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Incidence of post-contrast acute kidney injuries for trauma patients at a Swedish trauma centre

Degree Project in Medicine

Charlotta Kjällquist

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Supervisor: Jenny Skytte Larsson, MD-PhD

Co-supervisor: Ragnar Ang, Head of Trauma and Acute Surgery

Department of Surgery,

Institute of Clinical Sciences

Sahlgrenska Academy, University of Gothenburg

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List of abbreviations

AIS	Abbreviated Injury Scale
AKI	Acute kidney injury
CHF	Congestive heart failure
CI	Confidence interval
CI-AKI	Contrast-induced acute kidney injury
CIN	Contrast-induced nephropathy
CKD	Chronic kidney disease
CM	Contrast media
CRRT	Continuous renal replacement therapy
CT	Computed tomography
DM	Diabetes, both type 1 and 2
eGFR	Estimated glomerular filtration rate
ESUR	European Society of Urogenital Radiology
GCS	Glasgow Coma Scale
HOCM	High-osmolar contrast media
ICU	Intensive care unit
IOCM	Iso-osmolar contrast media
ISS	Injury Severity Score
IV	Intravenous
LOCM	Low-osmolar contrast media
MODS	Multi organ dysfunction syndrome
OR	Odds ratio
PC-AKI	Post-contrast acute kidney injury
RR	Respiratory rate
RTS	Revised Trauma Score
SBT	Systolic blood pressure
SCr	Serum creatinine
SD	Standard deviation
SU	Sahlgrenska University Hospital
SweTrau	Swedish Trauma Registry

Abstract

Title: Incidence of post-contrast acute kidney injuries for trauma patients at a Swedish trauma centre.

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Author: Charlotta Kjällquist, medical student at Sahlgrenska Academy, Gothenburg.

Introduction: The aetiology of post-contrast acute kidney injuries (PC-AKI) is currently debated. During recent decades studies have shown little or no difference in the incidence of acute kidney injuries among patients given contrast media (CM) as compared to patients not given CM during medical imaging.

Current guidelines at Sahlgrenska University Hospital (SU) recommend caution and at times contraindicates the use of CM for patients with renal impairment in order to reduce the risk of PC-AKI. These cautionary measures affect many patients such as elderly and diabetics.

Overestimating PC-AKI can lead to delay in management, impaired patient safety, and higher costs in health care.

Aim: To determine the incidence and possible risk factors of PC-AKI in trauma patients administrated intravenous CM during computed tomography (CT) at SU during 2018.

Method: This single-centre retrospective observational study of medical records comprises all trauma level I-II patients who underwent contrast enhanced CT at SU during 2018. Risk factors for renal impairment such as age, diabetes, pre-existing kidney- or heart failure and revised trauma score, injury severity score (ISS) and abbreviated injury scale (AIS) were examined to elucidate possible correlations.

Results: A total of 285 patients were included whereof 252 (88.4 %) patients received CM during CT (CM group), and 33 patients did not (non-CM group). 5.56 % of the CM group developed PC-AKI compared to 9.09 % in the non-CM group. Majority of the patients had normalised creatinine values within a week. Significant risk factors were pre-existing heart- and kidney failure, and high AIS and ISS. Multiple CM administration minimally increased the risk of developing PC-AKI.

Conclusions: A larger prospective study is needed to evaluate the risk of CM-induced PC-AKI, and in the long term a possibility to re-evaluate current guidelines to ensure best possible patient safety and lower health care costs.

Key words: Post-contrast acute kidney injury: Contrast media: Nephropathy: Trauma.

1. Background

1.2 Introduction

Intravenous contrast media (CM) is routinely used for medical imaging of trauma patients. Full circulatory optimization of the trauma patient before administration of CM is most often not possible due to the lack of time. To minimize the risk of complications and adverse reactions to the administration of CM, current guidelines for multi trauma patients at Sahlgrenska University Hospital (SU) recommend caution, and to consult the responsible radiologist before administration of CM to patients with estimated glomerular filtration rate (eGFR) below 45 ml/min [1]. These guidelines affect a large number of patients, for example elderly and patients with diabetes. Although guidelines are to be followed, individualised clinical decisions of giving CM to a patient or not is of paramount importance.

It is easier to optimize the patient before exposure to CM with preparations such as hydration, nephrotoxic drug withdrawal and adjustment of given CM-doses, in elective care, than in emergency care. For this reason, this study came to comprise only trauma patients [2].

During the evolution of CM, a history of adverse events has been recorded. Despite progress and development of the compounds and molecular structures of CM some issues are still present. The aetiology and incidence of post contrast acute kidney injury (PC-AKI) are currently debated. Several recent studies have shown none, or little, difference in the incidence of acute kidney injury (AKI) among patients given contrast media (CM) compared to patients not given CM during computed tomography (CT) scan [3-5]. Overestimating the risk of PC-AKI can lead to delay both in examination and treatment of the patient, resulting in impaired patient safety as well as increased costs in health care. Moreover, there is a risk for the patient if exposed to avoidable radiation due as a result of inconclusive primary imaging. Altogether, there are several incentives to try to determine the aetiology and incidence of PC-AKI. Therefore, this study has investigated the incidence of PC-AKI within trauma patients level I-

II and patients with an ISS > 15 (Injury severity score) who was administrated CM during computed tomography (CT) at SU during 2018. Trauma calls are evaluated and triaged by medical staff into trauma level I-IV due to the trauma mechanisms and patient parameters, where level I-II correspond to a higher risk of having severe injuries. ISS is a standardized scoring system used to assess trauma severity. The scale scores from 1 to 75, where scores > 15 is defined as a major trauma [6]. Both trauma level and ISS are estimated by using defined criteria [7, 8].

Kidney function is usually calculated by using eGFR. In Sweden the internationally standardized Malmoe-Lund formula is commonly used, containing the patients sex, age and SCr (Serum creatinine) to calculate eGFR [2]. This will result in a value measured in ml/min/1,73 m^2, which reflects the patients' renal function. This is a fast, inexpensive and easy method, contrary to the more exact method of true GFR which measures renal clearance of radioactive isotopes such as 51Cr-EDTA or ^{125}I-iodothalamate. Natural fluctuations of the kidney functions and of the creatinine clearance make the estimated calculations more unreliable compared to the more definite true GFR [9], but still the method is often used due to their effectiveness.

Several causes might contribute to a sudden kidney deterioration in trauma patients. Direct renal injury, hypovolemia, rhabdomyolysis and sepsis are some examples of conditions that can cause AKI, with or without the use of CM [10]. Pre-existing risk factors such as dehydration, kidney failure and the administration of nephrotoxic drugs are to be considered before administrating CM [2]. Other risk factors, that were included and evaluated in this study, is old age, diabetes (DM), congestive heart failure (CHF), pre-existing kidney failure and severe trauma. Many of these are factors known to increase the risk of developing nephropathy [11].

Common side effects to the administration of CM are flushing, nausea and shortness of breath. More severe reactions such as hypotension and anaphylaxis, are uncommon. A transient increase in SCr after administration of CM is considered normal [12], though underlying causes

of the more serious side effect, PC-AKI, is debated.

PC-AKI is defined as an increase in SCr > 26.5 μmol/L or > 1.5 times baseline, within 48-72 hours of intravascular administration of a contrast agent [13]. The natural fluctuation in kidney function and creatinine clearance can affect the SCr levels without other influence and should be considered when measuring SCr levels continuously. When compared, studies of non-trauma patients have shown no difference in the incidence of PC-AKI between groups given CM and not given CM [14, 15].

In the last decades the former consensus that CM is one of the main causes behind iatrogenic AKI has been questioned. Today's disunity about the true existence of PC-AKI divides the scientific opinion into two opposite fractions [16, 17]. On one hand there is the history of renal events and the long-time consensus of the use of CM risking induction of nephropathy [11, 18] and on the other hand recent studies have shown no differences in the incidence of PC-AKI in different patient groups given contrast compared to groups not given contrast during a CT-scan [3, 4, 19].

There is a confusion regarding the terminology and definition of renal function deterioration after administration of CM. The more comprehensive term of an acute renal dysfunction is AKI [20]. If this occurs within 48-72 hours of administration of CM the general term is PC-AKI, and if a causal relation between the administration of CM and decrease in renal function can be found it is called contrast induced acute kidney injury (CI-AKI). This was earlier known as "contrast induced nephropathy" (CIN), but as it refers to the nephropathy being a direct cause of the CM this term is now considered as an obsolete term [21].

2. Aim

The aim of this project is to determine the incidence of PC-AKI in patients triaged as a trauma calls level I-II and in patients with ISS > 15 after undergoing contrast enhanced CT, and furthermore to evaluate risk factors that can be of importance in the prevention of PC-AKI.

3. History of contrast media

The beginning of CM started not long after the discovery of x-rays by W. Röntgen in the late 19th century [22]. The requirement of sharper contrast of images soon led to the use of elements with high atomic numbers due to their radiopacity. The year after the discovery of x-rays (1896) E. Haschek and O.T. Lindenthal obtained one of the first images of a human vessel with contrast. By injecting an opaque mixture (Teichmanns mixture) of lime (calcium oxide), mercury sulphide (cinnabar) and petroleum into the artery of an amputated hand, they were able to visualize the vasculature of the hand, resulting in the first angiogram ever conducted [23]. Bismuth, lead, strontium, potassium and barium salts are other examples of elements experimented with as contrast agents during the evolution of imaging of the human body structures. Barium is one of few examples, except iodine, that is still in use today, now in gastrointestinal radiology. Many other substances were never safe enough to use on living humans. Iodine seems to be the only element safe enough to inject into humans in doses and concentration to gain sufficient radiopacity [24]. Iodine was, by accident, discovered to be a safe contrast agent in the early 1920s. By then iodine was commonly used as a syphilis treatment, and when Osborne et al. explored the fact that the urine in iodine treated patients was radiopaque, they performed and published the first pyelogram in 1923 at the Mayo clinic, Rochester MN [25, 26]. During the 1920s iodine became considered safe to use in human studies. Several scientists tried to increase the biological tolerance of other contrast agents by using different kinds of compounds, many of them including different forms of iodine.

Another big leap came about in Europe during the mid-20s. A. Binz and C. Räth were working with treatments against syphilis in Berlin. In the spirit of that time they synthetized hundreds of different chemical compounds, many containing pyridine, a five-carbon structure that can detoxify poisons. One of their compounds, Selectan, containing pyridine and iodine was extra interesting for their work and was sent out to medical colleagues in Europe. After

modification at Professor L.Lichwitz medical centre by his young co-worker, doctor M. Swick the result, “Uroselectan”, became the first clinical intravascular administrated urographic agent and also the introduction of modern angiography.

Binz and Räth patented the same compound as early as 1927, as one of their hundreds of chemical structures, but without Lichwitz or Swick its field of use might have never been discovered [24].

A.E. Moniz was another pioneer whose theory for reducing the toxicity of contrast agents was to increase the molecular size, which, in the late 1920s, resulted in Thorotrast (colloid thorium dioxide) [25]. This contrast medium was from the beginning considered safe due to its low range of acute and subacute side effects and was widely used until the 1950s. Quite soon after its introduction concerns about the long-term effects of this agent rose. In 1932 the “Pharmacy and North American Chemistry Councils” published a warning in Journal of the American Association (JAMA) about Thorotrasts possible long-term effects due to its radioactivity, and in the following years its oncogenic effects were proven in laboratory animals, though some of the experiments were hard to replicate [27, 28]. Later it became clear that the substance had a very long half-life and was extremely carcinogenic, and could cause malignancies in patients decades after being exposed [29].

The search for higher radiopacity inspired researchers to increase the possible amount of iodine atoms in molecules. In 1933, V.H. Wallingford was able to incorporate three iodine atoms on to a six-carbon-ring (para-aminoiodohippuric acid). Before this, all contrast agents had been based on five-carbon-rings. This resulted in a non-toxic radiopaque medium, excreted by the kidneys, and is today thought to be the first modern contrast agent. In further experiments with benzene rings, the active derivate, a free amine, was toxic why Wallingford exchanged it to an acetyl group. This resulted in Acetrizoate, an iodinated benzoic acid derivative, with lower toxicity but the disadvantage of causing significant pain on injection, probably due to its viscosity and ionic compound [25].

The need for sufficient radiopacity and low toxicity in the contrast medium seemed hard to balance.

During the 1950s small changes of already existing compounds resulted in less toxic CM but it was in 1968 with T. Almén, a Swedish clinical radiologist, the next large step could be taken. Almén had an idea that it was not the toxicity of the compounds that was the main issue any longer, but their effect on human homeostasis due to the osmotic effects of the agents. His idea did not receive much support from the pharmaceutical industry, except from a small Norwegian enterprise, Nyegaard A/S & Co. This collaboration resulted in the non-ionic metrizamide (Amipaque), the first low osmolality contrast agents. Today modified versions of Amipaque are used, the second generation of low osmolality CM (LOCM), due to their ability to be sterilized in autoclaves [24].

Even though all progress and success, from toxic, radioactive and painful agents to the ones used today, the causes and pathophysiology of some of the adverse effects are still not totally known. Both direct and indirect mechanism are implicated. Proposed direct mechanisms are for example apoptosis and necrosis of tubular epithelial cell due to toxicity of the compounds. Indirect effects considered include, for example, renal hemodynamic effects caused by an increase of endogenous vasoactive substance, due to reaction to the CM ,that diminish the renal blood flow causing medullar hypoxia and hence PC-AKI [30-32].

The osmotic effects of CM on homeostasis has led to the use of low- and iso-osmolar, all non-ionic, CM (IOCM), in Sweden today. This because they have a lower impact on homeostasis compared to high osmolar CM, even if all three forms are based on the same tri-iodinated benzene ring [33, 34] (see Figure 1). High osmolar CM (HOCM) have a much higher risk of adverse effects and is no longer recommended to be used for intravascular administration [35]. This should be taken into consideration when debating the existence of PC-AKI as much of the data regarding CM and AKI that is frequently used in discussions today, comes from an era when HOCM was standard use. This although HOCM is no longer used, but tend to

influence the debate still today [11].

The most commonly used CMs in Swedish health care is Omnipaque (Iohexol, LOCM) and Visipaque (Iodixanol, IOCM). Omnipaque is the CM mostly used within SU in adult patients [36], even though Iodixanol have been shown to reduce the risk for adverse events in patients with intraarterial administration of CM and in patients with pre-existing renal insufficiency [2, 37].

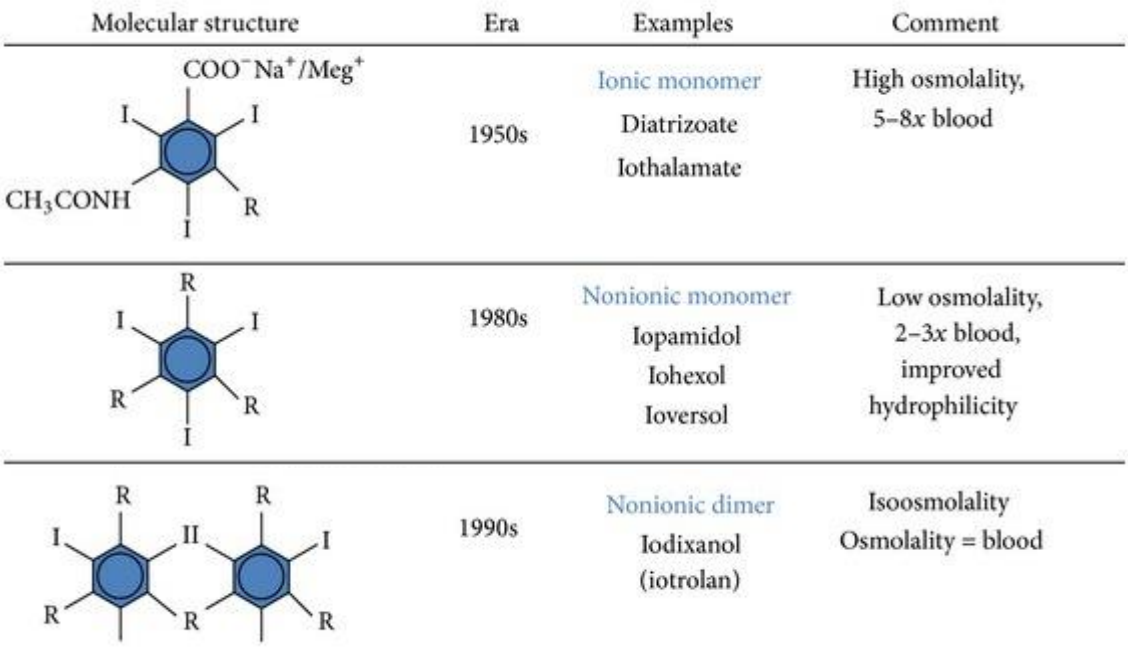

Fig. 1
Molecular structure of HOCM, LOCM and IOCM. Omnipaque (Iohexol) and Visipaque (Iodixanol) are the two contrast medias used at SU. Image adapted from Solomon, R [38].

4. Materials and methods

4.1 Study design

This is a retrospective observational study, comprising all patients triaged as trauma calls level I-II and all patients with ISS > 15 who was listed to undergo a CT at SU during 2018 (n = 975).

4.2 Study population and data collection

In total 975 patients were identified from the Swedish Trauma Registry (SweTrau), using the search criteria “trauma level I-II” and “ISS > 15” on patients that underwent CT during 2018 at SU. SweTrau is a Swedish national registry, focusing on severe trauma caused by traffic- and falling accidents and injuries due to other external violence since its start up in 2011 [39]. Its comprehensive patient material can for example form the basis for quality improvement or retrospective studies, such as this study.

Causes of non-eligibility were cancelled or unperformed CT-examinations, unauthorized access to medical records, wrong year, or faulty personal identify numbers, (n = 131). A total of 844 patients were eligible for inclusion.

For each included patient, files were reviewed within the medical record system Melior and as well as the laboratory system LabBest. Complementary x-ray data was collected from the radiology system used at SU; WebADAPT. The Abbreviated injury scale (AIS) was retrieved directly from the SweTrau-registry. All data were aggregated in a case report form to be transferred into a Microsoft Excel spreadsheet.

Exclusion criteria were as follows: death ≤ 48h from admission (n = 17), age < 18 (n = 69), discharged within ≤ 48h (n = 375), continuous renal replacement therapy (CRRT) secondary to multiple organ dysfunction syndrome (MODS) (n = 1) or MODS secondary to trauma (n = 3), and pre-existing kidney failure treated with dialysis (n = 1). In addition, some patient records were lacking sufficient SCr-data and were therefore excluded (n = 91).

A total of 159 patients from the SweTrau-list had performed a non-contrast enhanced CT, where 33 of them met the inclusion criteria and were therefore put in a control group (non-CM group).

Two hundred fifty-two patients met the inclusion criteria in the group that had had a CM enhanced CT (CM group). Hence a total of 285 patients were included in the study after exclusion criteria were met (see Figure 2).

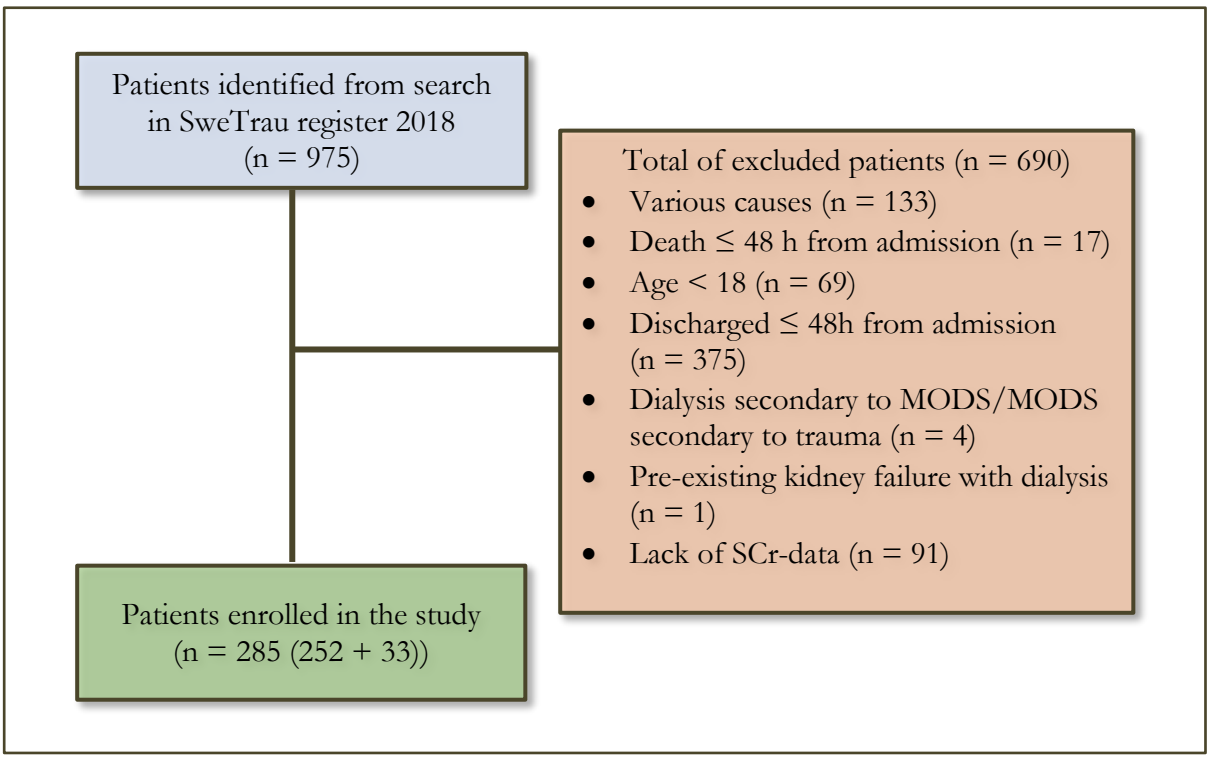

Fig. 2
Flowchart of inclusion and exclusion of the patients in the study." Various causes" such as; cancelled or unperformed CT-examinations, unauthorized access to medical records, wrong year, or faulty personal identify numbers.

4.3 Variables

Patient inclusion number, demographic data of age and sex were noted together with the pre-existing conditions of DM (type I and II), kidney- or heart failure if recorded in the patients' medical journal (see table 1).

Table 1: Demographic characteristics of CM group

Characteristics of CM group	n = 252 (%)
Age (y)	
> 18-74	200 (79)
≥ 75	52 (21)
Sex	
Male	176 (70)
Female	76 (30)
Diabetes (type I and II)	22 (9)
Pre-existing kidney failure	8 (3)
Pre-existing congestive heart failure	11 (4)

Y = Years. Values in parentheses are percentages.

SCr and eGFR were measured and calculated respectively at admission and approximately 72 hours later, as well the peak value in that interval. The patients' respiratory rate (RR), systolic blood pressure (SBP), GCS (Glasgow coma scale), ISS and AIS at admission were recorded.

The revised trauma score, (RTS) was calculated using the standardised formula for RTS = (0.9368 * GCS value) + (0.7326 * SBP value) + (0.2908 * RR value). The RTS is a general assessment of the patients vital signs and ranges from 0 to 7.8408 where a lower value of RTS correlates with a lower survival probability [40].

The AIS is an anatomically based injury severity score, ranging from 0 to 6, where a higher score indicates a more severe injury. The AIS was retrieved if the AIS was marked as an injury to the kidneys.

Some patients underwent their first or only CT at another hospital were but later transferred to SU whereas other patients were referred to other regional hospitals at discharge for rehabilitation. These patients were included if the SCr-measurements and procedures with CM and CT-examination were equivalent to the procedures at SU and relevant data were available.

Several patients (n = 36) had multiple CT-scans performed. If the scans were performed with CM and within 72 hours after each other they were considered as multiple scans. The SCr values for these patients were noted before the first CM administration and up to 72 hours after the last scan.

The patient data was further divided in the following subgroups: age 18-74 and ≥ 75, diabetics (type I and II), pre-existing chronic heart failure (CHF) and kidney failure, and their value of eGFR, RTS, AIS and ISS was listed to be able to detect differences between these groups.

4.4 Outcome measures

Primary outcome was the incidence of PC-AKI from admission and during the first 72 hours after IV-administration of CM. PC-AKI was defined as an increase in SCr of 26.5 μmol/L or > 1.5 times baseline, within 48-72 hours of intravascular administration of a contrast agent [13]. Changes in SCr and eGFR were calculated from baseline values at admission to the highest measured value within 72h after contrast administration. Within the non-CM group, the SCr was calculated from baseline values at admission to the highest measured level within 72 hours from admission.

4.5 Statistical methods

Data from the Excel spreadsheet were exported and analysed with SPSS Statistics 26 for PC (IBM). Logistic regression was used for calculation of result and test of significance. The value of significance was set as ≤ 0.05. For relevant data mean, median and standard deviation (SD) were calculated.

4.6 Ethical considerations

Retrospective data were collected from medical records for patients admitted to SU during 2018. Collection of data from journals was approved by the head of trauma care. Due to the retrospective study design, patients' consent was waived. Collected data was anonymized and patient identification numbers replaced by study inclusion numbers.

For future publication purposes, formal ethical approval has been submitted to the Swedish Ethical Review Authority and an approval is currently pending.

5. Results

5.1 Main results

A total of 14 (5.56 %) out of 252 patients in the CM group developed PC-AKI within 72 hours after CM administration. Amongst these patients, the ones that developed PC-AKI were older, had a higher ISS and a lower eGFR and RTS compared to the no PC-AKI-group (table 2). In total there was a higher percentage of pre-existing diseases within the PC-AKI-group compared to no PC-AKI-group: DM (21.43 % vs 7.98 %), CHF (21.43 % vs 3.36 %) and pre-existing kidney failure (14.29 % vs 2.52 %) (See table 2).

Table 2: Study population characteristics in contrast group

	All patients		No PC-AKI		PC-AKI	
	N (%), mean ± SD	Mdn	N (%), mean ± SD	Mdn	N (%), mean ± SD	Mdn
No. of patients	252 (100)	-	238 (94.44)	-	14 (5.56)	-
Age (y)	54 ± 21.2	53	53 ± 20.9	53	59 ± 25.8	68
Age group						
– 18-74	200 (79.4)	-	191 (80.25)	-	9 (64.29)	-
– ≥ 75	52 (20.6)	-	47 (19.75)	-	5 (35.71)	-
eGFR pre-CT	73.6 ± 20.56	74.00	74.1 ± 20.54	74.50	65.4 ± 19.88	63.00
RTS	7.175 ± 1.329	7.841	7.201 ± 1.295	7.841	6.728 ± 1.826	7.841
ISS	16 ± 11.5	14	16 ± 10.2	14	27 ± 19.7	21
AIS	7 (2.78)	-	5 (2.10)	-	2 (14.29)	-
Diabetes	22 (8.73)	-	19 (7.98)	-	3 (21.43)	-
CHF	11 (4.37)	-	8 (3.36)	-	3 (21.43)	-
Pre-ex. KF.	8 (3.17)	-	6 (2.52)	-	2 (14.29)	-

No. = number, percentage in parenthesis. ± SD = Standard deviation. Mdn = Median. (y) = Years.
eGFR = Estimated glomerular filtration rate. RTS = Revised trauma score. ISS = Injury Severity Score.
AIS = Abbreviated Injury Score. CHF = Congestive heart failure. Pre-ex. KF = Pre-existing kidney failure.

Seven (50 %) of the 14 patients who developed PC-AKI initially, did not meet the criteria for PC-AKI at 72 hours after administration of CM, as their SCr improved (see figure 3). Of the 7 remaining patients with persistent PC-AKI, 1 patient recovered day 7 after CM administration. Two patients had pre-existing kidney failure, and one recovered day 6 after administration of CM. One patient died from the complications of cardiac arrest due to spinal trauma shortly after 72 hours. Another patient received CRRT due to rhabdomyolysis, but

later than 72 hours after administration of CM. One patient suffered from prerenal kidney failure due to dehydration according to medical record. Two patients did not have sufficient data in their journals to confirm a recovery or not in SCr before discharge.

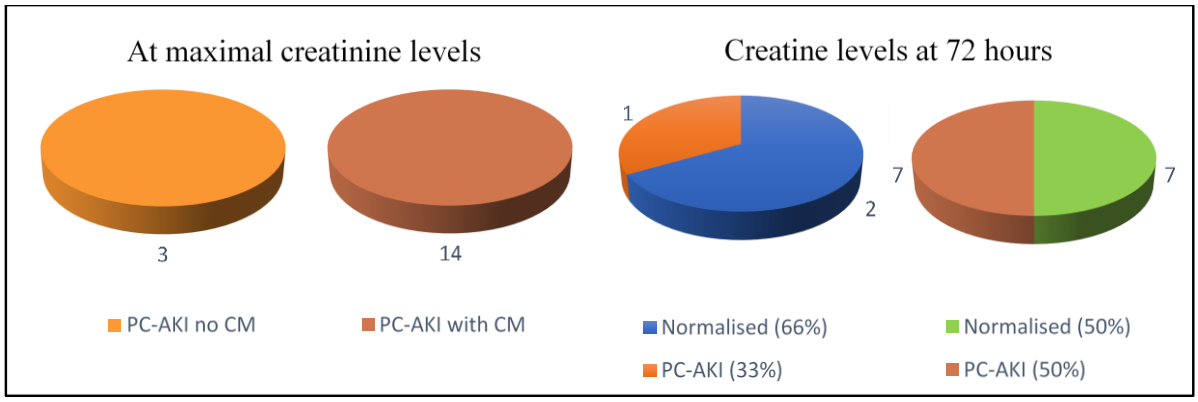

Fig. 3
Pie charts of PC-AKI/AKI patients at maximal SCr levels and at SCr levels at 72 hours

In the non-CM group (n = 33), 9.09 % (n = 3) developed AKI. Two of these patients had their SCr below the limit for AKI within 72 hours (see figure 3). For the last patient further data was missing. For both PC-AKI/AKI-groups the SCr mean initially increased with a subsequent decrease within the 0-72 hours (see figure 4).

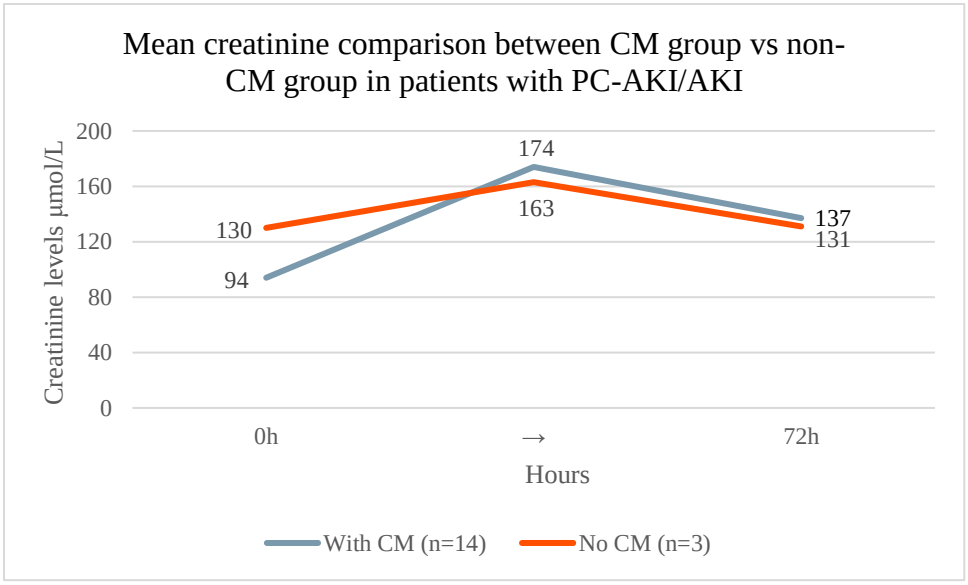

Fig. 4
Comparison of mean creatinine levels at 0-72 hours in patients administrated/not administrated contrast media during CT. n = Number of patients CM = Contrast media. PC-AKI = Post contrast acute kidney injury. AKI = Acute kidney injury.

Most patients that developed PC-AKI had a decrease in their SCr values within 72 hours (n = 10 in CM group, n = 2 in non-CM group). The remaining patients that developed PC-AKI had no decrease due to that their highest SCr value was also their last measured SCr value (n = 4 in CM group, n = 1 in non-CM group).

In between the PC-AKI/AKI-groups there was a higher total percentage of patients affected in the non-CM group, 9.09 % versus 5.56 % in the CM group. The demographics within the two groups with PC-AKI/AKI showed higher mean age and RTS as well as a lower eGFR and ISS in the PC-AKI-group. The incidence of pre-existing diseases was also more frequent within the PC-AK- group (see table 3).

Table 3: Study population characteristics with PC-AKI/AKI

	All patients with PC-AKI		CM group + PC-AKI		Non-CM group + AKI	
	N (%), mean ± SD	Mdn	N (%), mean ± SD	Mdn	N (%), mean ± SD	Mdn
No. of patients	17 (100)	-	14 (82.35) (5.56)	-	3 (17.65) (9.09)	-
Age (y)	63 ± 25.12	63	59 ± 25.8	68	81 ± 9.5	81
Age group						
– 18-74	10 (58.82)	-	9 (64.29)	-	1 (33.33)	-
– 74 and >	7 (41.18)	-	5 (35.71)	-	2 (66.66)	-
eGFR pre-CT	60.9 ± 21.52	60.9	65.4 ± 19.88	63	40.0 ± 18.36	32
RTS	6.814 ± 1.701	6.841	6.728 ± 1.826	7.841	7.216 ± 1.081	7.841
ISS	24 ± 18.5	24	27 ± 19.7	21	15 ± 4.9	17
AIS	3 (17.65)	-	2 (14.29)	-	1 (33.33)	-
Diabetes	4 (23.53)	-	3 (21.43)	-	1 (33.33)	-
CHF	4 (23.53)	-	3 (21.43)	-	1 (33.33)	-
Pre-ex. KF.	3 (17.65)	-	2 (14.29)	-	1 (33.33)	-

No. = number, percentage in parenthesis. ± SD = Standard deviation. Mdn = Median. (y) = Years.
eGFR = Estimated glomerular filtration rate. RTS = Revised trauma score. ISS = Injury Severity Score.
AIS = Abbreviated Injury Score. CHF = Congestive heart failure. Pre-ex. KF = Pre-existing kidney failure.

Risk factors for PC-AKI such as DM, CHF, pre-existing kidney failure, AIS, age, eGFR, RTS and ISS were analysed in the CM group as the risk in odds ratio (OR) within the PC-AKI group compared to the group that did not develop PC-AKI. In crude OR CHF, kidney failure, AIS and ISS came out as significant (see table 4). In adjusted multiple OR CHF, AIS and ISS was significant.

Table 4: Risk factors PC-AKI compared to no PC-AKI. Adjusted and crude OR.

	Adjusted multiple OR	95 % CI	P-value	Crude OR	95 % CI	P-value
DM	2.111	0.326-13.681	0.433	3.144	0.807-12.247	0.099
CHF	12.386	1.950-78.666	0.008*	7.841	1.824-33.705	0.006*
Pre-ex. KF	8.412	0.734-96.393	0.087	6.444	1.175-35.356	0.032*
AIS	9.112	1.146-72.460	0.037*	7.767	1.364-44.224	0.021*
Age group	2.817	0.524-15.147	0.228	2.258	0.723-7.051	0.161
eGFR	1.011	0.974-1.049	0.581	0.980	0.956-1.006	0.128
RTS	1.135	0.681-1.892	0.627	0.804	0.574-1.126	0.205
ISS	1.075	1.025-1.127	0.003*	1.054	1.019-1.090	0.002*

*OR= Odds ratio compared with those not diagnosed with PC-AKI. CI = Confidence interval. *Significant, P≤ 0.05. DM = Diabetes. CHF = Congestive heart failure. Pre-ex. KF = Pre-existing kidney failure. AIS = Abbreviated Injury Score. Age group ≥ 75 compared to age group 18-74. eGFR = Estimated glomerular filtration rate. RTS = Revised trauma score. ISS = Injury Severity Score.*

Further adjusted multiple OR, including all factors with p-value below 0.25, gave significant results in CHF, pre-existing kidney failure, AIS and in ISS (see table 5).

Table 5: Risk factors PC-AKI compared to no PC-AKI

	Adjusted multiple OR	95 % CI	P-value
CHF	12.840	2.213-74.504	0.004*
Pre-ex. KF	10.015	1.407-71.277	0.021*
AIS	7.537	1.013-56.108	0.049*
Age group	1.990	0.499-7.936	0.330
ISS	1.066	1.027-1.107	0.001*

*OR = Odds ratio compared with those not diagnosed with PC-AKI. CI = Confidence interval. *Significant, P ≤ 0.05. CHF = Congestive heart failure. Pre-ex. KF = Pre-existing kidney failure. AIS = Abbreviated Injury Score. Age group ≥ 75 compared to age group 18-74. ISS = Injury Severity Score*

Several patients had undergone multiple CT-scans with multiple CM-administration. If performed within 72 hours after each other, these repeated CT scans were counted as multiple scans. The SCr values were measured prior to the first CT and within 72 hours after the last examination. In the group of single performed CT-scans (n = 216) 5.56 % developed PC-AKI (n = 12). In the group of double performed CT-scans (n = 33) 6.45 % developed PC-AKI (n = 2). In the groups with 3 or more performed CT-scans (n = 3) no patient developed PC-AKI (see figure 5).

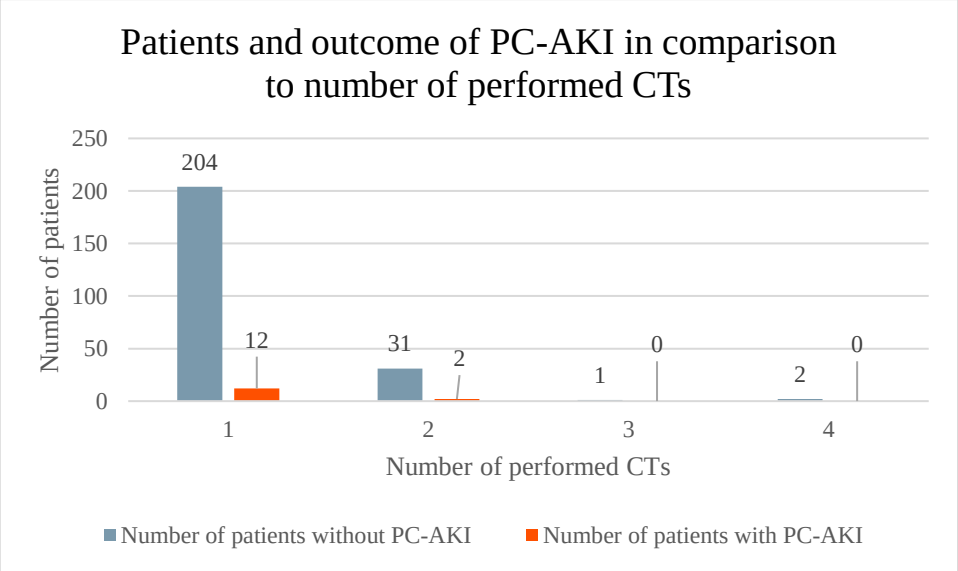

Fig. 5

Comparison of number of performed CTs and outcome of PC-AKI. CT = Computed tomography. CM = Contrast media. PC-AKI = Post contrast acute kidney injury.

6. Discussion

6.1 summary of main results

This study showed a 5.56 % incidence of PC-AKI in the CM group after contrast-enhanced CT (n = 14), and a 9.09 % incidence of AKI in the non-CM group after CT without administration of CM (n = 3) in patients at SU after trauma. These results are in accordance to other recent studies of the incidence of PC-AKI in contrast-administrated patients [3, 41, 42]. No statistical test was done to test for significance between these two groups as the patient material was insufficient in numbers. Although not tested for significance the result indicates that AKI is prevalent in both groups, administrated CM or not, and could be caused by other underlying factors than CM.

Significant risk factors, both in crude and adjusted OR, were pre-existing CHF and kidney failure as well as higher scores in ISS and AIS ($p < 0.005$). CHF, kidney failure and a higher score of ISS are known risk factors and often included in other studies [3, 10, 43, 44]. The AIS in the PC-AKI/AKI affected patients, both in the CM group and in the non-CM group, was equally at 3 points. The mean of AIS in the CM group was 2.8 (n = 5), and in non-CM group 3 (n = 1). Due to the small numbers of affected patients in this study, and the fact that AIS correlates with a higher score in ISS, it is hard to conclude if kidney trauma itself is the cause of AKI or not. Although the confidence interval (CI) is wide for most of the factors, the significance in both crude and adjusted multiple OR shows that there is a correlation between these factors and the risk of developing PC-AKI.

There was no statistically significant difference in DM, age, eGFR or RTS within the patients in the CM group that developed and not developed PC-AKI. Overall, the patient group that developed PC-AKI was older, had a higher ISS, a lower eGFR as well as RTS compared to the patients that did not develop PC-AKI.

Double administrations of CM seemed to marginally increase the risk for PC-AKI in the

patient group with double scans whereof 6.45 % (n = 2) developed PC-AKI compared to 5.56 % of the patients with single scans (n = 12).

Most PC-AKI/AKI-patients lowered their SCr values within 72 hours, except those whose highest SCr values also was their last measured values within 72 hours. Many of the PC-AKI/AKI-patients SCr levels were normalised within 72 hours (n = 7 + 2) and within a week most of the patients were back to baseline SCr values (n = 10 + 2). This indicates that an elevation in SCr is usually temporary and will often return to baseline within a few days which is similar to established data [21]. Only one patient with PC-AKI was treated with dialysis (CRRT), this after being diagnosed with rhabdomyolysis due to trauma.

6.2 Methodological considerations

This retrospective single centre study, which limits patient material, carries a risk for a several confounding factors that should be taken into account, such as low patient numbers and selection of patients, personal clinical assessments etcetera. A prospective multicentre study would have a greater coverage and would also provide results more applicable to other centres.

One of the ethical issues trying to illuminate the effect of CM in the risk of developing PC-AKI, is that the trial cannot be blinded. The patients cannot be declined the examination they need. Hence there is a potential risk of selection bias between the patient groups that receives and not receives CM. To tackle this problem the analytic technique of propensity score matching can be used. Combined with logistic regression and integration of the known risk factors for PC-AKI, including CM, this will give a propensity for each patient to end up in one of the groups, CM or no CM, and in that way compensate for eventual bias by comparing patients with equal propensity scores from each group [11].

Our patient group numbers were additionally not evenly balanced between the CM and the non-CM groups and therefore influences the reliability of the results between the groups. Due to the low patient numbers that developed PC-AKI/AKI no statistical test was applicable to test

for significance of the risk of PC-AKI/AKI between these groups. This makes it hard to draw any final conclusions for the incidence of PC-AKI/AKI although presence in both groups. With a larger patient material these statistical tests would be applicable. The presence of PC-AKI/AKI in both groups is of importance as it shows another cause than CM as the underlying causes of AKI in the non-CM group. Differences in pre-existing diseases, injury severity, clinical assessments of the benefit of CM in these patients or other existing factors that result in AKI without the exposure of CM can be the underlying cause. Further, characteristics between the groups that receives and not receives CM should be investigated to examine the cause of AKI present in both groups.

One factor that is often overlooked in the debate of PC-AKI is the fact that SCr levels naturally fluctuates during the day. More frequent sampling of SCr levels would reduce the risk of this to affect results.

Another weakness of this study was the number of patients that did not meet the inclusion criteria. The main cause of exclusion was due to discharge within 48 hours after arriving to hospital and the lack of laboratory data. In a future study this could be improved with follow-up in patients who were discharged within 48 hours and to measure their SCr in ambulatory clinics. A higher frequency of more laboratory samples would also help to allow a more robust material to analyse.

The significance of ISS as a risk factor for PC-AKI illustrates the need for measuring myoglobin in coming studies, especially within trauma patients, as rhabdomyolysis itself increases the risk of kidney failure [45]. There was not sufficient data registered on myoglobin levels to include this in the study.

One question that was not covered in this study was if the patients was given any preventive treatment to minimize the risk of side effects when administrating CM. Administrating IV fluids, isotonic sodium bicarbonate or giving oral acetylcysteine are examples of methods that

has been tested to lower the total risk of kidney related events which have been discussed in other papers [46, 47]. This would also be interesting to investigate in a future study.

7. Conclusions

This study showed an incidence of PC-AKI in 5.56 % of trauma patients given CM during CT. The incidence for PC-AKI was actually higher, 9.09 %, in patients not given CM. The reason to this higher incidence can only be hypothesized. Pre-existing diseases, higher age, nephrotoxic drugs, and dehydration can be part of the explanation, but these factors also contribute to the incidence of AKI in the CM group.

If the risk of PC-AKI is due to the CM itself or if other factors are more important is still unknown and needs to be investigated further. Prevailing evidence is not sufficient or concordant enough to draw definitive conclusions from. Obtaining knowledge of PC-AKI and prevent its impact on trauma patients is of great importance and relevance and can improve patient safety and potentially improve cost utilizations in health care.

The result of this study shows that there is a need for further research. A larger prospective study, preferably multi-centred, should be considered. The question remains if there is an increased risk of PC-AKI when using CM for CT. And if so, are there any potential avoidable risk factors or preventive methods that could be taken into considerations to avoid this situation?

Populärvetenskaplig sammanfattning

Förekomsten av akuta njurskador efter kontrastmedel hos traumapatienter på ett svenskt traumacenter

Kontrastmedel används rutinmässigt vid till exempel skiktröntgen och MR. Det injiceras vanligtvis in i vener och sprids från blodbanan ut i kroppens vävnader för att slutligen utsöndras via njurarna. Kontrastmedlet förtydligar kroppens organ och vävnader, men även skador och förändringar.

Samtidigt som röntgenstrålarna upptäcktes runt 1900-talets början förstod man att det gick att framhäva kroppens vävnader genom att tillföra ett mer röntgentätt ämne. Tidiga blandningar var dock så giftiga att de enbart användes i kadaver och djur. Sedan dess har man gjort stora framsteg och utvecklat kontrastmedlet för att minska dess risker. Trots detta finns det fortfarande frågetecken kring kontrastmedel och dess eventuella biverkningar. Från 1950-talet och framåt har kontrastmedlet diskuterats fram och tillbaka. Debatten startade när svårt sjuka patienter drabbades av försämrad njurfunktion och i värsta fall njursvikt efter att de fått kontrastmedel. Det verkade finnas en ökad risk hos de patienter som redan före administration av kontrastmedel hade dåliga njurvärden. Dagens kontrastmedel går dock inte att jämföra med de som användes under 1950-talet. Fortfarande gäller försiktighetsprincipen för patienter med nedsatt njurfunktion för att undvika eventuella komplikationer vid undersökningar med kontrast. Detta gäller till exempel äldre patienter, diabetiker etcetera. Men de senaste decennierna har det kommit studier vars resultat inte överensstämmer med synen att kontrastmedel skulle ge en ökad risk för njursvikt. Dessa rön ligger till grund för denna studie.

Genom att gå igenom journalmaterial från 2018 för alla patienter som inkommit akut till Sahlgrenska som allvarligt skadade patienter hoppades vi få en bättre överblick av hur kontrastmedel påverkar dessa patienter. Risken med att undvika att ge kontrastmedel till denna patientgrupp är att diagnosen fördröjs och därmed även behandlingen. I längden riskerar detta att ge en försämrad patientsäkerhet samt en högre totalkostnad för vården.

Totalt inkluderades 285 patienter. Trettiotre patienter genomgick en skiktröntgen utan kontrastmedel och användes som en jämförelsegrupp. Vi undersökte hur många som drabbades av försämrade njurvärden timme 0–72, men även vilka riskfaktorer som existerade innan undersökningen, såsom ålder, diabetes, hjärt- och njursvikt samt hur allvarligt skadade patienterna var.

Resultatet visade en relativt låg förekomst (5,56 %) av njurpåverkan hos patienter som fått kontrast, i jämförelsegruppen var förekomsten högre (9,09 %). Hjärt- eller njursvikt ökade risken för njurpåverkan men även svåra skador samt en direkt njurskada gav en ökad risk. Den akut försämrade njurfunktionen var oftast tillfällig och hade vanligtvis normaliserats inom en vecka. Det begränsade patientunderlaget måste tas med i helhetsbedömningen av vilka slutsatser man kan dra och hur till tillförlitliga resultaten är.

Vår slutsats är att det är svårt att påstå att kontrastmedlet i sig är orsaken till akut njurpåverkan. Därför behöver man titta närmare på möjliga underliggande orsaker till akut njurpåverkan utöver kontrastmedel, så som sjukdomar och andra riskfaktorer. Man bör även undersöka vilka patienter som får, och vilka som inte får kontrast. Det finns alltså ett behov av större framtida studier inom svensk sjukvård vars resultat kan ligga till grund för eventuella ändringar av nuvarande riktlinjer.

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