APGAR scale (Annexure II) asphyxia is labeled as present.

### Acute Kidney Injury in Newborns

AKI (Acute kidney injury) is familiar disease in the neonates which result very dangerous outcomes. In neonates' rate of AKI is high as compare to children and adults (Timovska, Cekovska & Trajkovska, 2015). It depends on various factors such as birth weight, age and services provides for neonates at the place of their birth. AKI is severe disease that injures kidneys. ARF (Acute renal failure) has been altered AKI. AKI illustrates by the unexpected decline of smooth kidney working. This defect results in irregularity of bodily electrolytes and liquids. It happens in fast reduction of GER (glomerular filtration rate) which result in withholding of nitrogenous desecrates goods and creatinine normally the reduction of urine productivity. Particularly in asphyxiated neonates, AKI may describe by regular urine output (UO). It is noted that around forty percent newborn babied carry

no oliguric AKI. It is also noted that infant babies carry large amount of water materials as compare to young people. Approximately neonates contain eighty percent more water bodies than adults. This result in body water materials as compare to people belong to other age clusters. For existence of AKI, urine outlet must more than "1.0 mL/Kg per hour".

In kids, occurrence of AKI is considerably less number as compare to newborn babies. In children it ranges from 8-24% with death rate range from10-61%. There is more change about existence of AKI in short weight infants (<1,500 grams), "low 5-minute APGAR score, birth intubation, lung distress syndrome and neonatal medication administration (nonsteroidal anti-inflammatory drugs, antibiotics)". The reasons about existence of AKI in infant babies are numerous. Normally these can further split into renal, pre-renal and post renal. Prerenal azotaemia considers as more ordinary kind of AKI in infant babies. It is happening in more than 80% cases, it occurs due to improper renal perfusion, which may be quickly cured which can result in better progress in urine production and renal utility. Renal damage of kidneys may prevail because of "parenchymal kidney damage". "Post-renal kidney damage" is result of UT obstacle by means of improper urine removal. Current study is based on measuring AKI with the help of measuring urea cretenine and adopts three levels of AKIs and their ranges are mentioned in the official definition of the AKI.

## Classification of Acute Kidney Injury

AKI which based on rapid dis-functioning of kidney, categorized by the quick decrease in the "glomerular filtration rate (GFR)", the whole process may happen within the hours. A non-functioning of the kidney is the reason for production of metabolic waste products such as urea, creatinine, destructed running liquid, other products which based on the acid homeostasis (Besen, Gobatto, Melro, Maciel & Park 2015; Lameire, Biesen, Hoste & Vanholder, 2009). AKI, it is not any distinctive health issue although it is a syndrome like the heterogeneous linked to the vast assemblage of pathophysiologic procedure of certain factors high intensity and etiology. From another point of view, AKI is frequently considered as the three broad pathophysiologic categories such as pre-renal, the intrinsic and the post renal. The first, Pre-renal type of AKI happen when hypo-perfusion of the kidney's reasons for the decrease in glomerular filtration rate without having any impact on the overt the parenchymal disaster.

Such etiologies related to pre-renal AKI consist on both conditions to reduce the volume and condition of reduced impactful arterial blood volume (EABV). Intrinsic AKI become the reason for different diseases including "the renal parenchyma, acute and quick progressive glomerulonephritis, acute interstitial nephritis, acute tubular injury and acute vascular syndromes and also atheroembolic disease" (Legrand, Mebazaa, Ronco & Januzzi 2014). "The most renowned etiology of intrinsic AKI is acute tubular necrosis as output from ischemia reperfusion injury, nephrotoxins/sepsis". "Post-renal (obstructive) AKI is the impact from the acute blockage of the urinary tract such as the partial or complete block to urinary flow". However, the high intensive post renal AKI happen with blockage in the bladder or both side ureteral blocking or even one side ureteral blockage with the loss or non-functionality of contralateral kidney, low and decreasing functioning in the kidney and it can be watched with the unilateral ureteral blockages, moreover with availability of normal contralateral kidney.

However the classification of such tripartite as a concept is really useful and the concept is may be overlapped. For example, prerenal AKI is linked such clinical parenchymal like injury and real time consistent pre-renal & post renal conditions may impact as the parenchymal affectation. This concept of AKI has replaced the older concept of "acute renal failure (ARF)" (Post, Kellum, Bellomo & Vincent 2017). Thus certain emergence of

the terminologies shows the real consideration and link among the proper functional kidney and its functionality and over the organ non-functioning is not dichotomous but also the other way like smaller to medium acute reduction in the kidney functionalities are linked with severe results. However the latest concept really unhide the bigger view of AKI related disease and real time effect but these terms still are not perfect and do not give a complete impact.

The terminology "Injury" reflects the presence of parenchymal organ loss, however the parenchymal like issue is not categorized as a acute non-functionality of kidney is linked with prerenal and post renal AKI (Hoste, Kellum, Selby, Zarbock, Palevsky, Bagshaw & Chawla 2018). Sometimes this terminology AKI is being used as parallel as the ATN, however these terminologies are not with the same meaning. ATN is being considered the one of the renowned condition of intrinsic AKI significantly in high level of illness patients; this reflects only one factor of the different etiologies of the AKI (Petäjä et al., 2017). Moreover, "still in patients with a standard presence of AKI in the setting of sepsis and ischemia reperfusion injury, there may be non-presence of concordance among the clinical syndrome and also the histopathologic outcomes defined by the terminology of ATN" (Nielsen, Skjøth, Søgaard, Kjældgaard, Lip & Larsen 2017; Chakraborty, Kaur, Guha & Batra, 2012).

### Proposed Hypothesis

$H_1$: To check/examine the frequency of the acute kidney injury (AKI) in the asphyxia neonatorum.
$H_2$: There is significant relationship of birth weight and severity of AKI by controlling gender.

## MATERIAL AND METHOD

### Research Design

This is cross-sectional study. Study conducted in department of pediatrics, Children hospital, Lahore. 6 months after approval of synopsis. A sample size of 200 is calculated at 5% confidence level of interval and 7% margin of error and taking expected of AKI is approximately 64%. Non probability sampling technique (Consecutive Sampling) is used for collection of data.

### Inclusion Criteria

- ✓ Term Neonates 72 hours of life (> 37 weeks as per antenatal scan)
- ✓ Neonates with asphyxia (as per defined in operational definition).
- ✓ Both gender

### Exclusion Criteria

- ✓ "Renal insufficiency which is detected by antenatal ultrasound".
- ✓ "Oligohydrominas which is detected by antenatal ultrasound".
- ✓ "Babies with history of maternal addiction of analgesia and sever infection".

### Techniques of Data Collection

After approval from ethical committee of Children hospital Lahore, informed agreement will be received by the guardians of patients earlier to include data of patient by ensuring the confidentiality of that particular respondent. For receiving the regular information addresses/telephone no/mobile no/e-mail Ids of guardians of patient will be gathered. Samples of blood will be used for checking AKI and its severity (operational definition). Benefits and risks of treatment will be described to the parents/patients /guardians. Weight of newborn will be checked at birth time by researcher. An established Performa will be used for recording and gathering the data from every patient.

## Data Analysis

Gathered data will be arranged and examined with the help of software of statistic name as SPSS version 22. Standard deviation and mean will be calculated for quantitative variables such as the birth weights APGAR scores. The percentage and frequency were calculated for qualitative variable such as AKI injury and severity on the basis of gender. Effect modifier such as Apgar score, birth weight and scores of gender is controlled with the help of data stratification. Chi square is used for final analysis. All the p values which are less than equal to 5 will be reflected as significant values.

## RESULTS AND DISCUSSION

### Demographic Analysis

*Gender*: The results show that frequency of Male Baby patient is 106 out of 201 and its percentage is 52.7. The female baby patient are 95 out of 201 and its percentage is 47.3%.
*Level of Education:* The results show that frequency of uneducated mother is 745 out of 201 and its percentage is 22.4 and mother who has primary education is 97 out of the 201 and its percentage is 48.3 as well as the mothers who have secondary and above education is 59 out of 201 and its percentage is 29.4.
*Employment level:* the results show level of employee and house wife and the frequency of employee are 61 out of 201 and its percentage is 30.3 and frequency of house wife is 140 out of 201 and its percentage is 69.7.
*Birth Weight:* The results show that the birth weight of baby patient and the frequency of <2.5 is 104 out of 201 and its percentage is 51.7. The frequency of > and =2.5 is 97 out of 201 and its percentage is 48.3.
*Mode of Delivery:* The results show the result about mode of delivery and the frequency of SVD is 55 out of 201 and its percentage is 27.4. Frequency of C-Section is 146 out of 201 and its percentage is 72.6.

### Disease Analysis

*APGAR Score Activity:* The results show that the frequency of 0.00= absent is 106 out of 201 and its percentage is 52.7 and also the frequency of 1.00= present is 95 out of 201 and its percentage is 47.3.
*APGAR Score Pulse:* The results shows that the frequency of 0.00=absent is 163 out of 201 and its percentage is 81.1 and also the frequency of 1.00=present is 38 out of 201 and its percentage is 18.9.
*APGAR Score Grimace:* The results further shows that the frequency of 0.00=absent is 100 out of 201 and its percentage is 49.8 and the frequency of 1.00=present is 101 out of 201 and its percentage is 50.2.
*APGAR Score Pulse:* The results shows that the frequency of 0.00=absent is 100 out of 201 and its percentage is 49.8 and frequency of 1.00 is 101 out of 201 and its percentage are 50.2.
*ASR:* The results show that the frequency of 0.00=not present is 132 out of 201 and its percentage is 65.7 and the frequency of 1.00=present is 69 out of 201 and its percentage is 34.3.
*AKI:* The frequencies about AKI shows that frequency of absent AKI is 64 out of 201 and its percentage is 31.8% and the frequency of present is 137 out of 201 and its percentage is 68.2 %.

Table 1 One-Sample Test

| | Test Value = 0 | | | | | |
|---|---|---|---|---|---|---|
| | T | Df | Sig. (2-tailed) | Mean Difference | 99% Confidence Interval | |
| | | | | | Lower | Upper |
| AKI | 20.691 | 200 | .000 | .68159 | .5959 | .7673 |

Table 2 One-Sample Test Severity of AKI

| | | Frequency | Percent | Valid | Cumulative |
|---|---|---|---|---|---|
| Valid | Absent | 64 | 31.8 | 31.8 | 31.8 |
| | Stage I (Mild) | 68 | 33.8 | 33.8 | 65.7 |
| | Stage II (Moderate) | 34 | 16.9 | 16.9 | 82.6 |
| | Stage III (Severe) | 35 | 17.4 | 17.4 | 100.0 |
| | Total | 201 | 100.0 | 100.0 | |

The above table shows the severity of AKI and the frequency of absent is 64 out of 201 and its percentage is 31.8. The frequency of the Stage-I (Mild) is 68 out of 201 and its percentage is 33.8 and frequency of Stage–II (Moderate)is 34 out of the 201 and its percentage is 16.9. The frequency of Stage –III(Severe)is 35 out of 201 and its percentage is 17.4. Overall, AKI patients are 137 and their overall percentage is 68 %. This means that 68% children with kidney disease are suffering from AKI. This result is very close to the result Gopal G (2014) who found that 64% of neonates were suffering from AKI. This slight different from the result of Durkan and Alexander (2011) their study indicates that 56% of neonates were suffering from AKI. This result is change due to the cultural and difference of facilities. As such research was conducted in Australia but the current study is conducted in Pakistan.

## Result of Chi Square

Table 3 Case Processing Summary

| | Cases | | | | | |
|---|---|---|---|---|---|---|
| | Valid | | Missing | | Total | |
| | N | Percent | N | Percent | N | Percent |
| Birth Weight | 201 | 100.0% | 0 | 0.0% | 201 | 100.0% |

* Severity of AKI

Table 4 Birth weight (Severity of AKI Cross Tabulation)

| | | | Severity of AKI | | | | Total |
|---|---|---|---|---|---|---|---|
| | | | Absent | Stage-I | Stage-II | Stage-III | |
| Birth weight | <2.5 | Count | 35 | 52 | 5 | 12 | 104 |
| | | % within Birth weight | 33.7% | 50.0% | 4.8% | 11.5% | 100% |
| | | % within AKI Severity | 54.7% | 76.5% | 14.7% | 34.3% | 51.7% |
| | > & =2.5 | Count | 29 | 16 | 29 | 23 | 97 |
| | | % within Birth weight | 29.9% | 16.5% | 29.9% | 23.7% | 100% |
| | | % within AKI Severity | 45.3% | 23.5% | 85.3% | 65.7% | 48.3% |
| Total | | Count | 64 | 68 | 34 | 35 | 201 |
| | | % within Birth weight | 31.8% | 33.8% | 16.9% | 17.4% | 100% |
| | | % within AKI Severity | 100% | 100% | 100% | 100% | 100% |

Table 5 Chi-Square Tests

| | Value | Df | Asymp. Sig. (2-sided) |
|---|---|---|---|
| Pearson Chi-Square | 39.824[a] | 3 | 0.0000 |
| Likelihood Ratio | 42.642 | 3 | 0.0000 |
| Linear-by-Linear Association | 12.346 | 1 | 0.0000 |
| N of Valid Cases | 201 | | |

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 16.41.

Chi square test is using for checking relationship of two categorical variables. This result checks the Effect modifier such as Apgar score with birth weight and scores of gender is controlled with the help of data stratification is shown in the above tables. Overall results

indicates that 31.8% baby patients are not suffering from AKI, 33.8% baby patients are suffering the from Stage-I (Mild), 16.9% baby patients are suffering the from Stage-II (Moderate) AKI and 17.4% baby patients are suffering the from Stage -III(Severe) AKI. Results indicates that 33.7% baby patients are not suffering from AKI, 50% baby patients are suffering from Stage-I (Mild) AKI, 4.8% baby patients are suffering the from Stage-II (Moderate) AKI and 11.5% baby patients are suffering the from Stage-III (Severe) AKI in the baby patients whose weight is less2.5 kg. Whereas, results indicates that 29.9% baby patients are not suffering from AKI, 16.5% baby patients are suffering the from Stage-I (Mild) AKI, 29.9% baby patients are suffering the from Stage -II(Moderate) AKI and 23.7% baby patients are suffering the from Stage -III(Severe) AKI in baby patients whose weight is greater or equal to 2.5 kg. All p values are 0.0000 which are less than 5. Thus, our hypothesis about the relationship of gender and severity of AKI is also accepted. In this result, we treat birth weight as control variable.

## CONCLUSIONS

This research designs to check the actuate kidney disease in newborn babies. A sample of 201 children is selected with the help of consecutive sampling from Children Hospital Lahore. Results indicate that there is significant relationship of birth weight and severity of AKI (Acute Kidney Injury) by controlling the gender. Additionally, there is significant relationship of gender and severity of AKI (Acute Kidney Injury) by controlling the birth weight. The frequency of severity of AKI is also significant. The results shows that 31.8% baby patients are not suffering from AKI, 33.8% baby patients are suffering the from Stage-I (Mild)AKI, 16.9% baby patients are suffering the from Stage-II (Moderate) AKI and 17.4% baby patients are suffering from Stage -III(Severe)AKI. All the p values are significant. Thus, our hypothesis about relationship of gender and severity of AKI, about the severity of AKI are accepted respectively.

The present study, from the results, proposed some recommended towards campaign the awareness programs about AKI and preventing programs of AKI for reduction of AKI. It is also recommended that hospitals will use the latest machineries and technology for treatment of AKI. It is also discouraged about cousin marriage which will result in less number of AKI. This is cross sectional research as data is collected from the respondents on single time point. In future, longitudinal researches will be conducted for generalizing the results. For generalizing the results, these kinds of the researches will also conduct in other hospitals where children departments are present. These kind of researches will also conducted in the other cities of Pakistan likewise Karachi, Faisalabad and Islamabad for generalizing the results of current study.

## REFERENCES

Bellomo, R., Kellum, J. A., & Ronco, C. (2012). Acute kidney injury. *The Lancet*, *380*(9843), 756-766.

Besen, B. A., Gobatto, A. N., Melro, L. G., Maciel, A., & Park, M. (2015). Fluid and electrolyte overload in critically ill patients: an overview. *World journal of critical care medicine*, *4*(2), 116.

Cataldi, L., Leone, R., Moretti, U., Zanardo, V., Attardo, G., Benini, D., & Cuzzolin, L. (2005). Potential risk factors for the development of acute renal failure in preterm newborn infants: a case-control study. *Arch Dis Child Fetal Neonatal Ed*, Vol. 90, pp. F514-519, 1359-2998.

Chakraborty, S., Kaur, S., Guha, S., & Batra, S. K. (2012). The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*, *1826*(1), 129-169.

Cuzzolin, L., Cataldi, L., Leone, R., Moretti, U., Martano, C., & Benini, D. (2005). Potential risk factors for the development of acute renal failure in preterm newborn infants: a case-control study. *Arch Dis Child Fetal Neonatal Ed*, Vol. 90, pp. F514-519, 1359-2998.

Durkan, A. M., & Alexander, R. T. (2011). Acute kidney injury post neonatal asphyxia. Journal of Pediatr. 158, 29–33.

Gavriatopoulou, M., Terpos, E., Kastritis, E., & Dimopoulos, M. A. (2016). Current treatments for renal failure due to multiple myeloma. *Expert opinion on pharmacotherapy*, 17(16), 2165-2177.

Hoste, E. A., Kellum, J. A., Selby, N. M., Zarbock, A., Palevsky, P. M., Bagshaw, S. M., & Chawla, L. S. (2018). Global epidemiology and outcomes of acute kidney injury. *Nature Reviews Nephrology*, *14*(10), 607-625.

Lameire, N., Biesen, W., Hoste, E., & Vanholder, R. (2009). The prevention of acute kidney injury an in-depth narrative review: Part 2: Drugs in the prevention of acute kidney injury. *NDT plus*, *2*(1), 1-10.

Legrand, M., Mebazaa, A., Ronco, C., & Januzzi, J. L. (2014). When cardiac failure, kidney dysfunction, and kidney injury intersect in acute conditions: the case of cardiorenal syndrome. *Critical care medicine*, *42*(9), 2109-2117.

Mehta, R. L., Kellum, J. A., & Shah, S. V. (2007). Acute Kidney Injury Network (AKIN): report of an initiative to improve outcomes in acute kidney injury. *Critical Care*. 11: R31.

Morizane, R., Lam, A. Q., Freedman, B. S., Kishi, S., Valerius, M. T., & Bonventre, J. V. (2015). Nephron organoids derived from human pluripotent stem cells model kidney development and injury. *Nature biotechnology*, *33*(11), 1193.

Nation, R. L., Li, J., Cars, O., Couet, W., Dudley, M. N., Kaye, K. S., & Tsuji, B. T. (2015). Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus. *The Lancet infectious diseases*, *15*(2), 225-234.

Nielsen, P. B., Skjøth, F., Søgaard, M., Kjældgaard, J. N., Lip, G. Y., & Larsen, T. B. (2017). Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *Bmj*, *356*, j510.

Petäjä, L., Vaara, S., Liuhanen, S., Ylinen, R., Mildh, L., Nisula, S., & Pettilä, V. (2017). Acute kidney injury after cardiac surgery by complete KDIGO criteria predicts increased mortality. *Journal of cardiothoracic and vascular anesthesia*, *31*(3), 827-836.

Post, E. H., Kellum, J. A., Bellomo, R., & Vincent, J. L. (2017). Renal perfusion in sepsis: from macro-to microcirculation. *Kidney international*, *91*(1), 45-60.

Timovska, S. N., Cekovska, S., & Trajkovska, K. (2015). The Acute kidney injury in the newborns. *Prilozi*, 36(3), 83-89.