Department of Anaesthesiology and Intensive Care Medicine
Helsinki University Central Hospital
University of Helsinki
Helsinki, Finland

ACUTE KIDNEY INJURY IN

SEVERE SEPSIS AND SEPTIC SHOCK

Meri Poukkanen

ACADEMIC DISSERTATION

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SUPERVISORS

Docent Ville Pettilä
Department of Anaesthesiology and Intensive Care Medicine
Helsinki University Central Hospital
Helsinki, Finland

Sari Karlsson, MD, PhD
Department of Intensive Care Medicine
Tampere University Central Hospital
Tampere, Finland

REVIEWERS

Professor Arvi Yli-Hankala
University of Tampere
Tampere, Finland

Docent Asko Järvinen
Division of Infectious Diseases
Department of Medicine, Helsinki University Central Hospital
Helsinki, Finland

OFFICIAL OPPONENT

Professor Konrad Reinhart
Director of Department for Anaesthesiology and Intensive Care
Jena University Hospital
Jena, Germany

To Tuomo and Veikka

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications referred to in text by their Roman numerals (I-IV). Articles have been reprinted with the kind permission of their copyright holder.

I   Poukkanen M, Vaara ST, Pettilä V, Kaukonen KM, Korhonen AM, Hovilehto S, Inkinen O, Laru-Sompa R, Kaminski T, Reinikainen M, Lund V, Karlsson S; the FINNAKI study group. Acute kidney injury in patients with severe sepsis in Finnish Intensive Care units. Acta Anaesthesiol Scand 2013, 57:863-872

II   Poukkanen M*, Wilkman E*, Vaara ST, Pettilä V, Kaukonen KM, Korhonen AM, Uusaro A, Hovilehto S, Inkinen O, Laru-Sompa R, Hautamäki R, Kuitunen A, Karlsson S; the FINNAKI Study Group. Hemodynamic variables and progression of acute kidney injury in critically ill patients with severe sepsis: data from the prospective observational FINNAKI study. Crit Care. 2013; 17(6):R295.
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III   Poukkanen M, Koskenkari J, Vaara ST, Pettilä V, Karlsson S, Korhonen AM, Laurila JJ, Kaukonen KM, Lund V, Ala-Kokko TI; the FINNAKI Study Group. Variation in the use of renal replacement therapy in patients with septic shock: a substudy of the prospective multicenter observational FINNAKI study. Crit Care. 2014;2014:18(1):R26

IV   Poukkanen M, Vaara ST, Reinikainen M, Selander T, Nisula S, Karlsson S, Parviainen I, Koskenkari J, Pettilä V; The FINNAKI Study Group. Predicting one-year mortality of critically ill patients with early acute kidney injury. Critical CareI (Submitted)

LIST OF ABBREVIATIONS

ACCP/SCCM	American College of Chest Physicians/Society of Critical Care
ADQI	Acute Dialysis Quality Initiative
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
APACHE	Acute Physiology and Chronic Health Evaluation
ATN	Acute tubular necrosis
AUC	Area under the receiver operating characteristic curve
BUN	Blood urea nitrogen
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CO	Cardiac output
Cp	Concentration of a substance in plasma
Cr	Creatinine
CrCl	Creatinine clearance
CRF	Case report form
CRRT	Continuous renal replacement therapy
Cu	Concentration of a substance in urine
CVP	Central venous pressure
DAMP	Damage-associated molecular pattern
DIC	Disseminated intravascular coagulation
FICC	Finnish Intensive Care Quality Consortium
GFR	Glomerular filtration rate
GoF	Hosmer-Lemeshow goodness-of fit
HES	Hydroxyethyl starches
HVHF	High volume hemofiltration
ICU	Intensive care unit
IHD	Intermittent hemodialysis
IL-6/18	Interleukin-6/18
iNO	Inducible nitric oxide
KDIGO	Kidney Disease: Improving Global Outcome
KIM	Human kidney injury molecule
L-FABP	Liver fatty acid-binding protein
MAP	Mean arterial pressure
MDRD	Modification of Diet in Renal Disease Medicine
MRI	Magnetic resonance imaging
NGAL	Neutorophil gelatinase-associated lipocalin
NO	Nitric oxide
ΔOF	Difference in the number of failed organs between on day 3 versus day 1 in the ICU
OR	Odds ratio

PAMP	Pathogen-associated molecular pattern
Qu	Urine flow rate
RIFLE	Risk, Injury, Failure, Loss, End-Stage
ROC	Receiver operating characteristic
RRT	Renal replacement therapy
SAPS	Simplified Acute Physiology Score
SIRS	Systemic inflammatory response syndrome
SMR	Standardized mortality ratio
SOFA	Sequential Organ Failure Assessment
SSC	Severe Sepsis Campaign
svO_2	Mixed central venous saturation
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor α

ABSTRACT

Background: Severe sepsis and septic shock are the main causes of acute kidney injury (AKI) in the intensive care unit (ICU). The care of these patients includes restoration of haemodynamics by fluid resuscitation and vasoactive treatment. Development of septic AKI has been shown to associate with lower mean arterial pressure (MAP) levels. The treatment of AKI is supportive. No generally accepted guidelines for indication or optimal timing for initiation of renal replacement therapy (RRT) exist. Apart from life-threatening indications, the initiation of RRT is mainly based on clinical judgment. The short- and long- term mortality rates of these patients are high. The long-term mortality of hospital survivors with AKI remains increased for several years after critical illness. The objectives of this study were to assess the incidence and 90-day mortality of ICU-treated patients with severe sepsis associated AKI (I), to evaluate the impact of early haemodynamics on development of AKI (II), to assess the differences in proportion of administration of RRT in patients with septic shock (III), and to develop predictive models for one-year mortality among all ICU-treated patients with AKI (IV). AKI was defined and staged by Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Patients: All patients and analyses were performed using data from the FINNAKI study, which was a prospective, observational study conducted in 17 Finnish ICUs between September 1, 2011 and February 1, 2012. Study I comprised 918 adult patients, who fulfilled the criteria for severe sepsis 24 hours preceding ICU admission or within the first five days in the ICU. Study II included 423 patients with severe sepsis diagnosed within 24 hours of ICU admission. Study III comprised patients with septic shock (N=726). In study III the participating ICUs were divided into high-RRT ICUs and low-RRT ICUs by the proportion of patients with septic shock treated with RRT. In study IV, 774 patients with early AKI (diagnosed within 24 hours of ICU admission) were analysed.

Main results: Of the 918 patients with severe sepsis, 488 had AKI (53%, 95% confidence interval, CI 49.9-56.5%). The population-based incidence of ICU-treated severe sepsis associated AKI was 0.32 (95%CI 0.30-0.34)/ 1000 adults/year. The 90-day mortality rate of the patients with severe sepsis associated AKI was 186/488 (38.1%, 95% CI 33.7-42.5%) compared to 106/430 (24.7%, 95%CI 20.5-28.8) in patients with severe sepsis without AKI, (P<0.001). Patients with severe sepsis associated AKI were older, had

more comorbidities, and daily chronic medications than those without AKI. Patients with AKI were more severely ill in terms of higher maximum SOFA (Sequential Organ Failure Assessment) score (P<0.001), had higher lactate concentrations (P<0.001), and they received more often mechanical ventilation (P<0.001) and vasoactive treatment (P=0.004) than patients without AKI. The most severe AKI, KDIGO stage 3, was independently associated with 90-day mortality (OR 2.6, 95%CI 1.8-3.7). Patients with severe sepsis and development of AKI had lower time-adjusted MAP (95%CI), 74.4mmHg (68.3-80.8), than those patients without progression of AKI, 78.6 mmHg (72.9-85.4 mmHg, P<0.001).

The proportion of RRT-treated patients in patients with septic shock ranged from 3% to 35 % across Finnish ICUs. This variation between high- and low-RRT ICUs was explained by differences in case-mix and in severity of organ dysfunction. Indications for and modality of RRT did not differ between ICU groups. The group of ICU (high-RRT or low-RRT ICU) did not increase the risk of fatal outcome in these patients.

The one-year mortality among patients with AKI was 39.8% (95%CI 36.3-43.3). A predictive model for one-year mortality for patients with early AKI based on data available by the third day in the ICU (D3 model) performed fairly well with an AUC -value (95%CI) of 0.80 (0.753-0.846) and a bootstrapped AUC-value (95%CI) of 0.79 (0.77-0.80). Advanced age, mechanical ventilation on D3, number of co-morbidities, higher modified SAPS II score, the highest bilirubin value by D3, and the lowest base excess value on D3 were predictors of one-year mortality on D3 model. The severity of AKI, or the presence of severe sepsis, did not remain as predictors for one-year mortality.

Conclusions: Over half of the patients with severe sepsis had AKI. These patients had a worse outcome, but only AKI KDIGO stage 3 was independently associated with 90-day mortality. Avoidance of time-adjusted MAP below 73mmHg may be beneficial for prevention of the progression of AKI in patients with severe sepsis. Despite 10-fold variation in proportion of RRT in patients with septic shock, the 90-day mortality of these patients was similar between high-RRT ICUs and low-RRT ICUs. The D3 model might be clinically useful in identifying patients with high risk for long-term mortality but it requires further validation.

1. INTRODUCTION

Severe sepsis and acute kidney injury (AKI) are both common syndromes that are encountered in the intensive care unit (ICU). The proportion of patients presenting severe sepsis upon admission to the ICU has been reported to be approximately 9% to 12%.[1-5] An increasing trend in the presence of severe sepsis in ICU-treated patients has been observed.[1,5] In France, the proportion of patients with severe sepsis among all ICU admissions increased from 8.4% in 1993 to 14.6% in 2001[1]; and in Australia and New Zealand an increase from 7.2% in 2000, to 11.1% in 2012 was seen.[5] A similar change has also been seen in the U.S. for hospitalized patients with severe sepsis.[6,7]

The incidence of AKI in patients with severe sepsis treated in the ICU ranges from 23% up to 67%.[8-23] The short-term mortality in patients with severe sepsis associated AKI has ranged from 16% up to 70%. [8,10,11,16,18,20-22,24-28] The treatment of severe sepsis associated AKI includes treatment of severe sepsis according to the Severe Sepsis Campaign (SSC) guidelines[29] and supportive treatment of AKI. The cornerstones of treatment of severe sepsis are restoration of haemodynamics with appropriate fluid resuscitation and vasoactive treatment when needed.[29] Recent studies have shown increase in mortality and in need for renal replacement therapy with administration of hydroxyethyl starches (HES).[30-34] According to the updated SSC[29] and KDIGO[35] (Kidney Disease: Improving Global Outcome) guidelines starches should not be used in severe sepsis.[29,35] Norepinephrine is advocated to be administrated to restore the blood pressure in severe sepsis associated AKI when resuscitation with fluids is inadequate to normalize blood pressure.[35] When infused directly into a renal artery, norepinephrine has induced renal vasoconstriction[36,37] and an increased renal vascular resistance has been observed with high doses (up to 1.6µg/kg/min) of intravenous norepinephrine.[38] However, with lower doses of norepinephrine (0.2-0.4µg/kg/min) renal vascular resistance has decreased and renal blood flow has not changed or has increased.[39-42]

The historical paradigm of reduced renal blood flow and acute tubular necrosis (ATN)[43] has been strongly challenged by advanced measurements of renal blood flow.[42,44-51] In addition, histopathological findings of renal tubular necrosis have not provided evidence of ATN.[52,53] A systematic review of the histopathology of septic AKI, including six human and 14 experimental studies, concluded that the current human and experimental data do not support the theory of ATN as the mechanism of septic AKI.[54] Hypotensive

episodes with mean arterial pressure (MAP) below 65-82mmHg have been shown to increase the risk of AKI and the related administration of RRT in patients with severe sepsis.[12,55-57]. The sufficient MAP level remains to be clarified and may vary in different patient groups.

No specific treatment for severe sepsis associated AKI exists and, thus, the treatment of AKI is supportive. Renal replacement therapy (RRT) is used in 9% to 70 % of patients with severe sepsis associated AKI. [8,11,16,17,20,24,58,59] Part of the large variation is explained by differences in study population, but also by lack of guidelines regarding indications and proper timing of RRT. The initiation of RRT is mainly based on local protocols and on the clinical judgment of the attending physician. For haemodynamically unstable patients, such as patients with septic shock, continuous RRT is recommended.[35,60] The optimal RRT practice for patients with severe sepsis associated AKI may be unique due to the distinct pathophysiology of septic AKI.[61] However, according to current data, the high volume hemofiltration (HVHF) that aims to purify the blood of inflammatory mediators has not shown any beneficial effect (reduced mortality or improvement of organ dysfunction) in septic AKI, and therefore it is not recommended as a treatment for septic AKI.[62,63]

Prognostic models for hospital mortality have been used for ICU-treated patients since the 1980s.[64-71] Considering the high costs and resource use of ICU-treated patients with AKI, an instrument to estimate the possibility of futile intensive care treatment is crucial. Although the long-term mortality of survivors of ICU-treated AKI patients has been found to be increased for up to 10 years,[25,72-79] no prediction model for long-term mortality exists. Most of the present AKI-specific models provide estimates for short-term mortality.[80-83]. In addition, these models have performed poorly when externally validated.[84,85] A model developed by using data on RRT-treated patients may not be applicable to patients with less severe AKI without customization and validation.[86] Moreover, none of the AKI-specific models have used current definitions RIFLE (Risk, Injury, Failure, Loss and End-stage renal disease), AKIN (Acute Kidney Injury Network), or KDIGO to define and stage AKI. Recent improvements in survival of patients with severe sepsis[5,87] and in patients with AKI[26] may have improved the outcome of patients with AKI. Therefore, a novel AKI-specific predictive model for long-term mortality, defining AKI by current classification, is needed.

2. REVIEW OF THE LITERATURE

2.1 Definitions

2.1.1 Severe sepsis and septic shock

Sepsis is a host's response to proven or suspected infection with at least two systemic inflammatory response syndrome (SIRS) criteria.[88] The SIRS criteria encompass alterations in body temperature, heart rate, respiratory rate, and leukocytes. Severe sepsis is defined as sepsis with organ dysfunction. Septic shock is severe sepsis with hypotension or hypoperfusion, which is not reversed with adequate fluid resuscitation. Patients treated with vasoactive therapies may not be hypotensive at the time of perfusion derangements, yet they should be regarded to have septic shock.[88] Table 1 includes definitions of SIRS, hypotension, hypoperfusion, and organ failures. The Surviving Sepsis Campaign (SSC) Guidelines Committee has updated and specified the symptoms and diagnostic criteria for severe sepsis, but the aforementioned basic principals have not been changed.[29,89-91] Another concept for staging sepsis, called PIRO, was published in 2003.[89,92] The elements of the PIRO concept are: Predisposition (premorbid illness, age, and comorbidities); Insult (injury, infection); Response (signs of sepsis); and Organ dysfunctions.[89] In future PIRO may develop into a reliable score for staging sepsis and to predict hospital mortality outcome in patients with sepsis, but further validation and customization of the model is needed.[93-96]

Table 1. Definitions of systemic inflammatory response syndrome (SIRS), hypotension, hypoperfusion, and organ dysfunction [88]

	Definition
SIRS	**Temperature** >38°C or <36°C **Heart rate** >90/minute **Respiratory frequency** >20 breaths/minute or pCO2 <4.3kPa **Leukocytes** >12 x 10^9 /l or <4x10^9 /l or >10% immature (bands) forms
Hypotension	Systolic blood pressure <90mmHg or reduced ≥40 mmHg from baseline
Hypoperfusion	For example lactic acidosis, oliguria or alteration in mental status
Organ dysfunction	Altered organ function resulting in disability to maintain homeostasis

2.1.2 Acute kidney injury (AKI)

Acute kidney injury (AKI) is a syndrome characterized by sudden disruption in renal function of regulating fluid and electrolyte compositions of the body and excreting waste products of metabolism. The definition of AKI has been based on serum creatinine level and on urine output. The nomenclatures, acronyms, and definitions of AKI have varied extensively in previous literature. In 2004, Acute Dialysis Quality Initiative (ADQI) commenced the first unifying definition and staging of AKI by presenting RIFLE criteria, which consist of three acute (Risk, Injury, and Failure) and two clinical outcome categories (Loss and End-stage renal disease) for kidney injury.[97] The RIFLE criteria defined and staged AKI by elevation in serum creatinine from baseline, by decrease in estimated glomerular filtration, and by diminished urine output. To increase the sensitivity of the RIFLE criteria, the Acute Kidney Injury Network (AKIN) published the AKIN criteria,[98] which comprise three severity stages for AKI. The AKIN criteria modified the timeframe for increment of serum creatinine from 7 days to 48 hours, required no baseline serum creatinine, included an absolute increase in serum creatinine of ≥26.5μmol/l as a criterion of AKI, and staged RRT-treated patients to the worst AKI stage. Thus far, RIFLE and AKIN criteria have been validated by numerous studies including more than 500,000 patients.[99] In comparison, to identify patients with AKI in the same study

population, the RIFLE and AKIN criteria have performed quite similar.[9,100] However, Lopes and colleagues found that the AKIN criteria showed a higher detection rate of AKI,[101] while in the study by Joannidis and colleagues the RIFLE criteria identified more patients with AKI.[102] The most recent definition of AKI, the Kidney Disease: Improving Global Outcome (KDIGO) criteria, is a combination of the RIFLE and AKIN criteria.[35] All of these classifications stage AKI by the worst fulfilled criteria, either urine output or creatine. The definition and stages of RIFLE, AKIN, and KDIGO criteria are presented in Table 2.

Severe sepsis associated AKI implies the fulfillment of the criteria for both severe sepsis[88] and AKI[35,97,98] simultaneously.

Table 2. Definition and classification of AKI by RIFLE, AKIN, and KDIGO criteria.

RIFLE[97]	AKI should occur within 7 days and be sustained for >24 hours.	
	Serum Creatinine (SCr)/ GFR	**Urine output**
Risk	Increased SCr x 1.5 **or** decrease in GFR >25%	<0.5ml/kg/h for ≥6 hours
Injury	Increased SCr x2 **or** decrease in GFR >50%	<0.5ml/kg/h for ≥12 hours
Failure	Increased SCr x 3 **or** SCr ≥353.6 µmol/l with acute increase of ≥44.2µmol/l **or** decrease in GFR >75%	<0.3ml/kg/h for ≥24 hours **or** anuria for ≥12 hours
Loss	Complete loss of renal function for >4 weeks	
End-Stage	Need for RRT for >3 months	
AKIN [98]	Increase in serum Creatinine must occur <48 hours.	
	Serum Creatinine	**Urine output**
Stage 1	≥26.5 µmol/l increase <48 hours **or** 1.5-2-fold from baseline	<0.5ml/kg/h for > 6 hours
Stage 2	2- to 3-fold from baseline	<0.5ml/kg/h for >12 hours
Stage 3	>3-fold from baseline **or** ≥353.6 with acute increase of 44.2 µmol/l or RRT	<0.3ml/kg/h for 24 hours **or** anuria for 12 hours
KDIGO[35]	Increase in serum Creatinine ≥26.4µmol/l within 48 hours or ≥1.5 times baseline, which is presumed to have occurred in preceding 7 days.	
	Serum Creatinine	**Urine output**
Stage 1	Increase ≥26.5µmol/l <48 hours **or** 1.5-1.9 times baseline	<0.5ml/kg/h for 6-12 hours
Stage2	2.0-2.9 times baseline	<0.5ml/kg/h for ≥12 hours
Stage 3	>3.0 times baseline **or** ≥353.6µmol/l **or** initiation of RRT	<0.3ml/kg/h for ≥24 hours **or** anuria for ≥12 hours

AKI acute kidney injury; AKIN Acute Kidney Injury Network; GFR glomerular filtration rate; KDIGO the Kidney Disease: Improving Global Outcome; RIFLE Risk, Injury, Failure, Loss and End-stage; RRT renal replacement therapy. AKI is staged by the worst fulfilled criteria, either urine output or serum creatinine.

2.2 Evaluation of renal function

2.2.1. Glomerular filtration rate (GFR)

High renal blood flow, approximately 20% of cardiac output, is required to produce a large amount of glomerular filtrate to excrete waste products.[103] The amount of blood flow extensively exceeds the need of renal oxygen demand. Renal arteries supply blood flow to the kidneys. After multiple divisions of arteries, blood finally flows to a renal corpuscle and to glomerular capillaries through afferent arterioles. Thereafter, filtrated blood flows away from glomerular capillaries via efferent arterioles.[104] In the renal corpuscle, protein-free plasma-like fluid filters from the glomerular capillaries into Bowman's space (glomerular filtration). The glomerular filtration is dependent on the surface area and permeability of the capillaries and on the glomerular filtration pressure. The glomerular filtration pressure is glomerular capillary pressure (= capillary hydrostatic pressure moving fluid out of the capillary) subtracted from the plasma oncotic pressure (retains fluid in the capillary) and hydrostatic pressure in Bowman's capsule (oppose fluid movement from the capillary).[103] Resistance of the afferent and efferent arterioles determines the glomerular capillary pressure. The pressures in the renal corpuscle are illustrated in Figure 1.
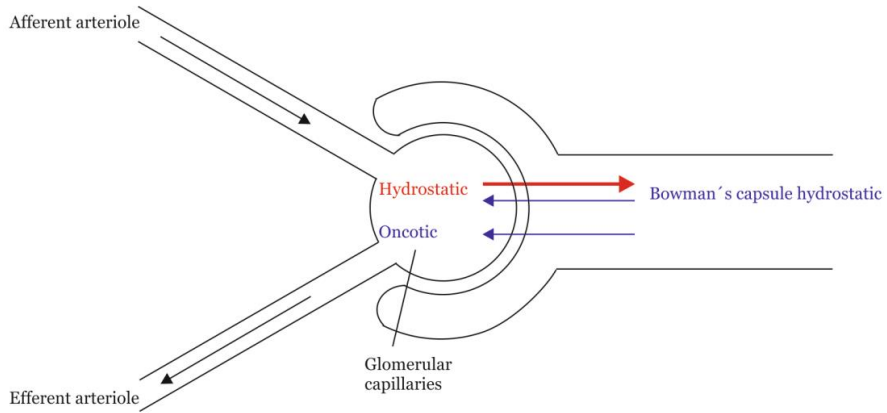
Figure 1. Pressures in the renal corpuscle effecting glomerular filtration pressure. Modified from Power I, Kam P. Principles of physiology for the anaesthetist, 2008, with permission by Taylor & Francis Group.[103]

Glomerular filtration rate (GFR) is recommended as the best measure of kidney function.[35] GFR is measured indirectly by administering substances, which freely filtrate across the glomerular capillary membrane and are not reabsorbed or excreted by the tubules; such as inulin, iothalamate, iohexol, and sinistrin.[105,106] GFR can be calculated according the following equation:

$$\textbf{GFR} \text{ (ml/min)} = \frac{C_u \times Q_u}{C_p}$$

C_u= Consentration of a substance in urine (mg/ml)
C_p= contration of a substance in plasma (mg/ml)
O_u= Urine flow rate (ml/min)

2.2.2 Estimations of GFR

Creatinine and urine output

Serum or plasma creatinine concentration and urine output are the most usual surrogates for GFR to detect and diagnose AKI in daily clinical practice. Creatinine is a late surrogate of renal function. Nearly 50% of kidney function is lost, before creatinine rises. As creatinine is a functional marker, it does not describe renal parenchymal cell injury. In addition, age, gender, race, diet, hydration status, and muscle mass modify production of creatinine.[107,108] Theoretically, changes in urine output reflect changes in GFR, but various etiologies, such as obstruction in urinary track and use of diuretic medication, can cause alteration in urine output without deterioration in GFR. Although oliguria has been shown to significantly associate with occurrence of new AKI (defined by RIFLE classification using solely creatinine criteria), the oliguria has only a fair predictive ability for subsequent new AKI (area under receiver operator characteristic curve, AUC 0.75).[109] Currently all modern AKI classifications (RIFLE, AKIN, and KDIGO) define and stage AKI on the basis of creatinine and urine output.[35,97,98]

Creatinine clearance (CrCL)

The clinical feasibility of GFR measurements with exogenous substances is poor. Creatinine clearance (CrCl) is routinely accepted as an estimate of GFR.[103,110] Creatinine is freely filtered across the glomerulus capillary membrane and is not reabsorbed. Yet, it is not an optimal measurement for GFR estimation due to the small amount of tubular excretion of creatinine causing overestimation of the true GFR.[108] Measurement of CrCl requires steady state and, thus, it is unsuitable for clinical practice for critically ill patients with unstable clinical conditions and changing volume status. Equations for estimating GFR have been developed. The most commonly used are Cockroft-Gault[111], simplified four variable equation of the Modification of Diet in Renal Disease (MDRD)[107], and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[112] formulas. These equations adjust patient's creatinine value to age, weight, gender, and ethnic group. Table 3 presents these three equations.

The Acute Dialysis Quality Initiative has recommended the MDRD equation.[97] According to a recent review the CKD-EPI creatinine equation is more accurate than MDRD[113] and the CKD-EPI creatinine equation is also recommended for estimating GRF by the KDIGO 2012 clinical guideline for chronic kidney disease.[114] However, no single equation is optimal across all populations and all equations cause bias. [113,115]

Table 3 Equations of the glomerular filtration rate (GFR)

Cockroft-Gault equation[111]	$\mathbf{CrCl}$ (ml/ml) = $\dfrac{(140\text{-}Age) \times Weight}{72 \times Cr}$ (x 0.85 if female)
MDRD equation[107]	**GFR** (ml/min/1.73m^2) = 186 x Cr $^{(-1.154)}$ x Age$^{(-0.203)}$ x (0.742 if female) x (1.212 if Afro-Americans)
CKD-EPI equation[112]	**GFR** (ml/min/1.73m^2) = 141 x min (Cr/κ,1)$^{\alpha}$ x max(Cr/κ,1)$^{-1.209}$x 0.993^{age} x (1.018 if female) x 1.159 if Afro-Americans)

Cr = serum creatinine (mg/ml); κ = 0.9 for male / 0.7 for female; α = -0.411 for male / -0.329 for female; min= minimum SCr / κ or 1; max = maximum SCr / κ or 1

2.3. Incidence of septic AKI and severe sepsis

In general ICU patients, the incidence of AKI varies from 6% up to 67% depending on the study population.[9,17,116-128] Among critically ill patients the aetiology of AKI is multifactorial and severe sepsis is the most common contributing factor to AKI. Of critically ill patients with AKI, 20%-67% have concomitant sepsis, severe sepsis, or septic shock.[9,116,121,122,125,126,129] The incidence of severe sepsis associated AKI treated in the ICU has varied from 13% up to 78% depending on the severity of sepsis and definition of AKI.[8-23] In the FINNSEPSIS study[3], acute renal failure (renal SOFA points ≥3) was present in 23% of patients with severe sepsis and in the SOAP study in 51%[130]. The proportions of patients with AKI among septic patients treated in the ICU are shown in Table 4.

The population-based incidence of severe sepsis associated AKI is uncertain. The FINNAKI study, covering 85% of the adult population in Finland, reported the population-based incidence of ICU-treated AKI as 0.746/1000 adult population/year.[121] Previously only two studies have reported the population-based incidence of ICU-treated AKI to be 2.147/1000 adult population/year [131] and 2.9/1000 adult population/ year[132]. Regrettably, those studies represented only a specific region in Scotland[131] and a single county in the U.S. [132]

The proportion of patients with severe sepsis in ICU admissions has been approximately 9% to 12%[1,2,4,5] and the population-based incidence of severe sepsis has varied from 0.46 to 3.00 /1000 adults/year.[1,133-138] According to the FINNSEPSIS study, the population-based incidence for severe sepsis was 0.38/1000 adult/years in 2005 in Finland. The number of patients with sepsis has shown to increase globally.[5-7,136] The annual increment of 8.2% (between 1993 and 2003)[6] and 17.8% (between 2000-2007)[7] in hospitalized patients with severe sepsis has been reported in the U.S. Likewise, an increasing trend in ICU-treated patients with severe sepsis has been found in Australia and New Zealand and in France.[1,5,26] However, despite the increasing incidences of both severe sepsis and AKI, the proportion of septic AKI in ICU-treated AKI has not been found to increase.[26]

Table 4. Studies reporting the proportions of patients with acute kidney injury (AKI) and renal replacement therapy (RRT) in the patients with sepsis treated in the intensive care unit

	Study desig n	Pts	Severity of sepsis	Time frame	Definition of AKI	Proportion of AKI	RIFLE R (%) Stage 1 (%)	RIFLE I (%) Stage 2 (%)	RIFLE F (%) Stage 3 (%)	RRT (%)
Bagshaw 2008[9]	R, M	33 375	sepsis	<24 hours	RIFLE / AKIN	42.1 / 43.4	16.2 / 18.4	16.3 / 12.0	9.6 / 13.0	- / -
Bagshaw 2009[12]	R, M	4 532	septic shock	<24 hours after onset of hypotension	RIFLE	64.4	16.3	29.4	18.7	-
Gurjar 2013[21]	R, S	406	sepsis	ICU stay	RIFLE	31.0	-	-	-	-
Hoste 2003[8]	R, S	185	sepsis[1]	14 d ICU	SCr≥176.8 μmol/l	16.2	-	-	-	11.4
Kim 2012[28]	R, S	291	severe sepsis	72 hours	RIFLE / AKIN	55.5 / 59.2	13.6 / 17.0	20.8 / 15.1	21.1 / 27.2	33.3
Lopes 2009[13]	R, S	315	sepsis	ICU stay	RIFLE / AKIN	29.2 / 31.4	7.0 / 8.3	8.3 / 6.3	14.0 / 16.8	9.2
Lopes 2010[39]	R, S	426	sepsis	ICU stay	RIFLE	32.4	6.1	8.0	18.3	9.6
Murugan 2010[14]	P, M	572	severe sepsis	Hospital stay	RIFLE	52.1	-	-	-	-
Oppert 2008[11]	P, M[2]	401	severe sepsis	1 day	SCr>2 x upper limit or UO < 0.5 ml/kg/h for 4 hours	41.4	-	-	-	17.5
Payen 2012[20]	P, M	176	severe sepsis	48 hours	AKIN[3]	73.3	42.6 (Stage 1 and 2)		30.1	20.5
Peng 2014[40]	R, S	211	sepsis	-	KDIGO	47.9	10.1	7.5	32.8	-
Piccinni 2011[17]	P, M	149	sepsis	ICU stay	RIFLE	77.8	14.8	19.5	36.9	22.8
Plataki 2011[18]	R, S	390	septic shock	ICU stay	RIFLE	60.7	12.3	19.2	29.2	-
Suh 2013[23]	R, S	992	sepsis	Hospital stay	RIFLE	57.7	27.9	18.3	11.5	4.0
White 2013[22]	P, S	246	sepsis[1]	ICU stay	RIFLE	65.4	19.5	14.2	31.7	NA
Yegenaga 2004[58]	P, S	217	sepsis	2 weeks	SCr>177μmol/l or UO<400ml/24h	13.4	-	-	-	6.0
Yegenaga 2010[16]	P, M	139	SIRS/sepsis	ICU stay	RIFLE	56.8	19.0	17.9	17.9	10.8

1) patients with surgical sepsis 2) cross sectional study 3) modified AKIN classification; no-AKI, mild AKI (stage 1 and 2) and Severe AKI (stage3)

Pts number of patients; R retrospective, P prospective, M multicenter, S single centre; SCr serum creatinine; UO urine out

2.4 Pathophysiology of septic AKI

The understanding of the pathophysiology of septic AKI is markedly limited due to scarce histopathological data and limited abilities to measure the renal blood flow in patients during severe sepsis associated AKI. The knowledge on the pathophysiology of septic AKI is mainly based on experimental studies. Based on observations in animals[141,142] and humans[25] with hypodynamic shock, ischemic insult due to reduced renal blood flow and subsequent renal vascular vasoconstriction has been considered as the main cause of the septic AKI.[43] However, recent experimental[44-49] and human studies[42,50,51] have shown that renal blood flow is preserved or even increased during severe sepsis suggesting that alteration in glomerular filtration pressure and in intrarenal distribution of blood flow are more important factors in the pathophysiology of septic AKI than renal ischemia. Sparse findings of tubular injury in renal histopathological findings have supported this theory in animal studies.[52,54] In line with this, histopathological evidence of acute tubular necrosis (ATN) was observed in only 22% of patients with sepsis associated AKI[54] and post-mortem kidney biopsies of patients with sepsis associated AKI have shown heterogeneity of the histopathological changes.[53] Currently, the pathophysiology of septic AKI is suggested to be multifactorial including alterations and disturbances in glomerular filtration pressure and in intrarenal distribution of blood flow, inflammation, oxidative stress, apoptosis, microcirculatory disorders, mitochondrial dysfunction, and organ cross-talk.[143,144]

2.4.1 Alterations in renal blood flow

Under physiological conditions, autoregulation of regional blood flow ensures constant organ blood flow within an organ specific range of blood pressure. Below the autoregulation threshold, organ blood flow decreases almost linearly.[145] The optimal goal for MAP during severe sepsis and septic shock to restore renal blood flow and prevent kidney injury is unclear. SSC guidelines suggest targeting a MAP ≥ 65 mmHg during severe sepsis.[29] The results of studies regarding optimal blood pressure during severe sepsis have been versatile. In patients with septic shock, MAP levels between 72 and 82mmHg have been associated with lower incidence of AKI.[57] In another study, MAP below 75 mmHg was found to predict the need of RRT[56]. A recent randomized, controlled trial (RCT) comparing a low MAP-target (65-70mmHg) to a high MAP-target (80-85 mmHg) among patients with septic shock found no difference in the overall rate of renal dysfunction between

different MAP-target groups.[146] A difference is only seen in patients with chronic hypertension, where the incidence of a doubling of the plasma creatinine or use of RRT was reported to be lower with higher MAP-target when compared to the low MAP-target group. [146] The observed MAP-levels exceeded the targeting MAP-levels in both groups, however. In the low-target group (65-70mmHg), MAP-levels were mainly between 70 and 75 mmHg, and in the high-target (80-85 mmHg) group between 80 and 90mmHg.[146] Lower MAP has also been shown to associate with increased incidence of AKI in septic pigs.[147] To the contrary, no beneficial effect of norepinephrine increased MAP, from 65 to 85 mmHg, was found on renal function or in blood lactate levels among patients with septic shock.[148,149]

In septic AKI, renal blood flow has been shown to vary by cardiac output referring to impairment of autoregulation.[48,150] Decreased renal vascular resistance and increased renal blood flow with simultaneously diminished GRF with increased serum creatinine have been observed in experimental studies with hyperdynamic sepsis. [44,45,48,49,151-153] A review of 159 animal studies with induced sepsis concluded that the renal blood flow was preserved or increased and the cardiac output was the predictor of renal blood flow in two-thirds of studies.[48] Likewise, in patients with sepsis-associated AKI renal blood flow has been found to be normal or increased by using a renal vein thermodilution catheter.[50]

In the absence of diminished renal blood flow, the reduced GFR is suggested to be a consequence of decreased glomerular filtration pressure caused by dilatation of both the afferent and efferent glomerulus arterioles with more intensive dilatation in the efferent arteriole.[154] This view has been supported by administration of angiotensin II[153] and arginine vasopressin[155,156] in severe sepsis. Infusion of angiotensin II, a vasoconstricting hormone with preferential effect on efferent arteriole, in hyperdynamic septic sheep restored renal haemodynamic to normal with a subsequent marked increase in urine output and an enchanced creatinine clearance.[153] Similarly, administration of arginine vasopressin improved urine output and creatinine clearance in septic sheep[155] and in patients with septic shock, has been associated with decreased progression of AKI and reduced risk of RRT.[156] However, controversial results have been reported. Reduced renal blood flow despite maintained cardiac output has been found in septic pigs with AKI referring to uncoupling between systemic (reduced) and renal (increased) vascular resistance.[157] Septic pigs with AKI had greater inflammatory and oxidative stress suggesting that development of septic AKI could be induced by both inflammation and alterations in renal circulation.[157]

Non-invasive, reliable, and repeatable methods to measure renal blood flow are unavailable. Direct measurement of renal blood flow with a percutaneous thermodilution catheter is overly invasive for clinical use. Renal Doppler ultrasound is a promising, noninvasive, reproducible, and simple tool, which may be used to assess the renal vascular resistance.[150,158] High renal arterial resistive index (RI) has been observed in patients with septic shock and development AKI.[159,160] In addition, a significant decrease in RI has been observed when increasing MAP from 65 yo 85 mmHg with norepinephrine during septic shock.[42] However, the value of a single RI measurement to predict septic AKI has proven to be insufficient.[160] Another noninvasive method is cine-phase contrast magnetic resonance imaging (MRI), which has shown diminished renal fraction of cardiac output.[51,150] Although cine-phase MRI is accurate, it is highly time-consuming and logistically difficult, especially for critically ill patients with multiple organ supportive treatments, such as mechanical ventilation, RRT, and invasive haemodynamic treatments.

Taken together, reduced renal blood flow does not seem to be a uniform explanatory factor of development of AKI during severe sepsis. In addition, considerable variability in renal blood flow has been observed in different phases of septic AKI (development, established, or recovery) in individual patients.[152,154]

2.4.2 Microcirculatory alterations

In addition to numerous experimental studies, sepsis-induced alterations in microcirculation have also been observed in human studies.[161-167] Microcirculation comprises small vessels: arterioles, capillaries, and venules. Capillaries are mainly responsible for oxygen and nutrient exchange and elimination of cellular waste products. Perfusion heterogeneity is characterized by an increased proportion of intermittently or non-perfused capillaries leading to disturbances in oxygen diffusion with subsequent differences in oxygenation.[168] During sepsis, these derangements in the renal microcirculation (for example sluggish blood flow and shunting) have been described to cause oxidative stress.[143] The disturbances in microcirculation in patients with sepsis have been shown to associate independently with mortality[163,164,169] and with the development or progression of organ dysfunction.[164,170] The higher MAP-level from 65 to 85 mmHg has been observed to improve the microcirculation assessed with near-infrared spectroscopy, increased mixed venous blood oxygen saturation (svO$_2$) and reduced blood lactate concentration.[165]

2.4.3 Inflammation

Experimental and human studies have emphasized the importance of the redundant inflammation reaction in the development of severe sepsis associated AKI.[14,171-175] The first-line host defense for pathogen is innate immunity, which recognizes pathogens by pathogen recognition receptors, including Toll-like receptors (TLRs).[171,176] TLRs recognize pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) with subsequently release of cytokines, such as tumor necrosis factor α (TNF-α), IL-6, and interleukin-8 (IL-8) into the circulating blood.[143,144,176] Higher blood levels of IL-6 have been reported in patients with severe sepsis associated AKI, compared to patients without AKI.[14,20,172] TNF-α injures tubular cells directly and soluble TNF-receptor levels have been found to be independently associated to mortality among patients with septic AKI.[177] Inflammatory stimuli increase the production of nitric oxide (NO) by activation of inducible NO (iNO). The role of NO is both beneficial and detrimental during sepsis. NO is necessary for the maintenance of the renal blood flow during sepsis.[178] However, overexpression of NO inhibits mitochondrial respiration leading to cell damage.[143] In addition, the overproduction of NO causes disturbances in microcirculation, which may lead to shunting, sluggish blood flow, hypoxia, and further amplification of the inflammation signal.[143,179]

2.4.4 Apoptosis

Under physiological conditions, mitosis and apoptosis (genetically programmed cell death) are in balance.[176] The role of apoptosis in septic AKI is controversial. In post-mortem examinations, signs of apoptotic processes were observed in proximal and distal tubules of every patient with septic shock[53]; and in endotoxin induced AKI, apoptosis has been found in tubular cells.[180] Based on the important role of the caspase enzyme in development of apoptosis, several studies have found that caspase inhibitor prevented apoptosis with a simultaneous decrease in the inflammation in the kidney.[181,182] Controversially, the recent experimental study has found no sign of increased apoptosis in septic AKI.[52] Thus, the clinical significance of apoptosis in septic AKI remains unclear. [176,183] It has been suggested that to benefit of an individual cell survival, the cellular energy consumption is reprioritised and cellular metabolism is downregulated resulting in organ dysfunction.[184]

2.4.5 Mechanical ventilation

The harm that mechanical ventilation causes to the kidneys is increasingly recognized. In experimental studies, mechanical ventilation with high tidal volume has been found to associate with changes in epithelial cells, renal dysfunction, and greater tubular apoptosis.[185,186] Similarly, ventilation with high tidal volume caused increased NO with subsequent microvascular leakage in kidneys and proteinuria.[187]

2.5 Biomarkers of septic AKI

Current classifications for AKI are based on changes in serum Cr and urine output, which both reflect changes in kidney function and are not markers for kidney cell damage. The distinct pathophysiology in septic AKI may lead to expression of specific biomarkers in serum and urine.

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein released from neutrophils and it is also expressed in low concentrations in kidneys, lungs, and in gastrointestinal tissue.[188] NGAL is filtered by the glomerulus and reabsorbed in the proximal tubule. Both plasma and urine NGAL has been shown to increase in acute tubular injury[188,189] and in sepsis.[190-193] Significantly higher NGAL levels (plasma and urine) have been found in adults and children with sepsis associated AKI than in patients without sepsis associated AKI.[191,192,194] The ability of NGAL to predict AKI in patients with sepsis has varied within AUCs 0.67-0.89.[191,194-196] Interleukin-18 (IL-18) is a pro-inflammatory cytokine, which is produced by mononuclear cells, macrophages, and non-immune cells, including renal tubular injury.[197-199] Increased plasma IL-18 has been observed in sepsis and in numerous inflammatory diseases, such as arthritis, inflammatory bowel diseases, psoriasis, and multiple sclerosis.[200] Higher urinary IL-18 levels have been found in patients with septic AKI than in patients with non-septic AKI.[201,202] Cystatin-C is a surrogate of GRF. It is freely filtered by the glomerulus and subsequently reabsorbed completely in the proximal renal tubule.[200] Thus, the presence of cystatin-C in urine may indicate tubular epithelial damage. Among patients with sepsis, the urinary cystatin C has been shown to predict AKI with an AUC value of 0.71.[203] Further validation and clinical studies of all the new biomarkers of AKI are needed, especially among critically ill patients with severe sepsis.

2.6 Risk factors of septic AKI

Severe sepsis is the dominant risk factor for AKI in critically ill patients and approximately half of severe sepsis patients have concomitant AKI.[9,11-14,16-18,20,22-24,140] While assessing the patient's risk of developing AKI the intensity, severity, and duration of exposure should be considered, as well as patient-related risk factors.[35] Table 5 lists the factors found to associate with higher risk of AKI in patients with sepsis. These risk factors for AKI are identical for all critically ill patients.

Table 5. Risk factors for AKI in patients with sepsis

Patient-related risk factors
Advanced age [12,16,23,204]
High body mass index [12,18]
Co-morbidities
        Chronic kidney disease [12,23]
        Chronic obstructive pulmonary disease[12]
        Coronary artery disease[12], heart failure[12], hypertension [23]
        Diabetes[12,23,204]
        Ethanol abuse[12]
        Hematologic malignancy[12]
        HIV/AIDS[12]
        Liver failure[12,204]

Use of angiotensin converting enzyme inhibitor or angiotensin receptor blocker[18,23]
Low baseline GFR[18,23] / higher baseline creatinine[23,204]

Risk factors related to critical illness
Administration of hydroxyethyl starches[30,32,33,204,205]
Blood transfusions[18]
Cardiac/thoracic surgery[204]
Delay in initiation of an effective antimicrobial treatment[18]
Greater aberrancies in acute physiology (in haemodynamic, respiratory rate, and Glasgow Come scale) and in laboratory measurements (leukocytes, bilirubin, lactate, and pH),[24]
Higher severity of illness scores[12,16,23,24,204]
Increased intra-abdominal pressure[206-209]
Medical admission[24]
Positive blood culture[23]
Source of infection: Abdominal[12,18] or genitourinary infection[12]
Use of iodinated contrast dye[23,204]
Use of vancomycin,[35,210] amphotericin B[35], furosemide[35], aminoglycosides[35]

In addition to increased risk of AKI, hydroxyethyl starches (HES) have been reported to associate with an increased risk of RRT in patients with sepsis.[30,32,33,204,205] Recent meta-analysis have reported a relative risk of 1.36 to 1.41 for RRT among patients with sepsis receiving HES.[31,34,211] Interestingly, the use of 20% human albumin has also been suggested to associate with risk of AKI in one study.[204]

The renal perfusion pressure is decreased by increased intra-abdominal pressure (IAP). In critically ill patients the threshold of IAP for predicting AKI has been found to be as low as 12 mmHg. [207] In patients with septic shock, increased IAP has been associated with increasing serum creatinine levels.[209]

Prolonged hypotension (defined MAP< 65 mmHg or a systolic pressure <90 mmHg) prior to initiation of antimicrobial treatment,[12] and MAP levels below 75-82 mmHg have been shown to increase the risk of renal failure.[55-57] The critical MAP threshold for development of AKI among patients with severe sepsis has been discussed in detail in the chapter on Pathophysiology of septic AKI (section 2.4).

2.7 Treatment of septic AKI

Treatment of septic AKI includes effective treatment of severe sepsis and supportive treatment of AKI. Guidelines for management of severe sepsis and septic shock (SSC guidelines) were initially published in 2004[90], and have been revised in 2008[91] and 2013.[29] These guidelines comprise detailed recommendations on the administration of adequate antimicrobial treatment, of early resuscitation of hemodynamic, and of supportive therapies.[29] Up to date, no curative therapy for septic AKI exists and the treatment is mainly supportive, focusing on the avoidance of known risk factors for septic AKI.

2.7.1 Antimicrobial treatment of infection

Administration of an effective antimicrobial therapy within an hour after the onset of hypotension has been found to reduce hospital mortality in patients with septic shock.[212] A delay in antimicrobial treatment has been associated

with increased risk of AKI[18] and mortality.[213-215] Adequate antimicrobial dosage adjustment for patients with severe sepsis associated AKI is challenging, especially in RRT-treated patients. In addition to alteration in renal function, fluctuating volume status, disturbances in haemodynamics, and decreased drug protein binding further complicate drug dosing.[216] Many antimicrobial drugs are significantly cleared by RRT and availability of therapeutic drug monitoring is limited with the exception of vancomycin and aminoglycosides. A growing body of evidence has shown that current dosing regimens are not adequate in critically ill patients. A meta-analysis including 14 studies with 1229 patients treated with a β-lactam antibiotics concluded that extended or continuous infusion resulted in lower mortality compared to short-term infusion in hospitalized patients with various infections (pneumonia, abdominal and genitourinary infections, and ICU acquired infections).[217] Among patients with severe sepsis not treated with RRT, an improvement in clinical cure (disappearance of symptoms related to the infection) has been found with continuous infusion of a β-lactam.[218] Yet, no difference in hospital survival was found.[218] Insufficient concentrations of β-lactam antibiotics have been demonstrated with standard dosage regimens in 19% up to 41% of critically ill patients, including RRT-treated patients[219], and underdosing of β-lactam antibiotics has been found to increase the risk of fatal outcome.[220] Therapeutic targets of vancomycin have been more consistently achieved with continuous infusion compared to intermittent dosing in critically ill patients.[221,222] The increased intensity of continuous renal replacement therapy (CRRT) was associated with a need for higher dosage regimens in order to achieve sufficient vancomycin concentration.[222]. Guidelines regarding drug dosing in acute kidney diseases are scarce and mainly modifications of guidelines for chronic kidney disease (CKD) patients.[216] In addition to antimicrobial treatment, source control such as drainage of an abscess debridement of infected tissue and removal of potentially infected device should be sought and intervention should be undertaken, when needed.

2.7.2 Treatment of haemodynamic dysfunction

Fluids

None of the currently available fluids is ideal for resuscitation of patients with severe sepsis associated AKI. Higher mortality rate[30,211] and need for RRT[30-33,204,211] have been reported in patients with severe sepsis receiving

HES. Yet, controversial results have been reported. No association between use of starches and renal dysfunction, RRT, or mortality has been found in patients with severe sepsis or septic shock.[223,224] Use of HES has also been reported to be associated with an increased number of red blood cell transfusions.[30-32,34,204,211] Guidelines have advocated not using HES for fluid resuscitation among patients with severe sepsis or patients with AKI.[29,35] Increased risk of AKI and decreased survival has been found in critically ill patients with hypoalbunemia.[225] Albumin may have some unproven beneficial effect in patients with severe sepsis or septic shock when substantial amount of crystalloids have already been administered.[29] A post-hoc, non-randomized subgroup analysis (in patients with severe sepsis) of the SAFE (Saline versus Albumin Fluid Evaluation) study suggested potentially reduced mortality in patients resuscitated with albumin compared to those receiving saline (30.7% vs. 35.3%, P=0.09).[226] Administration of albumin did not impair renal function.[227] A meta-analysis concluded that the use of albumin for fluid resuscitation of patients with sepsis was associated with reduced mortality compared to other fluids such as Ringer lactate, 0.9% saline, 6% HES, 10% Pentastarch, Hetastarch and gelofusine.[228] However, a multicenter, open-label trial with 1818 patient with severe sepsis resuscitated with albumin or crystalloid found no beneficial effect of albumin on renal SOFA score, on need for RRT, or on 28 or 90 day mortality rates.[229] Recently, excess chloride load has reported to have adverse effects in critically ill patients, including an increasing risk of AKI and need for RRT. [230,231] Thus, balanced solutions such as Ringer's and Hartmann's solutions might be more suitable for fluid resuscitation in critically ill patients with increased risk of AKI.[232]

Little evidence exists regarding the optimal amount of fluid to reach the targets. Strikingly, reduced mortality rate has been found in febrile African children, who were withheld standard fluid administration with either 0.9% saline or 5% albumin solution.[233] Thus, concerns about the previously used liberal fluid therapy have arisen, as excess fluid accumulation has been shown to be associated with adverse outcome in septic shock,[234] in patients with AKI,[235] in critically ill RRT-treated patients,[236] and in development of AKI in surgical ICU.[237] Therefore, liberal administration of fluids is suggested to be avoided and administration of fluids should be guided by evaluation of patient's fluid status and fluid responsiveness (changes in CO after administration of fluid bolus).[238] Positive fluid responsiveness has been defined as ≥15% increase in CO or stroke volume after administration of fluid.[239,240]

Vasoactive treatment

Administration of vasoactive therapy is often required to correct persistent hypotension and to retain adequate blood pressure. Of the patients with severe sepsis associated AKI from 56% up to 86% have received vasoactive treatment.[12,13,16,20,24,58]

Norepinephrine is a potent vasoconstrictor that acts via α-adrenergic receptors. In experimental studies, marked renal vasoconstriction and increased renal vascular resistance have been observed after infusion of norepinephrine into renal artery[36,37] or with intravenous high doses (up to 1.6µg/kg/min) of norepinephrine.[38] Decreased vascular resistance with increased renal blood flow has been found with lower doses of norepinephrine (0.2-0.4µg/kg/min).[39] In human studies, norepinephrine has been shown to increase creatinine clearance and urine output in septic shock[40,41] and to decrease the renal resistance index assessed by Doppler ultrasonography.[42] However, excess augmentation of MAP by norepinephrine has led to increased renal resistance[42] and increasing MAP over 70mmHg by vasopressors has increased the risk of circulatory failure, metabolic acidosis, and thrombosytopenia.[56]

For years "low-dose" dopamine (<5µg/kg/min) has been used for its presumed renoprotective effects based on findings in experimental studies and healthy humans.[241-243] The protective effect on dopamine has not been confirmed in clinical studies.[244-248] The results of current studies have not supported the use of dopamine, as it does not prevent AKI, reduce need for RRT, or improve outcome, and may even worsen renal perfusion.[246,249-251] Accordingly, SSC guidelines recommend norepinephrine as a first choice vasopressor and that "low-dose" dopamine should not be used.[29] In the presence of myocardial dysfunction the treatment with dobutamine is recommended. Recent experimental and human studies have reported beneficial effects (increased microvascular blood flow, and improvements in organ functions) of levosimendan in sepsis[252-255], but further investigations are needed.

2.7.3 Renal replacement therapy (RRT)

Of the patients with septic AKI, 4% to 70% of patients receive RRT.[8,11,16,17,20,23,24,58,59] Excluding the absolute indications for RRT such as hyperkalaemia, severe metabolic acidosis, overt uraemia, fluid overload with pulmonary oedema, and specific drug intoxications[190], the decision to initiate RRT is mainly based on clinical judgment. The B.E.S.T. (Beginning and Ending Supportive Therapy for the Kidney)- study reported marked practice variation for RRT worldwide[256] and corresponding results have been found among European intensivists.[257] In these studies, oliguria[256,257], high serum or plasma urea or creatinine,[256,257] fluid overload,[256,257] metabolic acidosis,[256] and hyperkalaemia[257] were the main indications for initiation of RRT. Despite a growing number of studies, no broad guidelines regarding timing, indication, modality, or dose of RRT exist.

The definitions of early and late initiation of RRT are based on different thresholds of urea and creatinine levels, or on varying time frames. Early hemofiltration has reported to prolong the need for mechanical ventilation and vasoactive treatment.[258,259]. However, patients with sepsis associated AKI treated with early RRT (defined as urea <35.7 moll/l, inception of CRRT ≤24 hours after diagnosing sepsis, or by time from ICU admission/initiation of vasopressor infusion to initiation of RRT) have survived better.[260-263] Recent reviews[264,265] and a meta-analysis[266] concluded that critically ill patients may benefit from early RRT. Instead of single laboratory values or timeframes, the decision to initiate RRT is advocated to be based on wider clinical evaluation of the patient with concern for fluid balance and nutrition, severity of underlying diseases, degree of other organ dysfunction, and likelihood of renal recovery.[35]

Studies from the 1990s reported greater haemodynamic stability and suggested favorable survival with CRRT compared to intermittent haemodialysis (IHD) in critically ill patients.[267-271] Recent studies have not supported this theory,[268,272,273] however, patients with unstable haemodynamics have been converted from IHD groups to CRRT, leading to a significant bias.[272,274] Better achievements of fluid balance targets have been shown with CRRT than IHD.[275] As CRRT is suggested for haemodynamically unstable patients[35], it is a reasonable modality of patients with severe sepsis or septic shock. Of the prescribed RRT, European intensivists administered CRRT to patients in 88% of cases [257]

Uncertainty of the optimal dose of RRT for patients with severe sepsis associated AKI persists. Ronco and colleagues published the landmark study regarding the dose of RRT in critically ill patients.[276] In a subgroup analysis of patients with sepsis they found that effluent rate over 45ml/kg/h was associated with improved outcome.[276] The randomized RENAL (The Randomized Evaluation of Normal versus Augmented Level), the ATN (Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network), and the observational DO-RE-MI (DOse REsponse Multicentre International collaborative Initiative) studies showed no reduction in mortality by intensive RRT.[277-279] Thus, a CRRT dose of 20-25 ml/kg/h is recommended by KDIGO[35] and other reviews regarding AKI or CRRT.[60,280]

It has been theoretized that high-volume hemofiltration (HVHF) could be beneficial in septic AKI by purifying inflammatory mediators from the bloodstream.[281] Previous small, single centre studies reported decreased vasopressor doses[282] and improvements in haemodynamics in patients treated with HVHF.[283,284] The IVOIRE study [high-volume (70ml/kg/h) vs. standard-volume (35 ml/kg/h) hemofiltration] found no reduction in 28-day mortality and in duration of mechanical ventilation, RRT, or vasoactive treatment.[62] Accordingly, HVHF is not recommended for treatment of septic shock associated AKI.[62] This recommendation was supported by a meta-analysis of four RCTs. [63]

2.8 Outcome

2.8.1 Short and long-term mortality

Most studies have reported short-term mortality rate (ICU or hospital mortality) or mortality rate at 28 days after ICU admission. The short-term mortality rates for severe sepsis associated AKI have ranged from 16% to 70%. [8,10-12,16,18,20-22,24,25,27,28] Few reported long-term mortality rates have varied from 36% up to 67%.[11,12,14] Mortality rates in patients with severe sepsis-associated AKI from recent studies are presented in Table 6. Patients with septic AKI have increased short-term mortality compared to non-septic AKI[8,10,24] and to patients with sepsis but without AKI.[10,11,13,14,16,18,20,28]

Multiple studies have reported an increased mortality rate for hospital survivors after critical illness up to 2-10 years after hospital discharge.[285-290]

Among critically ill patients, AKI has been shown to increase long-term mortality.[25,72-79] Even mild AKI (KDIGO stage 1) has been found to reduce 10-year survival in critically ill patients.[291] In Finland, mortality rates of 57% at 1 year, and 70% at 5 years, have been observed among RRT-treated patients.[78]

Table 6. Mortality rates of sepsis associated AKI

	Study design	Severity of sepsis	Patients with AKI	Mortality (%)			
				ICU	Hospital	28-day	90-day
Neveu 1996[25]	P, M	sepsis	157		74.5		
Hoste 2003[8,28]	R, S	sepsis	30	53.3	56.7	-	-
Bagshaw 2007[24]	P, M	sepsis	833	-	70.2	-	-
Bagshaw 2008[10]	R, M	sepsis	14 039	19.8	29.7	-	-
Oppert 2008[11]	P, M	Severe sepsis	166	64.6	67.3	-	67.3
Bagshaw 2009[2]	R, M	Septic shock	3 373[a]	53.4	59.5	-	58.4
Lopes 2009[13]	R, S	sepsis	99	-	52.5	-	-
Yegenaga 2010[16]	P, D	sepsis	79	-	65	-	-
Plataki 2011[18]	P, S	Septic shock	237	-	48.5	-	-
Kim 2012[20]	R, S	Severe sepsis	183[b]	-	-	59.2	-
Payen 2012[20]	P, M	Severe sepsis	129	-	-	32.6	-
Gurjar 2013[21]	R, S	sepsis	126	52	-	-	-
Legrand 2013[237]	R, S	Severe sepsis	69	39	45	38	-
Suh 2013[23]	R, S	sepsis	573		16.4		
White 2013[22]	P, S	sepsis	161	17	24	-	-
Peng 2014[140]	R,S	sepsis	101	-	-	46.5	-

D dual center; M multiscenter; P prospective; R retrospective; S single center; [a]patients with septic shock and persistent hypotension prior to initiation of antimicrobial therapy [b]defined by RIFLE criteria within first 72 hours in the ICU

2.9 Predictive models

Predictive models have been used in intensive care to classify individual patients on the basis of severity of illness and, thereafter, to predict the risk of hospital mortality of a group critically ill patients.[64-71] In addition, predictive models have been used to evaluate the ICU performance and in benchmarking, to assess resource use, and to include more homogeneous patients groups in clinical trials. [292-294] After careful consideration supported by clinical judgement, these models may be useful in clinical-decision-making and for estimation of the prognosis of an individual patient.

2.9.1 General ICU models

The two most common general predictive models for hospital mortality for ICU-treated patients are Acute Physiology and Chronic Health Evaluation (APACHE)[64] and Simplified Acute Physiology Score (SAPS)[68]. Both of the models have been updated several times; APACHE II-IV[65-67], and SAPS II[69] and 3.[70,71] All of these models include variables regarding chronic health status preceding acute illness, physiologic measurements of acute illness, and type of ICU admission (elective/emergency and medicine/operative). For the physiologic measurements, the worst value within the first 24 hours in the ICU is included in the models [65-67,69,295,296] except SAPS 3,[70,71] in which the timeframe for physiological values is limited for one hour preceding and after ICU admission. The models need to be separately customized for different geographical regions for better performance. The SAPS 3 model provides customized equations for several geographical regions (Australasia, Central/South America, Mediterranean, North America, and Central/Western/Eastern/North/Southern Europe).[70,71]

Organ dysfunction score, the Sequential Organ Failure Assessment (SOFA), has been primarily developed to describe the organ dysfunction in patients with severe sepsis, but later it has been applied in non-septic patients as well.[297] The function of six organs (respiratory, cardiovascular, renal, hepatic, central nervous system, and coagulation) are assigned daily according to the severity of dysfunction (normal to organ failure). Although the SOFA score has not been developed to predict mortality, a review comprising 18 studies concluded that in predicting hospital mortality, SOFA-based models performed only slightly worse than APACHE II or III scores and were competitive with SAPS II.[298] For predicting hospital mortality, the SOFA score has been used in a heterogeneous way: SOFA score on admission or at

a predefined time during ICU stay, the max SOFA score (highest daily SOFA score), total max SOFA score (sum of the highest scores of each organ system during the entire ICU stay), mean SOFA score (average of all total SOFA score), and delta SOFA (difference in predetermined time point during ICU stay).[298]

2.9.2 AKI-specific predictive models

Most AKI specific models provide estimations of the hospital mortality[80-82,299] or 60-day mortality.[86,300,301] Some of these models are obsolete due to variations in definition of AKI and poor performance in external validation.[59,84,302,303] In addition, one model is based on data on only RRT-treated patients,[86] and therefore, does not apply to patients with less severe AKI. Despite increased long-term mortality among critically ill patients with AKI,[25,72-78] AKI-specific predictive models for long-term mortality are lacking. Table 7 summarizes characteristics of the models including the predictive factors.

AKI-specific models for hospital mortality

The model by Liano et al[80] has been based on data from a single centre and AKI has been defined as an abrupt rise in serum creatinine over 177 µmol/l The development cohort of this model comprised 228 patients and the model was internally validated. Thereafter the model has been externally validated resulting in AUC-values ranging from 0.7 to 0.78.[299,304]

Stuivenberg Hospital Acute Renal Failure (SHARF) score[81] has also been derived on data on patients with AKI in a single centre. AKI was diagnosed as serum creatinine exceeding 177 µmol/l or an increase of more than 50% in patients with CKD. The model comprises two measuring points: time of diagnosis AKI (T0) and 48 h later (T48)[81]. Both measuring points comprise the same predictors, which are presented in Table 7. The AUC-values of the model were 0.87 (T0) and 0.90 (T48) in the development cohort[81], but in multicentre patient population only 0.67 (T0) and 0.78 (T48)[82]. Therefore, the models were customized by including additional predictors: serum bilirubin, presence of sepsis and hypotension[82]. The discriminative power of customized SHARF score improved yielding AUC values of 0.82 (T0) and 0.83 (T48)[82].

A model by Mehta[299] and colleagues was derived from prospectively collected data on patients with AKI treated in four ICUs. AKI was defined according the blood urea nitrogen (≥14 mmol/l) or serum creatinine (≥177µmol/l) levels and for patients with CKD a sustained rise in creatinine of ≥88µmol/l from baseline value was required. The AUC-value of the original model (AUC 0.83) and the bootstrapped adjusted AUC-values (0.795-0.89) were in line.[299] However, in external validation an AUC-value of 0.670 was yielded.[85]

AKI-specific models for 60-day mortality

Chertow et al have developed two AKI-specific predictive models for 60-day mortality.[300,301] The first model was derived on data on patients with AKI with a sudden rise in creatinine of at least 88.4 µmol/l over 24 to 48 hours. The AUC of the model was 0.81 in the development cohort.[300] To improve the predictive power of the model, a new AKI-specific model with three different measuring points (the day of diagnosing AKI, the day of consulting nephrology, and the day of initiation of RRT) was developed.[301] Different variables remained predictors at discrete time points. These variables are presented in table 7. The performance of the model improved over time with increasing AUC-values for models: day of diagnosing AKI (AUC 0.62), consulting nephrology (AUC 0.68), and initiation of RRT (AUC 0.72).[301]

Predictive models for RRT-treated patients

The predictive model for 60-day mortality by Demirjian comprises 21 predictors based on the data from the ATN study.[86] The bootstrapped AUC value of 0.85 was significantly better than the corresponding AUC-values of APACHE II (0.68) and total SOFA (0.69) scores.[86] This new model needs to be externally validated before use in clinical practice.

Prediction of long-term mortality

The ability of the SHARF score to predict one-year mortality has been evaluated and the score yielded AUC values of 0.791 for T0 and 0.833 for T48.[74] However, the score was tested among survivors of development cohort of the original SHARF score and hence a good performance of the SHARF score was to be expected. Among RRT-treated patients, increased Charlson co-morbidity index, presence of liver disease, higher APACHE II score, septic shock and need for CRRT have been found to be risk factors for one-year mortality.[72] This model performed outstandingly with an AUC –value of 0.83. Validation and customizing are needed before applying these models to clinical use and in patients with less severe AKI.

External validation of the AKI-specific models

In external validation using the multinational database of B.E.S.T. study (1742 patients), none of the AKI-specific (Chertow's, Liano's, or Mehta's) yielded an AUC-value above 0.7, which is considered satisfactory for clinical use.[85,305]. Liano's model has also been externally validated in 238 RRT-treated patients receiving an AUC-value of 0.78.[306]

2.9.3 Predictive ability of general ICU-scores and AKI criteria among patients with AKI

In lack of AKI-specific instrument to predict hospital mortality, general ICU-scores (APACHE II-IV, SAPS II and 3, and SOFA scores) have been evaluated for their predictive ability among patients with AKI.[84,85,299,301,307-310] Only the customized SAPS3 has presented good discrimination with AUC-values of 0.8[283] and 0.82.[308] Patients with AKI have unique characteristics, which most probably influence the performance of general ICU score.

Likewise, the predictive abilities for hospital mortality of AKI criteria (RIFLE, AKIN, and KDIGO) have been evaluated.[304,311] AUC-value of RIFLE criteria was AUC 0.6 in hospitalized patients.[304] Among critically ill patients all three definitions had comparable prediction ability for hospital mortality with AUC-values of 0.733-0.74 for all three classifications.[311]

Table 7. Summary of the predictive AKI-specific models

	Design	Validation	Predictors
PREDICTIVE MODELS FOR HOSPITAL MORTALITY			
Liano (1993)[81]	228 AKI patients P,S	Internal validation (100 patients) External validation (25 patients)	Age, male, nephrotoxics, oliguria, hypotension, jaundice, coma, consciousness, and assisted respiration
SHARF (2000)[82]	197 AKI patients P, S		*Both T0 and T48 scores*: Age, serum albumin, protrombine time, respiratory support and heart failure
Mehta (2002)[300]	851 AKI patients, P, M	Internal validation, bootstrapping	Age, male , BUN, Cr, hematologic failure, liver failure, respiratory failure, heart rate, and urine output
SHARF (2004)[83]	293 AKI patients P, M		*Both T0 and T48 scores*: Age, serum albumin, protrombine time, respiratory support, heart failure, serum bilirubin, sepsis, and hypotension
PREDICTIVE MODELS FOR 60-DAY MORTALITY			
Chertow (1997)[87]	257 AKI patients R, M	Internal, bootstrapping	Male, oliguria, total bilirubin, ventilation, stroke or seizure, acute myocardial infarction, immunosuppression, bicarbonate, and albumin
Chertow (2006)[88]	618 AKI patients R, M	-	1) *Day on AKI diagnosis*: age, CKD, BUN, liver failure, sepsis or septic shock 2) *Day on consultation*: age, urine output, Cr, BUN, liver failure, ARDS, platelets < 150 x 10^6/ l, sepsis or septic shock 3) *Day of initiation of RRT*: age, urine output, Cr, BUN, liver failure, respiratory failure, platelets<100 x 10^6/ l, sepsis or septic shock
Demirjian (2011)[89]	1122 RRT-patients R, M	Internal, bootstrapping	Age, chronic hypoxemia, cardiovascular disease (angina, myocardial infarction, congestive heart failure), malignancy, immunosuppressive therapy, ischemic AKI, postoperative patient, at initiation of RRT: heart rate, MAP, daily urine volume, mechanical ventilation, $FiO_2 \geq 0.6$, interaction of mechanical ventilation and $FiO_2 \geq 0.6$, arterial pH and PaO_2, Cr, bicarbonate, phosphate, albumin, total bilirubin, INR, and platelet count

BUN blood urea nitrogen; Cr creatinine; FIO_2 fraction of inspired oxygen; INR internation normalized ratio; M multicenter; MAP mean arterial pressure; P prospective; RRT renal replacement therapy; S singe centre; SHARF Stuivenberg Hospital Acute Renal Failure

3. AIMS OF THE STUDY

The main aims of this study were to assess the incidence and long-term outcome of ICU-treated severe sepsis associated AKI in Finland and to identify factors predicting one-year mortality of critically ill patients with AKI.

The specific objectives were:

1. To determine the incidence and population-based incidence of severe sepsis associated AKI according to the new KDIGO classification in adult patients treated in Finnish ICUs. (I)

2. To assess possible changes in the population-based incidence of ICU-treated severe sepsis treated in Finnish ICUs. (I)

3. To evaluate the association of time-adjusted MAP and vasoactive treatment with development and progression of AKI among patients with severe sepsis, and their association with 90-day mortality. (II)

4. To scrutinize the variation in use of RRT in adult patients with septic shock treated in different Finnish ICUs. (III)

5. To develop and validate predictive models for one-year mortality for patients with early AKI. (IV)

4. PATIENTS AND METHODS

4.1 Patients

For all the studies (I-IV), patients were from the FINNAKI study.[121] The FINNAKI study was a prospective, observational, multicenter study conducted in 17 Finnish ICUs between 1 September 2011 and 1 February 2012. The participating 17 ICUs comprised 5 ICUs in university hospitals and 11 central hospital ICUs. The FINNAKI study included all emergency admissions and those elective postoperative ICU admissions with an expected stay for at least 24 hours. The following patients were excluded: 1) patients under 18 years of age, 2) intermediate care patients, 3) patients with chronic dialysis, 4) patients, who received RRT during the previous ICU admission, 5) transferred patients, who already included in the study for 5 days, 6) patients without sufficient language skills or not permanently living in Finland, and 7) organ donors. Of the 5853 consecutive admissions screened for eligibility, 2901 patients were included to the FINNAKI main study. Figure 2 illustrates the flow chart of the substudies included in this work.

Study I included consecutive patients, who fulfilled the criteria for severe sepsis 24 hours preceding ICU admission or within the first five days in the ICUs (N= 918). The statistical analyses regarding septic AKI were performed for these patients. Additionally, for assessment of the incidence of ICU-treated severe sepsis, patients (N= 73), who were initially excluded from the FINNAKI study due to chronic dialysis or re-admitted patients receiving RRT during the previous ICU admission, were screened for severe sepsis retrospectively.

For Study II including 918 patients with severe sepsis, 179 patients from four ICUs were excluded due to incomplete data on haemodynamics. In addition, patients, who fulfilled the criteria of severe sepsis later than 24 h after ICU admission, died within the first 5 days in the ICU, or had development of AKI within the first 12 hours in the ICU, were excluded. The final study population comprised 423 patients with severe sepsis.
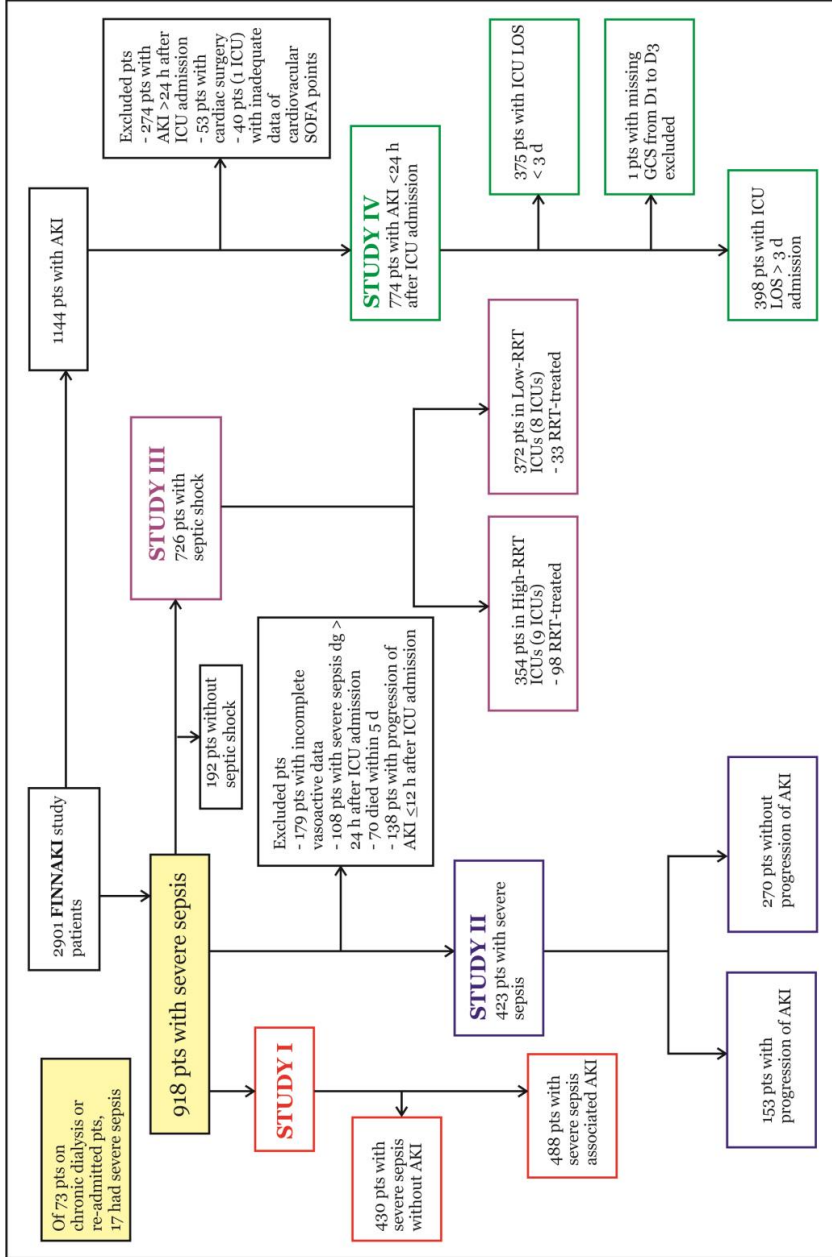
Figure 2. Study flow chart of studies I-IV. Pts patients. The number of patients with severe sepsis in the yellow boxes (935) was used for calculation of incidence of severe sepsis treated in the ICU.

Study III included patients, who fulfilled criteria for septic shock (N= 726). All FINNAKI study patients, who fulfilled the criteria for AKI during the first five days in the ICU, were evaluated for eligibility for **Study IV.** Patients, who fulfilled criteria for AKI later than 24 h after ICU admission or patients that underwent cardiac surgery, were excluded. In addition, 40 patients from one ICU with incomplete data on cardiovascular SOFA score were excluded. The final study population comprised 774 patients with early AKI.

For patients with multiple admissions, the first admission when criteria for severe sepsis was fulfilled were included in studies I-III and in study IV the first admission when AKI criteria were fulfilled.

Characteristics of patients in studies I –IV are presented in Table 8.

Table 8. Characterististics of patients in study I-IV.

	Study I	Study II	Study III	Study IV
Number of patients	918	423	726	774
Age, years (median,[IQR])	65 [54-75]	63 [51-74]	65 [55-75]	65 [55-75]
Male n (%)	329 (36)	276 (65)	464 (64)	268 (35)
Emergency admission n, (%)	894 (97)	415 (98)	704 (97)	744 (96)
Operative admission n, (%)	223 (24)	108 (26)	203 (28%)	216 (28)
SAPS II score, points (median, [IQR])	43 [34-55]	40 [32-49]	45 [35-58]	47 [36-62]
SOFA score on day 1 points (median, [IQR])	8 [6-10]	8 [6-10]	9 [7-11]	9 [7-12]
Length of ICU stay days(median, [IQR]))	4.0 [2.1-7.6]	4.6 [2.5-8.1]	4.5[2.38.2]	3.1 [1.6-5.8]

ICU Intensive Care Unit; IQR interquartile range, SAPS Simplified Acute Physiology Score; SOFA Sequential Organ Failure Assessment

4.2 Study designs and objectives

Study 1 was a predefined substudy of the prospective, observational, multicentre FINNAKI study. The aims of this study were to assess the incidence, population-based incidence, risk factors for mortality, and 90-day mortality of ICU-treated patients with severe sepsis associated AKI. In addition, for the calculation of the incidence of severe sepsis, patients excluded from the FINNAKI study due to, 1) chronic dialysis or 2) re-admitted patients, who received RRT during the previous ICU admission, were screened for severe sepsis retrospectively.

Study 2 was a predetermined substudy of the FINNAKI study. This study evaluated the association between early haemodynamics (the first 24 hours in the ICU) with a new onset or worsening of AKI during the first five days in the ICU, with special interest in time-adjusted MAP. The time-adjusted MAP was calculated by dividing the area under the curve of 10-minute median values of actual MAP values with aggregate time of MAP registration (= first 24 hours in the ICU or until progression of AKI). The AUCs and aggregate times below MAP threshold values (55 to 85 mmHg) were calculated. In addition, the association of vasoactive treatment and known risk factors for AKI were assessed. Figure 3 illustrates an example of the MAP area under curve (AUC) and MAP AUC under threshold 65 mmHg.
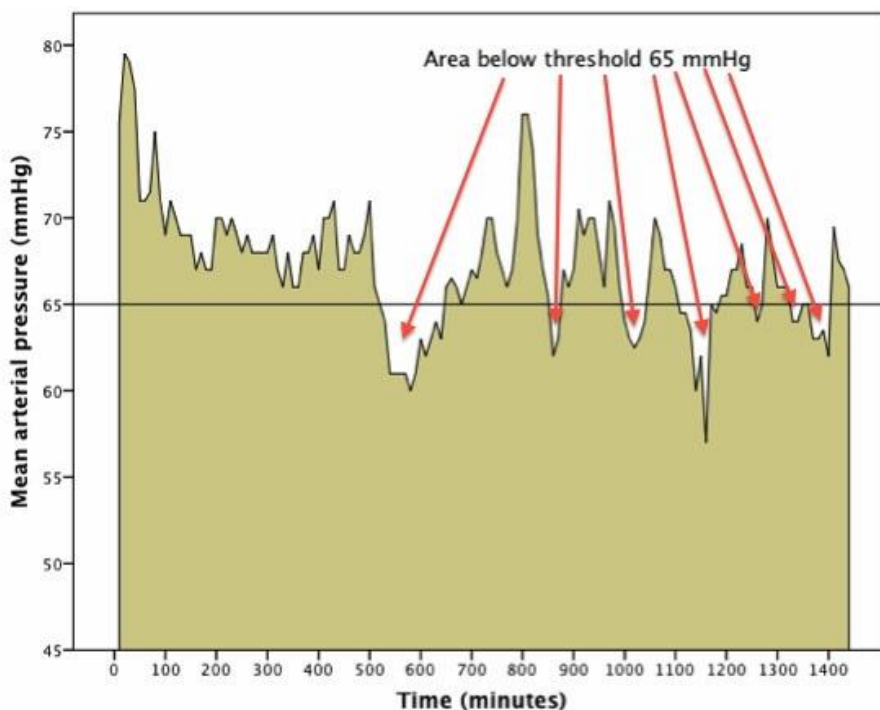
Figure 3. MAP values (mmHg) of an example patient with severe sepsis during the first 24 hours in the intensive care unit. The red arrows indicate areas below the threshold 65 mmHg

For **study 3,** patients with septic shock were retrieved from the FINNAKI study to assess the association between the proportion of RRT use among patients with septic shock and 90-day mortality. The participating 17 ICUs were divided into low-RRT and high-RRT ICUs by a median value of proportion of RRT. University and central hospital ICUs were equally represented in both ICU groups. The differences in indications, modalities, and complications of RRT, and in treatment restrictions between low- and high-RRT ICUs were evaluated.

Study 4 was a predetermined sub-study of the FINNAKI study. The aim of the study was to develop and validate predictive models for critically ill patients with AKI for one-year mortality on two time points: on admission to the ICU (admission model) and on the third day in the ICU (D3 model). The admission model only included predictors available prior to ICU admission. The D3 model included predictors available within the first three ICU days. The admission model comprised 744 patients and D3 model included patients with length of stay in the ICU at least three days, 398 patients.

Summary of study designs and the main aim of the studies are presented in Table 9.

Table 9. Summary of study designs

	Design	Study population	Aims
I	Prospective, predetermined	**918** patients with severe sepsis	To assess the incidence and 90-day mortality of severe sepsis associated AKI
II	Prospective, predetermined	**423** patients with severe sepsis	To evaluate the associations of early haemodynamic and vasoactive treatment with progression of AKI
III	Prospective, predetermined	**726** patients with septic shock	To evaluate the use of RRT and association between proportion of RRT use and 90-day mortality
IV	Prospective, predetermined	**774** patients with AKI	To generate predictive models for one- year mortality for early AKI patients

4.3 Data collection

Study data were retrieved from the national ICU quality database, Finnish Intensive Care Quality Consortium (FICC) maintained by Tieto Healthcare & Welfare Ltd, comprising routine dataset and supplement dataset collected by the study specific case report form (CRF). All the 17 participating ICUs belong to the FICC. Data were recorded for the first five days in the ICU. The routine FICC's dataset includes patients basic demographics, data on hospital and ICU admission and discharge, APACHE II, III, and International Classification of Diseases 10th diagnosis, severity of illness and organ dysfunction scores (APACHE II, SAPS II, and SOFA), and outcomes (length of stay in ICU and in hospital and ICU and hospital mortality).

In addition to routine dataset, data collection was expanded to record data of physiologic values regarding haemodynamics, vasoactive treatments, respiratory values, and laboratory values prospectively into the database. MAP-values were collected as median values of 2 or 5 minutes in the database of participating hospital and manually validated by trained study nurses for the first 24 hours in the ICU. The CRF included data of co-

morbidities, daily medications, health status, known risk factors for AKI, laboratory values prior to ICU admission, and daily evaluation of SIRS, infection, organ dysfunction, fluid balance, and RRT. Data on CRF were collected on the ICU admission and thereafter daily during the first five days in the ICU or until ICU discharge. After day five, data on given RRT were recorded twice a week. In addition, study physicians or nurses from each of the participating ICUs screened patients excluded from the FINNAKI study due to chronic dialysis or re-admitted patients who received RRT during the previous ICU admission for severe sepsis retrospectively. All data were managed anonymously with an individual study number for each patient. Patients' personal identity codes were only used to prevent inclusion of multiple admissions and to obtain survival data from the Finnish Population Register Centre.

For population-based incidence, the referral population of participating hospitals on 31st December 2011 was obtained from Statistics Finland (**http://www.stat.fi**). This referral population was used to calculate the population-based incidence of severe sepsis. For the population-based incidence of severe sepsis associated AKI the number of adults on chronic dialysis (N= 1527, provided by the Finnish Registry for Kidney disease[312]) was subtracted from the referral population.

4.4 Definitions

Acute kidney injury (I-IV)

Kidney Disease: Improving global Outcomes (KDIGO) criteria[35] were used in all studies (I-IV) to define and stage AKI by changes in serum creatinine and hourly urine output. The baseline serum creatinine was the latest value within a year preceding the study enrolment excluding a week prior to ICU admission. The modification in diet in renal disease (MDRD) equation, assuming a glomerular filtration rate (GFR) of 75 ml/min/1.73 m², was used to estimate the baseline creatinine for patients lacking baseline creatinine value as recommended by the ADQI Working Group.[97]

Acute and chronic health status (I-IV)

Presence of hypotension within 48 hours preceding ICU admission was defined as systolic blood pressure <90 mmHg for 1 hour and resuscitation as haemodynamic collapse requiring defibrillation, chest compression, or administration of epinephrine. Chronic kidney disease (CKD) was defined as functional or structural abnormalities of the kidney, or glomerular filtration rate (GFR) < 60ml/min/1.73m², at least one week prior to ICU admission.[35] Hypovolaemia and the presence of disseminated intravascular coagulation (DIC, defined by International Society on Thrombosis and Haemostasis[313]) were screened by an attending physician.

Severe sepsis and septic shock (I-IV)

Severe sepsis and septic shock were screened by the attending physician for 24 h preceding ICU admission and daily to the fifth day in the ICU by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria.[88]

Nosocomial infection (I)

An infection not present or incubating at the time of admission to the hospital, manifesting later than 48 hours after hospital admission was defined as nosocomial infection.[314,315].

Organ failure (OF) (I, III, IV)

Organ specific SOFA points ≥3 indicated organ failure[130,316]. ΔOF (IV) was calculated as difference in number of organ failure on between the third and the first day in the ICU.[317,318]

Vasopressor load (II)

Vasopressor load was calculated by the following formula: vasopressor load (µg/kg/min) = norepinephrine (µg/kg/min) + dopamine (µg/kg/min/2) + epinephrine (µg/kg/min) + phenylephrine (µg/kg/min/10).[56,319] Phenylephrine was not used for any patient during the study.

Low-RRT and High-RRT ICUs (III)

The proportion of RRT was calculated by dividing the number of RRT-treated patients with septic shock by total number of patients with septic shock in an individual participating ICU. The ICUs were divided into two groups, low-RRT and high-RRT ICUs, according to the median value of the proportion of RRT as a cut-off value.

Early AKI (IV)

AKI was defined as AKI, which was diagnosed within the first 24 hours in the ICU.

4.5 Outcome measures

Progression of AKI (II)

Progression of AKI was defined as a new onset of AKI or worsening of AKI by at least one KDIGO stage during the first five days in the ICU.

Standardized mortality ratio (III, IV)

The performance of the ICU and the developed predictive models were evaluated by the standardized mortality ratio (SMR), a ratio of observed deaths to predicted deaths. The SAPS II-based SMR (III) was calculated according to the original SAPS equation.[292] In study IV, the number of predicted deaths was calculated by using the developed AKI-specific models.

Mortality (I-IV)

The patients' vital status were determined at 90-day and at one-year after ICU admission. Death dates of patients were obtained from the Finnish Population Register Centre by personal identity codes. The Finnish Intensive Care Consortium provided the data on ICU and hospital mortality.

4.6 Statistical methods

The data are presented as absolute numbers (percentages) and medians (interquartile ranges, IQR). For comparison of two groups, the Mann-Whitney U-test was used for continuous variables and categorical variables were compared with the Chi-square test or the Fisher's exact test, when the number of cases in a sample was less than five. Backward stepwise logistic regression analyses (with significance of 0.05 for elimination) were performed to analyze associations between variables and outcomes and to calculate odds ratios (ORs) for independent predictors for outcome (I-IV). Variables with $P<0.2$ by univariable analyses were entered into the multivariable regression analyses (I-III). Discrimination of the model (the ability of a model to distinguish patients according to outcome) was evaluated by calculating the area under the receiver operating characteristic curve (AUC) (I, II, IV). The best cut-off values were assessed by the Youden Index method (II). [320,321] The Kaplan Meyer method was used for displaying the survival curves for patients experiencing severe sepsis-associated AKI (I).

Propensity score (III)

The propensity score of a patient describes the probability to receive the putative treatment conditional on the pre-treatment covariates.[322] The method is used to diminish the treatment selection bias and to adjust for differences in the characteristics between patients receiving and not receiving the treatment.[322,323] In study III, a propensity score for RRT was generated by logistic regression analysis. The following confounders related to the study endpoint (90-day mortality) or to the treatment (initiation of RRT) were entered: serum creatinine value, urine output on the first day in the ICU, age categorised by APACHE age groups[65], any co-morbidity, SAPS II score without age and renal components, and SOFA score without renal points on the first day in the ICU.

Development and validation of the predictive model (IV)

Candidate predictors were selected a priori based on previous studies or clinical judgment[324-328] and by univariable analyses between one-year survivors and non-survivors. Both models included only data available at that time point. In concordance with general ICU mortality prediction models, unknown or missing data regarding medical history were assumed to be normal.[65,69,71,329] The missing values of continuous data were imputed with median value of the variable. [326,330,331] To describe the course of severity of illness ΔOF (difference in number of OF on the third and first day in the ICU) was entered in the D3 model. As advocated the continuous variables were not categorized or dichotomized.[324,332-334]

The association of candidate predictors and one-year mortality was analyzed by multivariable logistic regression analyses with backwards elimination with significance level of $P<0.05$ for stepwise removal.[324-326,333] The performances of the models were assessed by discrimination, calibration, and precision. Discrimination of the model was assessed by concordance statistic (c-statistic) using the AUC-value.[305,335-337] An AUC-value of 0.5 represents the same as tossing a coin, whereas AUC values <0.7, >0.7, >0.8, and >0.9 are regarded as poor, acceptable, good, and excellent, respectively.[338-340] For clinical use, an AUC >0.7 is usually considered to be acceptable.[292] Calibration evaluates the correspondence between estimated probabilities of outcome and observed outcome.[324] Calibration of the model was assessed by the Hosmer-Lemeshow goodness-of fit (GoF) chi-squared test.[325,326] The P-value >0.05 of Hosmer-Lemeshow test indicates good calibration.[293]

Currently the most preferred method for internal validation is bootstrapping.[324,326] Bootstrapping method repeatedly draws samples with replacement from the original cohort.[324-326] Those samples are comparable but not identical to the original data set. The original model is developed and the model's performance is assessed in each bootstrapping sample resulting in a mean AUC-value.

In all studies (I-IV) a P<0.05 was considered significant. The time-adjusted MAP (II) was calculated using the NCSS software (Kaysville, UT, USA) and the bootstrapping was performed with R version 3.0.3 for Mac (R Foundation for Statistical Computing, Vienna, Austria). Otherwise all analyses were performed using SPSS Statistics versions 19-21 (IBM; Armonk, NY USA).

Missing data

Imputation techniques have been advocated to address missing values.[326,333] These techniques are based on available data on patients to estimate and to replace the missing data.[330,331] The missing values of continuous data were imputed with median value of the variable.[326](I, IV) Variables with notable (>5%) missing data were not considered as predictors.[333] The proportion of missing data on predictors ranged from 0 to 2.6% in the admission model and from 0 to 6.0% in the D3 model.

4.7 Ethical aspects

The Ethics Committee of the Department of Surgery, Hospital District of Helsinki and Uusimaa, approved the FINNAKI study protocol nationwide and the use of deferred consent. In addition, the Ethics Committees of each hospital district were informed of the FINNAKI study. A written study informed consent was obtained from patients or next of kin. The collection of data of deceased patients if an informed consent could not be obtained was approved by the Finnish National Institute of Health.

5. RESULTS

5.1 Incidence of severe sepsis associated AKI (I)

Of the 2901 patients included in the FINNAKI study during the 5-month study period, 31.6% (918) had severe sepsis. The incidence of AKI among ICU-treated patients with severe sepsis was 53.2% (488/918, 95% CI 49.9 - 56.5%). Of the 918 patients with severe sepsis, KDIGO stage 1 AKI was present in 21.1% (197), stage 2 10.6% (97), and stage 3 in 21.5% (197). RRT was administrated to 15.0% (138/918) during the first five days in the ICU. AKI was more common (59.6%, 433/726) in patients with septic shock compared to 28.6% (55/192) of patients with severe sepsis (P <0.001). The population-based incidence of AKI in ICU-treated patients with severe sepsis (95%CI) was 0.32 (0.30-0.34) /1000 adults /year.

Patients with severe sepsis associated AKI were older (66 years vs. 63 years, P=0.002) and had a higher BMI (27.4 kg/m^2 vs. 25.9 kg/m^2, P<0.001) than those without AKI. They were more severely ill (higher SAPS II score), received vasoactive therapy more often (P<0.001), and were mechanical ventilated more often (P=0.004). The proportions of patients with co-morbidities and points of severity of illness scores are presented in Table 10. Number of patients in APACHE II diagnostic groups in patients with severe sepsis with or without AKI is presented in Table 11. (unpublished data)

Table 10. CO-morbidities and severity of illness between patients with severe sepsis stratified by presence of AKI.

	Severe sepsis with AKI (N=488)	Severe sepsis without AKI (N=430)	P-value
Co-morbidities			
Atherosclerosis	16.3 (78/480)	12.6 (54/424)	0.14
Chronic liver failure	5.2 (25/482)	5.2 (22/425)	0.99
Chronic renal failure	9.9 (48/484)	2.8 (12/429)	<0.001
COPD	11.4 (55/481)	13.1 (56/426)	0.43
Diabetes mellitus	29.3 (143/488))	19.8 (85/430)	0.001
Hypertension	56.2 (272/484)	48.5 (207/427)	0.02
Immunosuppression	7.2 (35/481)	8.0 (34/426)	0.69
Systolic heart failure	10.8 (52/481)	10.8 (46)	0.99
APACHE [1]	27.0 [21.0-33.0]	21.0 [17.0-26.0]	<0.001
SAPS II	48.0 [38.0 – 61.0]	37.5 [30.0 – 46.0]	<0.001
SOFAmax	11.0 [9.0-14.0]	8.0 [6.0-10.0]	<0.001

COPD chronic obstructive pulmonary disease; APACHE Acute Physiology and Chronic Health Evaluation SAPS Simplified Acute Physiology Score; SOFA Sequential Organ Failure Assessment
[1] unpublished data

Table 11. The number (%) of patients with severe sepsis in APACHE II diagnostic groups stratified by presence of AKI (unpublished data)

APACHE II diagnostic group	Severe sepsis associated AKI (N=488)	Severe sepsis without AKI (N= 430)	P-value
Non-operative			
Respiratory	101(20.7)	158 (36.7)	<0.001
Sepsis	94 (19.3)	69 (16.0)	0.2
Gastrointestinal	50 (10.2)	24 (5.6)	0.01
Cardiovascular	47 (9.6)	26 (6.0)	0.05
Renal	26 (5.3)	0	<0.001
Metabolic	21 (4.3)	14 (3.3)	0.41
Neurological	15 (3.1)	25 (5.8)	0.42
Trauma	9 (1.8)	5 (1.2)	0.4
Postoperative			
Respiratory	11 (2.3)	12 (2.8)	0.6
Gastrointestinal	74 (15.2)	61 (14.2)	0.68
Cardiovascular	18 (3.7)	10 (2.3)	0.23
Renal	5 (1.0)	2 (0.5)	0.46
Neurological	3 (0.6)	10 (2.3)	0.46
Trauma	3 (0.6)	4 (0.9)	0.71
Other/missing	11 (2.3)	10 (2.3)	

APACHE Acute Physiology and Chronic Health Evaluation; AKI acute kidney injury

There was no difference in proportions of severe sepsis patients, with or without AKI, who received radio contrast dye prior to ICU admission (22.2% vs. 22.4%, P=0.946) (unpublished data). A significantly higher proportion of patients with severe sepsis-associated AKI (81.6%) received colloids (starch or HES), compared to patients with severe sepsis without AKI (68.5%, P<0.001) 24 hours prior to ICU admission or during days 1 to 5 in the ICU.

The majority of infections were community acquired in both groups of patients. Of the 648 blood cultures taken, 192 (29.6%) were positive. Of the positive blood cultures, 63% (121) were taken from patients with severe sepsis associated AKI. Details of infection between patients with severe sepsis with or without AKI is presented in Table 12.

Table 12 Data on infections in patients with severe sepsis stratified by presence of AKI

	Data available	Severe sepsis with AKI (N=488)	Data available	Severe sepsis without AKI (N=430)	P-value
Source of infection					
Abdominal	437	131 (30.0)	393	83 (21.4)	0.005
Genitourinary	437	39 (8.9)	393	19 (4.8)	0.02
Pulmonary	437	222 (50.8)	393	245 (62.3)	0.001
Soft tissue	437	47 (10.8)	393	37 (9.4)	0.52
			393		
Positive blood culture	353	121 (34.3)	302	71 (23.5)	0.003
Escherichia coli	121	28 (23.1)	71	8 (11.3)	0.04
Other gram negative bacteria	121	28 (23.1)	71	18 (25.4)	0.73
Enterococcus (faecium, faecalis)	121	8 (6.6)	71	4 (5.8)	0.79
Streptococcus pneumoniae	121	17 (14.0)	71	14 (19.7)	0.30
Staphylococcus aureus	121	9.1 (11)	71	8 (11.3)	0.63
Other coagulase negative stafylococci	121	12 (9.9)	71	6 (8.5)	0.74
Multiresistant bacteria*	121	2 (1.7)	71	1 (1.4)	0.90
Yeast	121	5 (4.1)	71	4 (5.6)	0.64
Other	121	21 (17.4)	71	13 (18.3)	0.87

*Multiresistant bacteria: methicillin-resistant staphylococcus aureus, vancomycin-resistant enterococci; extended spectrum beta lactamase.

In addition to 918 patients with severe sepsis, severe sepsis criteria were fulfilled in 23.3% (17/72) of the retrospectively screened patients, who were initially excluded from the FINNAKI study. Altogether 935 patients had severe sepsis during the study period. Using a corresponding 3-month study period and the same inclusion and exclusion criteria as in the original FINNSEPSIS study[3], the population based incidence of severe sepsis was 0.60 (95%CI 0.57-0.62)/1000 adults/year vs. 0.39/1000 adults/1000 (95% CI 0.37-0.41) in FINNSEPSIS (P<0.001).

5.2. Association with early haemodynamics and progression of septic AKI (II)

The development of AKI was present in 36.2% (153/423) of patients with severe sepsis within the first five days in the ICU. Patients with development of AKI had lower time-adjusted MAP (74mmHg, IQR 68-81mmHg) compared to those without progression (79mmHg, IQR 73-85mmHg, P<0.001). Except for the highest MAP threshold (85 mmHg), the areas under the mean arterial pressure (MAP AUCs) under all other MAP thresholds (55-80 mmHg) were larger in patients with progression of AKI compared to patients without progression of AKI. The best cut-off value for time-adjusted MAP for predicting progression of AKI by Youden method was 72.7 mmHg. A greater proportion of patients with development of AKI received norepinephrine or inotropes (P< 0.001 for both) during the first five days in the ICU. The maximum dose of norepinephrine was significantly associated with progression of AKI, only in the lowest quintile of time-adjusted MAP (47.2 – 69.5 mmHg, P<0.001).

Both time-adjusted MAP as a continuous covariate (OR 0.96, 95%CI 0.94-0.99) and time-adjusted MAP below 73mmHg as a binomial variable (OR 2.57, 95% CI 1.48-4.46) were independent predictors for development of AKI. (II)

5.3 Variation in use of RRT in septic shock associated AKI (I)

Of the 726 patients with septic shock, 436 (60.1%) had AKI and 131 patients (18.0%) received RRT. The proportion of RRT-treated patients with septic shock varied from 3% (2/76) to 16% (4/25) in the low-RRT ICUs and in the high-RRT ICUs from 19% (4/21) to 36% (36/99). Except high creatinine, indications for and modalities of RRT were similar in both ICU groups. The main indications and modalities of RRT are presented in Table 13. The median time for initiation of RRT in the high-RRT ICUs were 13.5 hours compared to 17.8 hours in low-RRT ICUs (P= 0.9). The SAPS II and SOFA scores did not differ between ICU groups, but patients treated in the high-RRT ICUs more often received organ supportive treatments such as mechanical ventilation (P<0.001), sepsis corticosteroid (P<0.001), and higher maximum doses of norepinephrine (P<0.001) during the first five days in the ICU. No difference in withholding of RRT existed between low- and high-RRT ICUs (7.5% vs. 4.5%, P=0.09). Patients with restricted RRT were older (69.0 vs. 65.0 years, P=0.009) and were more severely ill (SAPS II score 59.5 vs. 44.0, P<0.001) than patients without restrictions in RRT.

Table 13. Main indications and modalities of RRT in high- and low-RRT-ICUs.

	RRT-treated patients in the **Low-RRT ICUs**	RRT-treated patients in the **High -RRT ICUs**	P-value
Indication of RRT			
Oliguria	29/33 (87.9)	83/98 (84.7)	0.7
High creatinine	25/33 (75.8)	54/98 (55.1)	0.04
Acidosis	24/33 (72.7)	72/98 (73.5)	0.9
Hyperkalemia	9/33 (27.3)	2/98 (20.4)	0.4
Fluid overload	12/33 (36.4)	43/98 (43.9)	0.4
Modality of RRT during ICU stay			
Only CRRT	20/33 (60.6)	52/98 (53.1)	0.5
Only IHD	2/33 (6.1)	11/98 (11.2)	0.4
CRRT and IHD	11/33 (33.3)	35/98 (35.7)	0.8

ICU intensive care unit; RRT renal replacement therapy; CRRT continuous renal replacement therapy; IHD intermittent haemodialysis

5.4 Outcome (I- IV)

The 90-day mortality of severe sepsis associated AKI increased with severity of AKI. The 90-day mortality rates for patients with severe sepsis associated AKI, stratified by KDIGO stages and by RRT (I), are shown in Table 13. By multivariable regression analysis, comparing to patients with severe sepsis without AKI, KDIGO stage 3 AKI, but not less severe AKI, was independently associated with 90-day mortality with an OR (95%CI) of 1.937 (1.276-2.940). (I)

Table 14 90-day mortality rates in patients with severe sepsis stratified by presences of AKI and by the severity of AKI (KDIGO stages)[35](I)

Patients with severe sepsis (N=918)	90-day mortality
No-AKI (n=430)	24.7% (106)
Any AKI (n=488)	38.1% (186)
Stage 1 (n=194)	31.4 % (61)
Stage 2 (n=97)	35.1% (34)
Stage 3 (n=197)	46.2% (91)
RRT-patients (n=138)	49.3

The 90-day mortality was significantly higher in patients with severe sepsis and progression of AKI (32.7%) compared to patients without progression of AKI (18.9%, P=0.00) (II).

The mortality of patients with septic shock did not differ between low- and high-RRT ICUs (33.9% vs. 36.2%, P=0.5) (III). Likewise, 90-day mortality rates were corresponding in RRT-treated patients between low-RRT and high-RRT ICUs, 57.6% vs. 49.0% (P= 0.39). Low-RRT or high-RRT ICU or RRT were not associated with fatal outcome in multivariable analysis adjusted with age, admission type, SAPS II point without age and renal components, AKI on the D1 in the ICU, mechanical ventilation, the lowest BE value, prior to ICU, the highest norepinephrine dose during the first five days in the ICU and with propensity score for RRT. (III)

The mortality in critically ill patients with AKI at 1 year was 39.8%. (IV)

5.5 Predictive models for one-year mortality in patients with AKI (IV)

Among patients with AKI, one-year non-survivors were older (P<0.001), and more frequently noted chronic comorbidities (higher number of co-morbidities, P<0.001) and higher acute burden of illness (assesses as higher SAPS II, P<0.001) than the survivors. The development cohort for admission model comprised all 774 critically ill patients with early AKI and the D3 model included 399 patients, who stayed in the ICU for at least three days. The discrimination of the models improved with longer surveillance time from an AUC-value of 0.76 (admission model) to 0.80 (D3 model) in detecting patients with a risk for fatal outcome. The mean AUC-values by bootstrapping method (an average AUC of 1000 bootstrap samples) corresponded with the original models (0.75 for admission model and 0.79 for D3 model). The independent predictors for one-year mortality in D3 model were: advanced age, a high number of co-morbidities, poor premorbid functional performance, severity of illness, and mechanical ventilation on Day 3. Severity of AKI or presence of severe sepsis, were not predictors for one-year mortality. Table 14 shows the results of regression analysis with odd rations (OR, 95% CI) of all significant predictors of one-year mortality for both models.

Table 14. Predictors for one-year mortality in the admission model and D3-model for critically ill patients with AKI

ADMISSION MODEL		D3-MODEL	
Predictor	OR (95%CI)	**Predictor**	OR (95%CI)
Age, years	1.03 (1.02-1.04)	Age, years	1.04 (1.02-1.06)
Premorbid functional performance preceding the acute illness[a]	1.75 (1.15-2.68)	Modified SAPS II score [d]	1.03 (1.00-1.05)
Admission type according to SAPS II, compared to scheduled surgical		Number of co-morbidities	1.26 (1.05-1.52)
Unscheduled surgical	7.74 (1.65-36.23)	Mechanical ventilation on the D3	2.73 (1.62-4.61)
Medical	11.30 (2.45-52.01)	The lowest BE value on D3	0.92 (0.87-0.97)
Arteriosclerosis	1.87 (1.19-2.95)	The highest bilirubin within D1 to D3 [e]	1.02 (1.02-1.03)
Systolic heart failure	1.83 (1.13-2.95)		
Chronic liver failure	3.79 (1.89-7.43)		
Diabetes mellitus	0.59 (0.41-0.86)		
Malignancy	2.34 (1.43-3.83)		
Hypotension prior to ICU admission[b]	1.67 (1.20-2.31)		
Resuscitation prior to ICU admission[c]	2.34 (1.42-3.85)		

Admission model: [a]Premorbid functional performance defined as dependence of assistance in premorbid functional performance preceding the acute illness and compared to normal or disable to work. [b]Hypotension was defined as systolic blood pressure <90 mmHg for 1 hour, [c]Resuscitation was defined as haemodynamic collapse requiring cardiopulmonary resuscitation, defibrillation or administration of epinephrine D3 model: [d]Modified SAPS II score SAPS II score without points given for age, renal components, bilirubin, and type of admission, [e]The proportion of missing values of the bilirubin concentration within the first three days was 6.0%.

6. DISCUSSION

6.1. Incidence of severe sepsis and septic shock associated AKI

The incidence of ICU-treated severe sepsis associated AKI in this study (53%) was in line with results reported previously.[9-12,14-16,18,23,140]. Depending on the definition of AKI, however, and on the severity of sepsis, the incidence of sepsis associated AKI have ranged from 13%[58] up to 89%. In septic shock, the occurrence of AKI has been even more common.[12,13,18] In this study, AKI was found in 60% of patients with septic shock.

AKI was defined and staged by the KDIGO[35] criteria in the present study. The current AKI definitions identify patients with AKI somewhat differently. AKIN criteria have been shown to identify a few percent more patients with sepsis associated AKI and to classify more patients to the worst AKI stage compared to RIFLE.[9,13,28] In general ICU patients, AKIN criteria have not improved the ability to identify patients with AKI[100,341] and RIFLE criteria have shown better ability to detect patients with AKI.[102] The FINNAKI study reported identical incidences of ICU-treated AKI defined by KDIGO or by AKIN criteria (posthoc).[121] These three AKI classifications have also been validated in hospitalized patients (medical, surgical, neurological, oncological, and psychiatric patients) in Japan the KDIGO and RIFLE criteria identified patients with AKI similarly (11%), whereas less than half of these patients were defined as patients with AKI with the AKIN criteria.[123] Instead of multiple definitions of AKI, the use of three classifications is already an improvement, but to compare results between studies with comparable populations, AKI should be defined by one unified classification.

The population-based, ICU-treated, severe sepsis associated AKI incidence was 0.34/1000 adults/year. Regrettably, no population based incidence for severe sepsis associated AKI has been reported previously. The FINNAKI study reported population-based incidence of ICU treated AKI to the value of 0.75/ 1000 adults/year [121] and two other studies have reported incidences varying from 2.15 to 2.90 /1000/year. [131,132] These studies included patients from a limited area (Scotland[131] and county in U.S[132].) rather than nationwide, however.

During the present study, the population-based incidence of severe sepsis was 1.5-fold compared to the incidence reported in the year 2005. A corresponding increase in the incidence of sepsis has been reported globally,[1,5-7,136] despite the fact that the incidence of the most common causes of sepsis, such as pneumonia, intra-abdominal infection, and urinary track infection, have remained stable or have decreased.[342] To avoid bias in the comparison of incidence of severe sepsis between the FINNSEPSIS and present study: 1) a corresponding 3-month period, 2) the same ICUs, and 3) the exactly same inclusion and exclusion criteria were used. One plausible explanation for the detected increase in incidence of sepsis is that the information and increased knowledge of severe sepsis due to the FINNSEPSIS study[3] and the recently published international[29,90,91] and national[318,319] severe sepsis guidelines may have promoted better recognition of these patients. In addition, all ICU-treated patients, who did not fulfill the exclusion criteria, were included in the FINNAKI study and screened for severe sepsis and AKI. In the FINNSEPSIS study, ICU-treated patients, who filled the criteria for severe sepsis, were included in the FINNSEPSIS study. This difference in study enrolment may have increased the number of patients with severe sepsis during the FINNAKI study. According to the current literature, no other prospective study has compared the changes in incidence in ICU-treated severe sepsis in exactly identical ICUs and time period, and with the same criteria for severe sepsis.

6.2 Mean arterial pressure and progression of AKI

The hypotensive episodes (MAP below 73 mmHg) during the first 24 hours in the ICU were significantly associated with development or worsening of AKI in patients with severe sepsis. In close agreement, a MAP level between 72 and 82 mmHg has been previously suggested to be needed to avoid progression of AKI during septic shock[57]. In addition, MAP levels below 75 mmHg during the early phase of sepsis have predicted the need for RRT.[55,57] In a large RCT higher MAP-target (80-85 mmHg) during septic shock was only beneficial (less RRT) in patients with chronic arterial hypertension.[146] Although recent understanding of pathophysiology in septic AKI has elucidated the role of inflammation in development of septic AKI,[52,54,143,144,176,178] the aetiology of severe sepsis associated AKI is multifactorial and hypotensive episodes may predispose patients with sepsis to development of AKI. The optimal targeting MAP level is unclear, however , the findings of the present study suggest that avoiding MAP levels <73 mmHg may prevent the development of AKI in patients with severe sepsis. In

addition to optimal MAP level, evaluation of renal perfusion pressure is essential, especially in the presence of increased intra-abdominal pressure.

Patients with severe sepsis and progression of AKI received higher maximum doses of norepinephrine, but the maximum dose of norepinephrine was associated with progression of AKI only in the lowest quintile of time-adjusted MAP. Patients with development of AKI were more severely ill in terms of higher lactate concentrations, higher severity of illness score, and they received organ supportive treatments more often, and, thus, a plausible explanation is that the more severe disturbances in haemodynamics required higher doses of norepinephrine. Although norepinephrine has shown to increase renal blood flow and urine output and to improve microvascular circulation during sepsis[39,45,343,344], evidence of adverse outcome due to increasing vasopressor load in septic shock has been demonstrated.[56] On the basis of currently available evidence, restoration of blood pressure with administration of norepinephrine is more important than the eventual harmful effect of norepinephrine. However, excessive vasopressor load should be avoided.

6.3 RRT in severe sepsis and septic shock

Of the patients with severe sepsis, 15% were treated with RRT and of the patients with septic shock, 18% received RRT. These proportions are in line with reported studies of cases with a corresponding severity of sepsis and with the current available definition of AKI (RIFLE, AKIN or KDIGO criteria).[17,20] In patients with less severe sepsis, the reported proportions of RRT-treated patients have been less, <10%.[23,58,139] Across participating ICUs, 10-fold variation (3% to 36%) was found in proportion of RRT-treated patients with septic shock. The decision to initiate RRT is based on an opinion of the attending physician and on local protocols. A lack of consensus guidelines for indications for RRT may partly explain this large variation. Patients requiring RRT are severely ill and RRT is a highly complex treatment requiring expensive equipment. Therefore, the care of these patients may be centralized in some regions or countries. In the present study, all participating ICUs had the capacity to provide RRT, but the influence of the center policy regarding the initiation of RRT and inexperience in RRT can't be excluded. However, university hospital ICUs with proven experience and capacity to provide RRT were equally distributed in high- and low-RRT ICUs. In addition, the lowest (3%) and highest

proportion (36%) of RRT-treated patients among patients with septic shock were both presented in university hospital ICUs.

The most common indications of RRT (oliguria, high creatinine, acidosis, hyperkalaemia, and fluid overload) were in line with the B.E.S.T.-study and with the practice of European intensivists in low- and high-RRT ICU groups.[256,257] Apart from emergency indications, initiation of RRT integrates multiple aspects of patients' circumstances, such as progression and severity of AKI, pre-existing renal function and other co-morbidities, exposure of nephrotoxins, and prognosis of critical illness. Thus, the use of RRT varies between patients with corresponding severity of AKI. The treatment with RRT predisposes patients to complications related to RRT, such as hypotension, electrolyte disturbances, bleeding, punction complications and catheter-related infections. A study comparing conservative treatment (management of volume and hydration status, and restoration of electrolyte and acid- base homeostasis) with RRT found higher mortality in RRT-treated patients than in patients receiving conservative treatment.[345] Although the patients treated with RRT were more severely ill (higher SOFA and APACHE II scores) the worse prognosis in RRT-treated patients remained after adjustment for severity of illness.[345] In the present study, the mortality rates between high and low-RRT ICUs did not differ. Neither administration of RRT nor group of ICU (low-RRT or high-RRT ICU) were predictive for mortality.

In the present study, no differences in use of different modalities of RRT (only CRRT, only IHD or both CRRT and IHD) between high-and low-RRT ICU existed. European intensivists have been found to prefer CRRT.[257] In concordance, CRRT was used in 90% of RRT-treated patients with septic shock and CRRT was the most common modality in both high- and low-RRT ICUs. Patients with septic shock have unstable haemodynamic and IHD has been shown to be associated with haemodynamic instability more often than CRRT.[267,268,271]

In line with a previous study,[346] treatment restrictions were applied more often to RRT-treated patients (45%) compared to only a quarter of patients without RRT. Altogether, RRT was restricted in 10% of patients with septic shock (III). The proportion of restricted RRT was equal in both ICU groups. Congruent to the present results, age, severity of illness, and poor prognosis have been reported to associate with treatment restrictions in patients with AKI.[347] The decision to restrict RRT is difficult and should be based on the prognosis of the underlying critical illness and on the expected quality of life after intensive care. No differences in age, number of comorbidities, and severity of illness scores (non-renal SOFA score on day 1 in the ICU and

SAPS II score) existed in patients with restricted initiation of RRT between high-and low-RRT ICUs.

6.4 Outcome of severe sepsis associated AKI

The short-term mortality rates for patients with severe sepsis associated AKI were in line with Australian[10] and French[20] studies, but may be considered low compared to other previous studies reporting mortality rates over 40% and 75% for patients with septic AKI.[11,12,18,25,28] Some of the difference in mortality may be explained by differences in severity of sepsis (severe sepsis vs. septic shock[12,18]) and in the definition of AKI (RIFLE,[12,18] other definition of acute renal failure[11,25]). A cross-sectional one-day prevalence study from Germany has reported 90-day in-hospital mortality of 67% among patients with severe sepsis and AKI,[11] which is substantially higher than in the present study (38%). Patients with severe sepsis associated AKI were more often treated with RRT in the German study compared to the present study (42% vs. 28%) and they were older (71 years vs. 66 years, respectively), but APACHE II score of patients with septic AKI was lower in the German study (22 vs. 27). However, AKI was not defined by the current definitions (RIFLE, AKIN, or KDIFO) in the German study, and thus, the comparison of patient with septic AKI is not eligible.

The one-year mortality of critically ill patients with AKI (40%) was comparable to the mortality rate observed in patients with mild AKI[291] but lower than in studies reporting one-year mortality for critically ill patients with AKI of any severity.[74,348] Higher long-term mortality rates have been reported in RRT-treated patients.[72,78,349,350] These studies have included only patients with most severe AKI and thus, they are not directly comparable to the present study.

6.5 Predictive model for 1-year mortality in patients with AKI

In this study, two AKI-specific predictive models for one-year mortality among critically ill patients with AKI were developed. Mortality in survivors of critical illness after ICU treatment has been reported to remain high during the first months after hospital discharge.[290] Increased risk for long-term mortality in AKI survivors has been observed,[25,72,73,75-79,139,348] also in Finland.[78] The mortality rate of patients with AKI has not equalled the

average mortality of normal population until one year.[351] In addition, one-year mortality is a relevant patient-centered outcome compared to hospital mortality, which is influenced by discharge policy.[352] Only one of the AKI-specific (SHARF II) short-term mortality models has been tested for prediction of one-year mortality in the same multicenter cohort as it was developed.[74].

Most of the previous AKI-specific models are based on data available at a single time point. However, patients with progressing AKI have been observed to have a worse outcome than patients with stable or improving AKI.[353] Similarly, worsening of organ function up to four days after the onset of sepsis[318,354] or three days after initiation of RRT has been found to increase the risk of mortality.[355] Therefore, in this study two models at two different time points were developed (on ICU admission and on the third day in the ICU). The longer surveillance period improved the discrimination of the model from AUC-value of 0.76 (admission model) to 0.8 (D3 model). (IV) Corresponding improvement in discrimination of the model has also been found with the SHARF II model. [82]

In concordance with other AKI-specific models, a high number of co-morbidities, mechanical ventilation, and measurements reflecting organ dysfunction (the highest bilirubin value) were also predictors for long-term mortality.[80-83,86,301] However, contrary to the SHARF II-score[82] and Chertow's model[301], severe sepsis or AKI did not remain predictors for long-term mortality in the present models. Most of the AKI-specific models are developed on data from the 1990s. The advancements in definition, recognition and treatment of severe sepsis and AKI, and the improvement in general intensive care[5], may have improved the prognosis of these syndromes. In addition, due to differences in case-mix and changes in the definition of AKI, the previous AKI-specific models may no longer be applicable. None of the previous models have used any of the current definitions for AKI. This study adds novel predictive models for long-term mortality among critically ill patients with AKI. However, external validation is essential before the present model can be applied to clinical use.

6.6 Strengths and limitations of the studies

The present study has several strengths. First, the due to the large sample size with prospective data collection the results of the study I may be considered as generalizable to other populations. The participating ICUs covered the majority (85%) of the Finnish adult population[121] and represented both university and central hospitals. The data were collected using automated Internet interfaces and validated in the participating ICUs by educated study physicians and nurses. In addition, the study-specific additional data collected by CRF was audited in 9 ICUs (randomly chosen) by study investigators. Second, AKI was defined using changes in both urine output and creatinine, and most importantly, using the most recent KDIGO classification. Third, instead of short-term mortality with varying length of stay in ICU or hospital a fixed 90-day mortality was used as the endpoint for studies I-III and a patient-centered long-term outcome, one- year mortality for study IV. The vital status was obtained from the Population Register Centre. Fourth, in study 4 the proportion of missing data of only one predictor exceeded 5%. (IV) The missing values of continuous data were imputed with median value of the variable. (I, IV) As advocated, no continuous variable, and only one categorical variable, were dichotomized (IV). Internal validation was performed with the bootstrapping method (IV). Thus, in summary, the reliability and generalizability of the findings of the presented studies are high.

Multiple important limitations in this study need to be discussed, however. First, the FINNAKI study design was observational and, thus, able to detect only associations with no possibility to prove any causalities (I-IV). Second, AKI and severe sepsis were screened only for the first five days in the ICU (I-IV). The study design may have slightly underestimated the number of patients with AKI or severe sepsis. However, the critically ill patients with AKI have usually developed the worst AKI stage within the first few days (median 2 days) in the ICU.[119] In the FINNSEPSIS study, only 2.3% of patients with severe sepsis fulfilled the criteria for severe sepsis after the fifth day in the ICU. Third, and most importantly, only ICU-treated patients were screened (I-IV). A marked proportion of patients with severe sepsis are treated on wards.[3,356] Likewise a marked number of hospitalized patients with AKI are treated in the wards. The majority of these patients have mild disease and are treatable on the wards. In some of these patients, treatment restriction may have been applied due to severe co-morbidities, such as incurable malignancies. However, the aim of this study was to evaluate the incidence of ICU-treated severe sepsis associated AKI. For calculations of

incidence of ICU-treated severe sepsis, a part of the patients were screened retrospectively, and, thus, few severe sepsis cases may have been missed. In addition, the study was accomplished during the autumn and winter seasons, which may have influenced the occurrence of severe sepsis due to seasonal variation. Fourth, as recommended,[97] the MDRD equation was used to estimate a baseline Cr for patients lacking the baseline Cr value (I-IV). However, none of the current equations is optimal for all patients and causes bias.[113,115]

Study II was an observational study without randomization and predetermined targeting MAP levels and, therefore, no firm causal conclusion can be drawn about association of MAP level and progression of AKI. Second, additional haemodynamic measurements, such as CVP, CO, and SVO_2 were lacking and the only included parameters to describe the hypoperfusion were blood gas values and lactate concentrations. Third, intra-abdominal pressure (IAP) was measured only in a few (22%) patients with suspected high IAP by clinical judgment. Fourth, the exclusion of patients who died within the first five days in the ICU may have caused selection bias as these patients were most likely the most severely ill. However, these patients were excluded to diminish the impact of competing risks between progression of AKI and death.

In study III, the sample size was likely inadequate to show possible differences between high- and low RRT ICUs. The 10-fold variation in the use of RRT across the participating ICUs without influence on mortality calls for further evaluation in a larger study. Second, although propensity score[323] was included to regression analysis, the influence of local experience and practice in initiation of RRT can not be totally adjusted with propensity score.

In study IV, candidate predictors were mainly selected a priori based on previous literature and clinical judgment. Therefore, some significant factors may have been excluded. Second, although nearly 800 patients with AKI were included in the development cohort of the predictive model, a larger study population may be required to achieve better performance of the model. Third, customization and external validation would certainly improve the performance and clinical strength of our model. Fourth, due to a large proportion (31%) of missing values in neurologic evaluation in SOFA score on the third day in the ICU, it could not be included in the D3 model.

6.7 Clinical implications and future perspectives

AKI often complicates the course of severe sepsis and these patients often require organ supportive treatments. Despite advancements in intensive care the short- and long-term mortality rates are high in patients with severe sepsis. Earlier recognition of sepsis might lead to improved awareness and avoidance of additional risk factors related to sepsis and intensive care, such as hypotension, hypovolaemia, and administrations of nephrotoxins. This may be one of the most important possibilities to prevent the development of AKI and associated mortality.

For now, inflammation and overproduction of nitric oxide are suggested to play the key role in the development of severe sepsis associated AKI. Until better understanding on the precise pathophysiology of severe sepsis associated AKI, the haemodynamic circumstances that can predispose development of AKI, such as hypotension and hypoperfusion, should be avoided. On the other hand, targeting supranormal haemodynamic values with excess fluid administration or vasopressor load seem to be harmful. Further studies are needed to evaluate the association between different targeting MAP levels and especially renal blood flow over time. These studies should also take into account the severity of illness and try to standardize supportive haemodynamic treatment (fluid balance and vasoactive treatment).

The distinct pathophysiology of severe sepsis associated AKI enables fascinating possibilities to attempt to diagnose AKI earlier and to develop specific treatments for septic AKI. Detecting, removal, and prohibiting the inflammatory mediators in early phases of septic AKI could lead to better survival of these patients. The prohibition of the inflammatory cascade would prevent permanent cell damage and subsequent chronic renal failure requiring dialysis. Trials regarding caspase-inhibitors[181,357,358] are promising but require further investigation. Although the IVOIRE study did not confirm the beneficial effect of HVHF (high volume hemofiltration) in severe sepsis, theoretically the blood purification with HVHF remains an interesting prospect. Perhaps more advanced filters need to be developed to absorb the inflammatory mediators. In addition, particularly during HVHF, more advanced measurements of therapeutic concentrations of drugs are needed.
Animal studies with induced sepsis, administration of alkaline phosphatase has reduced the inflammatory response and mortality.[359,360] Alkaline phosphatase is an endogenous enzyme with the ability to reduce inflammation by detoxifying endotoxins through dephosphorylation. In addition, alkaline phosphatase converts the harmful extracellular adenosine

triphosphate into adenosine, which has anti-inflammatory and renal tissue protective traits.[361,362] The decreased expression of iNO in patients with sepsis [363] and improved CrCl in patients with severe sepsis or septic shock associated AKI[362] have suggested that alkaline phosphatase is a potential new treatment option for septic AKI. In the future, experimental and larger clinical trials are warranted for patient selection, timing and dosing of this treatment.

In the absence of absolute indications for RRT, the decision to initiate RRT is individual for each patient within the context of the patients' entire clinical condition. RRT is a highly invasive and costly treatment. Advantages and disadvantages should be considered before administration of RRT to avoid exposing patients to unnecessary harm. However, delaying initiation of supportive treatment may facilitate more severe organ dysfunction/failures. In the future, RCTs are needed to compare equally ill patients randomized to different therapeutic approaches and timing of RRT, possibly also including conservative treatment for AKI patients. Despite common use of RRT in developed countries, the consensus guidelines for indications, timing and also withholding of RRT remain lacking.

The objective assessment of an individual patient's severity of illness and prognosis is appealing. Predictive models are important instruments in identifying patients with inevitably poor prognosis to avoid futile care. In the future, lack of ICU beds may be a more pronounced problem. For now, predictive scores provide estimates of the number of patients predicted to decease among a group of similar patients. Nevertheless, they do not provide predictions of which patients will die. Therefore, decision-making for each individual patient treatment should not be solely based on predictive models. However, using these instruments to provide additional information in decision-making, together with clinical evaluation, is reasonable. A combination of several predictive models (for example SAPS II, daily SOFA score, and nursing workload) may provide a more accurate estimate of prognosis. A large prospective study designed for model developing and testing is needed to provide reliable AKI-specific score. Additionally, all new models need to be externally validated among patients from different geographical regions.

The mortality in hospital survivors of patients with AKI remains increased after hospital discharge. Even mild AKI has been shown to increase the risk of development of CKD and mortality. Reasonable follow-up, rehabilitation, prevention of use of nephrotoxic drugs and earlier diagnosis of possible CKD after hospitalization may improve the long-term survival of these patients in

the future. Longitudinal register studies of hospital survivors of patients with AKI are needed for organization of an optimal follow-up for these patients.

7. CONCLUSIONS

On the basis of the results of the study, the following conclusions are drawn:

1. In the Finnish adult ICUs, the incidence of severe sepsis associated AKI was 53%, which was largely consistent with studies using comparable definition of AKI. The population-based incidence of ICU-treated patients with severe sepsis associated AKI was 0.32/1000 adults/year.

2. The population-based incidence of severe sepsis was 1.5-fold (0.6 vs. 0.39/1000 adults/ year) compared to the incidence in year 2005.

3. Patients with severe sepsis and progression of AKI had lower time-adjusted MAP than those without progression. MAP-levels below 73 mmHg were associated with new onset and development of AKI. Progression of AKI was associated with higher mortality than in severe sepsis without AKI progression.

4. The proportion of RRT-treated patients in septic shock varied from 3% to 36% across Finnish ICUs. Differences in case-mix and severity of organ dysfunctions explained the 10-fold variation in the proportion of RRT-treated patients in low- and high-RRT ICUs. No difference in 90-day mortality existed between low and high-RRT ICUs among patient with septic shock (34% vs. 36%).

5. Severity of illness, advanced age, poor premorbid functional performance, a high number of co-morbidities, and mechanical ventilation on Day 3 were independent predictors of one-year mortality, but presence of severe sepsis or severity of AKI of was not. The D3-model performed fairly well judged by an AUC of 0.8.

8. ACKNOWLEDGEMENTS

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