Acute kidney injury in trauma and cardiac arrest patients

Thesis for the degree Philosophiae Doctor (Ph.D.)

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2. Acronyms and abbreviations

ACCP	American college of chest physicians
ACEI	Angiotensin converting enzyme inhibitor
ADQI	Acute dialysis quality initiative
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ALS	Advanced life support
ARB	Angiotensin II receptor blocker
ARF	Acute renal failure
ATN	Acute tubular necrosis
ATPase	Adenosinetriphosphatase
AuROC	Area under the receiver operating characteristics curve
BE	Base excess
BLS	Basic life support
°C	Degrees Celsius
CA	Cardiac arrest
C_{cr}	Creatinine clearance
CI	Confidence interval
CI-AKI	Contrast-induced acute kidney injury
CK	Creatine kinase
CKD	Chronic kidney disease
cm	Centimetres
CPC	Cerebral performance category
CPR	Cardiopulmonary resuscitation
CRRT	Continuous renal replacement therapy
CVVHD	Continuous veno-venous haemodialysis
CVVHDF	Continuous veno-venous haemodiafiltration
CVVHF	Continuous veno-venous haemofiltration
DOI	Digital object identifier
ECG	Echocardiogram
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
F	French
GCS	Glasgow coma scale
GFR	Glomerular filtration rate
GN	Glomerulonephritis
h	Hour
HCO_3^-	Bicarbonate
ICD	International classification of disease
ICU	Intensive care unit
IGFBP	Insulin-like growth factor-binding protein
IHD	Intermittent haemodialysis
IL	Interleukin
ISS	Injury severity score
IQR	Interquartile range
K	Dialyzer clearance of urea
K^+	Potassium
KDIGO	Kidney disease - improving global outcome
kDa	Kilo Dalton

kg	Kilogram
KIM	Kidney injury molecule
L	Litre
L-FABP	Liver-type fatty acid-binding protein
m	Mili
m^2	Square meter
MDRD	Modification of diet in renal disease
min	Minute
µ	Micro
n	Number
Na^+	Sodium
NCT	National clinical trial
NGAL	Neutrophil gelatinase-associated lipocalin
NORCAST	Norwegian cardiorespiratory arrests study
NSAID	Non-steroid anti-inflammatory drug
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
OUHU	Oslo university hospital Ullevål
P_{Cr}	Plasma creatinine concentration
PD	Peritoneal dialysis
PEA	Pulseless electric activity
pH	Pondus hydrogenii
PhD	Philosophiae Doctor
PNO	Poor neurological outcome
r	Correlation coefficient
RCF	Relative centrifugal force
RIFLE	Risk, injury, failure, loss and end-stage renal disease
ROC	Receiver operating characteristics
ROS	Reactive oxygen species
ROSC	Return of spontaneous circulation
RRT	Renal replacement therapy
RTS	Revised trauma score
SAPS	Simplified acute physiology score
SCCM	Society of critical care medicine
S_{Cr}	Serum creatinine concentration
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
SOP	Standard operating procedure
SPSS	Statistical package for social sciences
t	Time
TIMP	Tissue inhibitor of metalloproteinase
TLR	Toll-like receptor
TNF	Tumour necrosis factor
TTM	Targeted temperature management
U_{Cr}	Creatinine concentration in urine
V	Volume of distribution for urea
Vdt	Urine flow rate
VF	Ventricular fibrillation
VT	Ventricular tachycardia

3. List of papers

Paper I

Beitland S, Moen H, Os I. Acute kidney injury with renal replacement therapy in trauma patients. Acta Anaesthesiol Scand 2010; 54(7): 833-40.

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Paper II

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Paper III

Beitland S, Nakstad ER, Stær-Jensen H, Drægni T, Andersen GØ, Jacobsen D, Brunborg C, Waldum-Grevbo BE, Sunde K. Impact of acute kidney injury on patient outcome in out-of-hospital cardiac arrest: A prospective observational study. Acta Anaesthesiol Scand 2016; 60(8):1170-81.

DOI: 10.1111/aas.12753

Paper IV

Beitland S, Waldum-Grevbo BE Nakstad ER, Berg JP, Trøseid AMS, Brusletto BS, Brunborg C, Andersen GØ, Sunde K. Urine biomarkers early predict acute kidney injury and patient outcome after out-of-hospital cardiac arrest. Crit Care 2016; 20(1):314.

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4. Introduction

Acute kidney injury (AKI) is a feared complication in intensive care unit (ICU) patients where the kidneys rapidly fail to regulate fluid and/or metabolic waste products in the body [1-4]. AKI is quite common in ICU patients [5, 6], with variable incidence rates depending on the population studied and definitions used. The structural damage and/or functional impairment of the kidneys are caused by chronic risk factors acting together with acute illnesses and/or injuries [7-10]. Treatment of AKI is correction of the underlying condition and general supportive care of organ functions; the most severe cases need renal replacement therapy (RRT) temporary replacing the normal blood-filtering function of the kidneys [11]. AKI is associated with increased short-time morbidity, mortality and health care costs [12-15]. Survivors are also predisposed to chronic kidney disease (CKD) and have reduced long-time survival [16-19].

A better understanding of the pathophysiology of AKI has emerged in recent years [20-22] and uniform definitions are developed [23-25]. There are, however, still many shortcomings in the understanding of the disease process and patient care [26, 27]. One is that AKI is a quite heterogeneous condition [5] with deficient understanding of different patients groups and treatment alternatives [11, 28-32]. Another is that mortality in ICU patients with AKI remains high despite many attempts to improve prevention and treatment [32-35]. Finally, AKI becomes clinically evident when the decline in kidney function is quite advanced [36, 37], and it would be preferable to have early predictive biomarkers [38, 39].

This thesis focuses upon AKI in trauma- and out-of-hospital cardiac arrest (OHCA) patients who are two relatively small and heterogeneous subgroups of ICU patients. The primary aims were to investigate the occurrence of AKI and impact on patient outcome in both patient groups. Secondary aims were to evaluate the quality of RRT in trauma patients, and to examine the utility of urine AKI biomarkers in OHCA patients.

5. Background

5.1 Intensive care unit

An ICU is a hospital department that provides highly specialized health care to patients with severe and life-threatening illnesses and/or injuries. ICU departments may consist of variable patient groups such as mixed-, surgical-, medical-, neurological- or paediatric ICUs. Critically ill patients have reversible latent or manifest failure of one or several organ functions, including the central nervous system, cardiovascular system, lungs, liver, kidneys and coagulation system. ICU patients require constant, close monitoring and support from specialized equipment and medications to ensure improvement of these organ functions. The personnel working in the ICU are multidisciplinary consisting of doctors, nurses, physiotherapists and other groups working in teams closely following each patient. Among critically ill patients there is a substantial acute morbidity and mortality, and among survivors many suffer long-time physical and/or psychic disability [40, 41].

A huge challenge in the interpretation of studies performed in the ICU is that there is a considerable variation in critical care services across the world [42, 43]. There is large site-to-site variability in the ICU population, the treatment they receive, and their outcomes limiting the external validity of ICU studies [42]. In order to overcome these shortcomings, validated scoring systems are developed in order to have uniform reporting systems enabling comparisons of patient cohorts. The severity of illness early during ICU stay may be assessed by the Simplified acute physiology score (SAPS) [44], and the extent of organ failures during ICU stay might be measured using the Sequential organ failure assessment (SOFA) score [45].

5.2 Trauma

Trauma mainly affects young males and is the sixth leading cause of death and the fifth leading cause of significant disability worldwide [46, 47]. Trauma mechanisms are typically motor vehicle accidents or falls, and is often divided into non-penetrating (blunt) and penetrating injuries. The severity of trauma is usually assessed using the Injury severity score (ISS) [48], major trauma is often defined as ISS above 15 [47]. Pre-hospital stabilization includes management of airway, breathing and circulation in addition to securing the patient with a cervical collar and a scoop stretcher [49]. Rapid transportation of severely injured patients directly to a trauma centre improves outcome [49].

In-hospital management by a multidisciplinary trauma team includes a primary survey to detect organ dysfunctions and injuries. After immediate care of life-threatening injuries that might include surgery, a secondary survey is performed with a more detailed head-to-toe assessment [49]. Post-trauma care has changed during the last years, especially regarding the handling of severe bleeding. Recent European guidelines recommend the use of early imaging techniques for detection of free fluid in patients with suspected torso trauma, and that patients with significant intra-thoracic, intra-abdominal or retroperitoneal bleeding and haemodynamic instability undergo urgent intervention [50]. In parallel to this, acute bleeding patients are treated with hypotensive resuscitation with restricted use of fluids, massive transfusion protocols including blood component therapy, as well as treatment of acidosis and hypothermia [50]. Immediate post-traumatic deaths are usually due to apnoea, severe brain injury or severe, uncontrolled bleeding leading to circulatory collapse. In contrast, late deaths are often related to infections, organ complications or withdrawing of treatment due to futility. Among survivors, massive tissue injury, bleeding, coagulopathy and/or infection after trauma may severely affect organ functions; the kidney function is further challenged by skeletal muscular necrosis, i.e. rhabdomyolysis.

The incidence of AKI in trauma patients is estimated to be 15-48 % [51-56], but more robust data are warranted. Post-traumatic AKI is only a small proportion of severe AKI observed in the ICU [5]. There are few trauma patients in need of RRT, and usually the kidney function is restored in survivors [10]. Important risk factors for post-traumatic AKI are pre-existing CKD and other co-morbidities, advanced age, African-American race, obesity, severe injuries, rhabdomyolysis, blood product administration, haemoperitoneum and mechanical ventilation [10, 57-59]. Importantly, development of AKI in trauma patients is associated with increased patient mortality [51, 54, 55, 60, 61]. Trauma survivors may end up with long time complications including pain, reduced quality of life, physical disability and/or post-traumatic stress disorder [62, 63].

5.3 Cardiac arrest

Cardiac arrest (CA) is one of the most common causes of death in industrialised countries mainly affecting male, middle-aged and/or elderly people [64, 65]. In a recent European multinational study the incidence rate of OHCA was on average 84 per 100.000 inhabitants per year with large variation across countries [66]. Cardiac causes, as acute myocardial infarctions, chronic ischemia and acute primary arrhythmias are the most frequent causes of arrest. Non-cardiac causes, like respiratory disease, cerebrovascular disease, trauma, asphyxia and intoxications have a worse prognosis [67, 68]. OHCA is most often grouped according to the initial cardiac rhythm registered on the echocardiogram (ECG), i.e. ventricular tachycardia (VT), ventricular fibrillation (VF), pulseless electric activity (PEA) or asystole. The shockable rhythms (VT and VF) are usually associated with cardiac aetiology, PEA represents a wide range of aetiologies, and asystole is often the terminal rhythm as a sign of severe asphyxia [69, 70]. CA patients must receive immediate cardiopulmonary resuscitation (CPR) in order to achieve return of spontaneous circulation (ROSC). CPR has traditionally been divided into

basic life support (BLS) provided by bystanders consisting of chest compression and rescue breathing, and advanced life support (ALS) delivered by health-care professionals adding defibrillation, advanced airway management and intravenous drug therapy. Data from a large study indicate that 28 % of OHCA victims achieve pre-hospital ROSC, and as many as 59 % are transported to hospital, but again with large variations across sites [71]. The quality of care depends on five factors in the so-called "chain of survival": Immediate recognition of the CA, early CPR, early defibrillation, early ALS and post-resuscitation care [72].

In-hospital treatment after CA has improved during the last years focusing upon development of standard operating procedures (SOP) involving coronary reperfusion, targeted temperature management (TTM), haemodynamic optimisation in addition to control of seizures and blood sugar levels [73-75]. Initial survivors after CA have considerable morbidity and mortality [76, 77] related to the so-called post cardiac arrest syndrome [78, 79] characterized by ischemia and/or reperfusion injuries, activation of coagulation and inflammation, and subsequent occurrence of multiple organ failure [78, 79].

AKI affects 12-81 % of the CA survivors and becomes clinical evident median 1-2 days after the arrest [80-85]. Between 4-33 % of patients with AKI will need RRT [81, 84-86], but only a small proportion of those are RRT dependent after 30 days [85]. Risk factors for AKI in CA victims are pre-existing renal insufficiency, non-shockable rhythm, long time to ROSC and post-resuscitation shock [85]. Development of AKI in CA victims is associated with increased risk of death [81, 84-86], whereas the impact on neurological outcome remains unsettled [82, 84, 86]. Neurological outcome after CA is usually assessed using the Cerebral Performance category (CPC) ranging from 1 to 5, stages 1 or 2 are considered to be a good functional outcome [87, 88].

5.4 Acute kidney injury

AKI, previously named acute renal failure (ARF), must clearly be separated from CKD where there is progressive loss in kidney function evolving over a period above three months.

5.4.1 Definitions

Historically, there has been a huge challenge regarding the characterization of AKI as there were many different definitions that has hindered clinical research since it confounded comparisons between studies. In order to improve this, the Acute Dialysis Quality Initiative (ADQI) group developed the RIFLE (Risk, injury, failure, loss and end-stage renal disease) definition in 2004 [23]. The Acute Kidney Injury Network (AKIN) group published a slightly modified version in the AKIN definition in 2007 [24]. Later, the Kidney disease – improving global outcome (KDIGO) group published the KDIGO criteria in 2012 [25]. In all three definitions, the development of AKI has to be acute, and the worst of the serum creatinine and urine output criteria is used (Table 1). All definitions consider three variables related to:

- Time criteria: The change in kidney function has to be acute
- Glomerular criteria : Blood sample results and/or need of RRT
- Diuresis criteria: Urine output (measured as millilitre (mL)/kilogram (kg)/hour (h))

More recently, some have suggested that novel biomarkers of AKI should be included in AKI definitions, because biomarkers can identify kidney damage not otherwise detected [89]. A similar approach has been used in CKD where patients with normal or elevated estimated glomerular filtration rate (eGFR) have been included in they have other signs of kidney damage in blood samples, urine samples or imaging studies [90]. Although this might be a promising new era of AKI staging, biomarkers have yet not been included in AKI definitions.

Table 1: Definitions and staging of acute kidney injury

Time period

RIFLE	AKIN	KDIGO
Serum creatinine changes over 1-7 days, sustained for more than 24 hours	Acute serum creatinine changes occur within a 48-hour period during hospitalization	Serum creatinine changes ≥ 1.5 times baseline within 7 days*, or increases ≥ 26.5 µmol/L within a 48-hour time period**

Serum creatinine criteria

RIFLE		AKIN		KDIGO	
Risk	Increase in serum creatinine ≥ 1.5-2.0 times baseline or decrease in eGFR ≥ 25 %	Stage 1	Increase in serum creatinine ≥ 26.5 µmol/L or increase to ≥ 1.5-2.0 times baseline	Stage 1	Increase in serum creatinine ≥ 1.5-2.0 times baseline*, or ≥ 26.5 µmol/L**
Injury	Increase in serum creatinine ≥ 2.0-3.0 times baseline or decrease in eGFR ≥ 50 %	Stage 2	Increase in serum creatinine to ≥ 2.0-3.0 times baseline	Stage 2	Increase in serum creatinine ≥ 2.0-3.0 times baseline
Failure	Increase in serum creatinine ≥ 3.0 times baseline or decrease in eGFR ≥ 75 % or an absolute serum creatinine ≥ 354 µmol/L with an acute rise of at least 44 µmol/L	Stage 3	Increase in serum creatinine to ≥ 3.0 times baseline or serum creatinine ≥ 354 µmol/L with an acute rise of at least 44 µmol/L or initiation of RRT	Stage 3	Increase in serum creatinine ≥ 3.0 times baseline or increase in creatinine to ≥ 354 µmol/L or initiation of RRT
Loss	Complete loss of kidney function for more than 4 weeks				
ESRD	End-stage kidney disease for more than 3 months				

Urine output criteria

RIFLE		AKIN		KDIGO	
Risk	< 0.5 mL/kg/h for > 6 hours	Stage 1	< 0.5 mL/kg/h for > 6 hours	Stage 1	< 0.5 mL/kg/h for > 6 –12 hours
Injury	< 0.5 mL/kg/h for > 12 hours	Stage 2	< 0.5 mL/kg/h for > 12 hours	Stage 2	< 0.5 mL/kg/h for ≥ 12 hours
Failure	< 0.3 mL/kg/h for > 24 hours or anuria for 12 hours	Stage 3	< 0.3 mL/kg/h for > 24 hours or anuria for 12 hours	Stage 3	< 0.3 mL/kg/h for ≥ 24 hours or anuria for ≥ 12 hours

Table 1: Definitions and staging of acute kidney injury. RIFLE: Risk, injury, failure, loss, end-stage renal disease, AKIN: Acute kidney injury network, KDIGO: Kidney disease – improving global outcome, mL: millilitre, kg: kilogram, eGFR: estimated glomerular filtration rate, ESRD: End-stage renal disease, RRT: Renal replacement therapy. * = Serum creatinine changes ≥ 1.5 times baseline within 7 days. ** = Serum creatinine increases ≥ 26.5 micro(µ)mol/L within a 48-hour time period.

5.4.2 Incidence

The incidence of AKI varies across studies depending on the populations considered and the definitions used [91]. The occurrence of AKI in general ICU patients is reported to be 10-70 % [6], about one-third experiences AKI within 24 hours [8], and approximately two-thirds develops AKI during ICU stay [92]. The most common causes of AKI are sepsis, major cardiac-, vascular- or acute abdominal surgery [5]. Approximately 5 % of the general ICU patients are treated with RRT due to AKI [5]. Furthermore, the incidence of severe AKI necessitating RRT has increased over the last decades [93-95], and this constitutes a major burden of disease [96].

5.4.3 Risk factors

Data on causal relationship between assumed risk factor and AKI are lacking, while associations are more apparent. Multiple kidney insults, rather than one single factor, are often necessary to instigate AKI [97]. The primary disease process initiating AKI is often remote from the kidneys, being part of multiple organ failure [98]. Chronic and often unalterable risk factors for AKI are advanced age, diabetes mellitus, hypertension, congestive heart failure and CKD, while acute potentially avoidable risk factors are hypovolaemia, hypotension, hypoperfusion and/or exposure to known nephrotoxic drugs (Table 2).

Trauma patients are usually young and few have established risk factors for AKI [51]. However, they are predisposed to hypovolaemia, hypotension and hypoperfusion due to acute severe bleeding. Rhabdomyolysis may be present, and use of intravenous iodinated radiocontrast media may promote further kidney injury [51]. Although only a minority of trauma patients have direct injuries to the kidney and/or their vessels [99, 100], some might have elevated intra-abdominal pressure or urinary obstruction adversely affecting the kidney function [101, 102]. In contrast to trauma patients, CA patients often are middle-aged or

elderly with a high pre-arrest prevalence of diabetes mellitus, hypertension, congestive heart failure and CKD [81, 85]. These patients also have acute risk factors due to prolonged systemic hypoperfusion, post-arrest cardiogenic shock and use of intravenous contrast media [81, 85]. Both trauma- and CA patients are susceptible to a pro-inflammatory state with increased risk of severe sepsis that is considered to be a major contributor to AKI in the ICU [5].

Table 2: Nephrotoxic drugs

1. Cardiovascular effect	**3. Direct tubular effect**	**4. Immunologic activation**
a. General haemodynamic	a. Proximal tubuli	a. Acute interstitial nephritis
- Diuretics	- Aminoglycosides	- β-lactam antibiotics
- Vasodilators	- Cisplatin	- Vancomycin
- β-blockers	- Amphotericin B	- Rifampicin
b. Local vascular response	- Radiocontrast media	- Sulphonamides
- NSAIDs	- Immunoglobulins	- Ciprofloxacin
- ACEIs	- Mannitol	- NSAIDs
- ARBs	b. Distal tubuli	- Ranitidine
- Cyclosporine	- NSAIDs	- Cimetidine
- Tacrolimus	- Lithium	- Furosemide
	- ACEIs	- Thiazides
2. Other nephrotoxins	- Cyclosporine	- Phenytoin
- Heavy metals	- Cyclophosphamide	b. Acute glomerulonephritis
- Plant extracts	- Amphotericin B	- NSAIDs
	c. Tubular obstruction	- Heroin
	- Sulphonamides	- Gold
	- Methotrexate	- Penicillamin
	- Acyclovir	
	- Diethylene glycol	
	- Triamterene	

Table 2: Overview of nephrotoxic drugs classified based on the mechanisms behind toxic effects. NSAID: Non-steroid anti-inflammatory drug, ACEI: Angiotensin converting enzyme inhibitor. ARB: Angiotensin II receptor blocker.

6.4.4 Pathophysiology

The pathophysiology of AKI is complex and not fully understood. Much focus has previously been on observational studies in humans, concentrating upon systemic effects of AKI, and kidney organ structural- and functional alterations. The classical concept of acute tubular necrosis (ATN) has been challenge by current knowledge emerging a widened understanding of the disease process. AKI research has lately been extended to include interventional studies in animals, assessing structural and functional alterations on organ- and cellular level. These new areas of research might give new insight into the complex pathophysiology of AKI, and ultimately lead to better patient care [103].

In AKI there is often a combination of different pathophysiological mechanisms involved, commonly classified as pre-renal, renal and post-renal (Table 3) [103].

Table 3: Pathophysiological mechanisms involved in acute kidney injury

	Pre-renal	Renal	Post-renal
Occurrence	25-60 %	35-70 %	5-20 %
Causes	Decreased renal perfusion pressure	Damage to the four major structures of the kidneys	Obstruction of the urinary tract
Clinical conditions	- Reduced blood volume, blood pressure and/or blood flow	- Tubular damage might be ischemic and/or toxic - Glomerular damage may occur in severe acute glomerulonephritis (GN) - Interstitial damage may result from acute interstitial nephritis - Vascular damage to the intra-renal vessels may reduce renal perfusion	- Various clinical conditions such as prostate or gynaecological cancer, urethral stones or retroperitoneal fibrosis

Table 3: Overview of the pathophysiological mechanism involved in acute kidney injury.

Although limited data are available in trauma- and CA patients, we may assume that pre-renal mechanism are involved, due to bleeding in trauma patients and tissue ischemia and post-resuscitation shock in CA patients. The renal component consisting mainly of ATN may also

contribute, while post-renal AKI is less likely. All-over, the pathophysiology of AKI includes a wide range of anatomical and physiological alterations at systemic-, organ- and/or cellular level (Table 4) [103].

Table 4: Anatomical and physiological alterations in acute kidney injury

	Systemic effects	Organ effects	Cellular effects
Probable causes	Kidney effects of systemic disease and vice versa	Direct effects on the main structures of the kidneys	Cellular effects in the kidneys
Suggested mediators of effects	- Part of systemic inflammatory response syndrome (SIRS) with release of pro-inflammatory mediators, extravasation of leucocytes, increased oxidative stress and ion channel dysfunction - Part of multiple organ failure - Part of cardio-renal syndrome	- Tubuli might be obstructed. Tubular cells may lose their polarity, suffer cytoskeletal breakdown, detach from their basement membranes and have altered Na^+/K^+-Adenosinetriphosphatase (ATPase) function - Altered glomerular vascular resistance and filtration barrier - Interstitial inflammation - Increased vascular permeability, formation of microthrombi, and dysregulation of the intra-renal blood flow	- Pro-inflammatory response in the kidneys with release of pro-inflammatory mediators and activation of the compliment system - Impaired cellular energetics with formation of reactive oxygen species (ROS) and reduced antioxidant defence - Dysregulation of cell cycle with activation of caspases and reduced repair and regeneration capacity - Genetic predisposing

Table 4: Overview of purposed anatomical and physiological alterations in acute kidney injury.

AKI is part of a systemic pro-inflammatory process that may engender distant organ injury to the lungs, heart, liver, brain, gastrointestinal tract and bone marrow [12, 98, 104]. Heart disease and kidney disease often coexists [105], and one illness may adversely affect the other, termed the cardio-renal syndrome [106]. AKI patients may experience an early onset of multiple organ failure with related several fold increase in mortality [9, 107, 108]. Animal models suggest several mechanisms behind this pro-inflammatory state with distant organ injury in AKI (Table 5) [98, 109]. It is evident that AKI often is a part of multiple organ failure in trauma- and CA patients, mainly related to a pro-inflammatory state after trauma [110-112] and circulatory shock after CA [81, 85].

AKI may influence different renal structures, i.e. tubuli, glomeruli, interstitium and blood vessels. The tubular cells may lose their polarity, suffer cytoskeletal breakdown, and become detached from the basement membrane [113]. Desquamated cells may obstruct tubuli [114]. Evidence points to functional alterations in sodium reabsorption in the tubular Na^+/K^+-Adenosinetriphosphatase (ATPase) causing impaired sodium reabsorption [115]. Anatomical glomerular injury is modest in AKI patients despite loss of kidney function [20, 21]. The decline in glomerular filtration rate (GFR) might therefore be due to functional alterations. Indeed, it seems that increased sympathetic activity in sepsis might alter pre- and post-glomerular vascular resistance and thereby influence GFR [116]. The glomerular filtration barrier may also be altered in AKI [117]. Another pro-inflammatory mechanism may be over-expression of toll-like receptor (TLR) 2 in glomerular endothelial cells [118]. Interstitial injury in AKI is a result of a pro-inflammatory state leading to vasodilatation, increased vascular permeability and extravasation of leucocytes into the kidney interstitium [119]. The characteristic interstitial infiltrates are mostly composed of lymphocytes, macrophages, eosinophils and plasma cells with rapid transformation into areas of interstitial fibrosis [120]. Changes in the endothelium with increased vascular permeability and formation of microthrombi may lead to dysregulation of the intra-renal blood flow [103, 121]. Solid data are lacking with respect to how intra-renal mechanisms may contribute to AKI in humans. At least in septic patients, the concept of tubular ischemia resulting in ATN has been challenged [4].

There is a multitude of experimental research at cellular- and molecular levels suggesting possible players in the development of AKI. A pro-inflammatory response is observed with release of a myriad of mediators that promote inflammation from the leucocytes (interleukin (IL)-1, IL-8, eicosanoids and others) and the tubular epithelial cells (tumour necrosis factor (TNF)-α, IL-1, IL-6, Il-8 and others) [103], and this is further

enhanced by uncontrolled TLRs signalling and activation of the compliment system [103]. The outer renal medulla is sensitive to depletion of energy substrate and impaired mitochondrial activity, and this may be seen in AKI [103]. Furthermore, the formation of reactive oxygen species (ROS) might play a significant role in the genesis of AKI, and possibly also a reduced antioxidant defence mechanism [103]. Dysregulation of cell cycle has been observed in multiple models of AKI, as well as activation of caspases, i.e. enzymes playing an essential role as primary initiators of cell death [103]. Reduced repair and regeneration capacity have been observed in older animals [103], which may lead to chronic reduced function and thereby predispose for development of CKD [103]. Finally, genetic variation has been discussed in relation to AKI development, although no clear evidence of such a genetic predisposing has been found [122, 123]. The importance of these cellular mechanisms possibly contributing to AKI would need to be evaluated in humans. Excessive release of pro-inflammatory mediators [111, 124] in addition to increased formation of ROS [125] might be central sources of AKI in trauma- and CA patients.

5.4.5 Prophylaxis

A lot of research has been done on prophylaxis against AKI in different patients cohorts, and numerous interventions have been tested [126-135]. However, preventive strategies have so far mostly been disappointing [136]. Based on expert opinion, some general prophylactic measures have been advocated for AKI in ICU patients [137]:

- To identify high risk patients and follow their kidney function closely
- To avoid hypovolaemia, hypotension and/or hypoperfusion
- To be cautious in the use of nephrotoxic substances
- To ensure that the urinary tract is not obstructed

Special attention has been on contrast-induced acute kidney injury (CI-AKI), the most common iatrogenic cause of AKI after intravenous iodinated contrast media administration [126]. These agents may induce renal vasoconstriction, increase oxidative stress, and have direct tubular toxicity. Currently recommended measures to prevent CI-AKI is intravascular volume expansion with either isotonic saline- or sodium bicarbonate solutions [126].

Toxic substances from necrotic muscular cells observed in rhabdomyolysis are considered to be important contributors to AKI after trauma. Myoglobin may cause AKI through renal vasoconstriction, formation of intratubular casts, and the direct toxicity to tubular cells [138]. New research has also revealed that myoglobin increases oxidative stress, inflammation, endothelial dysfunction, vasoconstriction, and apoptosis [139]. Early and aggressive fluid resuscitation to increase urine output as in forced diuresis is agreed on as the main intervention for preventing AKI [138]. New drugs that target the harmful effects of myoglobin have been recently developed, and some have been proven to be successful in animal models of AKI due to rhabdomyolysis [139].

Unfortunately, no single preventive cure against AKI exists for trauma- and CA patients, but clinicians should still use the general recommendations mentioned above.

5.4.6 Diagnosis

AKI is usually diagnosed based on reduced urine output and/or elevated kidney markers in blood samples. A more comprehensive examination may be required to separate AKI from CKD, and to find potentially curable causes of AKI. Clinicians should explore known risk factors for AKI (age, hypertension, diabetes mellitus etc.), the duration of disease (CKD has duration above 3 months) and presence of kidney specific symptoms (weight gain, fatigue, nausea and pruritus). The physical examination should include clinical signs of cerebral

dysfunction (encephalopathy), cardiovascular dysfunction (tachycardia, hypotension and pericarditis) and fluid overload (peripheral oedema and pulmonary congestion). Blood sample analyses may detect retention of metabolic waste products (high creatinine and urea), electrolyte abnormalities (high potassium (K^+) and variable other electrolyte abnormalities), acid/base-abnormalities (low Pondus hydrogenii (pH), bicarbonate (HCO_3^-) and base excess (BE)) and biomarkers of rhabdomyolysis (high creatine kinase (CK) and myoglobin). Serum creatinine measurements have several limitations, as they are dependent on muscular mass, do not detect rapid changes in GFR, might be affected by conditions remote from the kidneys (dietary intake and rhabdomyolysis), and may be falsely measured using colorimetric methods (due to pseudocreatinines such as cephalosporins and others) [140]. Laboratories often provide an eGFR based on the measured serum creatinine concentration (S_{cr}) put into mathematical formulas, such as eGFR modification of diet in renal disease (MDRD) formula:

eGFR (mL/min/1.73 square meter (m^2)) =175×$(S_{cr})^{-1.154}$×$(Age)^{-0.203}$×(0.742 if female)×(1.212 if African)

Although creatinine- and eGFR levels are validated markers of kidney disease recommended to be used in CKD, they are of limited value in AKI due to lack of a steady-state situation [141]. Some therefore recommend to calculate GFR as urine creatinine clearance (C_{Cr}) based on the creatinine concentration in urine (U_{Cr}), urine flow rate (Vdt), and plasma creatinine (P_{Cr}) [141]:

C_{Cr} (mL/minute(min)) = [U_{Cr} x Vdt]/P_{Cr}

Radiographic imaging using Doppler ultrasound of the urinary tract should be done in AKI to exclude urinary obstruction. Additional analyses including chemical content of urine, urine dipstick analysis, microscopic evaluation of the urine sediment, serological tests and renal biopsy have limited value in AKI.

Several biomarkers have been proposed for early detection of AKI. An ideal biomarker should optimally have a reasonable sampling window, be easy to obtain, rapid to measure, change expression early during the disease process, provide high sensitivity and specificity, and be cost effective [38]. Current AKI biomarkers have several limitations as they are sensitive to sampling time, background noise, heterogeneity of patients and heterogeneity of disease processes. Additionally, the biomarkers have variable ability to discriminate between causes of AKI and to predict patient outcome.

An overview of the most promising AKI biomarkers is provided in Table 5. In order to improve biomarker performance, some advocate the use of several biomarkers [142], or that biomarkers should be combined with clinical patient data [143].

Table 5: Biomarkers of acute kidney injury

Biomarker abbreviation	Biomarker full name	Molecular size (kDa)	Source tested	Site of kidney expression	Biomarker rationale
Cystatin C	Cystatin C	13	Urine and serum	All nucleated cells	Glomerular filtration marker
NGAL	Neutrophil gelatinase-associated lipocalin	25	Urine and serum	Proximal and distal tubular neutrophils Epithelial cells	Inflammatory marker
KIM-1	Kidney injury molecule 1	38.7	Urine	Proximal tubular cells	Cell injury marker
IL-18	Interleukin 18	22	Urine and serum	Proximal tubular cells and leucocytes	Inflammatory marker
L-FABP	Liver-type fatty acid-binding protein	14	Urine	Proximal tubular cells	Cell injury marker
TIMP-2	Tissue inhibitor of metalloproteinase 2	21	Urine	Tubular cells	Cell cycle marker
IGFBP7	Insulin-like growth factor-binding protein 7	29	Urine	Endothelial, vascular, epithelial cells and others	Cell cycle marker
Angiotensinogen	Angiotensinogen	52	Urine	Kidney vasoconstrictor	Renin-angiotensin system activation marker

Table 5: Overview of biomarkers for acute kidney injury tested in intensive care unit patients. kDa: Kilo Dalton.

There are no specific recommendations for AKI diagnosis in trauma- and CA patients, but these patient groups may benefit from close monitoring of CK and/or myoglobin levels in blood in order to detect rhabdomyolysis [144]. Close collaboration with nephrologists should be encouraged, especially in cases with uncertain cause of the AKI [145].

5.4.7 General supportive treatment

It is vital to identify and treat the underlying condition causing AKI, as for instance sepsis or rhabdomyolysis. General supportive care of patients should be optimized including appropriate use of fluids, vasopressor and glycaemic control [25]. The kidney function should be closely monitored with frequent blood sampling and urine output measurements. Hypovolaemia, hypotension, hypoperfusion, use of nephrotoxic drugs and urinary tract obstruction should be avoided. Symptomatic treatment of AKI complications, such as fluid overload, hyperkalaemia and acidosis, may be used alone or in combination with RRT [25].

5.4.8 Renal replacement therapy

The use of RRT varies substantially across the world [146-148] despite the fact that international guidelines are developed [25]. In AKI, the primary aim of RRT is to temporary replace kidney function with elimination of fluid and metabolic waste products from the body. Secondary aims of dialysis therapy are to minimize complications of the disease process and the treatment, and finally to optimize patient comfort.

There is no consensus on when to initiate RRT, but international guidelines recommend that RRT should be emergently started when life-threatening changes in fluid-, electrolyte- and/or acid-base balance exist [25]. These guidelines also recommend that the decision on when to initiate RRT should be considered in a broad clinical context considering more than kidney function parameters [25]. It is uncertain whether early initiation of RRT

may have a beneficial impact on patient outcome compared to late initiation [30, 149-152], and the lack of a uniform definition of early and late initiation makes comparison of studies difficult.

The most commonly used RRT modality in the developed world has changed over years from peritoneal dialysis (PD), via intermittent haemodialysis (IHD), to various forms of continuous renal replacement therapy (CRRT). Although mortality rates in patients treated with IHD and CRRT are similar [153-155], haemodynamic stability is better preserved in CRRT [153]. It is uncertain whether the choice of dialysis modus affects the rate of chronic dialysis dependency [156, 157]. There are additionally different CRRT modalities such as continuous veno-venous haemodialysis (CVVHD), continuous veno-venous haemofiltration (CVVHF) and continuous veno-venous haemodiafiltration (CVVHDF) associated with similar patient outcomes [158, 159]. IHD and CRRT are considered complimentary therapies in recent treatment guidelines of AKI, but CRRT is recommended in haemodynamic unstable patients and in cases of increased intracerebral pressure or generalized brain oedema [25].

The optimal dose of RRT is uncertain, and in CRRT there is a discrepancy between prescribed dose and delivered dose due to interruptions during treatment [160]. Higher intensity RRT does not reduce mortality rates or improve renal recovery compared to conventional doses [34, 161, 162]. The currently recommended delivered doses in AKI is for IHD 3.9 Kt/V (dialyzer clearance of urea (K) multiplied by time (t) divided by the volume of distribution of urea (V)) per week and for CRRT 20-25 mL/kg/h [25], with adjustment during treatment in order to achieve goals of electrolyte-, acid-base-, solute- and fluid balance.

Treatment guidelines for AKI also include recommendations for the equipment used, including haemodialysis catheters, haemodialysis membranes, dialysate- and replacement fluids in addition to the use of anticoagulation [25]. Discontinuation of RRT in AKI should be

considered when dialysis is no longer required because kidney function has recovered adequately or in cases of futile treatment [25].

Withholding or withdrawing RRT is a complex decision that sometimes is necessary in order to reduce the burden of futile treatment to patients, relatives and the healthcare system. Withholding or withdrawing RRT depends on many interacting factors, which are unique for each patient and their families. An evidence-based guideline with specific recommendations has been available, however is infrequently employed to help decision making in clinical practice [163].

In a recent study of trauma patients with severe injuries, AKI with need of RRT occurred in 5 % of the patients [164]. In a systematic review and meta-analysis of patients with severe burn injuries, RRT was used in 3 % of the total population, and in 30 % of patients with AKI [28]. In another meta-analysis of CA victims, on average14 % of the patients were treated with RRT, but the frequency ranged from 4 % to 33 % in the different studies [85]. The trauma patients might need adjustment of CRRT due to extensive tissue necrosis with rise in metabolic waste products, and frequent interruptions during treatment. Important indications for RRT in trauma patients might be hypervolaemia due to initial fluid resuscitation and hyperkalaemia due to massive tissue damage. Withholding or withdrawing RRT might important issues in CA patients with lack of early guidelines to be used in the ICU. Rhabdomyolysis frequently occur in both patient groups, but how this affects the use of RRT remains unsettled [138].

The costs of RRT are substantial including expenses due to nurse staffing, anticoagulation, extracorporeal circuits in addition to dialysate- and replacement fluids [165]. In undeveloped countries patients still die because dialysis treatment is unavailable, but the use of PD, which is the cheapest and easiest method, is saving lives in many parts of the world.

5.4.9 Outcome

AKI in ICU patients is associated with an unfavourable survival rate that is worsened with the severity of the disease [8, 92]. Mortality seem to be closely linked to the development of multiple organ failure, and survival is dependent on the recovery of organ functions [166]. Despite recent advances in patient care, the acute mortality in severe cases with need of RRT is still around 50 % [167, 168]. There is also increasing evidence showing that AKI in the ICU is associated with reduced long-time survival of patients [18, 19]. Although data are limited, similar mortality findings have been observed in CA patients, and to some extent in trauma patients [56, 61, 85].

Data from general ICU patients show that few AKI victims become dependent on chronic RRT [18]. However, AKI is associated with increased risk of CKD as compared to an ICU control population without AKI [19]. Further, development of CKD is dependent on pre-morbid kidney function, cause of AKI, as well as presence of co-morbidities [168]. There is increasing evidence that AKI is especially harmful in CKD patients, leading to a worsening of the CKD [169]. Furthermore, AKI is also associated with later on increased risk for cardiovascular disease and congestive heart failure [170]. How this is in the subgroups of trauma- and CA patients remains unclear, sparse data in trauma patients show that few patients with post-traumatic AKI become chronic RRT dependent [10, 56].

There are some data available from general ICU patients revealing that RRT has an overall good acceptability, as over 90 % of patients indicated that they would undergo the same treatment again [18, 171]. Unfortunately, there are no such available data in trauma- and CA patients, but there is no reason to believe that these groups should be different from other ICU patients with respect to RRT acceptability.

6. Aims and research questions

The general aim of this thesis was to investigate AKI in two heterogeneous subgroups of ICU patients that are modestly studied, i.e. trauma- and OHCA patients. We had no specific hypotheses in our exploratory studies. The specific research aims and questions were:

1. To explore the occurrence of AKI necessitating RRT in trauma patients, and describe mortality and renal recovery in this patient group.

2. To evaluate the quality of RRT in trauma patients with AKI, focusing upon daily duration of CRRT, reasons for temporary interruptions and uraemic control.

3. To evaluate the occurrence of kidney disease in OHCA victims, and to explore the association between kidney disease and patient outcome.

4. To examine the utility of urine AKI biomarkers in OHCA victims, and their ability to predict AKI, mortality and/or neurological outcome.

7. Materials and methods

7.1 Study setting and design

This thesis includes four observational studies from Oslo University Hospital Ullevål (OUHU). OUHU is a community hospital for approximately 200.000 people and a regional hospital for 1.4 million people in Norway, with around 45.000 admissions per year. All four studies have single-centre observational cohort design; the trauma studies are retrospective (Paper 1 and II), whereas the cardiac arrest studies are prospective (Paper III and IV).
An overview of studies included in this thesis is provided in Table 6.

7.2 Study population

In the trauma studies (Paper I and II) adult (≥ 18 years) trauma patients were included if they developed AKI treated with RRT. Patients with CKD, and those who died within 24 hours, were excluded (Paper I and II). In the analysis of dialysis quality, patients with CRRT lasting less than 24 hours were excluded (Paper II).

In the CA studies (Paper III and IV) adult (≥ 18 years) comatose (Glasgow Coma Scale (GCS) ≤ 8 at admission) OHCA patients with ROSC (Paper III and IV) admitted to ICU treated with TTM were included in the Norwegian cardiorespiratory arrest (NORCAST) study registered at Clinicaltrials.gov (National clinical trial (NCT) number NCT01239420). The primary aim of this study was to assess predictors of outcome after OHCA (data yet not published). The NORCAST study had many exclusion criteria (dead before ICU admittance, in-hospital CA at another hospital, subarachnoid haemorrhage, other cause of coma, CPR< 5 minutes or spontaneous awakening, head trauma, age<18 years, intracerebral haemorrhage, unknown patient identity, transferred to another hospital, abdominal bleeding or previously included). In our *a priori* planned sub-studies on AKI patients we excluded those who died within 24 hours of ICU stay or for some reason did not receive active treatment

Table 6: Thesis overview

	Paper I	Paper II	Paper III	Paper IV
Study design	Retrospective cohort study	Retrospective cohort study	Prospective cohort study	Prospective cohort study
Study site	Oslo University Hospital Ullevål	Oslo University Hospital Ullevål	Oslo University Hospital Ullevål	Oslo University Hospital Ullevål
Study period	1996-2007	1997-2006	2010-2014	2010-2014
Data sources	Hospital registries Statistics Norway Norwegian Renal Registry	Hospital registries	Hospital registries	Hospital registries
Population	Trauma patients admitted with AKI and RRT (n=42)	Trauma patients with AKI and CRRT more than 24 hours (n=36)	Admitted OHCA patients (n=245)	Admitted OHCA patients with collected urine samples (n=195)
Intervention	Standard care	Standard care	Standard care	Standard care
Comparison	Epidemiological study of AKI with RRT	Study of CRRT quality	Epidemiological study of CKD and AKI	Diagnostic and prognostic utility of AKI biomarkers
Outcomes	Occurrence of AKI with RRT Mortality Chronic RRT dependency	Daily duration of CRRT and impact on uraemic control Reasons for CRRT interruption	Occurrence of CKD and AKI Mortality Neurological outcome	AKI biomarkers ability to predict AKI, mortality and neurological outcome
Biochemical analyses	Routine analyses in blood samples, no supplemental analysis	Routine analyses in blood samples, no supplemental analysis	Routine analyses in blood samples, no supplemental analysis	Routine analyses in blood samples. Additional urine biomarkers at admission and day three: Cystatin C, NGAL and [TIMP-2]·[IGFBP7]
Statistical analyses	Pearson's chi-square test Mann-Whitney U test Logistic regression analysis	Pearson's chi-square test Mann-Whitney U test Linear regression analysis	Pearson's chi-square test Fisher's exact test Mann-Whitney U test Independent sample T-test Kaplan-Meier log rank test Logistic regression analysis	Pearson's chi-square test Fisher's exact test Logistic regression analysis Receiver operating characteristics analysis
External approvals	Regional ethics committee Norwegian Data Inspectorate Norwegian Directorate for Health and Social Affairs	Regional ethics committee Norwegian Data Inspectorate Norwegian Directorate for Health and Social Affairs	Regional ethics committee	Regional ethics committee
Registrations	None	None	NCT01239420	NCT01239420

Table 6: Overview of studies included in this thesis. AKI: Acute kidney injury, RRT: Renal replacement therapy, n: number, CRRT: Continuous renal replacement therapy, OHCA: Out-of-hospital cardiac arrest, CKD: Chronic kidney disease. NGAL: Neutrophil gelatinase-associated lipocalin, TIMP: Tissue inhibitor of metalloproteinase, IGFBP: Insulin-like growth factor-binding protein. NCT: National clinical trial.

(Paper III and IV). In the analyses of AKI biomarkers, patients without collected urine samples and/or with known CKD were excluded (Paper IV).

7.3 Ethical considerations and approvals

The risk of participation in the studies was considered minimal since all studies were observational and patients received standard care.

The trauma studies (Paper I and II) were approved by the Regional Committee for Medical Ethics of Eastern Norway (Approved number REK 1, 408-06170 1.2006.2069). No patient consent was needed for this retrospective register and journal study according to the ethical approval, but written information was sent by postal mail to all included patients. The trauma studies (Paper I and II) were additionally approved by the Norwegian Data Inspectorate (Datatilsynet, reference number 06/1743-7/MOF), the Norwegian Directorate for Health and Social Affairs (Sosial- og helsedirektoratet, reference number 06/2655) and the hospital-based trauma registry (Approval dated 31th October 2007).

The OHCA studies (Paper III and IV) were approved by the Regional Committee for Medical Ethics of South-East Norway (Approval number REK S-O A Ref 2010/1116a). Written informed consent was obtained from the nearest family relative after admission and later from all patients who regained consciousness and were considered competent to give consent within six months. Patients were not considered for inclusion if the nearest family relative opposed it. Relatives were not asked for consent if the patient did not meet the inclusion criteria. Family relatives who were not present at the hospital were contacted by phone and had written study information sent by postal mail. The Regional Committee for Medical Ethics of South-East Norway approved the inclusion of some patients whose relatives were unreachable or failed to return their consent forms.

7.4 Study definitions

The study definitions used in the four papers are:

- *Trauma* was defined as patients having a trauma diagnosis code according to the International statistical classification of diseases and related health problems (International classification of disease (ICD)-9 and ICD-10), excluding diagnosis codes for late effects of trauma, foreign bodies and complications.
- *OHCA* was defined as absence of spontaneous respiration in a comatose patient receiving cardiopulmonary resuscitation.
- *ROSC* was identified as sustained electrical activity on the electrocardiogram, generating a palpable pulse.
- *AKI* was defined as patients having a diagnose code for acute renal failure, and/or a national procedure code for dialysis in Paper I and II, and as patients having AKI according to a modified version of the KDIGO criteria in Paper III and IV.
- *CKD* diagnosis was based on a positive medical history of chronic kidney disease.
- *RRT* was defined as PD, IHD or CRRT (any modality).
- *Severity of trauma* was assessed by the Revised trauma score (RTS) [172] and the ISS [48].
- *Severity of illness* was determined by the SAPS II score including 12 physiological variables and three disease-related variables generating a score ranging from 0 to 163 points [44].
- *Organ failure assessment* was done using the SOFA score assessing the respiratory, cardiovascular, liver, kidney coagulation and neurological systems generating a score ranging from 0 to 24 [45]. Organ failure was defined as a SOFA score ≥ 3, and multiple organ failure as organ failure of three or more organs.

- *Sepsis* was diagnosed according to the criteria from the American college of chest physicians/Society of critical care medicine (ACCP/SCCM) consensus conference [173].
- *Renal recovery* was defined as independency from RRT at the time of assessment.
- *Uraemic control* was defined as the percent changes in daily serum urea and creatinine concentrations.
- *Neurological outcome* was assessed using CPC assessed six months post-arrest, and was classified as good (CPC 1 or 2) or poor (CPC 3-5) neurological outcome (PNO).
- *Circulatory shock* was defined as systolic blood pressure less than 90 mmHg, or a decrease in systolic blood pressure of more than 40 % from baseline, and lasting more than one hour.
- *Volume load* was characterized as intravenous infusion of more than 500 mL of any fluid in less than half an hour.
- *Inotropic therapy* was defined as dopamine and/or dobutamine infusion.
- *Vasoactive therapy* was defined as norepinephrine and/or epinephrine infusion.
- *Rhabdomyolysis*: Peak serum CK above 10.000 U/L.
- *Urinary tract obstruction* was diagnosed based on radiographic descriptions and/or findings during abdominal surgery.
- *Fluid overload* was defined as a positive fluid balance leading to oxygenation problem (Paper II) or as an indication for RRT if it was mentioned as a reason for initiating RRT (Paper III).
- *Hyperkalaemia* was defined as serum potassium above 5.0 mmol/L.
- *Acidosis* was defines as whole blood pH below 7.25.
- *Uraemia* was defined as serum urea above 30 mmol/L.
- *Fluid input* was calculated as the sum of any fluids into patients.

- *Fluid output* was calculated as the sum of any fluids out of patients.
- *Fluid balance* was calculated as fluid input minus fluid output (perspiration not included).

7.5 Data collection

In Paper I and II, trauma patients with AKI undergoing RRT were identified from diagnosis and procedure codes, and several databases were crosschecked (hospital charts, medical records, trauma registry, intensive care registry and national renal registry) to ensure that no patients were lost. Data were collected from the patients' medical charts and routine biochemical analyses. Additionally, data on chronic RRT dependency (above three months) were obtained from the Norwegian Renal Registry including data from all patients receiving RRT for CRF in Norway. General population data were collected from Statistics Norway in order to calculate population based incidence rates of post-traumatic AKI necessitating RRT in the total population, and also separately in men and women.

In Paper III and IV, OHCA patients were consecutively enrolled using predefined inclusion and exclusion criteria outlined above. Most data were collected from the patients' medical charts, routine biochemical analyses and the hospital-based CA registry including prehospital data. Additional examinations were undertaken according to the aims of the study, including the collection of urine samples at admission and day three for the analyses of AKI biomarkers (outlined below). Moreover, data on six-month outcome (mortality and neurological recovery) were obtained during an extensive post-arrest consultation at OUHU, but the extended follow-up did not include data on kidney function.

7.6 Laboratory assays

The blood sample analyses included in this thesis were obtained from the patients on clinical indications, and no additional samples were collected for research purposes. For all papers (Paper I-IV) the biochemical blood sample analyses were performed at the Department of Medical Biochemistry, OUHU. These samples were analysed by bioengineers blinded for clinical data. The arterial blood gas samples were collected by ICU nurses not blinded for clinical data, and examined in blood gas analysers at the ICU.

For evaluating AKI biomarkers in OHCA patients (Paper IV), spot urine samples were collected from urine catheters at admission (0 to 6 hours post arrest) and day three. Samples were stored in a refrigerator up to 72 hours before frozen at - 70°C. After thawing, samples were centrifuged for five minutes at 20°C and 500 relative centrifugation force (RCF), aliquoted and refrozen. Thereafter, the urine samples were re-thawed and identical re-centrifuged before they were diluted 1/200 and run in duplicate according to the manufacturers' instructions. Cystatin C and NGAL were quantified using Bio-Plex Pro RBM Human Kidney Toxicity Assays panel 2 on the Bio-Plex 200 system (Bio-Rad Laboratories, Hercules, CA, USA).

The concentrations of TIMP-2 and IGFBP7 were measured using the NephroCheck^{TM} Test (Astute Medical, San Diego, CA, USA) calculating the product of both biomarker concentrations ([TIMP-2]·[IGFBP7]). A pilot study revealed that the studied biomarkers in urine were stable when stored in a refrigerator up to 72 hours prior to freezing, and when centrifuged after thawing [174]. Based on these results and previous studies [175, 176], we assume that our results regarding the AKI biomarkers are valid.

7.7 Statistical analyses

Statistical analyses were performed utilizing Statistical package for social sciences (SPSS) for Windows, version 15.0 (IBM Inc., Chicago, IL, USA) (Paper I and II) and 21.0 (IBM Corp., Armonk, NY, USA) (Paper III and IV). In Paper IV, we also used Stata 14 (StataCorp, College Station, TX, USA) in some of the analyses. In all instances, the level of statistical significance was set at a two-sided $p<0.05$.

The statistical analyses included in this thesis are briefly described below:

- *Pearson's chi-square test* (Paper I-IV): Categorical, unpaired data were expressed as number (percent), and compared using Pearson's chi-square test. This test evaluated how likely it was that the observed difference between data sets arose by chance, and this probability was calculated as the p-value.
- *Fisher's exact test* (Paper III and IV): Categorical, unpaired data with small sample size (expected value below 5) were expressed as number (percent), and compared using Fisher's exact test. This test evaluated how likely it was that the observed difference between data sets arose by chance, and this probability was calculated as the p-value.
- *Mann-Whitney U test* (Paper I-III): Continuous, independent data with skewed distribution were expressed as median (interquartile range (IQR)), and compared using Mann-Whitney U test. This test evaluated if one population had larger values compared to another population, and this probability was expressed as the p-value.
- *Independent sample T-test* (Paper III): Continuous, independent data with normal distribution were expressed as mean (± standard deviation (SD)), and compared using independent sample T-test. This test determined if two data sets were statistically significant different from each other, and this probability was expressed as the p-value.

- *Logistic regression analysis* (Paper I, III and IV): Logistic regression analysis measured the relationship between a categorical dependent variable and several independent variables. The test estimated probabilities that the relationship between variables arose by chance using a logistic function, and this probability was expressed as the p-value.
- *Linear regression analysis* (Paper II): Linear regression analysis was used to calculate the relationship between the continuous, dependent variable and the explanatory, independent variable. The relation between variables was expressed as the correlation coefficient (r), and the p-value of the regression line expressed the probability that the relationship between variables arose by chance.
- *Kaplan-Meier survival curve* (Paper III): Survival distribution of different populations was compared using Kaplan-Meier survival curve, and tested by the log rank test. This test evaluated how likely it was that the observed mortality in different groups arose by chance, and this probability was calculated as the p-value.
- *Identifying independent risk factors* (Paper IV): Variables with $p<0.25$ in the univariate logistic regression analyses were considered candidates for the multivariate model if they had less than 15 % missing data. Independent risk factors were identified using a multivariate logistic regression model and a manual backward stepwise elimination procedure. Multivariate analyses were preceded by estimation of correlation between risk factors. Evaluation of the predictive accuracy of the models was assessed by calibration and discrimination. Calibration was evaluated by the Hosmer and Lemeshow goodness-of-fit test. A statistically non-significant Hosmer and Lemeshow result ($p>0.05$) suggests that the model predicts accurately on average. Discrimination was evaluated by analysis of the area under the Receiver operating characteristics (ROC) curve. The ROC plot is as a visual presentation of sensitivity

versus 1-specificity. The area under the ROC curve (AuROC) is calculated indicating the level of discriminating ability, where 0.5 is considered as no discriminating value, whereas 1.0 indicate perfect discriminating ability. An acceptable discriminatory capability was defined as an AuROC above 0.7 in our study. Chi-square tests for equality of AuROCs were additionally performed to evaluate whether the differences in ROC plots occurred by chance, and this probability was expressed as a p-value.

- *Handling of repetitive measurements* (Paper II): In cases of repetitive measurements in the same individual, median values calculated for each individual was used to ensure that calculated p-values were not invalidated by dependent data set.
- *Handling of missing data* (Paper III and IV): Missing data may be handled by different statistical methods. We generally handled the missing data by using only available data, with the exception of the body weight of OHCA patients that were assumed to be 70 kg in females and 80 kg in males if unknown.
- *Out of range measurements* (Paper IV): Some of the measured concentrations were out of range for the assays used in the analyses of AKI biomarkers. In the statistical analyses, measured levels below the lower range were set as 0, whereas concentrations above the upper range were set as 100.000.

8. Results

8.1 Paper I

The study included 42 adult trauma patients admitted to OUHU between 1996 and 2007 with AKI necessitating RRT. Median age of the patients was 46 years, and 86 % were male. Patients were severely injured with a median ISS 36. RRT were initiated 1-25 days after trauma and lasted for 1-43 days. The mode of RRT was mainly CVVHDF, but some also received CVVHD or PD. Treatment was often switched to IHD after haemodynamic stabilization.

The population based incidence of post-traumatic AKI with RRT was 1.8 (95 % confidence interval (CI) 1.5-2.1) persons per million inhabitants per year. In trauma patients admitted to hospital incidence of AKI necessitating RRT was 0.5 ‰ (95 % CI 0.3-0.7 ‰), of those treated in ICU 8.3 % (95 % CI 5.9-10.8 %). The odds ratio (OR) for post-traumatic AKI requiring RRT was higher in males than females in the general population (OR 5.6, 95 % CI 2.2-14.0) as well as in the trauma patients admitted to hospital (OR 4.4, 95 % CI 1.9-10.3) and ICU (OR 4.5, 95 % CI 1.9-10.7). Assessing risk factors for AKI, 71 % received iodinated radiocontrast agents, 41 % had rhabdomyolysis and 12 % had urinary tract obstruction. Mortality was 36 % at three months and 40 % one year after the trauma. Age was a risk factor for death after one year with 57 % (95 % CI 7–109 %) increased risk for each 10 years added. None of the survivors were dialysis-dependent three months or one year after their traumatic event.

In additional unpublished subgroup analysis, we found that time from trauma to initiation of RRT was similar in patients with and without rhabdomyolysis (median 5.0 days versus 7.5 days, p=0.20, respectively) (Two-tailed Mann-Whitney U test) (Figure 1).

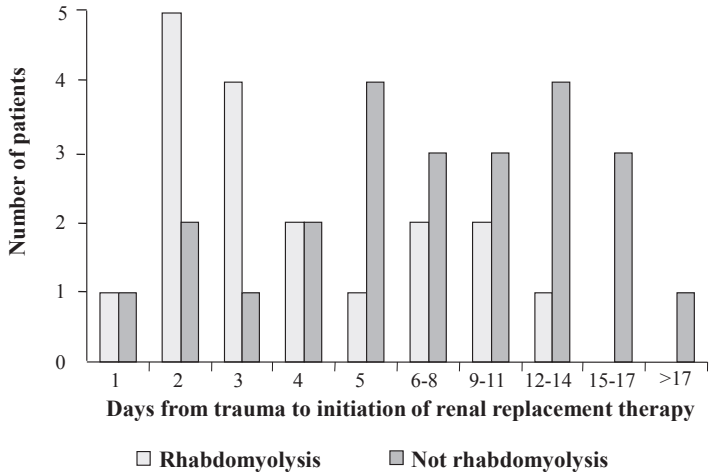


Figure 1: Time from trauma to initiation of renal replacement therapy in trauma patients with acute kidney injury grouped according to precense of rhabdomyolysis.

Further, the mortality rate in patients without rhabdomyolysis was lower at three months (17 % versus 50 %, p=0.03, respectively) and one year (22 % versus 54 %, p=0.04, respectively) compared to patients with rhabdomyolysis (Two-sided Pearson's chi-square test) (Figure 1).

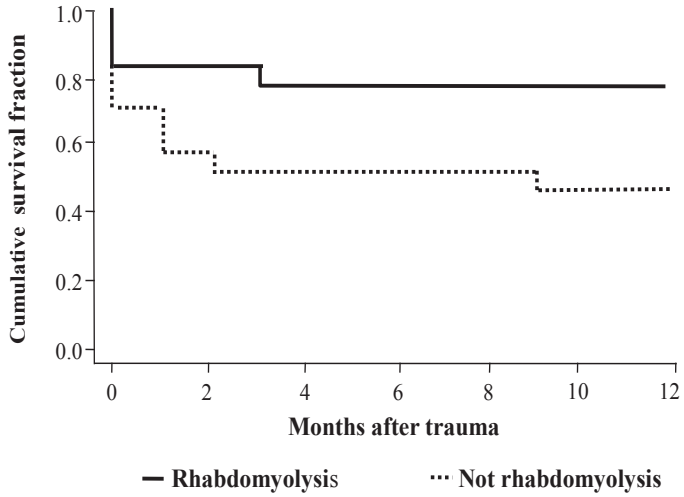


Figure 2: Kaplan-Meier survival plot in trauma patients with acute kidney injury and renal replacement therapy grouped according to precense of rhabdomyolysis.

8.2 Paper II

The paper included 36 adult trauma patients who developed AKI with need of CRRT lasting for more than 24 hours. Median age of the patients was 48 years, 86 % were males and 43 % had rhabdomyolysis. The mode of RRT was initially CVVHDF in all patients, but treatment was often switched to IHD after haemodynamic stabilization.

Data from the first five days of CRRT revealed that the median (interquartile range (IQR)) time per day with CRRT was 19 (15-21) hours, or 78 % of the possible operative time. Serum concentrations of urea increased during CRRT with median 5 % per day, whereas serum levels of creatinine deceased with median 5 % per day. There was a significant correlation between daily CRRT duration and daily changes in serum urea and creatinine concentrations (Δ urea, $r=0.60$, $p<0.01$ and Δ creatinine, $r=0.43$, $p=0.01$). CRRT interruptions were caused by filter clotting (54 %), therapeutic interventions (25 %), catheter related problems (10 %), filter time out (6 %) and diagnostic procedures (6 %). With the dialysis dose achieved in these patients, 19.1 and 14.1 hours per day of CRRT were required in order to maintain stable levels of urea and creatinine, respectively. In subgroup analysis comparing the reasons for CRRT interruption, those with rhabdomyolysis had more frequent therapeutic interventions (38 % versus 12 %, $p<0.01$) and less frequent filter time-out (2 % versus 10 %, $p=0.04$) compared to patients without rhabdomyolysis, respectively. Patients with and without rhabdomyolysis had a similar correlation between median daily CRRT duration and median Δ urea ($p=0.71$) as well as median Δ creatinine ($p=0.36$).

In additional unpublished analysis comparing patients with and without rhabdomyolysis, a difference in daily CRRT duration was present the first three days during treatment, but not from day four (Table 7).

Table 7: Daily duration of continuous renal replacement therapy

Dialysis (hours per day)	Rhabdomyolysis (n=17)	Not rhabdomyolysis (n=22)	p-value
Day 0 (n=39/17/22)	17.0 (12.0-21.5)	23.0 (17.8-24.0)	0.02
Day 1 (n=35/15/20)	18.0 (13.0-21.0)	23.0 (20.0-24.0)	0.01
Day 2 (n=33/13/20)	12.0 (6.5-21.5)	22.0 (19.0-24.0)	0.03
Day 3 (n=31/12/19)	14.0 (7.5-21.0)	22.0 (16.0-24.0)	0.05
Day 4 (n=24/9/15)	19.0 (18.0-23.0)	22.0 (11.0-24.0)	0.69

Table 7: Daily duration of continuous renal replacement therapy (CRRT) in trauma patients with acute kidney injury (AKI) grouped according to precense of rhabdomyolysis. Data are presented as median (interquartlie range) and compared using two-tailed Mann-Whitney U test. N: Number.

In detailed analysis of blood sample results during the first five days of CRRT, we further explored the daily changes in urea-, creatinine-, bicarbonate-, base excess-, potassium- and CK concentrations (Figure 3).

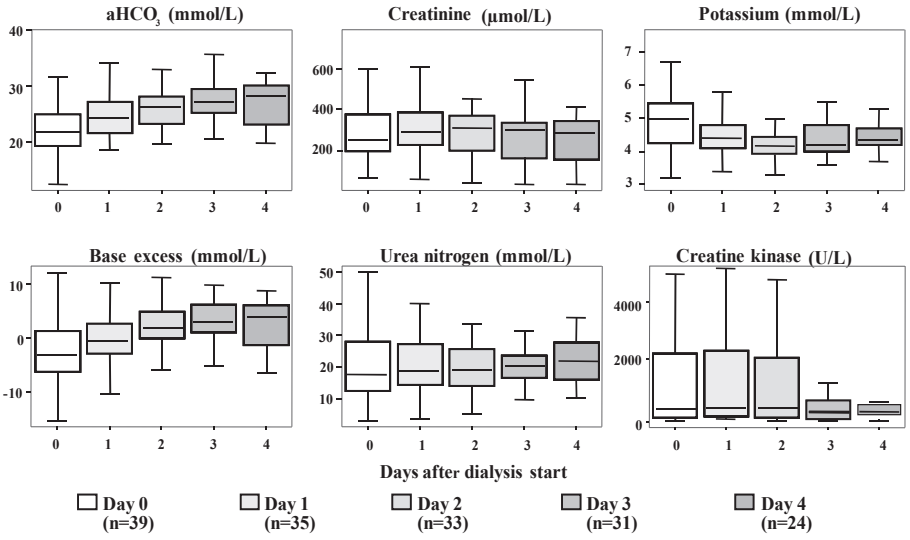


Figure 3: Blood sample analyses from the first five days after initiation of continuous renal replacement therapy in trauma patients with acute kidney injury treated. Data are presented as box plots with medians in 25th and 75th percentile boxes where outliers and extreme values are deleted.

8.3 Paper III

The study included 245 adult resuscitated, comatose OHCA patients with mean age 61 years and 84 % males. CA was witnessed in 87 %, bystander CPR was performed in 87 %, initial shockable rhythm was present in 67 %, and median time to ROSC was 25 minutes. All patients were treated according to our SOP including the use of TTM with target temperature set at 33 °C (degrees Celsius) for 24 hours.

Among the included patients, 4 % had previously known CKD and 46 % developed AKI. The 112 patients with AKI consisted of 58 (52 %) stage 1, 28 (25 %) stage 2 and 26 (23 %) stage 3, respectively. Overall six-month outcome revealed that 46 % died and 50 % had good neurological outcome. There was a significant difference in cumulative six-month survival in the compared kidney function groups ($p<0.01$), with favourable survival rates in patients without kidney disease. In univariate analyses, the presence of AKI was significantly associated with six-month mortality (OR 3.17, 95 % CI 1.95-5.43, $p<0.01$) and good neurological outcome (OR 0.28, 95 % CI 0.16-0.48, $p<0.01$). RRT was used in 18 patients with AKI, and indications for RRT were acidosis in 94 %, fluid overload in 72 %, hyperkalaemia in 50 %, rhabdomyolysis in 22 % and uraemia in 11 % of patients. AKI patients with and without RRT had comparable six-month mortality (50 % versus 61 %, respectively, $p=0.40$) and good neurological outcome (44 % versus 35 %, respectively, $p=0.42$), even after excluding those patients where RRT was withheld due to futility.

In additional unpublished subgroup analyses time from OHCA to initiation of RRT was similar in patients with and without rhabdomyolysis (median 1 day versus 1 day, p=0.43, respectively) (Two-tailed Mann-Whitney U test) (Figure 4).

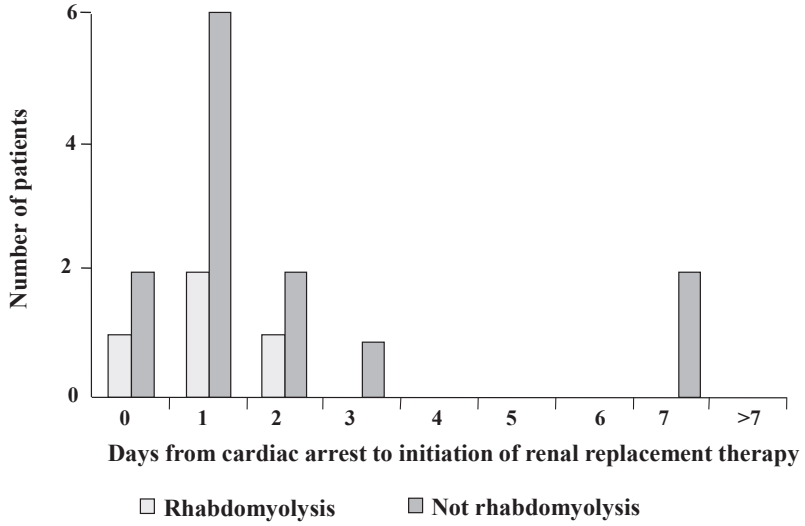


Figure 4: Time from cardiac arrest to initiation of renal replacement therapy in out-of-hospital cardiac arrest patients with acute kidney injury grouped according to precense of rhabdomyolysis.

Further, there were no statistical significant differences in outcomes when comparing patients with AKI KDIGO stage 3 with and without RRT (Table 8).

Table 8: Outcome in patients with and without renal replacement therapy

Assessed outcomes	AKI stage 3 with RRT (n=18)	AKI stage 3 without RRT (n=8)	p-value
CPC 1-2 at 6 months	6 (33)	1 (13)	0.352
Dead at 6 months	9 (50)	7 (88)	0.189

Table 8: Outcome in out-of-hospital cardiac arrest patients with acute kidney injury stage 3 comparing patients with and without renal replacement therapy. Data are expressed as number (percent) and compared using two-sided Fisher exact test. AKI: Acute kidney injury, RRT: Renal replacement therapy, CPC: Cerebral performance category, n: Number.

8.4 Paper IV

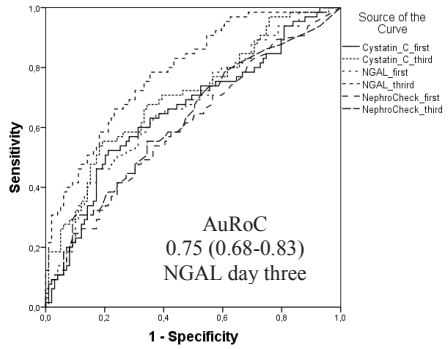
This paper included adult resuscitated, comatose OHCA patients with spot urine samples collected for AKI biomarker analyses. Among the 195 patients, 85 % were males and mean age was 60 years. The OHCA was witnessed in 85 %, 66 % had initial shockable rhythm and median time to ROSC was 25 minutes. AKI occurred in 45 % of the patients, with 27 %, 12 % and 7 % with KDIGO stage 1, 2 and 3, respectively. Overall six-month outcome revealed that 45 % died and 51 % had good neurological outcome. In all additional analyses, calculations were performed on PNO.

In univariate analysis, cystatin C and NGAL concentrations at admission and day three were independent risk factors for AKI, mortality and PNO, whereas [TIMP-2]·[IGFBP7] levels was only a risk factor for AKI at admission. The highest OR (95 % CI) was for AKI NGAL at day three with OR 5.65 (2.81-11.3), for mortality NGAL at admission with OR 4.51 (2.46-8.28) and for PNO NGAL at day three with OR 4.21 (2.18-8.12). In multivariate analysis combining clinical parameters and biomarkers, the AuROCs (95 % CI) were 0.774 (0.700-0.848), 0.812 (0.751-0.873) and 0.819 (0.759-0.878) for AKI, mortality and PNO, respectively. The discriminating power was not uniformly improved in models combining biomarkers and clinical parameters when compared to the use of biomarkers alone. In subgroup analysis exploring the biomarkers ability to predict severe AKI (KDIGO stage 2 and 3) compared to mild AKI (KDIGO stage 1), cystatin C and NGAL at day three were statistically significant better in predicting severe than mild AKI.

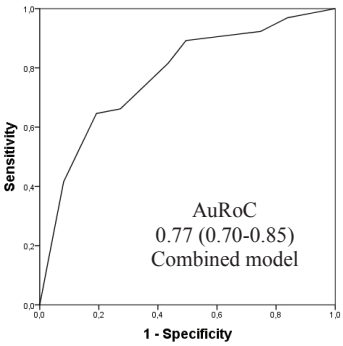
In additional unpublished results we present the AuROC curves for the AKI biomarkers' ability to predict AKI, neurological outcome and mortality alone, and in the best models combining biomarkers and clinical parameters (Figure 5).

Prediction of AKI (n=164)

Biomarkers alone



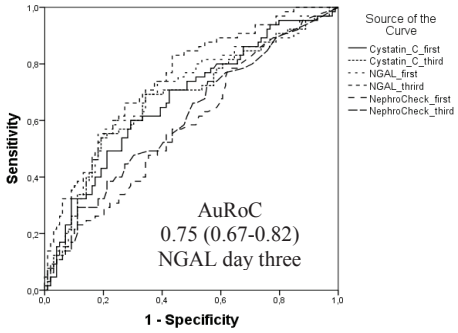
Best model with biomarker and clinical parameters



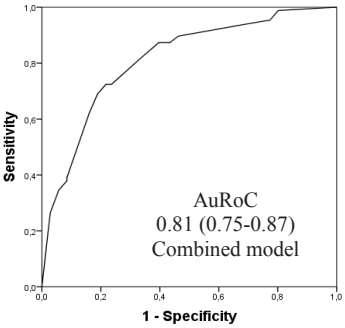
Parameters in model
SOFA score day 0
Serum urea day 0
Urine NGAL day 3

Prediction of mortality (n=164)

Biomarkers alone



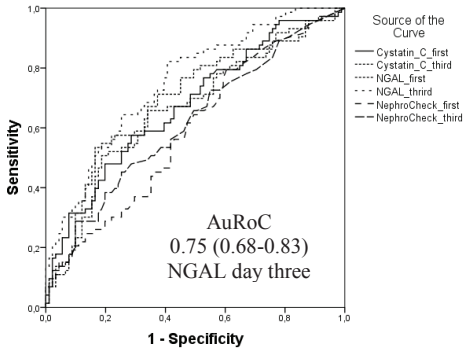
Best model with biomarker and clinical parameters



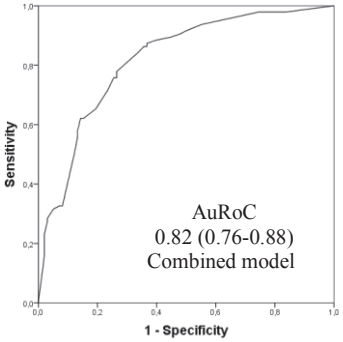
Parameters in model
Lack of initial VT/VF
Presence of AKI
SOFA score day 0
Urine NGAL at admission

Predictors of poor neurological outcome (n=164)

Biomarkers alone



Best model with biomarker and clinical parameters



Parameters in model
Lack of Initial VT/VF
Presence of AKI
Whole blood base excess day 0
SOFA score day 0
Urine Cystatin C at admission

Figure 5: Area under the receiver operating characteristics plots for the predictive models for acute kidney injury mortality and poor neurological outcome in cardiac arrest patients. Data are presented as area under the curve (AuRoC) with 95 % confidence interval for the best models. SOFA: Sequential organ failure assessment, NGAL: Neutrophil gelatinase associated lipocalin, VT/VF: Ventricular tachycardia/ ventricular fibrillation, AKI: Acute kidney injury.

9. Discussion

9.1 Paper I

Comparing epidemiological data on post-traumatic AKI in previous and present studies is challenging due to many different definitions of trauma and AKI. The reported occurrence of AKI after trauma has ranged from 0.1% to 31 % [10, 177, 178]. In more recent studies of severely injured trauma patients applying modern AKI criteria, the incidence of post-traumatic AKI is reported to be 15-48 % [51, 53-56], and RRT is described to be used in 6-15 % of trauma patients admitted to the ICU [53, 54].

We found that the occurrence of post-traumatic AKI with RRT was 0.5 ‰ of all hospitalized trauma patients, whereof many suffered only minor trauma with low ISS [179]. In agreement with previous findings, we found that 8.3 % of major trauma patients admitted to ICU had AKI necessitating RRT [53, 54]. Additionally, we calculated a population based incidence of post-traumatic AKI with need of RRT being 1.8 persons per million inhabitants per year.

The risk of developing post-traumatic AKI was in our study several times higher in males compared to females, which has been observed in many other studies [55, 56, 177, 180], although one study showed the opposite [8]. The gender difference in our study persisted even after adjustment for the actual number of males and females, suggesting that men may be more prone to develop post-traumatic AKI than women. We did, however, not adjust for the severity of trauma, and the observed gender difference might be due to more severe injuries in males compared to females. Nevertheless, in one study on risk factors for post-traumatic AKI, diabetes mellitus, male sex and severe injury were strongly associated with AKI development [8].

An interesting finding in our study was the frequent use of nephrotoxic agents compared to previous reports of post-traumatic AKI [10, 177]. Iodinated radiocontrast agents

were administrated to 29 % of the patients during computer topography, 5 % during angiography and additionally 38 % during combined computer topography and angiography [179]. Radiocontrast agents were often used during diagnostic and/or therapeutic interventions of spleen-, liver- and/or pelvic bleedings [181-183]. The limited clinical data on contrast agents as a risk factor for AKI in trauma patients are showing conflicting results [54, 56, 184, 185], and it seems like these agents are currently being used in most major trauma patients [56]. In studies comparing low and high exposure of iodinated radiocontrast agents, the use of high exposure has not been associated with increased risk of post-traumatic AKI [8, 184, 186].

We observed a relatively high incidence of urinary tract obstruction (12 %) as a possible contributing cause of AKI, including 2 % with obstruction of the urinary catheter, and 10 % with obstruction of both ureters. As all major trauma patients had urinary catheters inserted, one should expect that urinary tract obstruction was a rare risk factor for AKI in this patient group. Post-renal AKI has previously been reported to occur in 2.5 % of trauma patients and in 10 % of general ICU patients suffering from AKI [177, 187, 188]. Urinary tract obstruction in trauma victims might be due to traumatic injuries such as retroperitoneal haematoma blocking the ureter, or as part of an intrapelvic compartment syndrome [189, 190]. Additionally, some of the patients in our study underwent pelvic- or abdominal packing as part of damage control surgery [191], and how this might cause post-renal AKI in trauma patients deserves more research.

After publication of our study, there has been focus on the potential adverse effects of fluids containing hydroxyethyl starch in different patient cohorts. While these products have been associated with development of AKI and adverse outcome in septic patients [192, 193], it has not been certainly confirmed in surgical patients [194]. Although we lack data in our patient cohort, we know that fluids containing hydroxyethyl starch was commonly

used at our hospital during the study period. The use of such fluids in trauma patients was associated with decreased incidence of AKI in one study [195], while several other studies have shown the opposite [56, 196].

AKI is a strong predictor of mortality in trauma patients [51, 54-56, 61], and fatality rates in post-traumatic AKI with need of RRT has been described to be around 50 % [177]. In comparison, the mortality in our small patient group was 40 % after one year, and the good outcome might be due to young age and good health status prior to the trauma. Our observation that increased age was a risk factor for death was not surprising, as this has previously been shown in general ICU patients [44, 197] and trauma patients with AKI [56]. Unfortunately, we are unable to perform a long-time follow-up of our study population in order to explore the extent of complications such as chronic pain, reduced quality of life, physical disability and/or post-traumatic stress disorder.

Renal recovery in unselected ICU populations has been reported to occur in 78-95 % of the patients, and is obviously dependent on the definition of renal recovery and the time period considered [5, 16, 198]. As in two other studies of post-traumatic AKI, we found that no patient required chronic RRT [10, 56]. Considering long-time effects of AKI on the development of CKD, one year observational time is relatively short, and it would be interesting to follow the patients' kidney function over a longer time period. The overall good renal recovery rate observed in our study population was probably because our patients were relatively young, and that those with known CKD were excluded from the study.

9.2 Paper II

Our study revealed that the trauma patients received CRRT median 19 hours per day, i.e. 78 % of the total possible time [201], still comparable to the 19-23 hours per day in previous studies of general ICU patients with AKI undergoing RRT [35, 199, 200]. Probable reasons

for the relatively short daily CRRT duration in our patients might have been bleeding limiting anticoagulation, absence from the ICU due to diagnostic procedures and/or therapeutic interventions, and/or technical difficulties in maintaining dialysis circuit patency.

We observed that the daily CRRT duration to maintain serum concentrations were above 19 hours per day for urea, and only around 14 hours per day for creatinine. A clear limitation to these data, however, is that we were unable to present exact data on the delivered CRRT dose in the studied population. In contrast, 16 hours of CRRT per day was needed to maintain serum concentrations of both urea and creatinine in a previous study of mixed ICU patients [35]. The observed difference in daily RRT duration for maintaining urea and creatinine concentrations between trauma patients and general ICU patients could be explained by extensive muscular damage [202, 203], which may cause increased production of protein degradation products such as urea.

Filter clotting was the main reason for interruptions of CRRT in previous studies of mixed ICU patients, accounting for 74-78 % of the temporary discontinuations [35, 200]. The reasons for temporary interruptions during CRRT in our study was filter clotting (54 %), therapeutic interventions (25 %), catheter related problems (10 %), filter time out (6 %), and diagnostic procedures (6 %). Our study certainly revealed that there is a potential for improvement, since most of the CRRT interruptions were due to technical difficulties such as filter clotting or catheter-related problems.

There was no difference in the time interval from trauma to initiation of RRT in our patients with or without rhabdomyolysis. However, those with rhabdomyolysis had a better survival rate, and we might speculate that the observed difference in mortality was because they were younger with less chronic co-morbidity compared to patients without rhabdomyolysis. Additionally, those with rhabdomyolysis had shorter daily duration of CRRT the first three days after initiation of RRT. A plausible reason might be that they often

suffered from severe bleeding and underwent diagnostic and/or therapeutic interventions remote form the ICU. Another interesting finding in the blood sample analyses of total patient cohort was that some of the patients developed a metabolic alkalosis a few days after initiation of CRRT (Figure 3). Although we do not know the reason for this, it might be due to the RRT and/or the use of forced alkaline diuresis frequently applied in these patients prior to initiation of RRT.

Although clinical data on RRT quality are available in general ICU patients, data are lacking in the ICU subgroup of trauma patients. Trauma patients might differ from other ICU patients in several aspects of CRRT; first, the muscular damage might lead to a rise in metabolic waste product such as urea that should be eliminated from the body through the kidneys. Second, trauma patients are initially threatened by severe bleeding limiting the use of anticoagulation during CRRT. Third, frequent diagnostic procedures and therapeutic interventions remote from the ICU limit the time available for CRRT. In summary, we might speculate that trauma patients should receive increased dialysis doses during CRRT compared to other ICU patients, especially in the initial phase. However, there are no such specific treatment recommendations adjusted for trauma patients.

9.3 Paper III

In a recent systematic review and meta-analysis, overall incidence of AKI after CA was 37 % [85], and among the included studies ranging from 12 % to 81 % [80-85]. In comparison, we found that 46 % of the OHCA victims developed AKI within three days [204]. Reported occurrences of AKI may wary due to several factors including study population, as OHCA and in-hospital CA are different subgroups of CA victims [205]. In a study of mixed CA patients, in-hospital CA was found to be an independent predictor of AKI development [84], possibly because of pre-existing disease leading to hospital admission and/or other causes of

the CA. AKI occurrence also depends on the AKI definition used, and time period considered. Moreover, several factors such as pre-morbid status, pre-hospital factors, extent of reperfusion injuries and post-resuscitation care will affect the development of AKI. Finally, it is reasonable to assume that the quality of care may influence the extent of organ failures, but such parameters are difficult to measure in clinical studies [206]. CKD was present in 4 % of the patients in our study, comparable to previous CA studies [81, 84]. However, CKD was present in 10 % of a large population-based Norwegian cohort with similar age [207], and it is likely that the true prevalence of CKD in our study population was underestimated, because we based our CKD diagnosis on the medical history [204].

In our study we found that chronic hypertension, malignant disease, unwitnessed CA, long time to ROSC and high SAPS II- and SOFA scores were risk factors for AKI [204]. Pre-existing CKD and hypertension are known risk factors for AKI in general ICU patients, and high severity of illness scores are considered to be markers of multiple organ failure often present in patients with severe AKI [208]. In CA patients, unwitnessed CA, non-shockable rhythm and long time to ROSC are factors associated with unfavourable outcome [85, 124, 209]. A remarkable finding in our study was that rhabdomyolysis, a previously undescribed risk factor for severe AKI after OHCA, was present in 2 % of the patients without kidney disease, 10 % of the AKI patients, and 28 % of the AKI patients undergoing RRT. Additionally, our unpublished sub-group analysis revealed that CA patients with and without rhabdomyolysis had similar time from CA to initiation of RRT, although a low number of patients was studied. A recent systematic review and meta-analysis revealed that the serum CK level predicted rhabdomyolysis-induced AKI, even if the correlation between serum CK level and AKI occurrence was stronger in cases of traumatic rhabdomyolysis compared to other causes of rhabdomyolysis [144].

AKI after CA was associated with increased mortality in a recent systematic review and meta-analysis, but the effect on neurological outcome was unsure since the observed increased risk was not confirmed after corrections for confounders [85]. In our study, published after this review, we found that six-month mortality and neurological outcome were favourable in patients without kidney disease compared to those experiencing AKI, also in data adjusted for confounding factors [204]. The outcome findings regarding mortality and neurological outcome are often similar, since dead people are rated with a CPC of 5 [87, 88]. In order to improve outcome after CA, optimizing and standardizing our current approach to CA resuscitation and post-resuscitation care is essential [210], and future studies are needed to evaluate different treatment alternatives.

The reported use of RRT in CA patients with AKI has been 4-33 % [81, 84-86]. We found that 16 % of our OHCA patients with AKI underwent RRT, and that RRT was withheld due to futility in 9 % of the AKI patients. Interestingly, six-month mortality and neurological outcome were similar in AKI patients with and without RRT, even after excluding those where RRT was withheld due to futility. This finding was confirmed in our unpublished sub-group analysis revealing a similar prognosis in CA patients with AKI stage 3 with and without RRT, although the number of patients was low. In previous CA studies, AKI with use of RRT was identified as an independent predictor of bad outcome in a large registry study [211], but was not associated with unfavourable outcomes in three recent studies [81, 84, 86]. Many studies have therefore reported a relative good outcome in CA patients undergoing RRT, and there might be several reasons for this observation. A plausible explanation might be that clinicians perform well in selecting patients with anticipated good prognosis for RRT. An alternative hypothesis is that the use of RRT may have beneficial effects in this patient group, possibly by removing circulating harmful substances from the body. Post-cardiac arrest patients are sepsis-like with early excessive cytokine release [212],

and the use of RRT has been associated with beneficial effects in septic patients [213, 214]. Moreover, the use of RRT has in rhabdomyolysis shown to increase the clearance of muscular degradation products [138], improve mitochondrial function and inhibit cell apoptosis [215]. One clinical study revealed that the use of high-volume haemofiltration in OHCA patients was associated with improved survival [216], but more studies are indeed warranted.

9.4 Paper IV

The currently available biomarkers aimed to predict AKI have many shortcomings limiting their clinical use [38, 217, 218]. In general ICU patients, cystatin C, NGAL and [TIMP-2]·[IGFBP7] measured in blood and/or urine are among the best predictors of subsequent AKI [142, 219-221]. In CA patients there are some data revealing that NGAL measured in blood within four hours after ROSC is a predictor of AKI [209]. In agreement with this, we found that cystatin C, NGAL and [TIMP-2]·[IGFBP7] concentrations measured in spot urine of OHCA patients at admission were predictors of AKI. At day three cystatin C, NGAL, but not [TIMP-2]·[IGFBP7], was able to predict subsequent AKI, possibly due to the relatively short half-life of the latter markers. In a subgroup analysis, we additionally observed that urine cystatin C and NGAL levels at day three performed better in predicting moderate to severe AKI (KDIGO stage 2 and 3) compared with mild AKI (KDIGO stage 1). This is interesting, since worsened AKI severity is associated with increased need of RRT and reduced survival [222].

The biomarkers cystatin C, NGAL and [TIMP-2]·[IGFBP7] have in general ICU patients been prognostic predictors of mortality [223-225]. In two recent CA studies, NGAL levels measured in blood samples were able to predict mortality [124, 209], and in one of the studies NGAL concentrations also predicted neurological outcome [209]. Likewise, we found that the urine levels of cystatin C and NGAL, but not [TIMP-2]·[IGFBP7], were statistically

associated with mortality and PNO. We might speculate that cystatin C and NGAL are markers of whole body ischemia and reperfusion injuries, whereas TIMP-2 and IGFBP7 probably are more kidney-specific markers.

Predictive models of outcome after CA are warranted since futile treatment is a huge problem in medical practice. Patients may have late awakening after OHCA, and clinicians must be cautious in not prematurely terminate life in patients with the potential for full neurological recovery [226]. In fact, two studies of CA patients have revealed that more than half of the deaths among initial survivors were associated with withdrawal of active ICU treatment [75, 227]. Many efforts have therefore been suggested in order to improve prognostication after CA, but we still lack a reliable tool for the early prediction of poor outcome in these patients [228].The addition of biomarkers to clinical parameters have been suggested in order to improve outcome prediction after CA [229-231], but as in our study the discriminating power between favourable and unfavourable outcome is limited. However, in one study, a multimodal scorings system consisting of seven patient parameters at an early stage after ICU admission had a good ability to predict neurological outcome at ICU discharge [231]. Due to the restrictions of such predictive models, they are not ready for use in clinical practice to decide treatment allocation of patients. Recent European guidelines for post-resuscitation care therefore recommend a multimodal strategy with prolonged observation in cases with uncertain outcome [73]. We hope that the main results from the NORCAST study will contribute to improved prognostication after CA, especially since the clinicians were blinded for prognostic markers in order to avoid self-fulfilling prophecies in the study.

9.5 Methodological considerations

In assessing internal validity, the key concept is whether observed changes can be attributed to the exposure and not to other possible causes. Internal validity is therefore a question of study quality in observational studies, and whether the compared groups really are comparable. The most important domains to be considered in cohort design are presented in Table 9 where the papers in this thesis are assessed to be of high, unclear or low quality judged by the author of this thesis.

Table 9: Assessment of the quality of studies included in this thesis

Domains considered	Paper I	Paper II	Paper III	Paper IV
Selection bias Are compared patients from the same cohort and time period?	High	High	High	High
Selection bias Are there any losses to follow-up? How are these accounted for?	High	High	High	High
Information bias Are the methods used to collect data adequate or not?	Unclear	Unclear	High	High
Information bias Are exposures and outcomes measured objectively?	Unclear	Unclear	High	High
Confounding factors Are confounding factors adequately controlled for?	Low	Low	Unclear	Unclear
Statistical power Do the studies have adequate statistical power?	Low	Low	Unclear	Unclear
Other bias Are there other factors present that could limit the quality assessment?	Low	Low	Low	Low

Table 9: Assessment of the quality of studies included in this thesis.
Domains with unclear and low quality are discussed in the text.

In the trauma studies (Paper I and II), it is unclear to which extent the retrospective design may have influenced the quality of data collection. Not all outcome variables were objectively measured, as for instance the reasons for temporary interruptions during CRRT that to some degree was dependent on the author's judgement. Moreover, no confounding factors for the association between AKI with need of RRT and mortality were considered or controlled for, although some were likely to be present. Finally, the number of patients included was only 42 and 36, resulting in a limited statistical power and a probability for false negative effect (type II error).

In the OHCA studies (Paper III and IV), there might be confounding factors for the association between exposure (AKI) and outcome (mortality and neurological outcome) not adequately controlled for. As an example, we were unable to assess the confounding effect of RRT because no patients without AKI received RRT. Additionally, the possible confounding effect of withholding and/or withdrawing treatment was neither assessed. Furthermore, although there were 245 and 195 patients included in these studies, an *a priori* sample size calculation would be preferable. Finally, a general limitation to the quality assessment of all papers presented is, off course, the authors ability to evaluate own work marked as "other bias" in Table 9.

External validity is considered as the transferability of results, meaning whether the results can be applied in other settings. The key question in assessing external validity is the degree to which the conclusions in a study would hold for other persons in other places and at other times. There are several limitations to the generalizability of our results, as the studied populations (trauma and OHCA patients) are quite differently handled around the world, depending on recourse availability and established medical practice. Additionally, pre-hospital handling, in-hospital care and rehabilitation of these patient groups may vary across sites limiting the external validity of our findings.

All studies included in this thesis (Paper I-IV) have additional limitations to the design of cohort studies that should be taken into account in the interpretation of the results. Since the included patients are not randomized, there might be systematic differences between compared groups. Furthermore, the association observed between risk factors and outcomes does not necessarily mean that there is a causal relationship. In the trauma studies (Paper I and II), it would be preferable to include all severities of AKI, and to have a control group of trauma patients without AKI. Moreover, the quality of the studies would be improved if we could present exact data on the prescribed and delivered CRRT doses. Finally, it would probably also be appropriate to replace the Pearson's chi-square test with the Fisher's exact test in the analysis of some of the data with very few observations in each group. In the OHCA studies (Paper III and IV), a longer time period than six months follow-up would have been preferable. The occurrence of kidney disease was probably underestimated since CKD was diagnosed based on the medical history, and AKI criteria were applied for only three days with missing bodyweight information in some of the patients. In Paper IV, there were several limitations to the measurement of biomarkers as the time from CA to urine sampling varied both at admission and at day three. The urine samples collected at admission could potentially be diluted with urine present in the urinary bladder prior to the arrest. Moreover, the urine samples were not handled exactly as recommended, but we still consider the results to be valid based on results from previous studies and our pilot study [174-176].

The papers included in this thesis also have some methodological strengths. Cohort design is suitable for calculating incidence rates and examinations of multiple effects of a single exposure. Cohort studies are also appropriate for development of new hypothesis that could be tested out in subsequent trials [232]. In all studies (Paper I-IV), the included patients came from the same cohort and time period, using defined inclusion and exclusion criteria and with no loss to follow-up. In the trauma studies (Paper I and II), several registries were

crosschecked during the inclusion of patients, making it unlikely that patients were missed. Additionally, a uniform registration process was secured as only one investigator collected the data, intending to use clear and commonly applied definitions of variables. In the epidemiological study (Paper I), the setting with a single regional trauma referral centre made it possible to present population based incidence data, and the Norwegian Renal Registry made it possible to present reliable data on renal outcome.

In the OHCA studies (Paper III and IV), there were many included patients enhancing the statistical power of the study. Additionally, there was a prospective study design and *a priori* planned collection of data. Commonly applied definitions of variables were used, and kidney disease was classified using up-to date CKD and AKI definitions. Patients were treated according to our SOP documenting good and stable outcome over time [74, 75, 204]. Generally, we aimed to follow international recommendations for reporting of data from OHCA patients and observational studies [88, 233]. Finally, the AKI biomarkers were tested using some of the most promising biomarkers available in a population with a high pre-test probability of the considered outcomes (Paper IV).

9.6 Implications for clinical practice and future research

Paper I revealed that nephrotoxic agents and urinary tract obstruction might be important risk factors for AKI in trauma patients. These findings indicate that trauma patients undergoing angiographic embolization and/or damage control surgery should be closely followed afterwards in respect to their kidney function, and that alternative treatment options should be considered in high-risk patients. The importance of these findings should be evaluated in future studies considering both effects and side effects, and maybe compare it with other treatment alternatives of acute bleeding. Indeed, it would be feasible to facilitate trials comparing different interventions.

Paper II showed that trauma patients received inadequate RRT doses in order to achieve uraemic control, and technical difficulties were frequent causes of temporary interruptions. Since 2006 we have implemented educational programs for RRT run by dedicated ICU nurses. Our department has developed a CRRT protocol with standardized indications for CRRT, weight adjusted dialysis doses, and criteria for discontinuation of CRRT. Finally, we have changed anticoagulation during CRRT from systemic heparin to regional citrate. More studies on RRT quality in this patient group is certainly needed, and future studies of increased RRT dose, timing of initiation of RRT and/or improvement of technical skills would be preferable and very interesting.

Paper III showed that OHCA patients developing AKI with and without RRT had a similar prognosis, although those with RRT were more severely ill. Noteworthy, the clinicians have to consider these findings when deciding which patients should be offered RTT or not. Handling of AKI in CA patients and the use of RRT was not even mentioned in the most recent European or American guidelines for post-resuscitation care [73, 234]. We need to perform more clinical studies evaluating the effects of RRT after CA, and also evaluate consequences and treatment of rhabdomyolysis as a risk factor for AKI after CA.

Paper IV revealed that urine cystatin C and NGAL at admission and day three were independent risk factors for AKI, mortality and PNO in resuscitated, comatose OHCA patients. Unfortunately, these findings have limited value in clinical decision making since the biomarker levels overlapped in the compared groups. However, these biomarkers might be useful in clinical research in risk stratification of patients, as subjects with moderate biomarker levels probably have the most modifiable disease process and are suitable for inclusion in randomized clinical trials. In future studies, it would be possible to improve the performance of biomarkers with proper selection of patients, optimal sample collection and/or combined with other parameters.

There is an increasing incidence of AKI and use of RRT that is expected to rise even further [67, 94, 235, 236], in a recently published multicentre study 57 % of ICU patients experienced AKI, and 13.5 % were treated with RRT [222]. We therefore need more high-quality research on AKI further exploring risk factors, pathophysiology, prophylaxis, diagnosis, treatment, prognosis and follow-up. Future studies should include a wide variety of study designs (including experimental laboratory research, observational studies, interventional trials and systematic reviews), and the available research results should be graded for quality or certainty of evidence, and result in practical treatment recommendations available for bed-side health personnel. Considering the substantial complexity of the disease process, there seems to be no emerging miracle cure available. However, there are some promising alternatives for future improvements out of the scope of this thesis, including new functional tests of kidney function, remote ischemic preconditioning, haemodynamic optimization, immune-modulating RRT filters, drug dosing during AKI and/or RRT, timing of RRT initiation, and the use of recombinant embryonic stem cells. Future studies should also explore long-time outcomes after an episode of AKI, including factors influencing renal recovery and the effects of ambulatory follow-up.

10. Conclusions

The conclusions regarding the specific research questions are:

1. AKI necessitating RRT following traditional criteria was rare among trauma patients, and the risk of this complication was higher in males compared to females. The mortality of post-traumatic AKI with RRT was modest, and renal recovery was excellent among survivors as none was dependent on RRT one year after trauma.

2. Trauma patients with AKI and RRT had relatively short median CRRT duration, and there was an association between daily CRRT duration and uraemic control defined as daily changes in blood creatinine- and urea concentrations. The patients achieved inadequate RRT dose in order to achieve uraemic control, and a relatively large proportion of the temporary CRRT interruptions were due to technical difficulties.

3. Kidney disease occurred in about half of patients successfully resuscitated from OHCA, and was associated with unfavourable six-month mortality and neurological outcome. AKI patients with and without RRT had comparable mortality and neurological outcome, even after excluding patients where RRT was withheld due to futility.

4. Urine cystatin C and NGAL concentrations at admission and day three were independent risk factors for AKI, mortality and poor neurological outcome in resuscitated comatose OHCA patients, whereas [TIMP-2]·[IGFBP7] levels only predicted AKI at admission. The discriminating power was not uniformly improved in models combining biomarkers and clinical parameters compared to the use of biomarkers alone.

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12. Reprints of Paper I-IV