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INCIDENCE, BIOMARKERS, AND OUTCOME OF ACUTE KIDNEY INJURY IN CRITICALLY ILL ADULTS

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ACADEMIC DISSERTATION

To be presented with the permission of the Medical Faculty
of the University of Helsinki, for public examination in
Biomedicum Helsinki, Lecture Hall 3, Haartmaninkatu 8,
on may 23rd 2014, at 12 noon.

HELSINKI 2014

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You miss 100%
of the shots you don't take.

-Wayne Gretzky

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LIST OF ORIGINAL PUBLICATIONS

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I   Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkanen M, Karlsson S, Haapio M, Inkinen O, Parviainen I, Suojaranta-Ylinen R, Laurila JJ, Tenhunen J, Reinikainen M, Ala-Kokko T, Ruokonen E, Kuitunen A, Pettilä V; FINNAKI Study Group. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Medicine. 2013 Mar;39(3):420-8.

II   Nisula S, Yang R, Kaukonen KM, Vaara ST, Kuitunen A, Tenhunen J, Pettilä V, Korhonen AM; FINNAKI Study Group. The urine protein NGAL predicts renal replacement therapy, but not acute kidney injury or 90-day mortality in critically ill adult patients. Anaesthesia & Analgesia (In Press)

III   Nisula S, Yang R, Poukkanen M, Vaara ST, Kaukonen KM, Tallgren M, Haapio M, Tenhunen J, Korhonen AM, Pettilä V; FINNAKI study Group. Predictive value of urine interleukin 18 in evolution and outcome of acute kidney injury in critically ill adult patients. British Journal Of Anaesthesia. (Submitted)

IV   Nisula S, Vaara ST, Kaukonen KM, Reinikainen M, Koivisto SP, Inkinen O, Poukkanen M, Tiainen P, Pettilä V, Korhonen AM. Six-month survival and quality of life of intensive care patients with acute kidney injury. Critical Care. 2013 Oct 22;17(5):R250.

LIST OF ABBREVIATIONS

ACCP/SCCM	American College of Chest Physicians/Society of Critical Care Medicine
ACEI	Angiotensin-Converting Enzyme Inhibitor
ACS	Abdominal Compartment Syndrome
ADQI	Acute Dialysis Quality Initiative
AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
APACHE	Acute Physiology and Chronic Health Evaluation
ARB	Angiotensin II Receptor Blocker
ARF	Acute Renal Failure
ATP	Adenosine Triphosphate
AUC	Area Under (the ROC) Curve
CI	Confidence Interval
CKD	Chronic Kidney Disease
CO	Cardiac Output
Cp	Concentration of substance in plasma
CPB	Cardiopulmonary Bypass
Cr	Creatinine
CrCl	Creatinine Clearance
CS	Cardiac Surgery
CRF	Case Report Form
CRS	Cardiorenal Syndrome
CRRT	Continous Renal Replacement Therapy
Cu	Concentration of substance in urine
CV%	Coefficient of Variation
DIC	Disseminated Intravascular Coagulation
ELISA	Enzyme-Linked Immunosorbent Assay
EQ-5D	The EuroQol quality of life questionnaire
FICC	Finnish Intensive Care Consortium
GFR	Glomerular Filtration Rate
HES	Hydroxyethyl Starch
HRQol	Health-related quality of life
HRS	Hepatorenal Syndrome
ICD-10	International Classification of Diseases 10th revision
ICU	Intensive care unit
IDI	Integrated Discrimination Index
IHD	Intermittent haemodialysis
IL-18	Interleukin 18
IL-6	Interleukin 6
IQR	Interquartile Range
ISTH	International Society on Thrombosis and Hemostasis
kDa	kilo Dalton
KIM-1	Kidney Injury Molecule 1

KDIGO	Kidney disease: improving global outcomes criteria
LOS	Length-Of-Stay
LR+	Positive likelihood Ratio
LR-	Negative likelihood Ratio
MDRD	Modification in Diet in Renal Disease
NGAL	Neutrophil Gelatinase-associated Lipocalin
NHP	Nottingham Health Profile
NO	Nitric Oxide
NRI	Net Reclassification Improvement
NSAID	Non-Steroidal Anti-inflammatory Drug
OR	Odds Ratio
QALY	Quality Adjusted Life Year
Qu	Urine flow rate
QWB	Quality of Well-being Scale
RAAA	Renin-Angiotensin-Aldosterone System
RBF	Renal Blood Flow
RCT	Randomised-Controlled Trial
RIFLE	Risk, Injury, Failure, Loss, End-stage criteria
RRT	Renal replacement therapy
ROC	Receiver Operating Characteristic
SAPS	Simplified Acute Physiology Score
SF-36	Short-Form 36
SIP	Sickness Impact Profile
SOFA	Sequential Organ Failure Assesssment
TIMP-2	Tissue inhibitor of metalloproteinases 2
TISS	Therapeutic Intervention Scoring System
TLS	Tumour Lysis Syndrome
TNFα	Tumour Necrosis Factor α
UH	University Hospital
UO	Urine Output
VAS	Visual Analogue Scale

ABSTRACT

Aims

The objectives of this study were to evaluate the incidence, risk factors, and outcome of acute kidney injury (AKI) in adult intensive care unit (ICU) patients in Finland, and to test the ability of two new biomarkers to predict AKI, renal replacement therapy (RRT), and 90-day mortality in a large group of unselected ICU patients.

Materials and methods

A prospective, observational FINNAKI-study was conducted in 17 Finnish ICUs and all admitted patients were screened for eligibility during the study period of five months (1st of September 2011 to 1st of February 2012). All adult emergency admissions and elective admissions with an expected stay over 24 hours were included. AKI was defined with the Kidney Disease: Improving Global Outcomes (KDIGO) criteria and the patients were screened for five days. Urine samples were collected from all eligible patients. Study data were collected from the Finnish Intensive Care Consortium (FICC) prospective database and with a study Case Report Form (CRF).

Study I included all patients in the FINNAKI study and evaluated the incidence and risk factors for AKI and reported the 90-day mortality of patients with AKI.

In study II, urine neutrophil gelatinase-associated lipocalin (NGAL) was measured from a set of patients with samples available from the first 24 hours of admission. The analyses were performed with a commercially available ELISA kit (BioPorto®). The ability of NGAL to predict AKI, RRT, or 90-day mortality was evaluated.

In Study III, urine interleukin-18 (IL-18) was analysed from a set of patients with a sample available from ICU admission. The analyses were performed with a commercially available ELISA kit (Cusabio Biotech®). This study evaluated the ability of IL-18 to predict AKI, RRT, or 90-day mortality.

Study IV evaluated the long-term outcome of patients with AKI by assessing their 6-month mortality and the survivors' health-related quality of life (HRQol) at ICU admission and six-months later with the EQ-5D questionnaire. Study IV included FINNAKI study centres that had a follow-up-rate of over 70% concerning the EQ-5d data.

Main results

Study I included 2901 patients, of whom 1141 (39.3%, 95% Confidence interval, CI 37.5 - 41.1%) developed AKI during the first five days. The proportions of patients in the different stages of AKI were 499/2901 (17.2%, 95% CI 15.8 - 18.6%) in stage 1, 232/2901 (8.0%, 95% CI 7.0 – 9.0%) in stage 2, and 410/2901 (14.1%, 95% CI 12.8 – 15.4%) in stage 3. RRT was initiated for 272/2901 (9.4%, 95% CI 8.3% - 10.5%) patients during the first five days. The population-based incidence of AKI was 746 (95% CI 717 - 774) per million adults per year. Patients that developed AKI were older and more severely ill, and had more chronic comorbidities than patients without AKI. Hypovolaemia prior to ICU admission,

administration of diuretics or colloids (HES or gelatin) prior to ICU admission, and chronic kidney disease were independent risk factors for AKI. Of the 1141 AKI patients, 385 (33.7%, 95% CI 30.9 – 36.5%) died within 90-days.

Study II included 1042 patients from 15 study centres. In this population, urine NGAL predicted AKI with an AUC (95% CI) of 0.733 (0.701 – 0.765), RRT with an AUC (95% CI) of 0.839 (0.797 – 0.880), and 90-day mortality with an AUC (95% CI) of 0.634 (0.593 – 0.675).

Study III included 1439 patients from 17 study centres. Urine IL-18 predicted the development of AKI with an AUC (95%CI) of 0.586 (0.546-0.627), initiation of RRT with an AUC (95% CI) of 0.655 (0.572-0.739), and 90-day mortality with an AUC (95% CI) of 0.536 (0.497-0.574).

Study IV included 1568 patients from 10 study centres of whom 1190 were alive at six months. Of the AKI patients, 224/635 (35.3%, 95% CI 31.5 - 39.1%) died during six months. Of the six-month survivors, 959/1190 (80.6%) answered the EQ-5D. The EQ-5D index for AKI patients at six-months (0.676, Interquartile range, IQR 0.520-1.00) was lower than for the age- and sex-matched general population (0.826, IQR 0.812-0.859) but equal to that of patients without AKI (0.690, IQR 0.533-1.00). There was no significant change in the EQ-5D over six-months for either patient group (mean change 0.024 for patients with AKI and 0.017 for patients without AKI). Despite their measured lower HRQol, AKI patients evaluated their quality of life to be as good as that of the age- and sex-matched general population at six-months after the ICU treatment: EQ-5D visual analogue scale (IQR) for patients with AKI was 70 (50-83), and for the general population 69 (68-73).

Conclusions
Incidence of AKI among critically ill patients was high. Hypovolaemia, diuretics, and colloids prior to ICU admission were independently associated with the development of AKI. In this population, urine NGAL was statistically associated with the need to initiate RRT, but the transformation of this result into clinical practice is complicated. Urine NGAL lacks power to predict AKI or 90-day mortality. Urine IL-18 has no adequate power to predict AKI, RRT, or 90-Day mortality in critically ill adult patients. AKI is associated with significantly increased 90-day and 6-month mortality. The HRQol of all ICU patients was lower than that of the age- and sex-matched general population already before ICU treatment. This HRQol did not change during critical illness or during a six-month follow up. Despite their lower HRQol, AKI patients felt their health was equal to that of the general population.

Keywords
Acute kidney injury, critical illness, health-related quality of life, interleukin 18, mortality, neutrophil gelatine-associated lipocalin, renal replacement therapy

1. INTRODUCTION

Acute kidney injury (AKI) refers to a syndrome encompassing kidney damage from mild injury to total loss of function that seriously disturbs the homeostasis of fluid and electrolyte balances[1].

A uniform definition for acute kidney injury has existed only since 2004, when the Acute Dialysis Quality Initiative (ADQI) proposed the Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE) criteria for AKI[2]. Since then two modifications of the RIFLE: Acute Kidney Injury Network (AKIN) (2007)[3], and Kidney Disease: Improving Global Outcomes (KDIGO) (2012)[1] have emerged. All of the three modern definitions are based on changes in serum or plasma creatinine (Cr) and urine output (UO).

Clinical symptoms may be scarce in the early stages of AKI. As the kidney injury progresses and affects the glomerular filtration rate (GFR) Cr starts to rise. Oliguria or anuria may develop early, but sometimes the UO remains intact for quite long. Later in the course of AKI the severely diminished GFR manifests as electrolyte and acid-base disturbances, most often as elevated potassium and acidosis.

Though described already in 1941[4] after limb crush injuries, pathogenesis of AKI is still poorly understood. Several different pathways have been proposed and studied; none of which seems to explain the big picture alone[5-8]. The arising consensus suggests that AKI is a syndrome with several different predisposing factors and mechanisms of pathophysiology. A growing amount of data supports the idea that risk for AKI increases with a growing "burden of illness" whether chronic or acute[1].

The traditional division of kidney failure to pre- and post-renal causes has been widely abandoned as the complex nature of the kidney injury syndrome has unfolded[1]. Extra-renal causes, without actual kidney damage, such as depletion of fluids or urinary track obstruction naturally still exist but are rare causes for AKI in the intensive care environment. Also these causes, when identified, are quite easy to treat and usually without long-term damage to the kidney or other organs. In the ICU, AKI is usually multifactorial with both chronic conditions and acute events contributing to the development of kidney injury[9]. Sepsis is the most common single underlying cause for AKI[10].

In the diagnosing and staging of AKI, Cr and UO act as surrogates for glomerular filtration rate, however prominent weaknesses in both as kidney injury markers exist[11-13]. A vigorous search for new kidney injury biomarkers has been going on for several years. A hope of easily measurable markers that would be more sensitive and specific to actual injury in the kidneys, would react earlier in the course of AKI, and would be less prone to bias in different physiological situations[14] remains.

The incidence of AKI in Finland is unknown. In studies evaluating the incidence of AKI defined by any of the three current classifications, 11%[15] to 67%[16] of ICU patients developed AKI depending on the population studied and the study design. No studies using the newest KDIGO criteria exist.

AKI has significant consequences. It is associated with morbidity[17] and permanent loss of kidney function[18]. All severity stages of AKI are associated with significantly higher short-[19] and long-term mortality[20]. AKI increases hospital expenses up to two-fold[21] and achieving quality adjusted life years in the treatment of AKI patients is expensive[22]. No prospective multicentre studies have evaluated the outcome of ICU patients with acute kidney injury in Finland.

The aim of this study was to evaluate the nationwide incidence of ICU treated AKI, search for risk factors associated with the development of AKI, assess two promising new AKI biomarkers (urine NGAL and urine IL-18), and to study the outcome of patients with AKI.

2. REVIEW OF THE LITERATURE

2.1. Definition of acute kidney injury (AKI)

Acute kidney injury is any insult to the kidney, resulting in sudden loss of function leading to disruption of fluid and electrolyte homeostasis. The visible and measurable symptoms of AKI include oliguria or anuria and accumulation of products normally excreted by the kidneys such as Cr, urea, and potassium, which as the situation progresses leads to acidosis[8].

The first consensus criteria for AKI (RIFLE, Risk, Injury, Failure, Loss, End-stage) were proposed in 2004[2], and supplemented with some changes by the Acute Kidney Injury Network resulting in the AKIN criteria[3] a few years later. In 2012 KDIGO (Kidney Disease: Improving Global Outcomes) released the latest guidelines for diagnosing and staging AKI[1]. Figure 1 illustrates these three classifications for AKI. With the consensus criteria, the term acute kidney injury (AKI) replaced the formerly used acute renal failure (ARF). Defining a unified criteria was a vital improvement in the field of AKI, for over 35 different definitions for ARF were previously used[23] making comparison of studies challenging. A modified RIFLE for small children and infants was published in 2007[24].

Serum Cr concentration and urine output are the basis of all the three current criteria (Figure 1). In brief, the AKIN classification supplemented the RIFLE with a small change (≥ 26.5 µmol/l) in Cr as a criterion for stage 1 AKI, and narrowed the observation period for change in Cr to 48 hours. Data from comparison of RIFLE and AKIN, showed, however, that the two classifications partly identified different patients[19]. The KDIGO criteria was then developed aiming to correct this by combining elements from both previous classifications. According to data the Cr criteria seem to identify more patients having AKI than the UO criteria[15,25], however some patients are only recognized with the UO criteria[19,25,26].

The traditional classification of AKI into pre-renal, post-renal, and intrinsic AKI has largely been abandoned due to lack of correlation with histopathological findings[27], outcome[28] or the current classification of AKI[1].

In some specific kidney disorders (e.g. acute interstitial and glomerular nephritis, some viral infections, and vasculitic illnesses) the clinical manifestation is similar to AKI, however, as kidney diseases with no current association to critical illness these conditions are out of the scope of this study.

Due to the nature of the definition, AKI is a syndrome with extremely varying clinical manifestation from patients with a small and transitional rise in creatinine, to patients with total loss of kidney function.

RIFLE

CREATININE / GFR

Increase x 1.5 OR
GFR decrease > 25%

Increase x 2 OR
GFR decrease > 50%

Increase x 3 OR GFR decrease > 75%
OR ≥ 353.6 µmol/l with acute increase
of ≥ 44.2 µmol/l

R

I

F

URINE OUTPUT

< 0.5 ml/kg/h for ≥ 6 hours

< 0.5 ml/kg/h for ≥ 12 hours

< 0.3 ml/kg/h for ≥ 24 hours OR
anuria for ≥ 12 hours

AKIN

CREATININE

1.5- to 2-fold from baseline OR
≥ 26.5 µmol/l increase (48h)

2- to 3-fold from baseline

>3-fold from baseline OR
≥ 353.6 µmol/l with an acute increase
of ≥ 44.2 µmol/l OR RRT

1

2

3

URINE OUTPUT

< 0.5 ml/kg/h for > 6 hours

< 0.5 ml/kg/h for > 12 hours

< 0.3 ml/kg/h for 24 hours OR
anuria for 12 hours

KDIGO

CREATININE

1.5 – 1.9 times baseline OR
≥ 26.5 µmol/l increase (48h)

2.0 – 2.9 times baseline

>3 fold from baseline OR
≥ 353.6 µmol/l OR
RRT

1

2

3

URINE OUTPUT

< 0.5 ml/kg/h for 6-12 hours

< 0.5 ml/kg/h for ≥ 12 hours

< 0.3 ml/kg/h for ≥ 24 hours OR
anuria for ≥ 12 hours

Figure 1. Risk, Injury, Failure, Loss, End-stage (RIFLE), Acute Kidney Injury Network (AKIN), and Kidney Disease: Improving Global Outcomes (KDIGO) criteria for diagnosing and staging AKI. RIFLE is presented without Loss- and End-stage- stages. Only one criterion (creatinine or urine output) needs to be filled per patient, and all patients are staged according to their worst stage. In AKIN the change in Cr must occur in 48 hours. In RIFLE, AKI should occur within 7 days and be sustained for more than 24 hours. In KDIGO the 1.5-fold change in Cr must be presumed to occur within 7 days. The ≥353.6 µmol/l change must include fulfilling stage 1 Cr criteria.

2.2. Measuring kidney function and damage

2.2.1. Glomerular filtration rate

The glomerular filtration rate (GFR) is the best measure for kidney function, and the normal values of GFR range from 90 - 130 ml per minute per 1.73 m[2] [29]. Figure 2 shows the equation for calculating GFR. It can be determined indirectly with intravenously injected substances that are freely filtered through the glomeruli. The gold standard for measuring GFR is the inulin clearance[30], but some other substances can also be used[31,32]. Measuring GFR with exogenous substances is too complicated and expensive for routine use, and the creatinine clearance (CrCl) is widely used and accepted as a surrogate[33-36]. CrCl can be computed from a collection of urine (24 hours) and Cr. Precise calculation of CrCl requires a steady state, which is rarely the case in critically ill patients[37].

$$\mathbf{GFR}\,(\mathrm{ml/min}) = \frac{\mathbf{Cu\ x\ Qu}}{\mathbf{Cp}}$$

Cu= Concentration of substance x in urine (mg/ml)
Cp= Concentration of substance x in plasma (mg/ml)
Qu= Urine flow rate (ml/min)

Figure 2. Calculating the glomerular filtration rate (GFR)

CrCl and hence GFR can be estimated from any of several equations of which the Cockroft-Gault[38], the Modification of Diet in Renal Disease (MDRD)[29,39], and the CKD-EPI[40] are the most relevant. These three equations are presented in Figure 3.

The MDRD normalizes the results to body surface area and might be more accurate than the Cockroft-Gault[41,42]. CKD-EPI is the most recent equation shown to be superior in comparison to the MDRD[40,43]. However, the MDRD is the equation currently recommended by the Acute Dialysis Quality Initiative[2]. Usually the 4-variable modification of the MDRD is used[44,45].

In AKI studies CrCl/GFR equations (most often the MDRD[46]) are used to estimate a baseline creatinine for patients lacking it by back calculating with the assumption of a normal GFR of 75 ml/min / 1.73 m[2]. Using any of the equations to estimate GFR may lead to over- or underestimation of the incidence of AKI[43,46-48].

a)

$$\text{CrCl (ml/min)} = \frac{(140 - \text{Age}) \text{ x Weight}}{72 \text{ x Cr}} \text{ x (0.85 for females)}$$

b)

$$\text{GFR (ml/min/1.73m}^2) = \frac{186 \text{ x Cr}^{(-1.154)} \text{ x Age}^{(-0.203)}}{} \text{ x (0.742 for females) x (1.212 for Afro-Americans)}$$

c)

$$\text{GFR (ml/min/1.73m}^2) = 141 \text{ x min(Cr / } \kappa, 1)^{\alpha} \text{ x max(Cr / } \kappa, 1)^{-1.209} \text{ x } 0.993^{\text{age}}$$
$$\text{x (1.018 for females) x (1.159 for Afro-Americans)}$$

Cr = Serum creatinine (mg/dl)
κ = 0.7 if female / 0.9 if male
α = -0.329 if female / -0.411 if male
min = minimum SCr/κ or 1
max = maximum SCr/κ or 1

Figure 3. a) The Cockroft-Gault[38], b) The Modification of Diet in Renal Disease, MDRD (simplified 4-variable equation without urea and albumin[45]), and c) The CKD-EPI[40] equations for estimating creatinine clearance or glomerular filtration rate.

2.2.2. Creatinine and urine output

The current classifications for AKI are based on Cr and urine output[1-3]. Though they are accepted as surrogates for GFR, both Cr and UO are prone to significant bias when used as markers for kidney function.

Normal serum creatinine levels vary according to age, sex, race, muscle mass, medications, and fluid status[11,12,49]. In addition, Cr is not only freely filtered in the glomeruli, but also actively excreted by the tubules; this rate of excretion depends on the serum Cr concentration[11,30]. Cr is insensitive to changes in the GFR; the concentration of Cr starts to rise when half of the kidney function has already been lost[50]. Changes in Cr are therefore slow after an injury to the kidneys[11].

The correlation of GFR and urine output is not linear. Urine output might be normal in AKI because of tubular injury and impaired concentration ability[1,13]. Low urine output can be a result of urinary track obstruction. In addition, diuretics or other medications may alter the diuresis. In very obese patients, the straightforward utilizations of urine output per weight (ml/kg/h) leads to overestimation of AKI[1,13].

2.2.3. Urea

Urea, and especially the urea to Cr ratio, has been used as a marker of kidney function in the hope of differentiating between transitory azotaemia (pre-renal azotaemia) and actual kidney injury (formerly acute tubular necrosis)[51]. However, a recent study reported that the urea to Cr ratio is not useful in differentiating between different types of AKI[52]. Urea is freely filtered in the glomeruli, as is Cr, but it also has significant reabsorption. Nor is urea produced at a constant rate[53]. Furthermore, several other factors such as steroid administration, nutritional status, and diet might affect the blood urea levels[54]. Elevated urea is independently associated with increased mortality[55] regardless of Cr and is included in many severity scores[56].

2.2.4. Urinalysis

Chemical analysis of urine (fractional excretion of sodium and urea) and urine microscopy have traditionally been a part of the clinical evaluation for patients with kidney disorders[57]. Some data suggest that evaluating the urine sediment[58], fractional excretion of sodium[59], or fractional excretion of urea[60] could differentiate between transient and persistent AKI, and predict worsening AKI or outcome[61,62]. However, urine sediment processing, any scoring systems, or appropriate timing of urinary microscopy in AKI diagnostics have not been standardized[63].

In several countries including Finland, urinalysis and urine microscopy performed by a nephrologist are no longer a part of the routine test pattern for acute kidney injury patients in the ICU[64,65], except for routine differential diagnosis between, for e.g., infection and AKI. A growing burden of evidence suggests that urine microscopy or biochemistry have no value in discrimination between types of AKI[66] or in predicting worsening AKI[67]. Recently, a multi-centre study in critically ill patients demonstrated poor ability of urinary indices to differentiate between transient and persistent AKI[68].

2.3. Pathophysiology of AKI

The pathophysiology of AKI is in many parts still unknown. Currently AKI is regarded as a complex, multi-etiological syndrome with several different pathophysiological mechanisms. Most of the current knowledge of pathophysiology of AKI comes from animal studies[69]. For many years, vasomotor disturbances and ischaemic injury were the main focus of attention in the study of aetiology of AKI[8]. Since then, growing knowledge on the mechanisms of AKI have shown that though important, ischaemic-reperfusion injury is only one of the mechanisms causing AKI[70].

2.3.1. Ischaemic-reperfusion injury

The kidneys maintain their perfusion pressure and glomerular filtration rate in different haemodynamic situations very efficiently by autoregulation with the afferent and efferent arterioles in each glomerulus reacting to vasoconstrictive and vasodilatory factors[7]. In the autoregulation range, the afferent arteriole reacts to decreased perfusion pressure with vasodilatation. In situations where the autoregulation is disturbed, such as extreme global hypotension, vascular thrombosis, vascular clamping, or oxygen depletion the response is vasoconstriction and reduction of GFR[8]. However, significant periods of isolated warm ischemia are tolerated by the kidneys without sustained injury[71]. Reperfusion following ischemia is also damaging to the tissues and this type of damage is often called ischaemic-reperfusion injury.

In situations where autoregulation fails, depletion of adenosine triphosphate (ATP) follows initiating the complex mechanisms leading from ischemia to injury. Damage to the endothelium and release of nitric oxide (NO) seems to play a role in local imbalance of vasoactive substances[72]. These reactions are accompanied by metabolic changes[8,73], activation of the coagulation system[74], and an inflammatory reaction[75]. The damaged vascular endothelium leads to increased permeability[76], and further increased leukocyte infiltration[77]. The damaged cells in the kidneys lose their cytoskeletal structure[78] and release more proinflammatory and chemotactic substances that further enhance the reaction[79].

Obstruction of the tubules by cell casts and back leak of glomerular filtrate to capillaries may contribute to the injury[80,81]. Reperfusion injury further damages the cells via oxidative processes[73]. Most tubular cells, however, usually remain viable[5,6,82]. Both necrosis[82] and apoptotic processes[83] have been seen in the damaged kidney cells.

2.3.2. Septic AKI

Sepsis is the most common predisposing factor for AKI in the critically ill[9]. Despite early assumptions[84], septic AKI is far more complex than just ischaemic-reperfusion injury resulting from poor haemodynamics or low RBF[70]. It seems that septic AKI is multifactorial, and the mechanism of development may vary significantly between patients[85,86]. It is poorly understood why only a minority of sepsis patients have a classical tubular necrosis when assessed histopathologically[87], and actually most renal tubular cells remain intact in septic AKI[82]. Most of the data on septic AKI have been derived from animal studies[88].

Animal models have suggested considerable variability in RBF in relation to systemic haemodynamic changes in sepsis[89]. In a recent study systemic haemodynamics and RBF were measured noninvasively from septic patients showing constantly reduced RBF in comparison to cardiac output (CO)[90]. Also, in previous studies RBF and GFR have been poorly correlated[6,85,91]. Thus, the loss of GFR in septic AKI can occur in the presence of a normal or even hyperdynamic RBF, and because of disturbed autoregulation uncoupling of systemic haemodynamics and RBF occurs[86].

In sepsis the excessive systemic inflammatory reaction most likely plays a key role in the development of kidney injury and multiple organ failure[92]. The release of various inflammatory mediators, from pathogens and from immune cells, induces direct toxicity to tubular cells and triggers a complex cascade of inflammation[89,93].

At the cellular level, immunomodulators such as tumour necrosis factor α, Interleukin 6, and leukotrienes[94] are suggested to cause apoptosis or even necrosis in tubular cells. In addition, the inflammatory stimulus induces the release of nitric oxide (NO) in response to endothelial damage causing disturbances in intrarenal hemodynamics[95] and shunting in the periglomerular system. It has been suggested that excess dilatation of the efferent arteriole compared to the afferent arteriole[96,97] would lead to "local hypotension" in the glomeruli and loss of GFR. In response, the renin-angiotensin-aldosterone (RAAA) system[98] is activated leading to increased renal vascular resistance[89], further decreasing RBF.

Oxidant stress, mitochondrial dysfunction, and microcirculatory abnormalities have also been proposed as contributors to septic kidney injury, but the role of these mechanisms remains unclear[86].
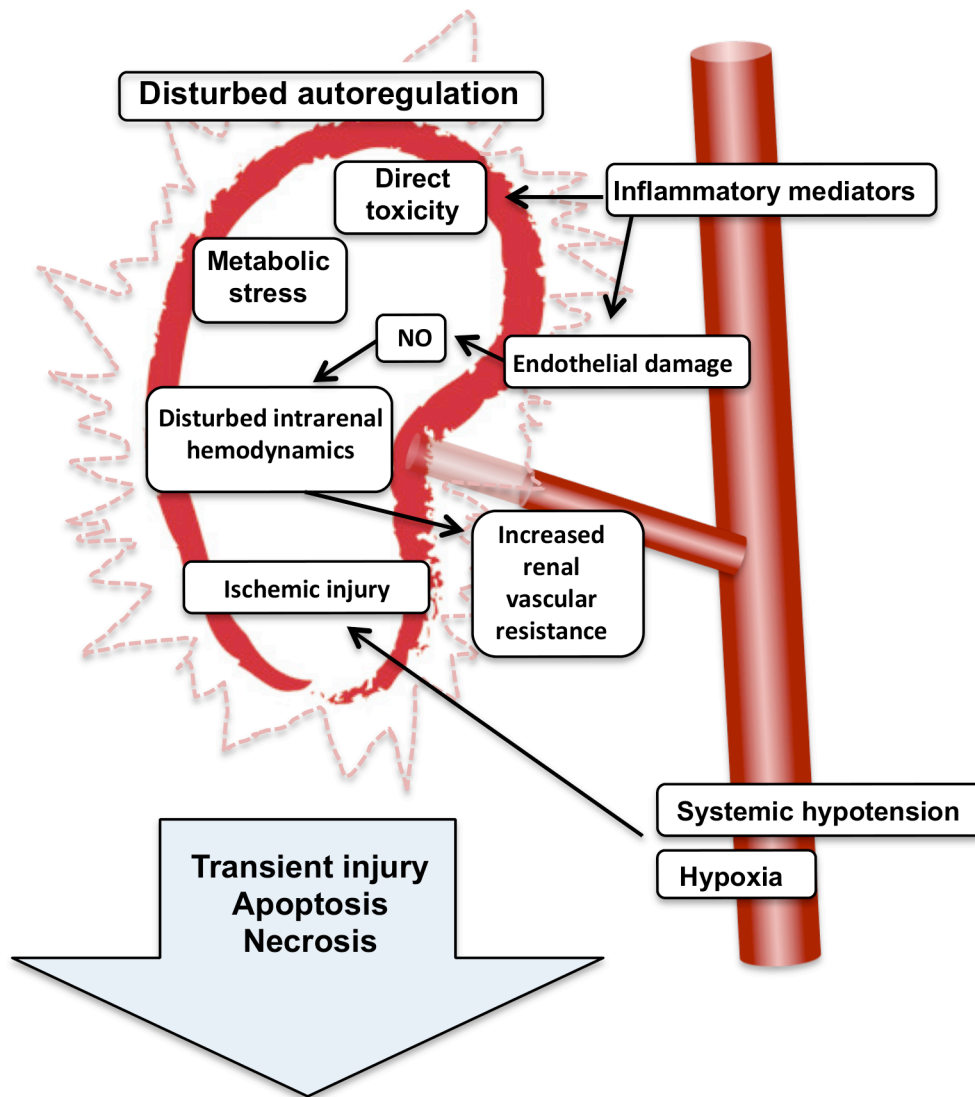
Figure 4. Schematic illustration of the pathogenesis of septic acute kidney injury.

2.3.3. Nephrotoxins

Several **drugs** and other substances frequently used in the ICU have direct or indirect effects on the kidneys. Indirect effects can be transmitted via influencing the systemic haemodynamics or modifying the pharmacokinetics of other drugs[99]. Direct damage to the kidneys can occur with various mechanisms: 1. by vasoconstriction (amphotericin, calcineurin inhibitors), 2. by altering the glomerular haemodynamic (non-steroidal anti-inflammatory drugs, ACE-inhibitors, angiotensin-converting enzyme inhibitor), 3. by toxic injury to the tubules (aminoglycosides, amphotericin, calcineurin inhibitors, methotrexate, contrast media), 4. by inducing interstitial nephritis (acyclovir), 5. by distal tubular crystal formation (acyclovir, methotrexate), 6. by thrombotic microangiopathy (calcineurin inhibitors), or 7. by osmotically induced tubular damage (immunoglobulins, starch)[100].

The excess release of myoglobin in **rhabdomyolysis** is damaging to the kidneys. Exact mechanisms of myoglobin induced AKI are unclear, but intrarenal vasoconstriction, direct and ischaemic tubule injury, and tubular obstruction are probably involved[101].

Tumour lysis syndrome (TLS) is a metabolic complication of cancer or treatment. In TLS the breakdown products of malignant cells induce hyperpotassinemia, hyperphosfataemia, hyperuricaemia, and hypocalcaemia, and often lead to AKI via calcium phosphate and uric acid crystallization[102]. Uric acid has more versatile effects by renal vasoconstriction, impaired autoregulation, oxidation, and inflammation[103].

2.3.4. Cardiorenal and hepatorenal syndromes

Simultaneous and bidirectional heart-kidney and liver-kidney disorders are classified as cardiorenal (CRS) and hepatorenal syndromes (HRS). Kidney injury often follows heart failure and vice versa as CRS due to systemic neurohormonal responses, reduced cardiac output, elevated venous pressure, and the following hypotension[104],[105].

The physiological consequences of acute liver failure are sepsis-like and often lead to acute kidney injury with multiple pathways including hypotension and renal ischemia, neurohormonal and immunological mechanisms, fluid accumulation and intra-abdominal hypertension due to ascites. The complex association between liver and kidney dysfunction is referred to as hepatorenal syndrome[106],[107].

2.4. Novel biomarkers of AKI

Due to known limitations in the current gold standard for AKI (creatinine and diuresis), new biomarkers to recognize AKI more sensitively, specifically, and earlier are needed. Figure 5 shows a timeline of developing AKI with regard to biomarkers. Both plasma and urine markers could be useful in AKI. Properties of an ideal biomarker would be:[108],[109]

1. must be generated by damaged, but not healthy cells.
2. concentration in the body must be proportional to the extent of the damage
3. should be expressed early after damage.
4. concentration should decrease rapidly after the acute injury to enable therapeutic monitoring.
5. should be easily, rapidly, and reliably measurable.

The biomarker levels in plasma and urine increase by several different and coincidental mechanisms[110]: excess synthesis in extrarenal tissues or release by circulating cells leads to elevated levels in plasma. Biomarkers in plasma can then be filtered into urine at varying rates. In situations of injury, reabsorption of the marker in the tubules can be impaired. Some biomarkers are produced in the kidneys (in e.g. tubular cells) or can be released from cells migrated into the kidneys[110].

Many potential biomarkers for AKI and adverse outcome associated with AKI have been studied to date[108,111-113] none of which have so far proven to be superior to others. In recent years probably the most studied new biomarker for AKI has been neutrophil gelatinase-associated lipocalin (NGAL) because of its biological plausibility and promising early studies[114].

Interleukin 18 (IL-18) is another promising biomarker with a known association to ischemic kidney injury and therefore a strong biological plausibility to be an AKI biomarker[115,116]. There is a lack of studies testing the predictive power of IL-18. The role of both these potential biomarkers in the ICU is unclear.
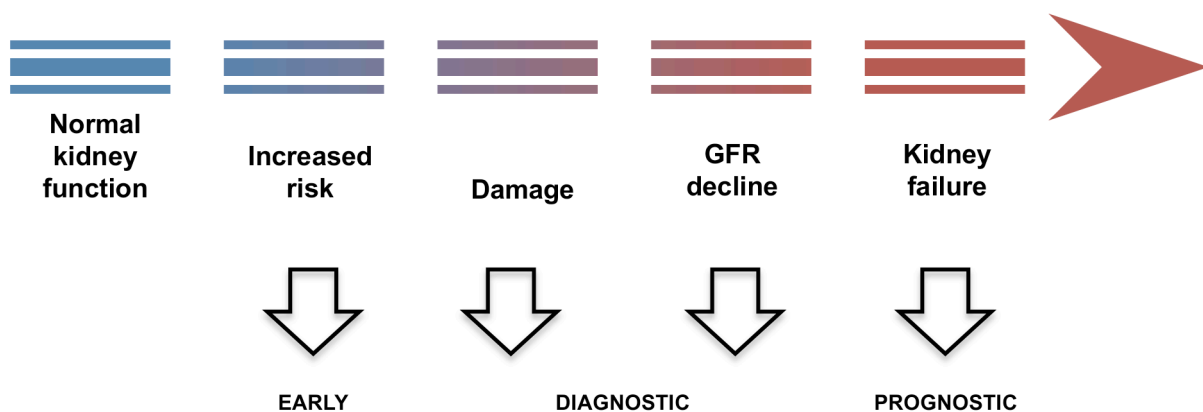
Figure 5. Biomarkers in the evolution of AKI. The current definition of AKI is based on markers (Cr and UO) that show decline in GFR or kidney failure. Biomarkers that show increased risk and/or early damage are needed. GFR, Glomerular filtration rate. Adapted from Bellomo and colleagues[70].

2.4.1. Neutrophil-gelatinase associated lipocalin

Neutrophil gelatinase-associated lipocalin (lipocalin-2) is a protein that was first found in human neutrophils[117], but has since been identified from many different tissues such as the lungs, stomach, trachea, colon, and the kidneys[118]. NGAL has several functions of which only some are known adequately. NGAL is found both in plasma and urine.

NGAL has an obvious role in the defence against microorganisms. It binds siderophores which are iron-binding molecules secreted by bacteria[119]. Furthermore, NGAL deficiency in animal models has led to increased sensitivity to certain bacterial infections[120,121]. NGAL also promotes epithelial cell differentiation[122], and might be involved in the repair process after kidney injury[123].

Generally, NGAL levels increase in various stress situations like acute infections, heart failure, inflammation, and malignant conditions[121,124-126]. Plasma NGAL is elevated in septic patients regardless of their AKI status[127,128].

What has made NGAL the focus of intense interest in the field of AKI is that it is one of the most upregulated genes in the early stages of ischaemic kidney injury, expressed mainly in the proximal tubules[129], and shown to rise (2h) and peak (6h) early after the insult on patients developing AKI[130]. In addition, recent data suggests that NGAL may protect tubular cells from ischaemic injury[131].

Plasma NGAL was found in early studies to be very sensitive and specific to identify early kidney injury in children undergoing cardiac surgery with areas under the curve (AUC) of 0.95[132], 0.96[133], and 0.998[114] (AUC of > 0.9 is excellent, AUC of 0.75-0.9 is good and AUC of 0.5-0.75 is poor). Results in critically ill patients have not been as coherently positive[134]. Table 1 summarizes studies that have included more than 20 patients in the evaluation of the role of NGAL in critically ill adult patients.

A growing body of evidence suggests that different molecular forms of NGAL exist[135]. Neutrophils predominately produce a 45 kDa homodimeric NGAL, and renal tubular cells predominately produce a 25 kDa monomeric NGAL. It is uncertain in what proportions each of the commercially available NGAL assays detect. Most of the monomeric NGAL in the urine is believed to originate from the renal tubular cells[135-137]. Immunosorbent assays that can identify the likely source of NGAL are beginning to emerge[138].

In a systematic review[134] from 2009, NGAL associated with AKI with a good pooled AUC (95% CI) of 0.815 (0.732-0.892) across settings. The corresponding AUC (95% CI) in cardiac surgery patients was a little poorer, 0.775 (0.669-0.867), and in critically ill patients was 0.728 (0.615-0.834). Of the different settings, NGAL was most reliable in predicting AKI after contrast medium with an AUC of 0.894 (0.826-0.950). NGAL predicted AKI significantly better in children, AUC 0.930 (0.883-0.968), than in adults, AUC 0.782 (0.689-0.872). In the same systematic review, the NGALs ability to predict RRT was combined to an AUC of 0.782 (0.648-0.917) and to predict hospital mortality to an AUC of 0.706 (0.530-0.747). Urine NGAL was found to be more accurate than plasma NGAL (AUC 0.775 versus 0.837)[134].

Ten studies with more than 20 patients in each have evaluated the predictive power of NGAL in critically ill adult patients[111,112,135,139-145]. There are three studies with NGAL from urine[111,112,145], three studies from plasma[139,140,142], and four studies from both[135,141,143,144]. The numbers of patients in these studies vary from 25[143] to 632[141]. All but two[141,142] report the ability of NGAL to predict new AKI instead of already established AKI, and the observation period for the development of AKI ranges from 12 hours[143] to 7 days[111,112,139,146]. The AUCs for NGAL for AKI prediction in the ICU setting vary from 0.48[144] to 0.956[139].

Seven of the ten studies also report AUCs for NGAL in the prediction of RRT[112,135,139-142,144]. The reported AUCs for NGAL with regards to initiation of RRT range from 0.26[144] to 0.89[141]. Six ICU studies[111,112,135,140-142] have evaluated the association of NGAL to mortality, the chosen mortality time point ranging from 7 days[112] to 90-days[142]. In only one of these studies evaluating mortality as an endpoint, the reported AUC was over 0.7 (0.83[111] for NGAL in prediction of 14-day mortality).

A recent study investigated the predictive powers of the different forms of NGAL in ICU patients, and demonstrated that both plasma and urine NGAL currently have a poor ability to predict AKI, RRT, or mortality even when discriminating between the different molecular forms of NGAL[135].

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Table 1. Studies evaluating the power of neutrophil gelatinase-associated lipocalin (NGAL) to predict acute kidney injury (AKI), renal replacement therapy (RRT), or mortality in adult ICU patients.

	Plasma or Urine NGAL	N	Setting	AKI	Established or new AKI	AKI AUC	RRT AUC	Mortality AUC
Constantin 2010[139]	P	56	S	RIFLE	N	0.956 (0.864-0.992)	0.788 (0.687-0.868)	-
Cruz, 2011[140]	P	301	S	RIFLE [c]	N	0.78 (0.65-0.90)	0.82 (0.70-0.95)	0.67 (0.58-0.77) ICU
De Geus, 2011[141]	P	632	S	RIFLE	E	0.77 ± 0.05	0.88 ± 0.06	0.63 ± 0.06 / hospital
De Geus, 2011[141]	U	632	S	RIFLE	E	0.80 ± 0.04	0.89 ± 0.04	0.64 ± 0.06 / hospital
Doi, 2011[111]	U	339	S	RIFLE	N	0.598 (0.521-0.670)	-	0.83 (0.69-0.91) / 14 d
Endre, 2011[112]	U	528	M	AKIN / RIFLE	N	0.68 (0.56-0.80)	0.79 (0.65-0.94)	0.66 (0.57-0.74) / 7 d
Glassford, 2013[135]	P	102 [a]	S	RIFLE	N	0.606 (0.491-0.722)	0.78 (0.579-0.982)	0.424 (0.271-0.578) / hospital
Glassford, 2013[135]	U	102 [a]	S	RIFLE	N	0.55 (0.418-0.683)	0.705 (0.49-0.92)	0.389 (0.258-0.519) / hospital
Linko, 2012[142]	P	369 [b]	M	RIFLE	E	-	0.73 (0.66-0.81)	0.58 (0.52-0.65) / 90 d
Mårtensson, 2010[143]	U	25 [a]	S	AKIN / RIFLE [c]	N	0.86 (0.68-1.0)	-	-
Mårtensson, 2010[143]	P	25 [a]	S	AKIN / RIFLE [c]	N	0.67 (0.39-0.94)	-	-
Royakkers 2012[144]	U	140	M	RIFLE	N	0.48 (0.33-0.62)	0.26 (0.03-0.50)	-
Royakkers 2012[144]	P	140	M	RIFLE	N	0.53 (0.38-0.67)	0.47 (0.37-0.58)	-
Siew, 2009[145]	U	451	S	AKIN	N	0.71(0.63-0.78)	-	-

P, Plasma; U, Urine; S, Single centre; M, Multicentre; RIFLE, Risk, Injury, Failure, Loss, End stage -criteria; AKIN, Acute Kidney Injury Network -criteria; E, Established AKI; N, New AKI; AUC, Area Under the Curve; RRT, Renal Replacement Therapy; ICU, Intensive Care Unit; [a] ICU patients with sepsis; [b] ICU patients with ventilatory support; [c] Both Cr and urine output criteria; Hospital, hospital mortality

2.4.2.Interleukin 18

Interleukin 18 (IL-18) is a member of the IL-1 cytokine family. It occurs intracellulary as an inactive precursor in monocytes and epithelial cells of the gastrointestinal tract[115]. The inactive form is activated by caspase-1, and then secreted mainly by macrophages or dendritic cells[147]. Free IL-18 in the cells is normally bound by IL-18 binding protein. The amounts of free IL-18 in the circulation are elevated with increasing imbalance between IL-18 and its binding protein after excess IL-18 production[115]. IL-18 promotes inflammation[115], and has a role in many autoimmune diseases[148], and ischaemic heart disease[149].

IL-18 is involved in ischaemic tubular necrosis as shown by animal studies in which IL-18-blocked mice were protected against ischaemic AKI[116,150]. IL-18 is shown to rise significantly in patients with acute tubular necrosis compared to healthy controls, and patients with various other renal diseases (urinary track infection, prerenal azotaemia, chronic renal diseases, renal transplant patients)[151]. In cardiac surgery patients, IL-18 started to rise 4-5h after cardiopulmonary bypass (CPB) and peaked at 12h[152]. IL-18 levels have been elevated in patients with sepsis, and especially in patients with gram positive infections[153].

The prognostic value of IL-18 in the prediction of AKI in an adult ICU setting has been investigated in five studies[111,112,154-156]. These studies all used urine IL-18 and are presented in Table 2. The AUC for IL-18 in the prediction of AKI ranges from 0.55[112] to 0.73[155].

Only one adult ICU study reports an AUC for IL-18 in the prediction of RRT (AUC 0.73) with only 14 patients meeting the endpoint[112].

Four studies (two of the studies in Table 2, one in cardiac surgery patients and one in RRT-patients) report IL-18 in association with mortality[111,112,157,158] with AUCs ranging from 0.53[157] to 0.83[111]. One ICU study reported the association of IL-18 with hospital mortality in hazards ratio 2.32 (95% CI 1.2 – 4.4)[155]. A recent study of serum IL-18 found an independent association of IL-18 with hospital mortality[158].

In a meta-analysis from 2013 the pooled AUC (95% CI) for IL-18 across all settings in prediction of AKI was 0.70 (0.66-0.74)[159], and in ICU patients 0.66 (0.62-0.70). In cardiac surgery patients IL-18 predicted AKI with a pooled AUC of 0.72 (0.68-0.76). Of the different settings, IL-18 predicted AKI best in children across settings: AUC 0.78 (0.75-0.82). In these studies, 4-6 hours after cardiac surgery was the optimal time point to measure IL-18[159]

Table 2. Studies on significance of urine interleukin 18 (IL-18) in prediction of acute kidney injury (AKI), renal replacement therapy (RRT), or mortality in adult ICU patients.

	N	Setting	AKI	Established or new AKI	AKI AUC	RRT AUC	Mortality AUC
Doi, 2011[111]	339	S	RIFLE	N	0.59 (0.51-0.67)	-	0.83 (0.68-0.91) / 14 days
Endre, 2011[112]	528	M	AKIN	N	0.55 (0.47-0.62)	0.73 (0.59-0.86)	0.68 (0.60-0.76) / 7 days
Metzger, 2010[154]	20	S	AKIN[a]	-	0.57	-	-
Parikh, 2005[155]	138[b]	M	-[c]	N	0.73	-	[d]
Siew, 2010[156]	391	S	AKIN	N	0.62 (0.54-0.69)	[e]	[f]

S, Single centre; M, Multicentre; RIFLE, Risk, Injury, Failure, Loss, End stage -criteria; AKIN, Acute Kidney Injury Network -criteria; E, Established AKI; N, New AKI; AUC, Area Under the Curve; RRT, Renal Replacement Therapy; ICU, Intensive Care Unit; [a] Both Cr and urine output criteria; [b] Patients with acute lung injury; [c] Cr >50% within 6 days; [d] Association with hospital mortality hazards Ratio 2.32 (95% CI 1.2-4.4); [e] Composite endpoint of dialysis or death during 28 days Odds Ratio 1.86 (1.31-2.64); [f] Association with hospital mortality Odds Ratio 2.02 (95% CI 1.41-2.89)

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2.5. Risk factors for AKI

In the ICU, AKI is usually multifactorial with several different insults affecting the kidneys in an additive way. The combined risk for each patient comprises both acute exposures and insults causing AKI, and chronic conditions and patient related factors that define how susceptible each patient is to develop AKI[1]. The type and intensity of the acute exposure is also of relevance. Estimating the absolute risk for AKI is challenging and attempts have been made to develop risk-prediction scores, but are mostly limited to patients after cardiac surgery[160-162] or contrast medium administration[163,164]. ICU patients are exposed to numerous potential factors causing AKI, and any critical illness per se is a risk factor for AKI.

Advanced **Age**[25,160,165-168] and **the female gender**[161,169] are associated with higher risk of developing AKI. Of chronic comorbidities **chronic kidney disease (CKD)**[16,170,171] is one of the factors most clearly associated with increased AKI risk, with even a mild elevation in Cr[172]. **Diabetes**[160,161,165,171] and **cardiac dysfunction**[160,161,170] also increase the susceptibility for AKI. In cardiac surgery patients, **pulmonary disease**[161] and **liver disease**[168,173,174] are risk factors for AKI. Increasing data suggest that **genetic factors**[175-180] predispose some patients for AKI. CKD, sepsis, liver failure, heart failure, and malignancies as comorbidities increase the risk for drug induced kidney injury[99].

Patients with **malignant** conditions might have a higher risk of AKI in the ICU[181]. Cancer can cause AKI either by direct invasion to the kidneys, via septic infections or by the patient being subjected to nephrotoxic chemotherapeutic agents[181]. **Tumour lysis syndrome** (TLS) is a metabolic complication of cancer or cancer treatment that often leads to AKI[102].

Sepsis is the most common underlying cause for AKI with up to 50% of AKI cases being related to sepsis[9,10,171,182-184]. Conditions that leads to severe **hypovolaemia**[171] or sustained **hypotension**[185] predispose patients to AKI.

The use of **hydroxyethyl starch** (HES) in ICU patients might be disadvantageous concerning kidney function. Three meta-analyses have concluded that the use of HES in critically ill patients can increase the risk for AKI[186-188]. HES compared to crystalloids increases the risk of severe AKI and initiation of RRT[189]. In AKI patients with severe sepsis HES was associated with increased need for RRT[190].

Albumin has been found to increase survival and decrease the incidence of AKI in chirrotic patients[191]. In ICU patients, however, no benefit from the use of albumin has been shown[192]. The evidence to date of **gelatin** in relation to AKI is inconclusive[193]. The use of gelatin in ICU patients is not recommended because of lacking apparent benefit and the affect gelatin has on clotting[194,195].

Excessive **fluid overload** has been acknowledged as a risk factor for AKI and adverse outcome[196]. How fluid accumulation leads to AKI is not totally understood. Known

pathways from fluid overload to AKI are abdominal hypertension or abdominal compartment syndrome (ACS)[197-200], and elevated venous pressure and venous congestion in the kidneys[201,202].

Major surgery[167] and especially **cardiac surgery**[203] with CPB are risk factors for AKI due to potential changes in haemodynamics, intravascular volume, delivery of oxygen, and the systemic inflammation reaction (systemic inflammatory response syndrome, SIRS) caused by the surgery and CPB[204].

Several **drugs** used in the ICU are known to be nephrotoxic[205]. Up to one quarter of severe AKI cases are somehow related to drug toxicity[9,206]. Table 3 lists potentially nephrotoxic drugs frequently used in the ICU.

Table 3. Potentially nephrotoxic drugs in the intensive care unit[99,207]

ACE inhibitor, ARB
Acyclovir
Aminoglycosides
Amphotericin
Contrast media
Calcineurin inhibitors (cyclosporine, tacrolimus)
Diuretics
Immunoglobulins
Metformin
Metotrexate
NSAID
Peptidoglycans (Vancomycin)

ACE inhibitor, angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; NSAID, Non-steroidal anti-inflammatory drugs

It has been estimated that **contrast media** are responsible for over 10% of the new AKI cases in hospitalized patients[208]. In ICU patients the risk for contrast media-induced AKI is due to co-existing AKI risk factors[209,210].

AKI is a known complication of **rhabdomyolysis** in which excessive release of myoglobin from muscle cells due to e.g. trauma or medications damage the kidneys[211,212].

2.6. Incidence of AKI

The **population-based incidence** of AKI defined by any of the modern definitions (RIFLE, AKIN, KDIGO) has been evaluated in only two studies[213,214] both using the RIFLE criteria for AKI. A retrospective study from one USA county area, representing a population of 124 277, reported a population-based incidence of 2900/million/year for ICU treated AKI[213]. A retrospective study from Scotland, representing a population of 523 390, evaluated the population-based incidence of hospital-treated AKI, which was reported as 2147 /million /year[214].

Data from a large Australian database suggested that the **incidence of AKI in the ICU** is increasing[215]. Since the unified criteria (RIFLE) for AKI were published, several studies have evaluated the incidence of AKI in the ICU[15,16,19,25,166-168,183,216-221]. These studies are presented in Table 4. The incidence of AKI in these studies varied significantly from 10.8%[15] to 67.2%[16]. The incidence of RRT ranged from 1.0%[168] to 11.9%[25]. All of the studies used the RIFLE or AKIN criteria for diagnosing and staging AKI, and in only half of them both Cr and UO criteria were utilized[15,16,25,166,167,216,221]. The observation period for development of AKI varied from 24 hours[217] to the entire hospital stay[16]. Large, multicentre retrospective registry studies, each with over 10 000 patients, have reported incidences from 22%[168] to 57.0%[221]. Altogether four[15,166,167,216] prospective studies have been published, the largest of which included 2 164 patients[15].

Two studies from Finland exist. Åhlström and colleagues reported an AKI incidence of 52% in a prospective, single-centre study with 658 patients[216]. Recently in 2012, Vaara and colleagues performed a large nationwide database analysis with over 20 000 patients and reported an AKI incidence of 26.6%[220]. Both of the Finnish studies used the RIFLE classification though Vaara and colleagues without UO data.

Table 4. Studies reporting the incidence of acute kidney injury (AKI) in intensive care unit (ICU) patients

	Patients	Study type	AKI definition	AKI %	Stage 1 / RIFLE R	Stage 2 / RIFLE I	Stage 3 / RIFLE F	RRT%	Observation period
Bagshaw, 2008[217]	120 123	R, M	RIFLE, Cr [a]	36.1	16.2	13.6	6.3	-	24 hours from admission
			AKIN, Cr	37.1	18.1	12.0	13.0		
Cruz, 2007[15]	2 164	P, M	RIFLE, Cr, UO	10.8	2.1	3.8	4.9	3.3	ICU stay
Hoste, 2006[16]	5 383	R, S	RIFLE, Cr, UO	67.2	12.4	26.7	28.1	4.1	Hospital stay
Joannidis, 2009[19]	14 356	R, M	RIFLE, Cr, [a] AKIN, Cr, [a]	28.5 35.5	7.6 7.5	11.1 7.2	16.8 13.8	-	2 days from admission
Lopes, 2008[25]	662	R, S	RIFLE, Cr, UO AKIN, Cr, UO	43.8 50.4	14.7 21.1	11.0 10.1	18.1 19.2	11.9	ICU stay
Mandelbaum, 2011[221]	14 524	R, S	AKIN, Cr, UO	57.0	38.5	14.1	4.3	-	ICU stay
Medve, 2011[166]	459	P, M	AKIN, Cr, UO	24.4	11.5	5.5	7.4	7.4	ICU stay
Ostermann, 2007[183]	41 972	R, M	RIFLE, Cr	35.8	17.2	11.0	7.6	4.4	ICU stay
Ostermann, 2008[218]	22 303	R, M	AKIN, Cr	35.4	19.1	3.8	12.5	8.3	ICU stay
Piccinni, 2011[167]	576	P, M	RIFLE, Cr, UO	65.8	22.0	22.6	21.2	8.3	ICU stay
Sigurdsson, 2012[219]	1 012	R, S	RIFLE, Cr	21.7	7.1	6.8	7.8	3.6	ICU stay
Thakar, 2009[168]	325 359	R, M	AKIN, Cr	22.0	17.5	2.4	2.0	1.0	ICU stay
Vaara, 2012[220]	24 904	R, M	RIFLE, Cr	26.6	10.3	8.1	8.2	6.8	ICU stay
Åhlström, 2006[216]	658	P, S	RIFLE, Cr, UO	52.0	25.5	17.2	11.2	7.1	3 days from admission

ICU, intensive care unit; P, prospective; R, retrospective; M, multicentre; S, single centre; AKIN, Acute Kidney Injury Network Criteria; KDIGO, Kidney Disease: Improving Global Outcomes criteria; RIFLE, Risk, Injury, Failure, Loss, End-stage criteria; Cr, Creatinine Criteria for AKI; UO, Urine Output criteria for AKI; [a] Cumulative 24h urine output

2.7. Prevention and treatment of AKI

No specific means to prevent or to treat of AKI are available[1]. The recognition of patients at risk before clinical symptoms are seen is therefore vital. The current guidelines for AKI recommend the following action for all patients at high risk for AKI: 1. discontinuing and avoiding nephrotoxic drugs if possible (including contrast medium), 2. optimizing haemodynamics and volume status, 3. starting functional haemodynamic monitoring, 4. monitoring of Cr and diuresis, 5. avoiding hyperglycaemia. In addition RRT and drug dosage changes should be considered for patients with established severe AKI[1].

2.7.1. Haemodynamics and vasoactive medication

Sustained systemic hypotension leads to renal hypoperfusion and may result in AKI[73]. Normally, reduced blood flow and ischemia are well tolerated in the kidneys, however the autoregulation of an injured kidney is disturbed[90] and a protocol-based management of haemodynamics in AKI prevention and treatment is recommended[1] and also found beneficial in high-risk surgical patients[185]. The optimal or adequate level of blood pressure in patients with risk of AKI or established AKI is, however, unknown[222,223].

The use of vasopressors is recommended when combined with fluids in patients with shock. The choice between different vasopressors is not unambiguous[1]. Despite the use of **dopamine** in low doses with the hope of preventing AKI, data to date do not give rationale for this use[224]. Furthermore, in comparison to norepinephrine, dopamine seems to be associated with an increased number of adverse events[225]. **Vasopressin** has been suggested to have beneficial effects in AKI patients, but definitive proof of vasopressin reducing AKI or improving outcome is lacking[226,227].

2.7.2. Diuretics

Loop diuretics are often used in patients with AKI or at risk of AKI[228]. **Furosemide** does not reduce mortality or the need for RRT in AKI patients, and it might have harmful effects on kidney function[228-230]. The use of furosemide is recommended only in some cases to treat volume overload[1].

2.7.3. Other medication

Fenoldopam[231] and **atrial natriuretic peptide**[232] have presented some promise in prevention and treatment of AKI, but data from adequately powered studies[233-236] have been unable to confirm these findings. Furthermore, existing data don't suggest benefit from human **insulin-like growth factor 1** (IGF-1)[237-239], or **erythropoietin**[240] to prevent or to treat AKI. Preliminary data from recent animal studies suggest that **cyclosporine** (a calcineurin inhibitor) might protect from AKI by blocking the inflammatory reaction[241].

N-acetylcysteine might be effective in preventing contrast-induced AKI[242], but in patients undergoing major surgery, without contrast medium exposure, no benefit in terms of need for RRT has been found[243]. Data on critically ill patients are scarce[244]. **Theophylline** has been shown to be renoprotective in asphyxic neonates[245-247], but data in adults are lacking. Another adenosine receptor antagonist, rolofylline, has recently been studied in patients with cardiorenal syndrome, but no positive effects on survival or kidney function were observed[248].

Data suggest that a tight **glycaemic control** (blood glucose target 4.5 to 6 mmol/l versus a target of ≤ 10 mmol/l) with insulin might reduce AKI in critically ill patients, and especially in surgical patients[249]. However, in these studies, an intensive glucose control significantly increased the risk for severe hypoglycemia[250]. The current international guidelines recommend a blood glucose target of 6.1 – 8.3 mmol/l[1].

2.7.4. Fluids

Adequate fluid therapy to restore intravascular volume and maintaining cardiac output and renal vascular flow in shock is recommended in the prevention of AKI[251]. Estimating fluid responsiveness and the adequate amount of fluid resuscitation in critical illness are, however, very complicated[198,252,253]. Furthermore, based on animal models, restoring the systemic blood pressure with fluid therapy does not necessarily lead to improved renal oxygenation[254,255]. Excessive fluid administration results in fluid overload and fluid overload is a risk factor for AKI[196].

Though 0.9% normal saline is widely used in fluid therapy, a growing body of evidence suggests that the use of saline leads to hyperchloremic metabolic acidosis[256,257], and can in addition to other adverse events, increase the incidence of kidney injury[258,259]. The use of balanced solution (e.g. Ringer's solution, Hartmann's solution) could be more advantageous in the critically ill than 0.9% saline[258,260]. On the basis of a large RCT, albumin (4%) presents no benefit in ICU patients compared to 0.9% saline[192]. The use of HES is not recommended in any ICU patients, as starches can increase the risk for AKI, need of RRT and mortality[187,190,192].

Intravenous isotonic sodium chloride (0.9% saline)[261] or infusion of sodium bicarbonate[262] given before and after contrast medium has been shown to prevent from contrast media-induced AKI. N-acetylcysteine might also offer a benefit in the prevention of contrast media-induced AKI for patients in high risk[242,263]. Although 0.9% sodium chloride was used in these studies, the current Finnish Guidelines for acute kidney injury recommend giving 1 ml/kg/h of balanced solutions 12 hours prior and 12 hours post contrast medium injection[207] due to the disadvantages associated with excess chloride administration[258,260].

Mannitol is a compound used to induce osmotic stress. It is derived from sugar and increases urine flow, but existing data are inadequate and do not indicate a beneficial effect in preventing AKI[264-266].

2.7.5. Renal replacement therapy

The purpose of RRT in AKI is to: a) normalize and maintain fluid, electrolyte and acid-base homeostasis, b) to prevent further injury to the kidneys c) to provide time for renal recovery, and d) to enable the use of certain supportive treatments (e.g. antibiotics) in situations where other treatments have failed[1].

Indications for RRT are not uniform, but traditionally severe acidosis, hyperpotassinaemia, severe fluid overload, anuria, uremic complications, and hypermagnesaemia leading to loss of deep tendon reflexes have been considered as absolute indication for RRT. Also, a rapidly worsening kidney function, severe sepsis, and the overall condition of the patient should be considered[1,267]. A multicentre study from Finland described oliguria, high creatinine, acidosis and fluid accumulation as the most common indications for RRT initiation, though most patients had several reasons listed[268]. Not all RRT is executed for AKI, and other indications include e.g. immunomodulation in sepsis, removal of toxic substances, or management of dystermia[267].

Despite extensive research, no consensus on the most beneficial timing of RRT exists though it has been suggested that early would be better than late[1,269]. Based on data from a multicentre study, RRT was generally initiated very early in the course of ICU treatment in Finland (41.9% on the first day)[268].

The modality of choice for ICU patients is typically continuous renal replacement therapy (CRRT), which is better tolerated in unstable patients and permits ongoing treatment for several days[270]. Intermittent treatments are usually offered later on in the course of critical illness when the patients are more stable. No clear difference has been shown between mortality in patients treated with IHD versus CRRT, however, CRRT is shown to be associated with haemodynamic stability[271]. Renal recovery might be better in patients treated with CRRT[272].

The lack of uniform guidelines on when and to whom to initiate RRT makes it a complex endpoint in studies and complicates the assessment of how RRT affects patient outcome[269]. AKI patients that fulfil any absolute indication for RRT are at high risk of dying without RRT, but on the other hand, patients with RIFLE F (Stage 3) AKI that don't receive RRT have been shown to have more treatment restrictions and lower severity scores that patients put on RRT[273].

2.8. Outcome of patients with AKI

2.8.1. Recovery from AKI

Most patients experiencing severe AKI with RRT recover completely or partially. Reported recovery (defined as RRT independency) rates vary from 75%[274] to 95.6%[275] at day 90, and from 90%[276] to 95%[277,278] at five years. However, even patients that are discharged dialysis-free have an increased risk of both CKD with RRT dependency[18] and mortality[17] in the future. Chronic conditions such as diabetes[170] and CKD are associated with nonrecovery from AKI[279].

2.8.2. Length-of-stay and costs for care

Length-of-stay (LOS) is an outcome subjected to bias, however, many studies evaluating the incidence of AKI also report ICU LOS for patients with and without AKI. All of these studies found that AKI patients stayed significantly longer in the ICU than patients without AKI (Table 5)[16,166,167,218,219].

Table 5. Length of stay in the intensive care unit (ICU) for patients with and without acute kidney injury (AKI)

Study	N	LOS AKI Median (IQR if available)	LOS no AKI Median (IQR if available)	P
Hoste, 2006[16]	5 383	4 (2-9)	3 (2-4)	<0.001
Medve, 2011[166]	459	4.5	2	<0.001
Ostermann, 2008[218]	22 303	7	2	<0.001
Piccinni, 2011[167]	576	7 (3-16)	3 (2-8)	<0.001
Sigurdsson, 2012[219]	1 026	4 (1-108)	2 (0-52)	<0.001

N, Number of patients; LOS, Length-of-stay; IQR, Interquartile range

It is estimated that treatment of patients with AKI increases the health care cost in the USA by 10 billion dollars annually[9,21]. According to studies, AKI doubles the costs for hospital treatment compared to patients without AKI[21,280-282].

In a Finnish study from 2005, the cost of one quality adjusted life year (QALY) for AKI patients receiving RRT were 222 000 € / QALY for the first year[282]. Another RRT-patient study from Finland reported calculations for all costs per hospital survivor during five years (85 540.6 €), and the cost utility of acute RRT (270 000 €/QALY)[22]. No conclusive accepted value for one QALY has been defined, but in excess of 50 000 USD (about 40 000 €) has been suggested[283].

2.8.3. Health-related quality of life

The health-related quality of life (HRQol) is the impact of patients' health status on their quality of life. HRQol is a multi-dimensional concept that includes physical, mental, emotional and social aspects. HRQol can be measured with any of several questionnaires including EuroQol (EQ-5D)[284], Short Form 36 (SF-36)[285], the Sickness Impact Profile (SIP)[286], the Quality of Well-being Scale (QWB)[287], and Nottingham Health Profile (NHP).

According to prior studies the HRQol of patients admitted to ICU is already lower than that of the general population before critical illness[288,289]. Increasing age and severity of illness may be associated with a poorer HRQol[290]. In RRT patients, existing CKD has been associated with a poorer HRQol after ICU treatment[291]. In ICU patients, an emergency admission, elevated Cr at admission, hypothermia, and metastatic cancer are predictors of poor recovery measured with the HRQol[292].

The HRQol of patients with AKI has been evaluated in two previous studies[20,293]. A recent prospective study concluded that the HRQol (measured with the SF-36) of patients with AKI at six months after ICU admission was similar to that of patients without AKI. The HRQol of AKI patients was also already lower compared to the general population at ICU admission[20]. Another study evaluating patients with postoperative AKI using the SF-36 found that despite having lower scores in physical functions at six months, AKI patients perceived their HRQol to be better than before admission to the ICU[293].

Other studies reporting HRQol of AKI patients have only included RRT patients[220,276,281,291,294-296], and have all reported impaired physical health compared to controls. Despite their loss of physical health, patients in these studies perceived their health was excellent[276], and even reported that they would undergo the same treatment again[294,295].

Two studies from Finland have reported the HRQol of RRT-patients[220,282]. A study from 2005 reported that the HRQol of RRT patients after ICU treatment was significantly lower compared to that of the age- and sex-matched general population[282]. The study from 2012 concluded that the HRQol of RRT patients was equal to that of patients without RRT at six months[220]. Furthermore, in both studies, RRT patients were as content with their lives as the general population[220,282].

2.8.4. Mortality

Studies evaluating mortality in AKI patients are presented in Table 6. Most of the studies have only focused on short-term mortality (ICU, hospital)[15,16,19,20,25,166,167,183,216-219]. The lowest ICU mortality of 28.4% was from a large retrospective study from 2007[183] and the highest ICU mortality of 54% from a small study with 183 patients[297]. In nine out of fourteen studies, hospital mortality was the chosen outcome[16,19,25,166,183,216-219]. Hospital mortality has a wide range of variation from 13.3%[16] to 49.1%[166].

No studies have reported the 90-day mortality in AKI patients treated in the ICU and only three studies have reported long-term mortality at six months[20,293,297]. In one prospective study the 6-months mortality of AKI patients was 46.5%[20]. In two retrospective studies the six-month mortality for AKI patients was 58.5%[297] and 38.0%[293]. Recently a sequentially matched analysis calculated, that the absolute excess mortality attributable to AKI at 90-days was 8.6%, and that statistically 19.6% of deaths (population attributable risk, 90-day mortality) among ICU patients could be avoided if there was no AKI[298].

Table 6. Studies reporting mortality for intensive care unit (ICU) patients with acute kidney injury (AKI)

	Patients	Study design	ICU Mortality %	Hospital Mortality %	90-day Mortality %	6-month Mortality %
Abosaif, 2006[297]	183	R, S	54	-	-	58.5
Abelha, 2009[293]	1 200	R, S	-	-	-	38.0
Bagshaw, 2008[217]	120 123	R, M	-	24.5	-	-
Cruz, 2007[15]	2 164	P, M	36.3	-	-	-
Hofhuis, 2013[20]	749	P, S	-	-	-	46.5
Hoste, 2006[16]	5 383	R, S	-	13.3	-	-
Joannidis, 2009[19]	14 356	R, M	-	36.4	-	-
Lopes, 2008[25]	662	R, S	-	41.3 (RIFLE) 39.8 (AKIN)	-	-
Medve, 2011[166]	459	P, M	39.3	49.1	-	-
Ostermann, 2007[183]	41 972	R, M	28.4	36.1	-	-
Ostermann, 2008[218]	22 303	R, M	31.1	40.4	-	-
Piccinni, 2011[167]	576	P, M	28.8	-	-	-
Sigurdsson, 2012[219]	1 012	R, S	-	37.6	-	-
Åhlström, 2006[216]	658	P, S	-	16.7	-	-

ICU; intensive care unit, M; Multi-centre, S; Single-centre, P; Prospective, R; Retrospective, AKIN; Acute Kidney Injury Network Criteria, KDIGO; RIFLE; Risk, Injury, Failure, Loss, End-stage criteria,

According to a systematic review from 2005, mortality of AKI patients has remained high throughout the years[299]. However, a study from 2007 suggested that mortality among AKI patients had decreased 3.4% annually from 1996 to 2005[215]. A major decrease in mortality of RRT treated patients was observed between 1988 and 2002 in a study published in 2006[300].

In most studies evaluating AKI patients' mortality, all or some RIFLE or AKIN stages have been independently associated with mortality[15,16,19,25,166,168,183,216-219]. However, even mild stages of AKI have been associated with increased mortality[16,21,184]. Advanced age[9,301] and existing comorbidities, such as diabetes[170,302] and CKD[21,183,218], seemed to increase the mortality among AKI patients. Recent data suggest that fluid overload[268,303] and HES use[190] in AKI patients are associated with excess mortality. Also, increasing severity of illness and number of organ failures[302], mechanical ventilation[9], sepsis[302] and a delayed ICU admission[9,301] have been associated with increased mortality in AKI patients.

2.9. Statistical methodology

2.9.1 Validity, bias and precision

Validity is the extent to which the study measures what it aims to measure and how well the results correspond to the real world (lack of systematic errors). Internal validity describes how well the cohort was selected, data recorded, and the analyses performed. External validity refers to how well the results can be generalized to other populations[304,305].

Study **bias** refers to the unknown or unacknowledged errors created during the design of the study, data collection, sampling, procedure, or choice of problem studied. The type of bias can be broadly divided into selection bias, information bias and confounding bias[304]. Selection bias occurs if the process of patient inclusion presents a systematic error. Information bias refers to imprecisely collected or classified data. Confounding bias is an error in the interpretation of associations and causalities between factors and outcomes[304,306].

Precision is the lack of random error in the study results. Confidence intervals (CI) can be used to measure precision. The narrower the CI the more precise the result. The usual method is to present the 95% confidence intervals, which are based on the hypothetical situation that the study was to be repeated many times. More precisely, when repeated infinitely often with 95% CI's, then 95% of the CIs would contain the "correct" value. More simply stated: with a 95% change the "correct" results lie between the interval[305,306]. Usually the CIs can be improved by increasing the sample size. In clinical studies, the lower 95% CI limit is often of importance representing the theoretical "minimal" value of the acquired result.

2.9.2 Statistical evaluation of biomarkers

Biomarkers are used to identify diseased individuals, to assess the severity of illness, to identify individuals at risk, to guide treatment, and to predict outcomes. To fulfil any of these tasks reliably, the biomarker should meet certain statistical criteria[307,308].

The performance of a biomarker is often described with sensitivity and specificity, which can be derived from a table combining the true disease state and the state indicated by the biomarker (Table 7 and Table 8)

Table 7. Diagnostic matrix for biomarker performance

	Disease	
Biomarker	**Sick**	**Healthy**
Positive	A (true positive)	B (false positive)
Negative	C (false negative)	D (true negative)

modified from Ray and colleagues 2010[307]

The sensitivity of the biomarker is the ability to identify true positives, and the specificity of the biomarker is the ability to identify true negatives. The positive predictive value of a biomarker is the likelihood that the positive result is a true positive, and the negative predictive value is the likelihood that a negative result is a true negative.

Table 8. Calculating the quantities describing biomarker performance

Sensitivity	A / A + C
Specificity	D / B + D
Positive predictive value	A / A + B
Negative predictive value	D / C + D
Positive likelihood ratio (LR+)	sensitivity / (1-specificity)
Negative likelihood ratio (LR-)	(1-sensitivity) / specificity

A, true positive; b, false positive; c, false negative; d, true negative

Positive likelihood ratio (LR+) can be described as the ratio of "true positives" to "false positives" (sensitivity / 1 – specificity), and the negative likelihood ratio (LR-) can be described as the ratio of "true negatives" to "false negatives". In general, the test in question is considered excellent if the LR+ is >10, good if the LR+ is 5-10, and poor if the LR+ is 1-5, but the clinical context should be considered when assessing relevance of likelihood ratios[307,308].

A receiver operating characteristic (ROC) curve is a graphical representation of likelihood ratios of individual measurements of the biomarker. Calculation of the area under the ROC curve (AUC) is a common way of assessing the discriminative power of a biomarker. In general, an AUC of > 0.9 is considered excellent, AUC of 0.75-0.9 good, and AUC of 0.5-0.75 poor. An AUC of 0.5 is equal to a roll of a dice[307].

The net reclassification index (NRI) and the integrated discrimination improvement (IDI) are sensitive tools for detecting additional benefit of a predictive marker[309-311]. NRI and IDI can be calculated with existing meaningful risk categories or as "continuous". In lack of established models for predicting the chosen outcomes, the continuous NRI can be applied by constructing multivariable models. When calculating the continuous NRI, each change (with and without the biomarker) in a probability improving the ability of the model to predict the true outcome, is assigned 1 and a change worsening the model is assigned -1. NRI is the percentage of patients whose classification improves by any amount for the marker in question (Figure 6). Integrated discrimination improvement (IDI) is calculated with the same principle using the change in the probabilities without converting them to 1 or -1[309-311].

$$\mathbf{NRI} \;=\; \left(\frac{\substack{\textbf{E+ patients} \\ \textbf{with improved} \\ \textbf{risk stratification}} \;-\; \substack{\textbf{E+ patients} \\ \textbf{with declined} \\ \textbf{risk stratification}}}{\textbf{Number of E+ patients}}\right) \;+\; \left(\frac{\substack{\textbf{E- patients} \\ \textbf{with improved} \\ \textbf{risk stratification}} \;-\; \substack{\textbf{E- patients} \\ \textbf{with declined} \\ \textbf{risk stratification}}}{\textbf{Number of E- patients}}\right)$$

E+ = Patients meeting the endpoint
E- = Patients not meeting the endpoint

Figure 6. Calculating the Net reclassification index (NRI)

3. AIMS OF THE STUDY

The main aims of this study were to evaluate the nationwide incidence of AKI in Finland, new biomarkers for diagnosis of AKI and outcome prediction, and the effect AKI has on the patients' outcome. Specific aims were:

1. To evaluate the incidence and population-based incidence of AKI in adult patients treated in Finnish ICUs (I)

2. To assess factors associated with development of AKI (I)

3. To evaluate the ability of urine NGAL to predict AKI, RRT, and 90-day mortality (II)

4. To evaluate the ability of urine IL-18 to predict AKI, RRT, and 90-day mortality (III)

5. To evaluate the effect of AKI on the health-related quality of life (HRQol) of ICU patients, and to assess factors associated with a good HRQol after ICU treatment in patients with AKI (IV)

6. To study the 90-day (I) and 6-month (IV) mortality of ICU patients with AKI.

4. PATIENTS AND METHODS

4.1. Patients

All patients in studies (I-IV) were from the prospective, observational FINNAKI study. The FINNAKI study was a prospective, multicentre, observational study with 17 ICUs from Finland participating in the study. During the five-month study period (1st of September 2011 to 1st of February 2012) all patients admitted to these ICUs (N=5 853) were screened for eligibility.

The FINNAKI study included all emergency ICU admissions and electively admitted patients, whose stay exceeded 24 hours. The study excluded:
1. Patients under 18 years of age
2. Re-admitted patients who received RRT during their previous admission
3. Elective ICU patients treated for less than 24 hours if discharged alive
4. Patients on chronic dialysis
5. Organ donors
6. Patients with no permanent residency in Finland or insufficient language skills
7. Patients transferred from another ICU if they had already participated in the study for 5 days
8. Intermediate care patients.

Study I included all FINNAKI study patients (N=2901). For **Study II** and **Study III**, a set of FINNAKI patients were randomly chosen from those with available urine samples. **Study II** included a total of 1042 patients from 15 different study centres with at least one urine NGAL sample analysed from the first 24 hours of ICU admission. **Study III** included 1439 patients from 17 different study centres with a urine IL-18 sample analysed from ICU admission. For **Study IV,** study centres that achieved a follow up rate of over 70% concerning the six-month EQ-5D were chosen. Study IV included altogether 1568 patients from 10 different study centres. Table 9 presents the numbers of patients in each study and Figure 7 illustrates a flow chart of studies I-IV.

Table 9. Numbers of patients in studies I-IV

Study	Number of patients	Criteria for selecting patients
I	2 901	All patients recruited to FINNAKI
II	1 042	A random set of patients with urine samples from the first 24 hours after ICU admission
III	1 439	A random set of patients with urine samples available from the time of ICU admission
IV	1 568	All patients from study centres with >70% EQ-5D follow-up rate at six months

EQ-5D, EuroQol Health-related quality of life questionnaire; ICU, Intensive Care Unit

In case of multiple admissions, the admission with the patient's highest KDIGO stage was chosen in all studies (I-IV). For patients that were transferred between two study ICUs during the first five ICU days, the data from these admissions were combined. Patient characteristics for all patients in studies I-IV are presented in Table 10.

The Ethics Committee of the Department of Surgery in Helsinki University Hospital gave approval for the FINNAKI study data collection and for the use of a deferred consent policy. The Finnish National Institute of Health gave approval for data collection from medical records of deceased patients lacking a written consent. For all other study patients a written, informed consent was obtained from the patient or proxy.
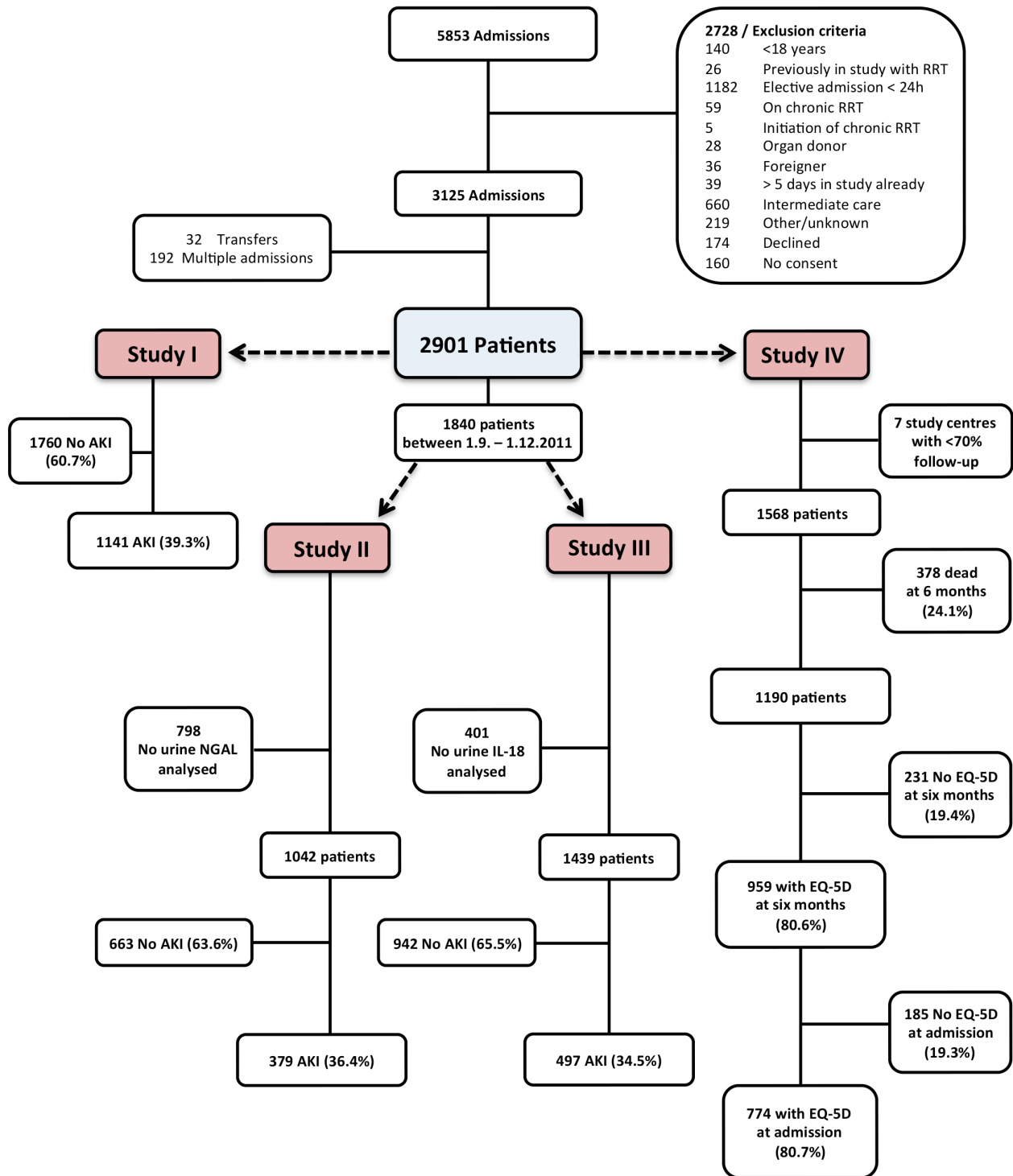
Figure 7. Flow chart of studies I-IV. RRT, Renal replacement therapy; AKI, Acute kidney injury; EQ-5D, EuroQol Health-related quality of life questionnaire.

Table 10. Characteristics of patients in studies I-IV

	Study I N=2901	Study II N=1042	Study III N=1439	Study IV N=1568
Age, years	64 (51-74)	63 (51-73)	63 (50-73)	65 (53-74)
Gender, male	1846 (63.6)	673 (64.6)	920 (63.9)	1015 (64.7)
Baseline Cr (µmol/l)	76 (61-93)	77 (62-92)	74 (60-91)	78 (63-95)
SAPS II score (points)	37 (28-50)	36 (27-48)	36 (27-47)	36 (27-49)
SOFA score (first 24 hours, points)	7 (4-9)	7 (4-9)	7 (4-9)	7 (5-10)
Emergency admission	2544 (87.7)	912 (87.5)	1286 (90.1)	1287 (82.1)
Surgical admission	1010 (34.8)	362 (34.7)	485 (33.7)	618 (39.4)
DIAGNOSTIC GROUP (APACHE III)				
Cardiovascular, operative	438 (15.1)	160 (15.4)	182 (12.6)	355 (22.6)
Cardiovascular, non-operative	390 (13.4)	154 (14.8)	189 (13.1)	231 (14.7)
Respiratory tract, non-operative	353 (12.2)	121 (11.6)	178 (12.4)	184 (11.7)
Metabolic	262 (9.0)	94 (9.0)	139 (9.7)	133 (8.5)
Neurological, non-operative	255 (8.8)	76 (7.3)	133 (9.2)	85 (5.4)
Gastrointestinal tract, operative	253 (8.7)	95 (9.1)	135 (9.4)	152 (9.7)
Gastrointestinal tract, non-operative	189 (6.5)	59 (5.7)	92 (6.4)	92 (5.9)
Trauma	186 (6.4)	63 (6.0)	99 (6.8)	70 (4.5)
Sepsis	182 (6.3)	67 (6.4)	89 (6.2)	99 (6.3)
Other (<5% each)	393 (13.5)	153 (14.7)	203 (14.1)	167 (10.7)

Values are presented as numbers (percentages) or median (interquartile range, IQR); Cr, creatinine; SAPS II, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assesssment; APACHE II, Acute Physiology and Chronic Health Evaluation

4.2. Study design

4.2.1. Study I

Study I described the whole FINNAKI study cohort. The aims of this study were to report the incidence, population-based incidence, risk factors, and outcome (90-day mortality) of patients with AKI in a consecutive, nationwide cohort of mixed critically ill adult patients.

4.2.2. Study II

This study evaluated the ability of urine NGAL to predict AKI, RRT, and 90-day mortality in critically ill adult patients. NGAL was analysed at ICU admission, at 12h and at 24 h if available. The highest NGAL was then selected for statistical analyses for each patient. Sensitivity analyses were performed first for all and then in subgroups excluding: 1) septic patients, 2) patients who had AKI or received RRT on admission day, and 3) patients lacking a true baseline Cr value.

4.2.3. Study III

This study assessed urine IL-18 as a diagnostic marker for AKI, and as an outcome marker predicting RRT, or 90-day mortality. IL-18 at ICU admission, and at 24 h, was analysed and the highest value was chosen for statistical analyses. The association of the change in IL-18 from admission to 24 h with AKI, RRT, and 90-day mortality was also analysed. The predictive powers of urine IL-18 and NGAL were also compared in patients with both biomarkers available.

Study III was originally designed to also evaluate the prognostic power of kidney injury molecule 1 (KIM-1) in the same patient population as IL-18, but the data concerning KIM-1 were excluded after analysis due to implausible results.

4.2.4. Study IV

This study described the long-term outcome of AKI patients assessed by the patients' health-related quality of life, and by their six-months mortality. The HRQol of the study patients was measured at admission and at six months with the EQ-5D questionnaire, and compared to the age- and sex-matched general Finnish population. Also, factors associated with a good quality of life after ICU treatment were assessed.

4.3. Data collection

Study data was collected from the Finnish Intensive Care Consortium's (FICC) prospective database and with a study specific case report form (CRF). Data were recorded for five days in the ICU for each patient. Collection was terminated early if the patient was discharged before day five.

All of the 17 study ICUs belong to the Finnish Intensive Care Consortium (FICC). The FICC database was originally established in 1994 for benchmarking purposes, has since expanded, and is currently handled by Tieto Healthcare & Welfare Ltd. The database routinely records patient demographics, APACHE III admission diagnosis, International Classification of Diseases 10th revision (ICD-10) diagnosis, ICU severity scores (SOFA, SAPS II, TISS), length-of-stay, and ICU- and hospital mortality. In addition the database records, an extensive set of physiologic data, most of which are automatically transferred via the clinical information systems from patient monitors, ventilators, and laboratory systems. Some data, such as the HRQol by EQ-5D scores and vital status at hospital discharge, are entered manually into the database. Before being saved into the central database, local processes by automated filters and trained personnel validate the data. The completeness of the data is routinely monitored and has been found to be good[312]. Some variables (e.g. hourly urine output) were added to the database for the purpose of this study. An automated calculator built into the database did calculations for the severity of the kidney injury with regard to UO.

A study specific CRF was developed to augment the data from the database. The ICU physician and/or nurse filled this CRF at admission, daily for five days, and at ICU discharge. Data collected with the CRF comprised of chronic and present health status, medications, information on possible risk factors for AKI, evaluation of severe sepsis, disseminated intravascular coagulation (DIC), other organ dysfunction, fluid balance, and RRT. The CRF variables were altogether 54% of the whole dataset. The reliability of this CRF data was monitored in eight randomly chosen study centres with a structured monitoring plan.

4.4. Population-based calculations

To perform calculations of the population-based incidence, the number of adults in the study area (participating hospital districts) in December 2011 was obtained from Statistics Finland. The Finnish Registry for Kidney disease provided the number of adults on chronic RRT. This number (N= 1 527) was subtracted from the whole population resulting in a reference population of 3 671 143 adults, which corresponds to 85.1% of the whole Finnish adult population.

4.5. Laboratory sample collection

Urine samples were collected from the study patients at ICU admission, 12 h, and 24 h. Urine was collected with a sterile technique from Foley catheters. The admission sample was taken immediately after admission or at 2 hours at the latest. The samples were aliquoted and either stored first temporarily at -20 °C, or immediately at -80 °C, where they were stored until assayed. The longest storage time at -80 °C was six months.

4.6. Laboratory assays

4.6.1. Neutrophil gelatine-associated lipocalin (II)

Urine NGAL was analysed with a commercially available enzyme linked immunosorbent assay (ELISA) following manufacturer's instructions (BioPorto® Gentofte, Denmark). The analyst was blinded to patient information.

The samples were diluted 1/50 and the validated ELISA method[313] had a measurement range of 10 to 1000 ng/ml with the chosen dilution. Out of range values were registered as the highest of lowest value (10 or 1000 ng/ml). The chosen kit shows good intra-assay precision (median coefficient of variation, CV% <5%), and inter-assay precision (CV% <10%). For the statistical analyses the highest NGAL of the first 24 hours was used.

4.6.2. Interleukin 18 (III)

Urine IL-18 was analysed with a commercially available enzyme linked immunosorbent assay ELISA kit (Cusabio Biotech® Wuhan, China), according to the manufacturer's instructions by an analyst blinded to patient information.

The samples were concentrated 2 fold, and with this the detection range of this method is 3.9 – 250 pg/ml. Out of range values were registered as the highest and lowest value. The IL-18 kit shows good intra-assay and inter-assay precision for samples tested from urine (CV% <10%). The highest IL-18 of the first 24 hours and the change in IL-18 from admission until 24 hours were used for statistical analyses.

Urine kidney injury molecule 1 (KIM-1) was also analysed from the same patient population with an immunosorbent ELISA (ALPCO® Diagnostics, Salem, USA) assay. Due to unknown reasons, over 90% of the results were below the detection limit. These data were then discarded because of an evident problem in some stage of the analysis (Nisula et al, unpublished data).

4.7. Definitions

4.7.1. Acute kidney injury

In all studies (I-IV), AKI was defined with the Kidney Disease: Improving Global Outcomes (KDIGO) criteria[1] with both daily Cr measurements and hourly urine output and a continuous moving baseline for both. The FINNAKI study was originally designed with the AKIN[3] criteria supplemented with a historical baseline Cr. The KDIGO criteria were published in 2012 concurrently with the study data collection, and when the data were analysed, the AKI staging in study population was calculated using the KDIGO criteria. This resulted in identical classification of the study patients. In all studies (I-IV) the baseline serum Cr was defined as the latest measurement from the previous year, however excluding the previous week. For patients lacking a baseline, the Modification of Diet in Renal Disease (MDRD) equation[39], assuming a glomerular filtration rate of 75 ml/min/1.73 m², was used as recommended by the ADQI[29]. The highest AKI stage for each patient was used in the incidence calculations. The patients' AKI and RRT status was screened for five days in the ICU (I, IV). For the biomarker studies (II, III), in evaluating samples from the first 24 hours of ICU admission, the screening period of AKI and RRT was limited to three days.

4.7.2. Sepsis and DIC

Evaluation of sepsis and severe sepsis, and DIC, were done daily using the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM)[314] and International Society on Thrombosis and Haemostasis (ISTH) criteria[315].

4.7.3. Risk Factors for AKI

In study I the potential risk factors for AKI were defined as follows: hypotension: systolic blood pressure < 90 mmHg for 1 hour, rhabdomyolysis: creatinine kinase (CK) > 5000 U/l or myoglobin > 5000 µg/l, hypovolaemia: hypovolaemia by clincans´ judgement, resuscitation: a haemodynamic collapse requiring chest compressions, defibrillation or administration of adrenalin, low cardiac output: inadequate systolic function + hypotension + signs of tissue hypoxia, massive transfusion: transfusion of more than 10 red blood cell units in 48 hours. Data on hypotension, hypovolaemia, low cardiac output, and massive transfusion were only recorded prior to ICU admission. Colloids before ICU admission included HES and gelatin, and during the ICU stay also albumin.

4.7.4. Renal replacement therapy

RRT was defined by either continuous or intermittent treatment initiated in the ICU during five days in study I and IV, and during three days in studies II and III. No specific indications for initiation of RRT were defined for this was an observational study and all study centres followed their routine guidance.

4.8. Outcome measures

4.8.1. Health-related quality of life (IV)

The EuroQol (EQ-5D) quality of life questionnaire was used to assess the health-related quality of life of the study patients a) at ICU admission (HRQol prior to critical illness) and b) at six-months after ICU admission. Collection of this data is a part of the FICC database routines. The ICU nurse presented the questions to the patient or proxy at the first eligible time after admission. The follow-up at six-months was carried out by mail or telephone. EQ-5D data obtained from proxies have been shown to be reliable[316,317].

The EQ-5D[284] is a validated tool in measuring HRQol in critically ill patients[318,319]. It has five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that are all assessed on a scale from 1 to 3. The answers are combined to an index score (range from 0 to 1) with population-based weight coefficients. The index scores can be used to compare different populations. As a part of the questionnaire, a visual analogue scale describes the respondent's self-rated health on a scale from 0 to 100. Based on previous data, a significant change in the EQ-5D index is 0.08, and for the VAS score 7[320,321].

4.8.2. Mortality (I-IV)

The 90-day and 180-day (6 months) mortality were obtained from the Finnish Population Register Centre (http://www.vrk.fi) using the study patients' social security numbers.

4.9. Statistical methods

Nominal data were presented as numbers (percentages). Continuous data (as not normally distributed) were presented as medians with interquartile range (IQR, 25th – 75th percentiles). Categorical variables were compared with the Chi-square test or the Fisher's exact test when appropriate, and continuous variables with the Mann-Whitney U-test. The Wilcoxon signed rank test was used to compare repeated measurements of EQ-5D (IV). Kaplan-Meyer survival curves were built for AKI patients (I). A backwards-conditional stepwise logistic regression analysis was performed to calculate odds ratios for independent association to AKI and 90-day mortality (I)

To evaluate the properties of biomarkers (II, III), receiver operating characteristics curves (ROC) were constructed and the areas under curves (AUC) with 95% confidence intervals were calculated. Best cut-off values with 95% CIs (II) were identified with the Youden index and the sensitivities, specificities, and positive likelihood ratios (LR+) were calculated. To evaluate the additive predictive power of the biomarkers, the continuous net

reclassification improvement (NRI) and integrated discrimination improvement (IDI)[309-311] were calculated. For this purpose, multivariable predictive models (enter model) for each endpoint were constructed by inserting variables proven significant in a univariable model. The model was then tested with and without the biomarker. Probabilities from these models were used to calculate the continuous NRI and IDI.

The sample size calculations of the FINNAKI study were based on targeting clinically significant 95% CIs of ± 2.0% for the incidence of AKI. In studies II and III sample size calculation were based on the 95% CI limits of AUC as previously described[322] targetting sample sizes providing clinically relevant CIs less than ± 0.05 (<0.1) for all endpoints using incidences for AKI, RRT and 90-day mortality from the whole study cohort.

A P-value of <0.05 was considered significant. As an exception, when selecting variables to the predictive models (III, IV) on the basis of univariable models, a P-value of 0.2 was considered adequate.

The Youden index and cutoff points (II) were calculated with MedCalc version 12.7.2 (MedCalc Software, Belgium) and all other analyses with SPSS version 19 - 21 (SPSS, Chicago, Ill., USA)

5. RESULTS

5.1. Incidence of AKI (I)

The total number of patients in each study centre varied between 59 and 419 (I). The incidence of AKI ranged from 20.7% to 53.5% in different study centres (Table 11). The **incidence of AKI** in the whole study population was 1141/2901 (39.3%, 95% CI 37.5 - 41.1%). KDIGO stage 1 AKI was present in 499 (17.2%, 95% CI 15.8 - 18.6) patients, stage 2 in 232 (8.0%, 95% CI 7.0 – 9.0) patients, and stage 3 in 410 (14.1%, 95% CI 12.8 – 15.4%) patients. RRT was initiated during the first five ICU treatment days in 272/2901 patients (9.4%, 95% CI 8.3% - 10.5%).

The **population-based incidence** of AKI in adult ICU patients, calculated from the number of adult inhabitants in the area of the participating hospital districts, was 746 (95% CI 717 - 774) per million adults per year.

Table 11. The numbers (percentages) of patients with acute kidney injury (AKI) in individual FINNAKI study sites (Nisula et al, unpublished results)

Site	AKI patients N (%)	
1	123/307 (40.1)	UH
2	153/286 (53.5)	UH
3	85/193 (44.0)	UH, CS
4	121/419 (28.9)	UH
5	107/314 (34.1)	UH
6	19/92 (20.7)	
7	46/141 (32.6)	
8	53/108 (49.1)	
9	61/165 (37.0)	
10	36/101 (35.6)	
11	61/120 (50.8)	
12	37/97 (38.1)	
13	51/113 (45.1)	
14	91/223 (40.8)	UH
15	28/63 (44.4)	
16	23/59 (39.0)	
17	46/100 (46.0)	

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); UH; University Hospital; CS, Cardiac Surgery

The total number of AKI patients, AKI patients stratified into different KDIGO stages and numbers of RRT patients in studies I-IV are presented in Table 12.

Table 12. Incidences of acute kidney injury (AKI) and renal replacement therapy (RRT) and numbers of patients in different KDIGO stages in studies I-IV

Study (N)	AKI	Stage I	Stage II	Stage III	RRT
I (2901)	1141 (39.3)	499 (17.2)	232 (8.0)	410 (14.1)	272 (9.4)
II* (1042)	379 (36.4)	168 (16.1)	81 (7.8)	130 (12.5)	83 (8.0)
III* (1439)	497 (34.5)	213 (14.8)	113 (7.9)	171 (11.9)	96 (6.7)
IV (1568)	635 (40.5)	280 (17.9)	119 (7.6)	236 (15.1)	162 (10.3)

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); RRT, Renal Replacement Therapy, KDIGO, Kidney Disease: Improving Global Outcomes Criteria *For studies II and III observation period for AKI and RRT was 3 days. Numbers are presented as count (percentage)

5.2. Risk factors for AKI (I)

In study I, patients that developed AKI were significantly older (median 66 versus 62 years), more often male (66.2% versus 62.0%), and had a higher baseline creatinine value than patients without AKI (median 78.0 µmol/l versus 73.0 µmol/l). Patients with AKI were generally more ill judged by SAPS (43 versus 33 points) and SOFA scores (first 24 hours median 9 versus 6), they required mechanical ventilation (74.8% versus 65.9%) and vasoactive treatment (78.1% versus 53.4%) more often, and had a higher lactate level (median 2.7 mmol/l versus 1.9 mmol/l) during the first 24 hours of their ICU stay. Emergency surgery prior to the ICU admission was significantly more common in AKI patients (24.5% versus 20.8%), but the type of admission (emergency/non-emergency, post-operative/non-operative) was not of significance.

As shown by Table 13, hypertension, arteriosclerosis, diabetes, systolic heart failure, and chronic kidney disease were significantly more common in patients with AKI than in patients without AKI. AKI patients had ACE-inhibitors or ARBs, NSAIDs, diuretics, metformin, statins, or corticosteroids more often as permanent medications than patients without AKI. Table 13 presents chronic co-morbidities and medications in patients with and without AKI.

Table 13. Co-morbidities and medication in patients with and without acute kidney injury (AKI).

	Data available	No AKI (N=1760) N (%)	AKI (N=1141) N (%)	P
Co-morbidity				
Chronic obstructive pulmonary disease	2883	148 (8.4)	116 (10.3)	0.058
Hypertension	2885	749 (42.8)	630 (55.5)	<0.001
Arteriosclerosis	2870	194 (11.1)	186 (16.5)	<0.001
Diabetes	2897	345 (19.6)	292 (26.6)	<0.001
Systolic heart failure	2874	176 (10.1)	159 (14.1)	0.001
Chronic kidney disease	2889	67 (3.8)	122 (10.8)	<0.001
Medication				
ACE-inhibitor or ARB	2839	555 (32.3)	481 (43.0)	<0.001
NSAID	2785	129 (7.6)	113 (10.3)	0.01
Diuretic	2847	398 (23.1)	410 (36.4)	<0.001
Aspirin	2845	449 (26.0)	334 (29.8)	0.016
Metformin	2854	188 (10.9)	161 (14.3)	0.004
Statin	2856	471 (27.2)	389 (34.5)	<0.001
Corticosteroids	2864	118 (6.8)	104 (9.2)	0.011

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); ACE-inhibitor, angiotensin convertase enzyme-inhibitor; ARB, angiotensin II receptor blocker; NSAID, non-steroid anti-inflammatory drug.

Acute events that were studied as possible risk factors for AKI are presented in Table 14. According to the results, severe sepsis, DIC, resuscitation, and administration of ACE-inhibitors or ARBs were significantly more frequent in patients who developed AKI both prior to ICU admission and when including time in the ICU before the development of AKI.

Rhabdomyolysis and emergency surgery were more common among AKI patients before ICU, but when including the ICU admission, there was no longer a significant difference. Concerning hypotension, hypovolaemia, low cardiac output, and massive transfusion data were only available prior to ICU, but all of these were significantly more common in patients that developed AKI. Peptidoglycan antibiotics were given in equal amounts to patients that did or did not develop AKI.

Contrast medium was more frequently given to patients that didn't develop AKI both before ICU and during the admission. Almost 40% of the patients that developed AKI received diuretics prior to their ICU admission, which was significantly more than to patients that didn't develop AKI. However, this was reversed when including the time in the ICU into the analysis. NSAIDs were given equally to patients that later on developed AKI and to those that didn't before ICU but less AKI patients received NSAIDs in the ICU. Also, patients that developed AKI received significantly more colloids prior to their ICU admission, but that difference no longer existed after including the time in the ICU.

Table 14. Events preceding acute kidney injury (AKI).

	NO AKI (N=1760) N / total / (%)	AKI (N=1141) N / total / (%)	*P*
Events before ICU admission			
Severe sepsis	299 /1760 (17.0)	367/1141 (32.2)	<0.001
DIC	16 /1750 (0.9)	41/1135 (3.6)	<0.001
Hypotension	303/1744 (17.4)	395/1117 (35.4)	<0.001
Rhabdomyolysis	37/1756 (2.1)	40/1138 (3.5)	0.015
Hypovolaemia	404/1754 (23.0)	467/1127 (41.4)	<0.001
Resuscitation	169/1757 (9.6)	150/1138 (13.2)	0.002
Low cardiac output	56/1758 (3.2)	81/1138 (7.1)	<0.001
Massive transfusion	46/1760 (2.6)	47/1141 (4.1)	0.017
Emergency surgery	366/1758 (20.8)	279/1139 (24.5)	0.012
Radiocontrast dye	454/1751 (25.9)	247/1134 (21.8)	0.006
Peptidoglycan antibiotics	131/1757 (7.5)	102/1136 (9.0)	0.081
ACE-inhibitor or ARB	388/1733 (22.4)	326/1108 (29.4)	<0.001
NSAID	152/1684 (9.0)	109/1084 (10.1)	0.201
Diuretics	428/1713 (25.0)	436/1104 (39.5)	<0.001
Colloids	439/1634 (26.9)	409/1086 (37.7)	<0.001
Events before day 5 (including 48-hours preceding ICU admission)			
Severe sepsis	365/1760 (20.7)	388/1141 (34.0)	<0.001
DIC	29/1759 (1.6)	52/1138 (4.6)	<0.001
Rhabdomyolysis	56/1760 (3.2)	41/1139 (3.6)	0.307
Resuscitation	194/1760 (11.0)	155/1138 (13.6)	0.021
Emergency surgery	504/1758 (28.7)	323/1139 (28.4)	0.445
Radiocontrast dye	550/1759 (31.3)	273/1137 (24.0)	<0.001
Peptidoglycan antibiotics	184/1760 (10.5)	119/1139 (10.4)	0.524
ACE-inhibitor or ARB	468/1760 (26.6)	340/1127 (30.2)	0.021
NSAID	226/1757 (12.9)	120/1125 (10.7)	0.043
Diuretics	1063/1760 (60.4)	597/1122 (53.2)	<0.001
Colloids	774/1760 (44.0)	513/1114 (46.1)	0.147

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); ACE-inhibitor, angiotensin convertase enzyme-inhibitor; ARB, angiotensin II receptor blocker; DIC, disseminated intravascular coagulation; Colloid, HES or gelatin (including albumin in the ICU); Hypotension, systolic blood pressure < 90 mmHg for 1 hour before ICU admission; Hypovolemia, by clinicans´ judgement before ICU admission; Low Cardiac Output, inadequate systolic function + hypotension + signs of tissue hypoxia before ICU admission; Massive transfusion, transfusion of more than 10 red blood cell units in 48 hours before ICU admission; NSAID, non-steroid anti-inflammatory drug; Rhabdomyolysis, CK > 5000 U/l or myoglobin > 5000 µg/l; Resuscitation, haemodynamic collapse requiring CPR, defibrillation or administration of adrenalin;.

In this study population, based on a logistic regression analysis, several conditions were independently associated with the development of AKI, including: 1) hypovolaemia prior to ICU admission, 2) administration of diuretics prior to ICU admission, 3) administration of colloids prior to ICU admission, and 4) chronic kidney disease Table 15 shows the model-based odds ratios (OR) for these variables.

Table 15. Factors independently associated with acute kidney injury (AKI)

Variable	Odds ratio	95% CI
Pre-ICU hypovolaemia	2.20	1.85 – 2.62
Pre-ICU diuretics	1.68	1.41 – 2.00
Pre-ICU colloids	1.35	1.13 – 1.61
Chronic kidney disease	2.64	1.88 – 3.71

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); Hypovolaemia, by clinicians' judgment; Colloids, gelatin in 52% of patients, starch in 40% of patients, and both in 8% of patients

5.3. Novel biomarkers for AKI

5.3.1. Neutrophil gelatinase-associated lipocalin (II)

At least one urine NGAL sample was analysed from altogether 1042 patients. The highest uNGAL value was below the detection limit in 107 (10.3%) patients and exceeded the upper limit in 184 (17.7%) patients. The numbers (percentages) of samples analysed at each time point of study patients still in the ICU, were 965/1042 (93%) at 0 h, 669/1006 (67%) at 12 h, and 817/848 (96%) at 24 h. In 56% of the patients, the highest uNGAL value was from the admission sample.

Receiver operating characteristic (ROC) curves for urine NGAL in the prediction of AKI, RRT and 90-day mortality are presented as Figure 8. The performance of the highest urine NGAL of the first 24 hours of ICU admission in the prediction of AKI, RRT, and 90-day mortality is presented in Table 16.

A sensitivity analysis excluding events on day 1, leaving 201 AKI patients and 45 RRT patients, resulted in AUCs (with 95% CI) of 0.668 (0.624 – 0.712) for NGAL in prediction of AKI, and 0.857 (0.805 – 0.909) in prediction of RRT. Table 17 presents the sensitivity analyses, excluding septic patients, events on day 1, and patients without a known baseline creatinine.
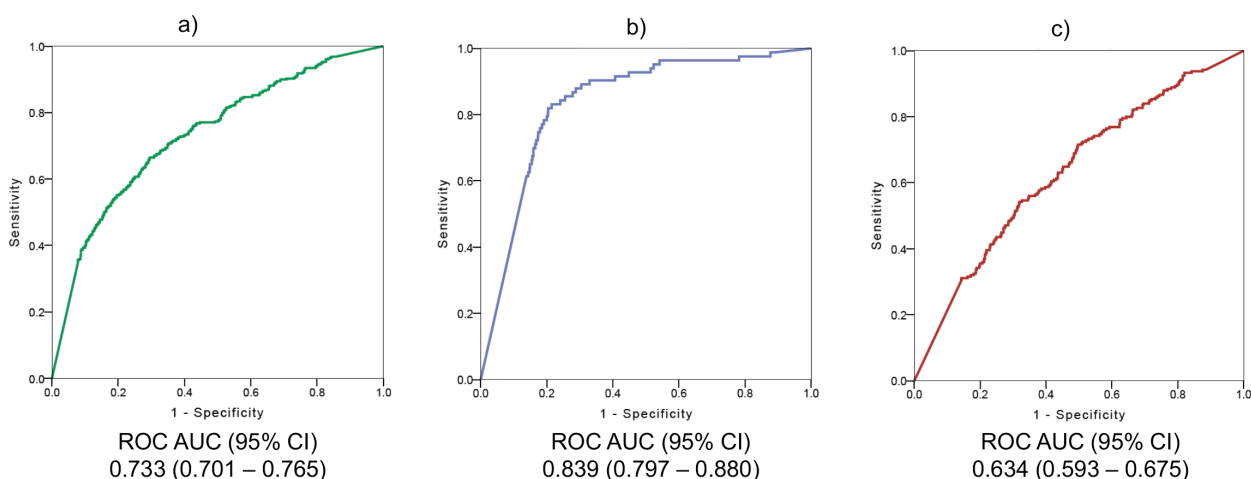
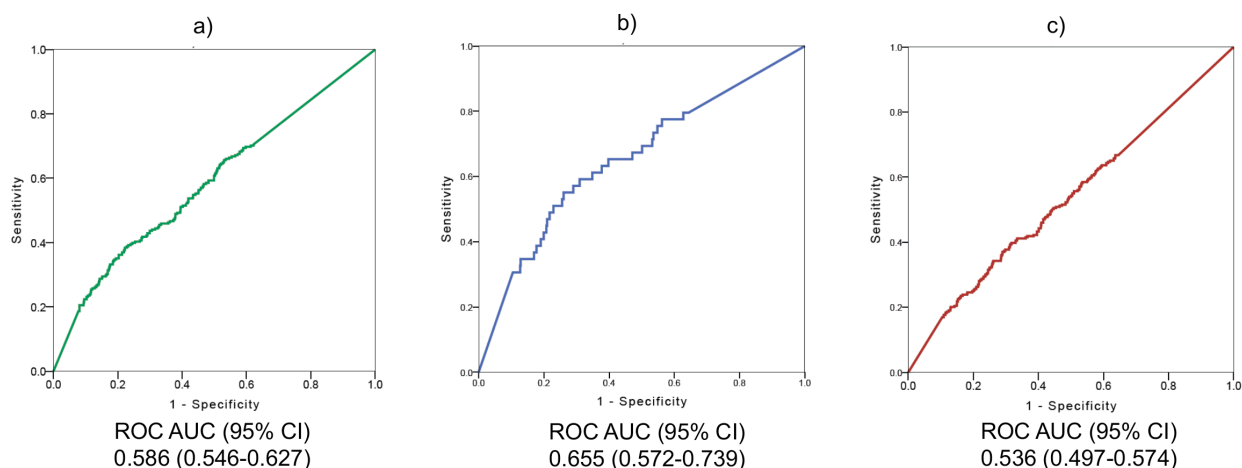| a)	b)	c)
ROC AUC (95% CI)	ROC AUC (95% CI)	ROC AUC (95% CI)
0.733 (0.701 – 0.765)	0.839 (0.797 – 0.880)	0.634 (0.593 – 0.675)

Figure 8. Receiver operating characteristics curves (ROC AUC with 95% Confidence Interval) for urine NGAL in prediction of a) acute kidney injury, b) renal replacement therapy, and c) 90-day mortality

Adding NGAL to the predictive models constructed for AKI, RRT, and 90-day mortality changed the probability–based ROC AUCs (95% CI) from 0.705 (0.672-0.738) to 0.752 (0.721-0.783) concerning AKI, from 0.938 (0.910-0.966) to 0.945 (0.918-0.972) concerning RRT, and from 0.821 (0.791-0.852) to 0.823 (0.793-0.854) concerning 90-day mortality.

Table 16. AUC's, sensitivities, specificities, best cut-off values, positive likelihood ratios, NRIs, and IDIs for urine NGAL (24-hour highest value) regarding prediction of acute kidney injury (AKI), renal replacement therapy (RRT), and 90-day mortality

	AKI (N=379)	RRT (N=83)	90-day mortality (N=225)
AUC (95% CI)	0.733 (0.701 – 0.765)	0.839 (0.797 – 0.880)	0.634 (0.593 – 0.675)
Sensitivity	0.665	0.831	0.542
Specificity	0.704	0.785	0.681
Cut-off ng/ml (95% CI)	157 (73 – 225)	449 (219 – 538)	229 (76 – 988)
LR+	2.24 (1.95 – 2.57)	3.81 (3.26 – 4.47)	1.70 (1.45 – 1.98)
NRI	56.9%	56.3%	15.3%
IDI	0.071	0.022	<0.001

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); AUC, Area Under the Curve; 95% CI, 95% Confidence Interval; LR+, Positive likelihood Ratio, NRI, Net Reclassification Index; IDI, Integrated Discrimination Improvement; RRT, Renal Replacement Therapy

Table 17. Sensitivity analyses for urine NGAL (24-hour highest value) regarding prediction of acute kidney injury (AKI), renal replacement therapy (RRT), and 90-day mortality.

	AUC (95% CI)
Non-septic patients (N= 554)	
AKI (N=162)	0.702 (0.654 – 0.750)
RRT (N=37)	0.863 (0.792 – 0.934)
90-day mortality (N=88)	0.600 (0.534 – 0.665)
Events on day 1 excluded	
AKI (N=201)	0.668 (0.624 – 0.712)
RRT (N=45)	0.857 (0.805 – 0.909)
Patients with known baseline Cr (N=665)	
AKI (N=253)	0.732 (0.692 – 0.771)
RRT (N=53)	0.847 (0.803 – 0.890)
90-mortality (N=166)	0.654 (0.607 – 0.700)

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); RRT, Renal Replacement Therapy; 95% CI, confidence interval; AUC, area under receiver characteristics curve

5.3.2. Interleukin 18 (III)

An admission IL-18 sample was analysed from 1439 patients, of which 1080 patients also had the 24 hours sample available. The 229 of the 497 AKI patients who had AKI on the first ICU day were excluded from the analyses concerning AKI as on endpoint, and similarly 47 of the 96 RRT patients were excluded from the analyses concerning RRT. Figure 9 illustrates the ROC curves for IL-18 in the prediction of AKI, RRT, and 90-day mortality.

ROC AUC (95% CI)
0.586 (0.546-0.627)

ROC AUC (95% CI)
0.655 (0.572-0.739)

ROC AUC (95% CI)
0.536 (0.497-0.574)

Figure 9. Receiver operating characteristics curves (ROC AUC with 95% Confidence Interval) for urine IL-18 in prediction of a) acute kidney injury, b) renal replacement therapy, and c) 90-day mortality

Table 18 presents AUC (with 95% CI), sensitivities, specificities, best cut-off values, and positive likelihood ratios (LR+) for the highest IL-18 during the first 24 hours in prediction of AKI, RRT, and 90-day mortality. Sensitivity analyses were performed to exclude the bias from septic patients and estimated baseline creatinine. The results of these sensitivity analyses are presented in Table 19.

Table 18. AUC's, sensitivities, specificities, best cut-off values, and positive likelihood ratios for urine IL-18 (24-hour highest value) regarding prediction of acute kidney injury (AKI), renal replacement therapy (RRT) and 90-day mortality

	AKI (N=268)	RRT (N=49)	90-day mortality (N=289)
AUC (95% CI)	0.586 (0.546-0.627)	0.655 (0.572-0.739)	0.536 (0.497-0.574)
Sensitivity	0.384	0.551	0.398
Specificity	0.778	0.739	0.683
Cut-off ng/ml (95% CI)	65	65	44
LR+	1.72 (1.41-2.08)	2.04 (1.54-2.69)	1.25 (1.06-1.47)

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); AUC, Area Under the Curve; 95% CI, 95% Confidence Interval; LR+, Positive likelihood Ratio, RRT, Renal Replacement Therapy

In the 1080 patients with both IL-18 samples available, the change in IL-18 from admission to 24 h predicted new AKI with an AUC (95% CI) of 0.557 (0.514 - 0.601). For prediction of RRT, the AUC (95% CI) was 0.531 (0.428 - 0.633), and the change in IL-18 produced an AUC (95% CI) of 0.489 (0.447 - 0.532) for 90-day mortality. Figure 10 shows the temporal changes in IL-18 from admission to 24h stratified by presence of AKI during the first three ICU days.
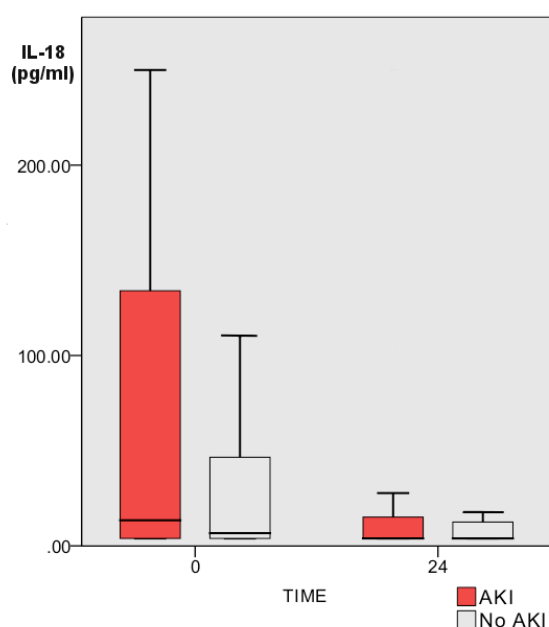
Figure 10. Boxplot of urine IL-18 on admission and 24 hours stratified by the presence of AKI during the first three ICU days in patients with both samples available (N=1080)

The multivariable model constructed to predict AKI in this population produced AUCs (95% CI) of 0.693 (0.649-0.737) without and 0.697 (0.653-0.741) with IL-18. In this model, chronic kidney disease, SAPS II (without age and renal points), SOFA (without renal points), highest lactate of day 1, severe sepsis, and IL-18 were independently associated with development of AKI. The model for 90-day mortality produced AUCs (95% CI) of 0.824 (0.795-0.854) without, and 0.824 (0.795-0.854) with, IL-18. Age, liver disease, SAPS II (without age and renal points), acute liver failure, and AKI were independently associated with 90-day mortality.

Table 19. Sensitivity analyses for urine IL-18 (24-hour highest value) regarding prediction of acute kidney injury (AKI), renal replacement therapy (RRT), and 90-day mortality.

	AUC (95% CI)
Non-septic patients (N= 749)	
New AKI (N=116)	0.563 (0.502-0.624)
RRT (N=16)	0.780 (0.668-0.893)
90-day mortality (N=98)	0.534 (0.472-0.597)
Patients with known baseline Cr (N=917)	
New AKI (N=174)	0.570 (0.519-0.620)
RRT (N=32)	0.643 (0.539-0.748)
90-mortality (N=212)	0.552 (0.508-0.597)

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); RRT, Renal replacement Therapy; 95% CI, confidence interval; AUC, area under receiver characteristics curve

5.3.3. IL-18 versus NGAL (III)

For 855 patients both the admission urine IL-18 and NGAL were available. Figure 11 shows the comparing ROC curves of IL-18 and NGAL for the chosen outcomes and Table 20 lists the corresponding AUCs (95% CI) of NGAL, IL-18, and IL-18 * NGAL (IL-18 times NGAL) in prediction of AKI, RRT, and 90-day mortality.

a) AKI   b) RRT   c) 90-day mortality
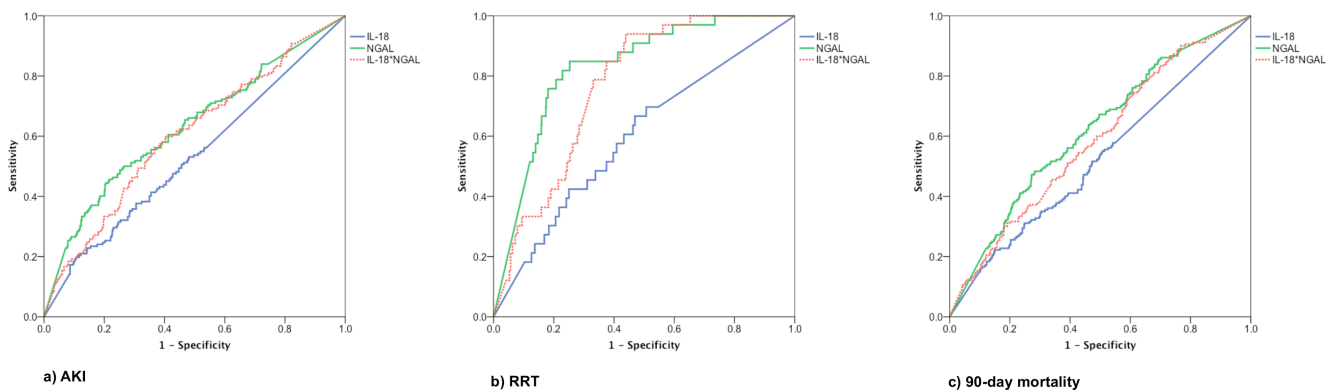
Figure 11. Receiver operating characteristic (ROC) curves for NGAL regarding prediction of a) acute kidney injury, b) renal replacement therapy, c) 90-day mortality

Table 20. AUCs (95% CI) of NGAL, IL-18, and IL-18 * NGAL in prediction of acute kidney injury (AKI), renal replacement therapy (RRT), and 90-day mortality

	AUC (95% CI)		
	AKI	RRT	90-day mortality
NGAL	0.631 (0.579-0.682)	0.827 (0.765-0.889)	0.618 (0.573-0.664)
IL-18	0.531 (0.479-0.584)	0.598 (0.498-0.697)	0.524 (0.476-0.573)
NGAL*IL-18	0.603 (0.553-0.654)	0.767 (0.708-0.826)	0.588 (0.542-0.634)

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); AUC, Area Under the Curve; 95% CI, 95% Confidence Interval; RRT, Renal Replacement Therapy

5.4. Outcome

5.4.1. Length-of-stay (I)

In this study population, the length-of stay (median, days with IQR) in the ICU was significantly longer in patients who developed AKI (3.7, 1.9 - 6.4 days) than in patients without AKI (1.9, 1.0-4.0 days). Also, the hospital stay was significantly longer in AKI patients (12, 6.0 - 22.0 days) compared to patients without AKI (9, 5.0 - 15.0 days).

5.4.2. Health-related quality of life (IV)

In study IV, 1190 of the 1568 patients were alive at six months, and of those, 411 (34.5%) had AKI. Of the six-month survivors, 959 (80.6%) answered the EQ-5D questionnaire (including 327 patients with AKI). For 774/959 (80.7%) patients, the admission EQ-5D was also available (including 268 patients with AKI). There was no difference in the characteristics of the six-month EQ-5D respondents and non-respondents. However, the patients that had not answered at admission (390/1568) had higher severity scores compared to the respondents (day 1 SOFA score 8 (6-10), as compared to 7 (5-9), and SAPS II score 40 (31-55), as compared to 35 (26-47)).

The mean change in EQ-5D index from admission to six months was 0.017 for patients without AKI, and 0.024 for patients with AKI. The mean difference between the changes in patients without and with AKI was 0.007 (-0.314 - 0.045) (P=0.728).

The six-month EQ-5D index and VAS scores of patients with AKI, patients with RRT, and patients without AKI, compared to the age- and sex-matched general population are presented in Table 21, and the distribution of answers in patients with and without AKI in Table 22.

Table 21. The EQ-5D index (scale 0-1) and VAS scores (scale 0-100) at six months for patients with acute kidney injury (AKI) and renal replacement therapy (RRT) compared to patients without AKI

	EQ-5D index		EQ-5D VAS	
	Study patients	General population	Study patients	General population
Patients without AKI (N=632)	0.690 (0.533-1.00) *	0.845 (0.812-0.882)	75 (60-87)	70 (68-77)
Patients with AKI (N=327)	0.676 (0.520-1.00) *	0.826 (0.812-0.859)	70 (50-83)	69 (68-73)
Patients with RRT (N=85)	0.676 (0.482-0.802)*	0.845 (0.819-0.882)	65 (50-80)*	70 (68-77)

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); RRT, Renal replacement therapy; *P <0.001, comparison between the study patients and age- and sex-matched general population. Values are presented as median (interquartile range, IQR).

Factors that were associated with a good HRQol (equal to the age- and sex-matched general population) were explored in a multivariable logistic regression model. Among the 327 AKI patients who responded at six months only, 1) the EQ-5D index at admission (OR (95% CI) 1.042 (1.024 - 1.060)/0.01 points), and 2) the lack of hypertension (OR 2.561 (1.141 - 5.750), were independently associated with a good HRQol. In comparison in the 632 patients without AKI only the EQ-5D index at admission was a factor independently associated with a good HRQol (OR 1.039 (1.028 - 1.049)/0.01 points).

Table 22. The distribution of EQ-5D answers at six-months in patients with and without acute kidney injury (AKI)

	Patients without AKI (N=632) %	Patients with AKI (N=327) %
Mobility		
I have no problems in walking about	54.3	48.6
I have some problems in walking about	39.7	43.4
I am confined to bed	6.0	8.0
Self-care		
I have no problems with self-care	77.8	72.2
I have some problems washing or dressing myself	16.6	22.0
I am unable to wash or dress myself	5.5	5.8
Usual activities (e.g., work, study, housework, family or leisure activities)		
I have no problems with performing my usual activities	59.2	54.7
I have some problems with performing my usual activities	32.4	34.6
I am unable to perform my usual activities	8.4	10.7
Pain/discomfort		
I have no pain or discomfort	47.9	43.4
I have moderate pain or discomfort	46.5	50.2
I have extreme pain or discomfort	5.5	6.4
Anxiety / depression		
I am not anxious or depressed	71.0	73.4
I am moderately anxious or depressed	26.3	23.5
I am extremely anxious or depressed	2.7	3.1

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria)

5.4.3. Short-term mortality (I)

The overall ICU- and hospital mortality in this population of 2901 adult ICU patients were 241/2901 (8.3%, 95% CI 7.3% - 9.3%), and 471/2901 (16.2%, 95% CI 14.9% – 17.6%). ICU mortality for AKI patients was 175/1141 (15.3%, 95% CI 13.2% - 17.5%)(Nisula et al, unpublished data), and hospital mortality for AKI patients was 292/1141 (25.6% 95% CI 23.0 – 28.2%) compared to 179/1760 (10.2%, 95% CI 8.7 – 11.6%) in patients with no AKI.

5.4.4. 90-day mortality (I)

The 90-day mortality in the whole study population was 678/2901 (23.4%, 95% CI 21.8% - 24.9%). By day 90 after admission 385/1141 (33.7%, 95% CI 30.9 – 36.5%) of the AKI patients had died compared to 293/1760 (16.6%, 95% CI 14.9 – 18.4%) of patients without AKI. Of the patients who received RRT, 106/272 (39.0%, 95% CI 33.1% – 44.9%) died within 90-days.

5.4.5. Six-month mortality (IV)

The crude six-month mortality in the study IV patient population was 378/1568 (24.1%, 95% CI 21.9 - 26.3%). Of the AKI patients, 224/635 (35.3%, 95% CI 31.5 - 39.1%), and 154/933 (16.5%, 95% CI 14.1 - 18.9%) patients without AKI, died during 6-months. For patients that received RRT, the six-months mortality was 63/162 (38.9%, 95% CI 31.2 - 46.5%)(IV). Figure 12 illustrates a Kaplan-Meyer survival plot of the 1568 study patients (IV) and Table 22 presents 90-day and 6-months mortality for patients stratified into different KDIGO stages.
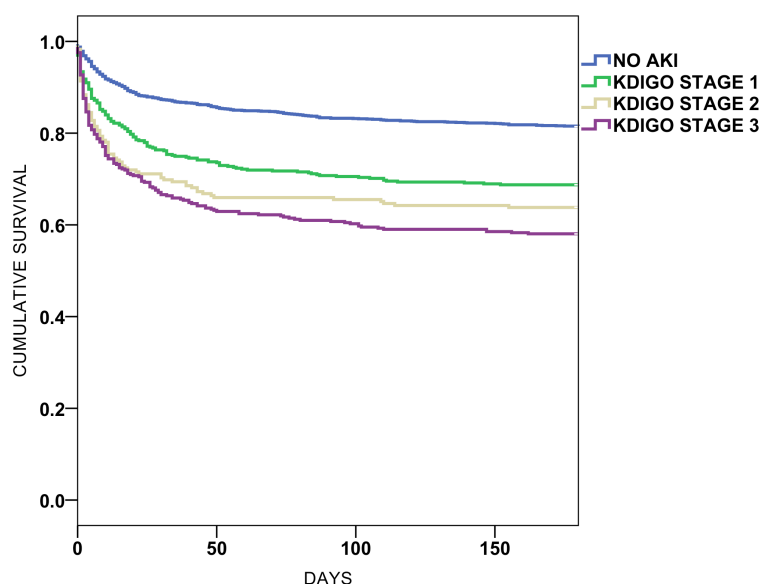
Figure 12. A Kaplan-Meyer survival plot of the 1568 study patients (IV) Stratified into different KDIGO (Kidney Disease: Improving Global Outcomes) stages.

Table 23. 90-day and six-month mortality of patients with acute kidney injury (AKI) stratified into different KDIGO stages

	Study I	Study IV
	90-day mortality	**6-month mortality**
	N (%)	**N (%)**
Stage 1	146/499 (29.3)	89/280 (31.8)
Stage 2	79/232 (34.1)	40/119 (33.6)
Stage 3	160/410 (39.0)	95/236 (40.3)

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); Numbers are presented as count (percentage)

In the 2901 patients in study I, all stages of AKI were independently associated with 90-day mortality. See Table 24 for odds ratios. In the same logistic regression analysis also age (OR 1.04), non-operative admission (OR 2.21), and highest lactate of the admission day (OR 1.17) were independently associated with 90-day mortality.

Table 24. Odds ratios (95% CI) for acute kidney injury (AKI) stages I-III for association to 90-day mortality

	OR	**95% CI**
AKI Stage I	1.71	1.31 –2.23
AKI Stage II	1.78	1.26 – 2.51
AKI Stage III	1.71	1.28 – 2.29

AKI, Acute kidney injury (by the Kidney Disease Improving Global Outcomes, KDIGO criteria); OR, Odds Ratio; 95% CI, 95% Confidence Interval

6. DISCUSSION

6.1. Incidence of AKI (I)

The **incidence of AKI in the ICU** in this study was 39.3%, which is in close agreement with four large retrospective studies[19,183,217,218] of which two used both RIFLE and AKIN criteria[19,217], one used AKIN (only Cr)[218], and one used RIFLE (only Cr)[183]. In two of these studies[19,217], however, the observation period for AKI was shorter (24 hours, and 2 days) suggesting a higher incidence result with an observation time comparable to this study (5 days). Surprisingly the prospective[15,166,167,216] studies had the largest variance in reported incidences (10.8%[15] to 65.8%[167]). Cruz and colleagues[15] reported the lowest incidence of 10.8% with the RIFLE criteria in a study with 19 ICUs from Italy including mostly small hospitals. Of note, in this study the first AKI stage instead of the highest was used for incidence calculations possibly explaining the low incidence. Only four years later another prospective, a multicentre study[167] from Italy also using RIFLE with 576 patients, reported a high incidence of 65.8%. There is no obvious explanation for the vastly different results in these two Italian studies. The highest reported incidence of AKI (67.2%) comes from a retrospective, single centre study with 5 383 patients[16] that defined AKI with the RIFLE criteria. In this study, the observation period for development of AKI included the whole hospital stay, which might partly explain the high incidence.

Study I was the first to evaluate the incidence of AKI with the KDIGO criteria. Since KDIGO combines RIFLE and AKIN by introducing both the "historical baseline Cr" from RIFLE and the "small rise of 26.5 μmol/l in Cr" from AKIN, it would be expected to increase the number of patients identified to have AKI. This presumption will have to be confirmed in future studies, but the result of study I seems to fortify that hypothesis with 9/14[15,19,166,168,183,217-220] of the prior studies reporting lower incidences.

Two studies from Finland have previously reported incidences for ICU treated AKI both using the RIFLE criteria. A large retrospective study by Vaara and colleagues[220] presented a lower incidence of 26.6%, but that particular study was designed to evaluate the incidence of RRT, and no urine output data were available and the Cr data were incomplete. Another study by Åhlström and colleagues[216] was a prospective study with both Cr and UO data available presenting an incidence of 52% for AKI in the ICU. That study was, however, a single centre study from a university hospital. As a tertiary care centre with complex patients, that same study centre in study I presented an almost identical incidence of 53.5%, highlighting the importance of multicentre design in epidemiological studies.

The incidences of AKI in the 17 different ICUs in study I varied from 20.7% to 53.5% most likely reflecting differences in patient characteristics and variance due to small sample size in the smaller study centres.

In study I, the **population-based incidence of ICU treated AKI** was 746/million adults/year. The only other study with population based incidence for ICU treated AKI reported a very high result of 2900/million/year[213]: the RIFLE was employed with both Cr and urine output criteria, but the reference population included only inhabitants of one county area in the USA rather than the whole country. Also, there was unlimited access to intensive care in that area, which might have affected the results. This hypothesis is supported by the fact that the incidences of other organ failures in that study were also exceptionally high. One retrospective study evaluated the population-based incidence of hospital treated AKI defined with RIFLE and reported an incidence of 2147/million/year[214]. Based on the population-based incidence in study I about 4000 adults develop AKI during their ICU treatment in Finland every year.

6.2. Risk factors for AKI (I)

In study I, patients that developed AKI were older and more severely ill judged by the SOFA score and SAPS II points, as well as the fact that they more often received vasoactives, mechanical ventilation, and had a higher admission day lactate. These findings are in concordance with a majority of epidemiological AKI studies reporting predisposing factors for AKI[16,25,166-168]. Of chronic comorbidities, hypertension (56%), systolic heart failure (14%), and medications suggesting cardiovascular diseases (ACEIs or ARBs (43%), aspirin (30%), diuretics (36%), and statins (35%)) were frequent in AKI patients in this study in concordance with two other studies reporting cardiovascular diseases to be significantly more common in AKI patients[167,168]. About one quarter of the AKI patients had diabetes compared to one fifth of the patients without AKI, which is in concordance with previous data[165,171]. CKD was present in over 10% of AKI patients compared to 4% of non-AKI patients and the baseline creatinine of AKI patients was significantly higher compared to patients without AKI. CKD has been reported as a predisposing factor for AKI in three other epidemiological studies[16,25,168]. Though the studies by Hoste and colleagues[16] and Piccinni and colleagues[167] found a medical admission to be associated with AKI, there was no significant difference in AKI incidence between surgical and non-surgical admissions in study I. Similar to several previous studies, severe sepsis was significantly more common among AKI patients in study I[25,166,167].

It was noteworthy in study I that contrast media were more seldom given to patients who later on developed AKI both before and during the ICU treatment, and therefore contrast medium did not associate with the development of AKI in study I, despite its established role as an AKI risk factor[323]. This suggests that treating physicians in the ICU, and also in the emergency departments and hospital wards, seem to acknowledge that contrast media should be avoided in patients showing any signs of AKI and in patients with cumulating risk factors for AKI.

Over 35% of AKI patients (P<0.001 compared to patients without AKI) received diuretics prior to their ICU admission, in spite of the fact that these patients most likely already

show signs of AKI (e.g. oliguria) at the time of receiving the diuretics. Including the time in the ICU, a majority of all patients (>50%) received diuretics, but this was significantly more frequent in patients without AKI. This finding suggests that treating personnel in the ICUs might be more aware of the potential disadvantages of diuretics in AKI compared to other hospital staff. However, the fact that over 50% of all ICU patients received diuretics at some stage leaves room for doubt as to whether diuretics are generally used excessively in critically ill patients.

Pre-ICU hypovolaemia and Pre-ICU hypotension were significantly more often observed in patients that later on developed AKI. In addition to probably independently contributing to the development of AKI[8] these might associate with the significantly increased use of colloids (HES or gelatin) in AKI patients. At the time of study I data collection, the most recent RCTs[187,190] showing a link between HES, excess renal failure, and mortality had not yet been published. These studies concluded that HES increased AKI and the need for RRT in ICU patients[189], and the need for RRT in septic patients[190] verifying the observational result of this study. Despite the fact that these data were not available, the use of colloids in the ICU in this study was significantly more rare in patients that developed AKI than in those that didn't.

Most of the studies reporting predisposing factors to AKI have been observational studies and therefore cannot establish causality (as opposed to RCTs). Logistic regression as a statistical method can be used to strengthen the findings of observational studies, but results should still be interpreted with caution. Only the studies by Hoste and colleagues and Medve and colleagues tested factors associated with AKI in a logistic regression model. They found that CKD, medical admission, malignancy, and SOFA score (Hoste), and SAPS II, Cr on admission and sepsis (Medve) to be independently associated with the development of AKI. Of these, only CKD was also an independent factor in study I. The other independent risk factors in study I (pre-ICU hypovolaemia, pre-ICU use of diuretics, pre-ICU use of colloids) were not tested in any of the other studies.

6.3. Novel biomarkers of AKI

6.3.1. Neutrophil gelatinase-associated lipocalin (II)

Study II showed that urine NGAL does not have adequate predictive value concerning AKI (AUC 0.733) or 90-day mortality (AUC 0.634) in critically ill adults. NGAL was associated with RRT (AUC 0.839), but conversion of this result into clinical use is complicated.

Results from studies evaluating the power of NGAL in predicting AKI in children undergoing cardiac surgery have been very promising and have set wide scale expectations for NGAL as an AKI biomarker. The less optimistic results in adults (pooled AUC of 0.775 in a systematic review[134]) undergoing cardiac surgery suggest, however, that adult patients have confounding factors concerning NGAL. Critically ill patients have a wide range of

chronic illnesses and the type and time of the kidney insult is variable. In these patients, the performance of NGAL has been clearly incoherent and yet unclear based on existing studies. In ten studies evaluating NGAL in the prediction of AKI in the ICU the AUCs range from 0.48[144] to 0.956[139]. Mårtensson and colleagues[138] and Constantin and colleagues[139] reported good to excellent results, but these were the smallest ICU studies with 25 and 88 patients, and the study by Mårtensson and colleagues only included septic patients. The study by De Geus and colleagues has been the largest study with 632 patients on adult ICU patients prior to study II[141], reporting an AUC of 0.77 for plasma and 0.80 for urine NGAL in AKI prediction.

Half of the studies actually report AUCs (0.68 to 0.78)[112,127,140,141,145], which are quite consistent with the results in study II. Also, the systematic review and meta-analysis from 2009 calculated a comparable pooled AUC of 0.728[134] for NGAL in prediction of AKI in critically ill patients supporting the findings of study II.

The majority of the seven studies that have evaluated the performance of NGAL in prediction of RRT[112,135,140-142,144], reported AUCs, which were comparable (0.78[135] to 0.82[140]) to the AUC of 0.839 in study II. Very weak performance for NGAL with AUCs of 0.26 from urine and 0.47 from plasma were reported by Royakkers and colleagues[144], but the numbers of endpoints in that study were really small (N=14).

Even with a quite good statistical association of NGAL with initiation of RRT in study II, the conversion of these results into clinical use is challenging for several reasons. First, the criteria for RRT initiation was not uniform[1] but rather based on individual choices by the treating physicians. Second, even with an association of NGAL with initiation or RRT, it is still unclear if the patient will benefit from this treatment as data on the optimal timing of RRT are still lacking[269], and it is difficult to evaluate the impact of RRT on the prognosis of these patients. The fact that NGAL associates with the decision to initiate RRT but not with AKI could reflect a poor or worsening general condition of these patients, rather than just poor kidney function.

Of the six studies that have assessed NGAL in mortality prediction[111,112,135,140-142], only one study from Finland by Linko and colleagues[142], used a long-term endpoint of 90-day mortality. That study reported comparable poor results (AUC of 0.58) to study II (AUC 0.634). Two studies used hospital mortality as an endpoint and also reported suboptimal AUCs of 0.389[135] to 0.64[141]. The study with 339 patients by Doi and colleagues[111] was the only one reporting a good AUC (0.83) for NGAL in mortality prediction, but 14-day mortality was found to be clinically irrelevant.

Heterogeneity among the studies on NGAL concerning study design, timing of samples, and the amount samples, is observed possibly explaining the incoherent results. The incidence of AKI in these studies varies from 14%[140] to 72%[127] reflecting probable differences in patient populations and the definition of AKI[324]. Also, it seems that immunoassays with different antibodies are not uniform in their performance in measuring NGAL[325,326]. The existing different molecular forms of NGAL and the lack of

knowledge in their measurement severely complicate NGAL's current use as a biomarker[135].

6.3.2. Interleukin 18 (III)

Study III showed that IL-18 has no prognostic power concerning AKI, RRT, or 90-day mortality in critically ill adult patients.

IL-18 yielded an AUC of 0.586 in predicting new AKI during the next 48 hours, which is in concordance with four[111,112,154,156] of the other studies of IL-18 in an ICU environment. The numbers of patients in those four studies vary from 20[154] to 528[112] and they report AUCs from 0.55[112] to 0.62[156]. Only the study by Parikh and colleagues[152], including 138 lung-injury patients, reports a marginally better AUC of 0.73 in prediction of AKI. Parikh and colleagues also reported an independent association of IL-18 with development of AKI (OR ranging from 2.3 to 3.7), which was also true in study III with an OR (95% CI) 1.003 (1.001-1.005). However, the overall AUC of the model in study III was poor (0.693) and changed only marginally when including IL-18 (0.697) suggesting no apparent role in AKI diagnostics. The recent meta-analysis on urine IL-18 by Liu and colleagues reached a pooled AUC of 0.66 for IL-18 in prediction of AKI in critically ill patients[159] which is in concordance with the results of study III.

It has been previously reported that IL-18 is an early marker of kidney injury that starts to rise in 2-4 hours, peaks at 12 hours, and stays elevated for 24-48 hours after the initial insult to the kidneys[130,152]. With most ICU patients there is significant delay between the onset of illness and admission to the ICU, and the early onset of the IL-18 rise might be one factor explaining its poor performance as a kidney injury marker in this group of patients. This hypothesis is supported by the finding in study III (figure 10) that the median concentration of IL-18 in AKI patients was decreasing from admission to 24 hours suggesting an earlier peak in IL-18.

Reliable data on the association of IL-18 with RRT have been missing. One study reported an AUC of 0.73, but in this study only 19 patients reached the endpoint of RRT and the observation period was substantially long (19 days)[112]. The study by Siew and colleagues presented a composite endpoint of death or dialysis during 28 days with only 17 patients fulfilling this endpoint. The adjusted OR for IL-18 was 1.76[156], but IL-18 was not significant for predicting dialysis alone. The AUC (0.655) for IL-18 in prediction of RRT in study III doesn't support the use of IL-18 for this purpose.

Study III found no association with urine IL-18 and 90-day mortality (AUC 0.536). The largest study on IL-18 prior to this, by Endre and colleagues[112] with 528 patients, reported hardly any better results (AUC 0.68). Doi and colleagues[111] found a slightly promising AUC of 0.83, but similar to the study by Endre and colleagues, the follow-up time for the endpoint chosen was too short to be clinically significant (14 days and 7 days). Altogether, data do not support the use of IL-18 in the prediction of mortality.

6.3.3. NGAL compared to IL-18 (III)

Like in the individual studies II and III, analyses of the admission NGAL and IL-18 from patients with both samples available showed that IL-18 is inferior to NGAL in predicting all of the chosen endpoints AKI, RRT, and 90-day mortality. However, even with NGAL the results were not compelling enough to be sufficient for clinical use (II and III). Siew and colleagues also compared NGAL to IL-18 and had comparable results[156]. They also found that adding IL-18 to NGAL didn't improve the AUC for detecting AKI. In study III it was chosen to multiply NGAL with IL-18, but the resulting AUC was inferior to that of NGAL alone in predicting all the endpoints (AKI, RRT, 90-day mortality).

6.4. Outcome

6.4.1 Health-related quality of life (IV)

Study IV showed that the HRQol of patients with AKI is not different from that of patients without AKI at ICU admission or at 6 months after ICU treatment. Moreover, the HRQol of both AKI and non-AKI patients is lower than the age- and sex-matched general population already at admission. And nor does it change significantly during critical illness.

Data on the HRQol of AKI patients are scarce with the exception of RRT patients. A recent single centre study by Hofhuis and colleagues[20] concluded that the HRQol of AKI patients was already lower at ICU admission compared to general population. Also, the HRQol at six months for AKI patients was almost similar to those without AKI (lower only in vitality and general health dimensions in AKI patients).

Despite their poorer health judged by the EQ-5D index, the patients in study IV (with AKI and without AKI) perceived their HRQol to be as good as that of the general population. Abelha and colleagues drew similar conclusions in a study with postoperative AKI patients with lower health scores but a perception of excellent health[293].

In study IV the HRQol of RRT patients was equal to that of AKI patients, but opposite to the results of the two earlier Finnish studies[220,282], RRT patients in study IV perceived their health (judged by the VAS score) to be significantly lower than that of other ICU patients.

6.4.2. Mortality (I, IV)

Though fixed and long-term outcomes have been recommended[327], the majority of studies on incidence and outcome of AKI have only reported short-term mortality rates for AKI patients[15,16,19,25,166,167,183,216-219,297]. The ICU mortality for patients with AKI ranged from 28.4%[183] to 54.0%[297] in previous studies, and the ICU mortality of 15.3% in study I was significantly lower. Also, the hospital mortality rate for AKI patients (26.5%) in study I was one of the lowest among all studies (13.3% to 49.1%)[16,19,25,166,183,216-219]. None of the other studies reported 90-day mortality rates and only three evaluate the 6-month mortality of patients with AKI[20,293,297]. The six-month mortality for AKI patients in study IV (35.3%) was lower than in the other studies ranging from 38.0%[293] to 58.5%[297].

Both short- and long-term mortality rates are low in studies I and IV compared to previous studies. Differences in study designs and patient populations explain some of the variation between studies. These studies did not consistently report severity scores, but on the basis of the given SAPS II points there was a large variation on how severely ill the ICU patients were; SAPSII points for patients without AKI ranged from 18[293] to 52[297] and for patients with AKI from 31[293] to 62[25] in the studies reporting outcome for AKI patients. The study by Abosaif and colleagues had the highest ICU and 6-month mortality, but also very high SAPSII scores for patients with and without AKI (51-52 points)[297]. Variations in the severity of illness most likely have an effect on not only the incidence of AKI, but also the outcome of the patients. In some countries or areas there is unlimited access to intensive care treatment. In Finland this is not the case, and ICU treatment has to be allocated for patients who are believed to benefit the most from it. This often means that moribund patients with poor chance of survival are not admitted to ICUs. This patient selection might improve the calculated outcomes of ICU patients. However, it has been shown that the outcomes of Finnish intensive care patients are generally good[312], and the overall hospital mortality of 18.4% (years 2001-2008) is low compared to two large European studies[328,329] with comparable severity of illness scores.

Bell and colleagues showed that most of the deaths among AKI patients occur within about 60 days[330]. The Kaplan-Meyer survival curve of patients from study IV supports this finding and suggests that a follow-up of less than this would be insufficient when assessing mortality. Furthermore, study I shows that if using either ICU- (15.3%) or hospital-mortality (26.5%) as the endpoint the total number of deaths would be severely underestimated (90-day mortality 33.7%).

Extrapolated from the population of study I, there are roughly 8000 ICU patients annually in Finland comparable to the FINNAKI study population (adult, ICU LOS >24 hours, non intermediate care, see inclusion and exclusion criteria of study I). Derived from the recently published study on mortality attributable to AKI in the ICU[298], about 350 lives among these patients could be saved in Finland every year if AKI could be avoided.

6.5. Methodological considerations

6.5.1. Validity, bias, and precision (I-IV)

Study I was the largest prospective study on the epidemiology of AKI in the ICU to date. The large sample size, multi-centre setting, and prospective design increase the validity of the study. Also, the study period of 5 months is estimated to be adequate, particularly when no evidence of a seasonal variation in the incidence of AKI exist. Furthermore, the population in the areas of the participating hospitals encompasses the majority (85%) of the adult population in Finland, and 17 out of the 25 intensive care units in Finland. All patients admitted to the ICUs during the study period were screened for eligibility. The data collection was extensive and relied on an automated and validated prospective database and audited CRF data. The latest definition of AKI with both the Cr and Urine output was utilized, which increments to the internal validity of these studies (I-IV). However, the limitations of an observational study persist. No certain causalities can be proven with this study design.

Due to the substantial size of the study I population and the multicentre setting, these results are inclined to be well generalizable to other cohorts. However, as can be shown by the large variation in the incidences of AKI in different study centres, some of these results might not compare to individual ICUs, but rather larger cohorts. Also, because of the ethnic structure of the Finnish population, these data are almost exclusively based on the Caucasian race, which should be acknowledged when applied to other ethnic groups. Finland represents a welfare state with a high-quality universal public healthcare system, generally a high level of education, and narrow socioeconomic gradients compared to many other countries[331]. This should also be acknowledged if implementing these results (I-IV) into other populations.

These studies (I-IV) most likely present only minor selection bias due to the complete screening of patients. The use of a deferred consent policy further reduces selection bias. In studies II and III an attempt was made to avoid bias by selecting the included laboratory samples at random and in a blinded fashion. Likewise, in study IV only centres with an adequate number of follow up data were included to avoid bias. The fact that urine samples cannot be collected from anuric patients presents a selection bias in studies II and III.

When assessing information bias, the data in these studies (I-IV) can generally be considered reliable due to the collection methods (see methods, data collection). However, about 50% of the variables were collected with the CRF, which presents an elevated risk of biased data as the CRF is filled out manually by the ICU staff. The study specific laboratory samples in studies II and III were assayed by the same individual in large batches with commercially available and validated kits, which reduces bias. Collecting data with questionnaires especially using proxies can present a bias. However, the EQ-5D has been validated in ICU patients[319] and information provided by proxies has proven reliable[316].

Confounding bias is unavoidable in an observational study assessing effects and exposures. It is acknowledged in these studies (I-IV) that no certain causalities can be drawn between associated factors. Multivariable logistic regression techniques were used in an attempt to minimize the effect of confounders.

In study I the targeted precision (95% CI ± 2.0%) in the incidence of AKI was achieved. Also the 95% CIs of the AUCs in studies II and III were within preferred limits with the exception of the CIs in AUC of IL-18 predicting RRT due to a small number of endpoints.

6.6. Limitations

Several limitations in these studies (I-IV) should be addressed. The FINNAKI study was an observational study and therefore only associations can be shown, and no absolute causality. In study I only AKI in the ICU was evaluated. The incidence of AKI outside ICUs is, however, also substantial. The screening period for AKI was 5 days, which rules out the possibility to identify AKI developing after that. However, according to available data the majority of AKI patients reach their highest AKI class during the first few days of their ICU stay (median 2 days IQR 1-3 to 1-7 days)[16]. Furthermore, according to a study in Finland the mean length of stay in the ICU was 3.1 +/- 5.3 days (median 1.3 days; quartiles 0.8 - 3.0 days)[332] also supporting the hypothesis that 5 days is a sufficient time to recognize most cases of AKI. When applying the KDIGO criteria for AKI, the MDRD equation was used to estimate a baseline creatinine when a measured value was not available. The use of any surrogate or estimated baseline Cr will result in some bi-directional misclassification of AKI. Studies have shown that this misclassification is more likely to occur in mild AKI than in more severe AKI[42,47,48,333]. Still, the latest consensus criteria for diagnosing and staging AKI (KDIGO)[1] includes a baseline Cr in the definition of AKI. Based on existing data, despite known shortcomings in the MDRD equation, it is the recommended method for estimating Cr by the Acute Dialysis Quality Initiative (ADQI)[334], and also the method most commonly used in studies regarding AKI[46]. In studies III and IV, sensitivity analyses were performed to exclude any bias from estimating baseline Cr. Concerning acute events preceding AKI, data on hypotension, hypovolaemia, low cardiac output, and massive transfusion were only recorded before the ICU admission. Since the majority of AKI patients developed AKI during the first few days in the ICU, this is not considered as a major factor of bias. Because of limitations in data collection it was not possible to differentiate between the different types of colloids (HES, gelatin, albumin) in study I. Therefore colloids before ICU admission included HES or gelatin and after ICU admission also albumin.

In studies II and III the laboratory samples were not from consecutive patients, but taken out from storage in random boxes without any knowledge of patient outcomes of properties. As shown in study II, patient demographics and numbers of outcomes were comparable to the original FINNAKI study cohort. The urine samples in studies II and III were not centrifuged prior to storage. Data show that centrifuging does not affect the stability of NGAL[335-337] or IL-18[338] in urine. It was chosen in studies II and III to report NGAL and IL-18 as absolute values and not normalized to urine Cr, though some studies[159,339] suggest that normalization would improve results. However, this is complicated because the amount of Cr excretion in different situations is highly variable[340].

In study IV, only patients from 10 out of 17 study centres were included due to lacking follow-up EQ-5D data. Study centres with over 70% response rate were chosen to avoid selection bias. Although excluding 7 sites, some data was still lacking: the EQ-5D data was available for 80% of the patients at six months. The admission EQ-5D was not available for 19% of the 6-month respondents.

6.7. Clinical implications

AKI is very common among critically ill adult patients. This was the first study to evaluate the incidence of AKI in a multicentre setting in Finland.

No specific treatment for AKI exists. Preventing the development or worsening of AKI by removing risk factors when possible is currently the main method of reducing the incidence of AKI. It is important to perceive the additive nature of chronic comorbidities and acute events as risk factors for AKI. The total risk of AKI for each patient is the sum of all the different potential risk factors concurrently involved. All critically ill patients are at elevated risk of AKI.

The use of many nephrotoxic substances (e.g. diuretics and colloids) in patients that developed AKI suggests that physicians could be better aware of potentially harmful drugs in patients at risk of AKI.

Aiming to reduce the incidence of AKI is important because AKI associates with significantly increased short- and long-term mortality - even in patients with the mildest stage of AKI. Because of this high mortality, patients with severe AKI and patients with AKI accompanied with other organ failures should be treated in appropriately equipped units with the possibility of haemodynamic, volume status, laboratory, and urine output monitoring

The health-related quality of life of patients admitted to ICUs is lower than that of the general population. Surprisingly, critical illness has no further effect on the HRQol of these patients. Furthermore, although AKI complicates and prolongs treatment, the surviving AKI patients' HRQol is as good as that of those who didn't have AKI. Most importantly, despite a lower objectively measured health, both patients with and without AKI perceive their quality of life as equal to that of the general population.

Urine NGAL, or IL-18, do not provide additional assistance in the prediction of ICU patient AKI or mortality. NGAL predicts the need for RRT, but since no unified criteria for RRT initiation or knowledge of the most beneficial timing, dose, and modality of RRT exist, this finding currently lacks clinical significance. Thus, urine NGAL or IL-18 should not be used in the prediction of AKI, RRT, or 90-day mortality in critically ill adult patients.

AKI is an important syndrome with significant consequences. All physicians should be familiar with the concept of AKI emphasizing those working in emergency departments, operating theatres, and intensive care units.

6.8. Future perspectives

The fundamental constraint in all AKI studies is the shortcomings in the way acute kidney injury can be defined and diagnosed. The current diagnostic criteria (gold standard) for AKI rely on creatinine and urine output in the absence of anything better. Cr and UO both are surrogates for glomerular filtration – in other words functional markers. As functional markers they lack sensitivity, specificity, and rapid timing to identify injury in the kidneys. The delay between the onset of injury and identifiable signs of AKI (loss of function) causes the therapeutic window, during which potential interventions could be tested or carried out, to be missed. More accurate ways of rapidly identifying acute damage in the kidneys are needed.

Currently medical imaging does not play a significant role in AKI diagnostics, but can mainly provide information on pre-renal (vascular) or post-renal (hydronephrosis) causes of AKI, and visualize macroscopic processes (malignancy, hematoma) influencing the kidneys. With evolving techniques, there is a hope for kidney imaging that would identify more subtle on-going processes or assess function. Renal blood flow can already be measured noninvasively with cine-phase contrast magnetic resonance imaging[90]. Doppler- and micro-vesicle contrast-enhanced ultrasonography are relatively new methods that may provide more information on renal perfusion in the future[341-343].

Though it would provide important information on AKI, acquiring kidney biopsies of all ICU patients is too invasive and complex for everyday clinical use with the current methods. Adequate creatinine clearance measurements would provide a clear picture of the functional capacity of the kidneys. Perhaps in the future, with method development, these procedures can be performed bedside in the ICU rapidly and inexpensively. GFR measurements alone would still, however, fail to provide any information on injuries that don't affect function. Are they relevant in terms of outcome? That remains to be studied.

An inaccurate gold standard[344] for AKI leads to a fundamental dilemma in biomarker studies: When comparing new biomarkers against Cr and UO markers that are more rapid in identifying AKI as we know it can possibly be revealed, but nothing new will be discovered in terms of identifying AKI outside the current criteria. Some data suggests that patients that have elevated damage markers but no loss of kidney function i.e. no AKI with the present criteria are at elevated risk of adverse outcome, such as RRT and mortality[345]. This might represent a population of patients that have "subclinical AKI", and recently the addition of damage markers to the criteria for AKI was suggested[14].

It is very interesting that NGAL, for example, predicts AKI in otherwise healthy children undergoing cardiac surgery[114], but lacks that power in critically ill patients. Just because the results against the current AKI criteria are poor, doesn't mean we should stop looking at NGAL or other markers in the ICU. However, wide scale further work is needed to identify what it actually is, that NGAL or the other somehow promising biomarkers react to or predict, and in which patients they should be used.

In any case the critically ill will always be an especially challenging group of patients concerning kidney injury biomarkers. First, due to significant heterogeneity concerning characteristics such as age, permanent illnesses, and type and severity of the acute illness. Second, because there rarely is a single identifiable insult to the kidneys but many taking place simultaneously, or possibly ongoing for days and with varying intensities. The identification of troponins to diagnose myocardial injury was a well-known success story in cardiology. However, an acute coronary event most often presents itself with known symptoms unlike AKI. Maybe with extensive research it will be learned bit by bit to construct a pattern of markers together identifying different pathophysiological processes causing AKI, markers predicting the severity and evolution of AKI, and markers predicting recovery or little chance of recovery from AKI.

Constructing AKI risk stratification models on the basis of existing data and implementing the models to clinical use could still increase awareness of AKI risk factors and help to further reduce the incidence of AKI. Still, more studies on factors predisposing to AKI are needed. The association of HES with AKI has been evaluated in two large RCTs[189,190]. Similar studies on e.g. haemodynamics, fluid balance, and drugs are wanted. Optimal timing, modality, and dose of RRT also remain unknown and require examination in further studies.

Establishing knowledge of a biomarker sensitive to predict AKI early on could lead to a clinical practice to measure this marker in emergency departments, operating theatres, or even hospital wards, and together with risk stratification models to guide admission to an ICU or treatment in general e.g. use of contrast media, antibiotics, or other potential AKI risk factors. Identifying early markers for AKI would also be crucial for planning RCTs concerning factors preventing AKI.

Interesting results on certain genetic variance predisposing patients to AKI[346], or protecting from AKI[176], should be further tested in studies with preferably large-scale genotyping. This is currently expensive and time consuming, but in the future AKI genetics will probably be an important field of extensive research.

Most of all, the basis of profound understanding of acute kidney injury would be for the pathophysiology of AKI to be completely unravelled. This would generate a logical path to identifying the risk factors, developing new diagnostic markers, and testing specific drugs for prevention and treatment of AKI.

7. CONCLUSIONS

1. The incidence of ICU treated AKI with the KDIGO criteria was 39%, and the population-based incidence of AKI in adult ICU patients 746 / million / year. Comparison to previous studies was difficult because of large variation in study designs.

2. Patients who developed AKI were older, more severely ill, and had more chronic illnesses and medications than patients without AKI. Events such as severe sepsis, resuscitation, hypovolaemia, hypotension, low cardiac output, massive transfusion, and emergency surgery were more common in AKI patients than other patients. In this population, diuretics, colloids (HES or gelatin), and hypotension before ICU admission, as well as chronic kidney disease, were independently associated with AKI.

3. Urine NGAL had poor association with the development of AKI and 90-day mortality in critically ill patients. Urine NGAL had a statistical association with the initiation of RRT, but as uniform criteria for initiation of RRT and data on the most beneficial timing of RRT are lacking, the transformation of this result into clinical practice is complicated.

4. IL-18 did not predict AKI, initiation of RRT or 90-day mortality in critically ill adult patients, and should not be used clinically for these purposes.

5. The HRQol of patients admitted to ICUs was lower than that of the age- and sex-matched general population already before ICU admission. The HRQol of patients who suffer from AKI remained unchanged during critical illness and was not different from that of patients without AKI six months after ICU admission. Despite their lower HRQol AKI patients (in exception to RRT patients) felt their health was similar to the general population.

6. Although both 90-day (34%) and six-month mortality (35%) in patients with AKI were high, mortality among AKI patients in Finland seemed to be lower than in several other countries.

8. ACKNOWLEDGEMENTS

Espoo, March 2014

Sara Nisula

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