Thesis

"The Impact of Preoperative Crystalloid Bolus on Acute Kidney Injury in Non-Cardiac Surgery: A Retrospective Study"

A Sub-Analysis of preliminary data from the prospective study 'Effect of Pre-operative Intravenous Crystalloids on Post-Induction Blood Pressure'

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Graz, 16.04.2025 Karim Lionel Bouzenna m.p.

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Zusammenfassung

Fragestellung: Die akute Nierenschädigung ist eine perioperative Komplikation. In der wissenschaftlichen Literatur zeigt sich wiederholt eine Assoziation zwischen der Inzidenz von akuter Nierenschädigung sowie perioperativer Hypotonie. Es ist unklar, ob eine präoperative Flüssigkeitsgabe einem perioperativen Blutdruckabfall und in weiterer Folge einem Nierenschaden entgegenwirken kann. Ziel dieser Arbeit ist es, retrospektiv mit präliminären Daten zu analysieren, ob die Intervention, also die präoperative Gabe eines kristalloiden Flüssigkeitsbolus, in der zuvor durchgeführten prospektiven Hauptstudie zu einer verringerten Inzidenz von akuten Nierenschäden geführt hat. Aufgrund unterschiedlicher pathophysiologischer Mechanismen bei der Entstehung von akuter Nierenschädigung bezieht sich diese Studie nur auf nicht-kardiale Operationen.

Methodik: Im Hinblick auf die Interventions- und Kontrollgruppe der Hauptstudie wurde eine retrospektive Kohortenstudie durchgeführt. Hierfür wurden Patient*innendaten der Hauptstudie im Zeitraum vom 02.11.2021 bis zum 28.08.2023 untersucht. Als primärer Endpunkt wurde die Inzidenz der akuten Nierenschädigung durch einen Anstieg des Serumkreatinins von 0,3 mg/dL innerhalb von 48 Stunden nach der Operation definiert. Die 30-Tage-Mortalität, der Bedarf von Nierenersatztherapie sowie die Dauer des Krankenhausaufenthaltes wurden als sekundäre Endpunkte mituntersucht. Die gesammelten Daten wurden deskriptiv aufgearbeitet und mit den jeweiligen statistischen Testverfahren analysiert. Auch die Assoziation von Alter, Geschlecht und Komorbiditäten mit der Inzidenz von akuter Nierenschädigung wurde mittels logistischer Regression überprüft.

Ergebnisse: Von 227 untersuchten Patient*innen konnten 147 in die Studie eingeschlossen werden. Insgesamt erlitten 18 Patient*innen eine akute Nierenschädigung. In der Kontrollgruppe lag die Inzidenz bei 15,85 %, in der Interventionsgruppe nur bei 7,69 %. Dieser klinische Unterschied zeigte kein signifikantes Ergebnis im Chi-Quadrat-Test ($p = 0,134$). Auch für die sekundären

Endpunkte sowie für die Assoziation von Alter, Geschlecht und Komorbiditäten konnte kein signifikantes Ergebnis festgestellt werden.

Interpretation: Obwohl eine Tendenz zu einer Assoziation von präoperativer Flüssigkeitsgabe und einer erniedrigten Inzidenz von akuter Nierenschädigungen erkennbar ist, konnte kein signifikantes Ergebnis festgestellt werden. Um die Fragestellung weiter zu erforschen, braucht es prospektive, randomisierte und zu der Fragestellung angepasste Studien mit ausreichender Fallzahl.

Abstract

Aim: Acute kidney injury (AKI) is a known perioperative complication. The scientific literature shows an association between the incidence of AKI and perioperative hypotension. It is unclear whether preoperative fluid administration can counteract a perioperative decrease in blood pressure and subsequently reduce the incidence of AKI. The aim of this study is to retrospectively analyse whether the intervention, i.e. the preoperative administration of a crystalloid fluid bolus, led to a reduced incidence of AKI in the previously conducted prospective main study. Due to different pathophysiological mechanisms in the development of AKI, this study refers only to non-cardiac surgery.

Methods: A retrospective cohort study was conducted with regard to the intervention and control groups of the main study. For this purpose, patient data from the main study were examined in the period from 02.11.2021 to 28.08.2023. The primary endpoint was defined as the incidence of AKI due to an increase in serum creatinine level of 0.3 mg/dL within 48 hours after surgery. As secondary endpoints the 30-day mortality, the need for renal replacement therapy and the length of hospital stay were investigated. The collected data were processed descriptively and analysed using the respective statistical test methods. The association of age, gender and comorbidities with the incidence of AKI was also analysed using logistic regression.

Results: Of the 227 patients analysed, 147 were included in the study. A total of 18 patients suffered an AKI. The incidence in the control group was 15.85% and only 7.69% in the intervention group. This clinical difference did not show a significant result in the chi-square test ($p=0.134$). Also no significant result was found for the secondary endpoints or for the association of age, gender and comorbidities.

Interpretation: Although a tendency towards an association between preoperative fluid administration and a reduced incidence of AKI is recognisable, no significant result was found. Prospective, randomised studies with a sufficient number of cases are needed to investigate this question further.

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1 List of Abbreviations

Abbreviation	Meaning
AKI	Acute kidney injury
ADQI	Acute Dialysis Quality Initiative
ARF	Acute renal failure
ASA	Classification of American Society of Anesthesiologists
BMI	Body mass index
BUN	Blood urea nitrogen
CO	Cardiac output
Δp	Pressure difference
D	Diffusion coefficient
e.g.	For example
F	Blood flow
GFR	Glomerular filtration rate
HR	Heart Rate
H0	Null hypothesis
H1	Alternative hypothesis
i.e.	That is
ICU	Intensive care unit
IOH	Intraoperative hypotension
JGA	Juxtaglomerular apparatus
LKH	Landeskrankenhaus
MAP	Mean arterial pressure
MINS	Myocardial injury after noncardiac surgery
PaO2	Partial pressure of oxygen
POQI	Perioperative Quality Initiative
Q	Power of the flow
RBP	Renal backpressure
RBF	Renal blood flow

RFP	Renal filtration pressure
R	Total systemic resistance
r	Radius
Scr	Serum creatinine
SD	Standard deviation
SV	Stroke volume
VSMC	Vascular smooth muscle cells
π	Pi

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4 Introduction

4.1 Physiology of Blood Pressure, Circulation and Perfusion

In large multicellular organisms like the human body, simple diffusion cannot meet the metabolic needs. Therefore, the circulation system is essential for survival, supplying the cells with oxygen, nutrients, hormones (and medication), while transporting the waste products to their elimination. Circulation also plays a key role in thermoregulation. (1)

The vascular system can be subdivided into a high-pressure system (left heart and arteries), and a low-pressure system (veins, lung vessels, and right heart, left atrium) including the capillaries, where metabolic exchanges happen. The heart pumps about 70-80 millilitres (ml) of blood per beat, called stroke volume (SV), 60-80 times per minute, called heart rate (HR) through both systems. SV multiplied by the HR equals the cardiac output (CO), which is a direct parameter of metabolic demand. To enable a demand-based, economic distribution of the CO, the resulting SBP is usually over 100 mmHg. (2)

The blood flow follows the laws of physics with a driving arterial-vein pressure difference of 95 mmHg between the left heart and the vena cava. Ohm's law describes that the power of the flow (Q) depends directly on the driving pressure difference (Δp) and indirectly on the total systemic resistance (R) (1,2):

$$Q = \frac{\Delta p}{R}$$

Furthermore, resistance in an ideal vascular system depends mainly on the radius of the vessel (r) and the viscosity of the fluid (η), resulting in the Poiseuille's Equation. Considering the length of the vessel (l) and pi (π), the blood flow (F) is therefore described as (1,2):

$$F = \frac{\Delta p * r^4 * \pi)}{(8 * \eta * l)}$$

Moreover, Fick's law describes diffusion between two liquids separated by a membrane, like in capillaries. The diffusion flux (J) of a particle depends on its diffusion coefficient (D), the exchange surface (A), the distance (L), and the difference in the concentration of the particle inside the blood (c_i) and outside (c_o, inside the extracellular milieu) (2):

$$J = D*A*\frac{(c_i - c_o)}{L}$$

So, for lipid soluble or hydrophobic substances like oxygen, carbon dioxide (CO_2), and also inhalational anaesthetics, the metabolic exchange rates are perfusion-limited (3).

The regulation of the circulatory system describes the coordination of essential variables like arterial pressure, cardiac output, and total systemic resistance, to ensure organ perfusion (3).

The regulation of blood pressure can be categorised into short-term, intermediate, and long-term modifications (1). Short-term blood pressure regulation is mediated by neural reflexes and happens within seconds. The primary sensors - the baroreceptors in the carotid sinus and aortic arch - are activated by the distention of the vascular walls, raising the firing rate of afferent nerves (glossopharyngeal and vagus nerves) projecting to the nucleus tractus solitarii. Here interneurons inhibit cardioacceleratory and vasomotor areas of the medulla oblongata, decreasing sympathetic activity and therefore reducing vasoconstriction and the activity of the pacemaker cells in the heart. This results in vasodilation and bradycardia lowering the blood pressure or vice versa. (3)

Secondary short-term regulation of blood pressure depends on peripheral chemoreceptors, located close to the baroreceptors, and central chemoreceptors in the medulla. Both are primarily responsible for the regulation of ventilation. However, their neural reflex leads to vasoconstriction of the blood vessels and bradycardia, if there is a decline in arterial oxygen partial pressure (PaO_2), a rise in arterial carbon dioxide partial pressure or hydrogen ions, and fixed ventilation. While increased ventilation results in an augmented heart rate, the effects of all these

neural reflexes rely on specific neurotransmitters and the location of their receptors (see Table 1). (1)

Table 1: Different receptors with their locations, pathways, neurotransmitters and effects. (1)

Receptor	*Location*	*Neural pathway*	*Transmitter*	*Effect*
Alpha 1 (α_1)	Vascular smooth muscle cells (VSMC)	Sympathetic	Norepinephrine	Vasoconstriction
Alpha 2 (α_2)	VSMC	Sympathetic	Norepinephrine	Vasoconstriction
Beta 1 (β_1)	Cardiac pacemaker cells	Sympathetic	Norepinephrine	Tachycardia
Beta 1 (β_1)	Cardiac myocyte	Sympathetic	Norepinephrine	Increase cardiac contractility
Beta 2 (β_2)	VSMC	Parasympathetic	Norepinephrine	Vasodilation
Muscarin 2	Cardiac pacemaker cells	Parasympathetic	Acetylcholine	Bradycardia
Muscarin 2	Cardiac myocyte	Parasympathetic	Acetylcholine	Decreased cardiac contractility

Intermediate control of circulation, effective after several hours, runs through the renin-angiotensin-aldosterone system (RAAS). A decrease in arterial pressure leads to an increased release of renin, an enzyme that converts angiotensin I to angiotensin II. Angiotensin II acts as a vasoconstrictor and stimulates the synthesis of aldosterone. Both decrease the renal output of sodium chloride and water, therefore elevating the blood volume, and the blood pressure. Finally, long-term regulation of arterial blood pressure relies on the salt and water balance and requires normal kidney function. (2)

The mean arterial blood pressure (MAP) makes it possible for organs to regulate their perfusion by demand and ensures that even the most peripheral tissues are

supplied. All organs receive the same MAP and control the required blood flow by several mechanisms, that change the local resistance due to vasoconstriction or dilation. Neural mechanisms rely on the autonomic nervous system. Furthermore, there are metabolic or endothelial mechanisms that influence local blood flow. For example, a decrease of local PaO_2 or nitric oxide (NO) can cause vasodilation. (1)

The muscular tone of the arterial walls reacts to the transmural pressure. So if the arterial pressure increases and stretches these layers of the wall, a cellular response results in calcium influx and an increased myogenic tone. This myogenic mechanism, called the Bayliss effect, plays an important role in the autoregulation of the kidneys and the brain. (2)

4.1.1 Autoregulation in the Brain, the Kidneys and the Heart

The cranial perfusion pressure (CPP) can be described as the difference between the MAP and the intracranial pressure (ICP). Due to the myogenic and metabolic mechanism the blood flow can remain constant as long as the systolic arterial pressure lies between 70-150 mmHg. This is called autoregulation and ensures constant blood flow despite varying blood pressure. (1)
The perfusion of the heart depends on its muscular activity. During systole, the constriction of the myocardium results in compression of the blood vessels. Consequently, the perfusion of the left heart happens during diastole, if there is sufficient diastolic blood pressure. With augmenting heart rate, the relative time of the diastolic phase decreases, resulting in a lower metabolic supply. (2)
Another organ relying on constant blood flow for its vital function is the kidney. Here, the autoregulation secures renal blood flow (RBF) and consequently glomerular filtration rate (GFR). The afferent arterioles react due to the myogenic mechanism to an increased blood pressure with vasoconstriction. The efferent arterioles constrict to counteract hypotension. Furthermore, there is the tubuloglomerular feedback mechanism: macula densa cells sense a higher luminal sodium- or chloride-concentration as an effect of an increased GFR resulting from a higher blood pressure. Subsequently, these cells release paracrine agents, which leads to constriction of the afferent arterioles, decreasing RBF and GFR. (1)

4.2 Perioperative Hypotension

4.2.1 Definition

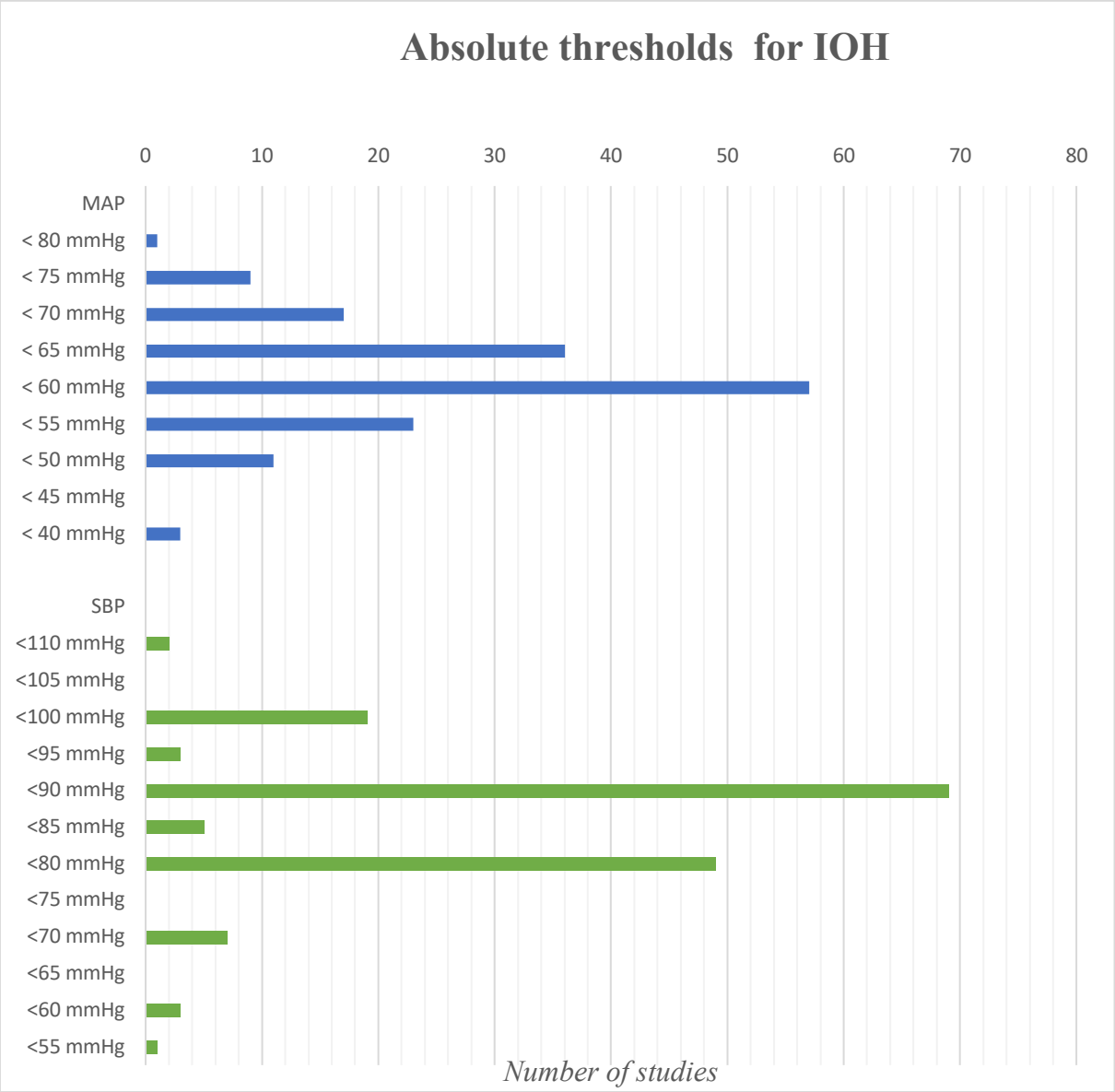
Perioperative hypotension can be categorised as pre-, intra- or postoperative hypotension (4). To estimate blood flow, organ perfusion, and oxygen delivery, anaesthesiologists monitor a patient's blood pressure as a surrogate parameter due to its ubiquitous availability and its easy and non-invasive measurement technique. (1,5,6)
Even with the lack of a universal definition for intraoperative hypotension (IOH), there is strong evidence for the association between perioperative hypotension and adverse events, namely organ injury as a function of arterial pressure severity and time. (4,7–10)
To prevent or decrease the likelihood of adverse events like myocardial injury, acute kidney injury (AKI), ischemic stroke, and death, which are associated with perioperative hypotension, there is a demand for blood pressure thresholds to guide intraoperative care (4,5). Furthermore, there is evidence for monitoring and individualised treatment of arterial pressure being beneficial for patient outcomes. (11)
Perioperative hypotension is associated with an increased 30-day mortality, and moreover, one-third of all hypotension episodes originate from the post-induction, but pre-incision period. Consequently, perioperative hypotension remains a clinically relevant and challenging topic for anaesthesiologists worldwide. (4,7,12,13)

Despite a few decades of research, there is a lack of a universal definition or an international consensus for a hypotensive threshold that the patient should not fall below during surgery (5). The difficulty of finding a universal threshold lies within the complexity of the clinical question: trying to connect a blood pressure value to an adverse event, considering the type of measurement (brachial cuff or radial arterial line, for example), the used threshold value (systolic blood pressure (SBP) vs. MAP), absolute or relative thresholds (like a 25% decrease from the baseline pressure), the uncertainty of when organ damage occurs (regarding pre-, intra and postoperative events not being independent of each other) and linking these

considerations to certain adverse events, like ischemic stroke or myocardial and kidney injury. Furthermore, the underlying reason for the hypotension and the complications of various treatments are other variables that have to be taken into account, just like patients' comorbidities and risk factors. And finally, there is the consideration that a certain blood pressure does not guarantee organ perfusion or intact oxygen delivery. (4,5)

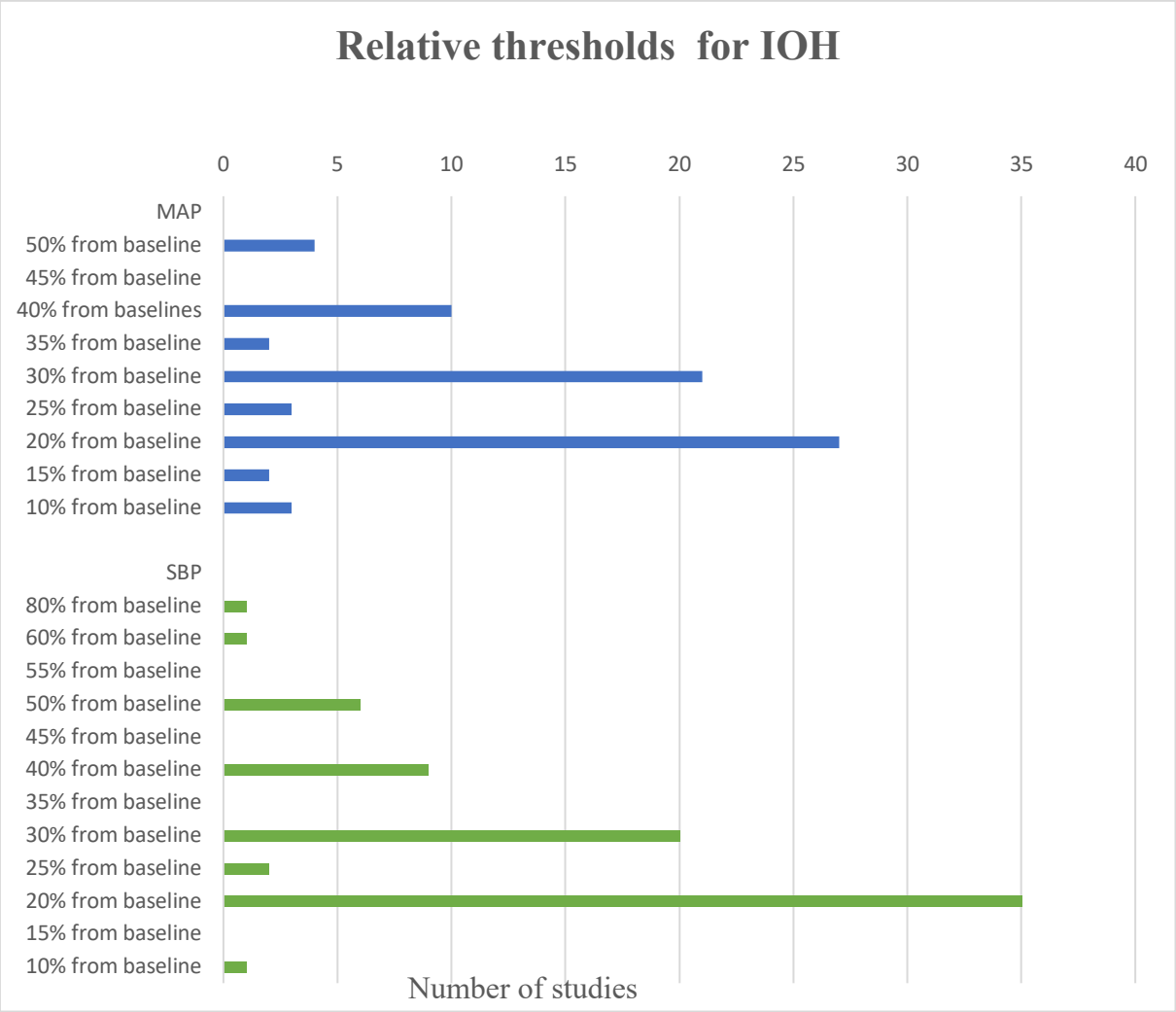
In 2007, Bijker et al. found over 140 definitions of perioperative hypotension, resulting in incidence rates from 5% to 99% in the scientific literature. (14)
In 2019, the Perioperative Quality Initiative (POQI) published a consensus statement, highlighting an SBP <100 mm Hg and MAP <60–70 mm Hg as intraoperative hypotension. Weinberg et al. published in 2022 a review, in which they investigated 318 studies for definitions of intraoperative hypotension, with the conclusion that the most frequently used definitions of intraoperative hypotension were an SBP < 90 mmHg, a MAP < 60 mmHg or a 20% decrease from the baseline measurement of either MAP or SBP. They also concluded that in studies that used absolute thresholds, there was a stronger association in detecting postoperative adverse events than in studies with relative thresholds. All in all, they emphasised that intraoperative hypotension should be defined as POQI suggested. The distribution of the used definitions is shown in Figures 1 and 2. (4,15)

Figure 1: Different definitions for intraoperative hypotension (IOH) as absolute thresholds, adapted from Weinberg et al. (15)



IOH: Intraoperative hypotension, MAP: Mean arterial pressure; SBP: Systolic blood pressure

Figure 2: *Different definitions for intraoperative hypotension as relative thresholds, adapted from Weinberg et al.* (15)



IOH: Intraoperative hypotension, MAP: Mean arterial pressure; SBP: Systolic blood pressure

4.2.2 Causes, Risk Factors, and Pathophysiology of Perioperative Hypotension

Pre- (A), intra- (B), and postoperative (C) hypotension have different causes and a variation of risk factors. However, the cause of hypotension is an important factor regarding possible adverse events. Generally, the risk of perioperative hypotension is higher in the elderly (age >50), in patients with a higher level in the Classification of the American Society of Anesthesiologists (ASA), and in

emergency settings. Hypotension can also occur in spinal anaesthesia, and is even more likely with the combination of spinal or epidural and general anaesthesia. Furthermore, there is evidence that withholding beta-blockers or angiotensin-converting enzyme inhibitors before surgery prevents adverse cardiovascular events. And that patients with chronic arterial hypertension are more likely to suffer adverse events after perioperative hypotension, as a result of the organ-dependent autoregulation being set on higher arterial pressures. (4–6,16–18)

Generally, the causes of hypotension can be categorised into three main groups (19):

1) Reduced cardiac preload
2) Reduced afterload
3) Reduced cardiac contractility

A) Preoperative hypotension, meaning a decrease in blood pressure in the post-induction but pre-incision period, is associated with diabetes, induction in head-up tilt positions, hypotension before induction (MAP < 70 mmHg), and with preoperative beta-blocker therapy or previous thyroid surgery. Also, the use of propofol, midazolam, and fentanyl as anaesthetic drugs and mechanical ventilation comes with a higher probability of hypotension. Furthermore, drugs can cause an allergic response with resulting hypotension. (16,19–22)

B) Intraoperative hypotension can be caused by blood loss, cardiac dysfunction, and due to the surgical intervention, itself. Cardiac dysfunction includes myocardial infarction, arrhythmias, and heart failure. (6,16)

C) Postoperative hypotension is poorly studied due to confounders and discontinuous measurement. It can be caused secondary to previously mentioned causes and also due to vasoplegia after cardiac surgery or due to sepsis. Furthermore, postoperative hypotension often remains undetected and, therefore, prolonged, due to broader intervals (4-6 hours) of routine vital sign assessment in surgical wards (16,23,24)

4.2.3 Complications and Adverse Events of Perioperative Hypotension

The main organs affected by perioperative hypotension are those whose perfusion depends on autoregulation, namely the brain, the heart and the kidneys. (3,23,25,26)

4.2.3.1 Cerebral Adverse Events

The main cerebral adverse events associated with perioperative hypotension are stroke and cognitive impairment, both of which are of major concern to patients. A stroke is defined as a regional or global neurologic deficit that persists over 24 hours. Reduced blood flow in ischaemic stroke can be caused by an embolus or relatively by a decreased perfusion due to hypotension. Additionally, this might worsen the damage caused by an embolus. Traditional risk factors for stroke like hypertension or atrial fibrillation add up with the risk of the surgical procedure (higher in carotid endarterectomies or surgical intervention on cardiac valves). However, there is evidence that perioperative hypotension has the largest population-attributable risk for perioperative stroke. This can be explained pathophysiologically, because hypotension can cause critically low perfusion in watershed zones of the brain. There are also considerations about a reduced threshold of functional autoregulation under the influence of anaesthetic drugs. (4,18,23,26)
Signs of cognitive impairment, usually measured by neuropsychological tests, in patients after surgery, are summarised under the term “Postoperative cognitive dysfunction”. (27,28)

4.2.3.2 Cardiac Adverse Events

Cardiac adverse events like myocardial infarction or myocardial injury are strongly associated with perioperative hypotension. A pathophysiologic explanation could be an increased oxygen supply and demand mismatch or due to an ischemia-reperfusion injury. Almost every myocardial infarction in a patient undergoing

surgery happens in the following 48 hours after the procedure. Myocardial injury occurs in over 10-20% of patients after general surgery. (23,29–32)
Myocardial injury after non-cardiac surgery (MINS) is defined as a rise in postoperative cardiac troponin concentrations that exceed the 99th percentile of the upper reference limit of the used assay. Other signs or symptoms are not required to fulfill the definition criteria, because the laboratory chemical changes are already strongly associated with short- and long-term mortality. (31,32)

4.2.3.3 Renal Adverse Events and Mortality

Perioperative hypotension is associated with acute kidney injury and has been identified as the most significant factor contributing to postoperative mortality (25,30). Wesselink et al. have reviewed 42 articles on the relationship between intraoperative hypotension, duration of hypotension and changes in odds ratio of adverse events (Mortality, MINS, AKI, Stroke) incidence in a systematic review. The results are shown in Table 2: (33)

Table 2: Association of harm with degree and duration of hypotension, using a heat map of combined data from 42 Studies, adapted from Wesselink et al. 2018 and Scott et al. 2024. (24,33)

		Odds ratio		
Intraoperative MAP Threshold	Duration In minutes	AKI	MINS	Mortality
<80 mmHg	≥1			
	≥5			
	≥10	1.02		1.02
	≥20	1.04		1.04
<75 mmHg	≥1			
	≥5			
	≥10	1.02		1.02
	≥20	1.09		1.09

<70 mmHg	≥1			
	≥5			
	≥10			1.04
	≥20			1.09
<65 mmHg	≥1			
	≥5			
	≥10		1.3	
	≥20		1.8	
<60 mmHg	≥1			
	≥5			
	≥10	1.8	1.5	
	≥20	2.3	2.5	1.2
< 55mmHg	≥1		1.3	
	≥5		1.5	1.2
	≥10	2.3	1.8	1.4
	≥20	3.5	2.5	2.0
< 50mmHg	≥1		1.3	
	≥5		4.4	2.4
	≥10	2.3	4.4	2.4
	≥20	3.5	4.4	2.4
< 45mmHg	≥1	1.6	1.3	
	≥5	1.6	4.4	2.4
	≥10	2.3	4.4	2.4
	≥20	3.5	4.4	2.4
< 40mmHg	≥1	3.8	1.3	
	≥5	3.8	4.4	2.4
	≥10	5.1	4.4	2.4
	≥20	5.1	4.4	2.4

Risk Category	Odds Ratio, Risk Ratio or Hazard Ratio
Mild	1<OR <1.4
Moderate	1.4 ≤ OR <2
High	≥2

MAP: Mean arterial pressure; AKI: Acute kidney injury; MINS: Myocardial injury after non-cardiac surgery

4.2.4 Therapeutic Management of Perioperative Hypotension

The meticulous management of perioperative blood pressure is paramount to prevent adverse events (23). The most frequently used interventions to increase arterial blood pressure are the administration of a fluid bolus, the reduction of the dose of an anaesthetic to a safe minimum, a bolus of vasopressors such as ephedrine, or a combination of these. All of them are effective regarding the augmentation of the arterial blood pressure level. Also, epinephrine or phenylephrine mixed with anaesthetic drugs can reduce post-induction hypotension. The use of two vasopressors is recommended when the target blood pressure level cannot be achieved with one vasopressor alone. Also, there is evidence for interventions like peristaltic pneumatic compression of the leg, elevating arterial blood pressure in non-critical patients. (6,21,34)

There is no consensus on which vasopressors should be used to prevent or treat perioperative hypotension. However, there are pathophysiological concerns about using purely alpha receptor agonist vasopressors due to the consideration of lower organ perfusion through vasoconstriction. Also, the effects of a certain substance on the plethora of adverse events remain mostly uncertain. (4,6)

Furthermore, there is limited evidence that individualised treatment with continuous norepinephrine perfusion until four hours after surgery could be superior to the use of an ephedrine bolus. (4,11)

In 2022, the Anesthesia Patient Safety Foundation held a Consensus Conference resulting in recommendations to address hemodynamic instability in patients. They emphasised that the optimal treatment for hypotension depends on the causes and varies between vasopressors, ionotropic substances, and fluids. (24)

4.3 Acute Kidney Injury

4.3.1 Definition

Acute kidney injury describes a syndrome characterised by a sudden decline in renal function. The term includes a variety of pathophysiologic processes resulting in a drop in GFR and retention of metabolic waste products. Therefore, in clinical practice, AKI is defined by its diagnostic criteria, indicating a loss of GFR. AKI replaces and expands the old term “acute renal failure (ARF)”. The expression ARF implies a dichotomous condition of either a healthy kidney or total organ failure. Instead, the new wording highlights current evidence that the loss of renal function is a process where even small changes are associated with adverse events. But the term injury is also criticised for its suggestion of parenchymal damage, which can be absent in AKI. (35,36)
The incidence of AKI in hospitalised patients is described in the literature as approximately 7-10%, while the prevalence in intensive care units (ICU) is up to 60%. (37,38)

4.3.2 Aetiology

The causes of AKI are summarised into three pathophysiologic categories (35):

1. Prerenal AKI involves all the reasons that lead to hypoperfusion of the kidney
2. Intrarenal or intrinsic AKI includes diseases that develop in the renal parenchyma
3. Postrenal or obstructive AKI results from obstruction of the urinary tract

However, overlap between these categories is possible, in particular renal hypoperfusion as the prerenal cause for AKI may result in parenchymal damage, leading to an allocation to intrinsic AKI. Furthermore, it appears that processes at the cellular level in renal tissues are decisive, whether systemic factors trigger AKI or not. (39)

4.3.2.1 Prerenal Causes of AKI:

The rise of nitrogen-containing molecules like urea and creatinine in the blood is called azotemia. Azotemia due to prerenal causes is therefore called prerenal azotemia. Prerenal causes of AKI involve diseases that lead to azotemia due to hypoperfusion of the kidneys, namely congestive heart failure, sepsis, volume depletion, and hemorrhage. Volume depletion is the loss of extracellular fluid due to burns, diarrhoea, vomiting, and the loss of intravascular fluid into the third space, i.e. the interstitium (edema), or into the body cavities (e.g. ascites). (35,40,41)

In sepsis and heart failure, the loss of fluid to the third space and hypotension add up to an increase in renal blood flow (RBF). (39,41)

In physiological circumstances, the kidneys receive 25% of the cardiac output with only 10% of it reaching the medulla. If the renal blood flow decreases, the filtration pressure in the glomeruli declines. There the juxtaglomerular apparatus (JGA) of each nephron reacts to reduced RBF due to stretch receptors in the vessel walls with the secretion of renin. This leads to the activation of the RAAS system. Hypotension, which can cause an increased RBF, also triggers the sympathetic system, resulting in further stimulation of the JGA due to ß1-receptors. (16,39,41)

In physiological conditions, the activation of the sympathetic system and RAAS leads to constriction of the efferent arterioles and higher resorption of sodium chloride, securing normal GFR. However, the kidney already uses 80% of its oxygen extraction to match the energy consumption of reabsorption processes. So if the GFR is secured in the process of higher sodium reabsorption, the oxygen demand rises. In pathologic conditions like sepsis, heart failure, or volume depletion, the increased Angiotensin II activity leads to a constriction of the afferent arteriole, therefore worsening renal blood flow and oxygen supply. This process can lead to azotemia without parenchymal damage. (1,35,39,41)

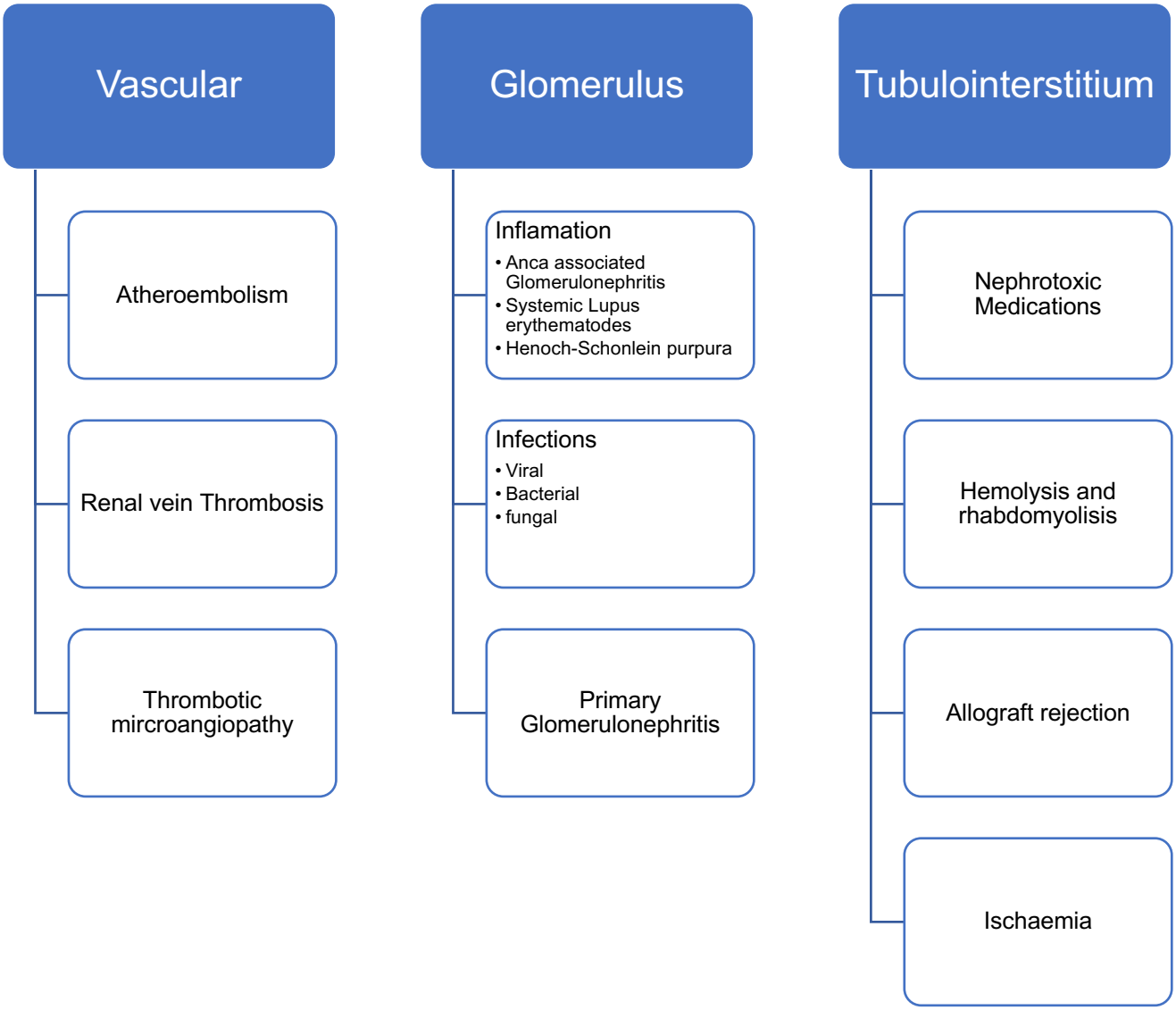
The oxygen demand-delivery mismatch triggers cellular pathways in the renal parenchyma, especially in the cells of the medulla, particularly tubular cells. Because of the low blood flow in the medulla and the oxygen shunt between afferent and efferent vessels, these cells react sensitively to ischemia, while at the same time, they are mainly responsible for sodium reabsorption. The death of

tubular cells due to hypoperfusion is called acute tubular necrosis. Therefore, hypoperfusion can lead to parenchymal damage, causing intrarenal AKI.(35,39,41) The knowledge of this pathophysiological process is mostly the result of animal studies. In clinical practice, AKI due to hypoperfusion is not verified through histopathological findings. Also, renal microcirculation is strongly influenced by its metabolic and neurohumoral mechanisms. Prostaglandins and NO for example can counteract vasoconstriction in afferent arterioles. It is not certain if hypotension initiates AKI or exacerbates intrinsic mechanisms. It is certain that prerenal azotemia is associated with higher hospitalisation rates and mortality. (37,39,41)

4.3.2.2 Intrarenal / Intrinsic Causes of AKI

Intrarenal or intrinsic causes of AKI are categorised according to the affected histopathological tissues (see Figure 3). Diseases of the vascular system can affect large vessels or small vessels and capillaries. Glomerular damage can be categorised into inflammatory or infectious processes. The renal tubular cells and the interstitium are the most commonly damaged due to hypoperfusion or nephrotoxic drugs. (35)

Figure 3: Intrinsic causes of AKI categorised by their affected tissue: vessels, glomerulus, or tubulointerstitial. (35,36)



4.3.2.3 Postrenal Causes of AKI

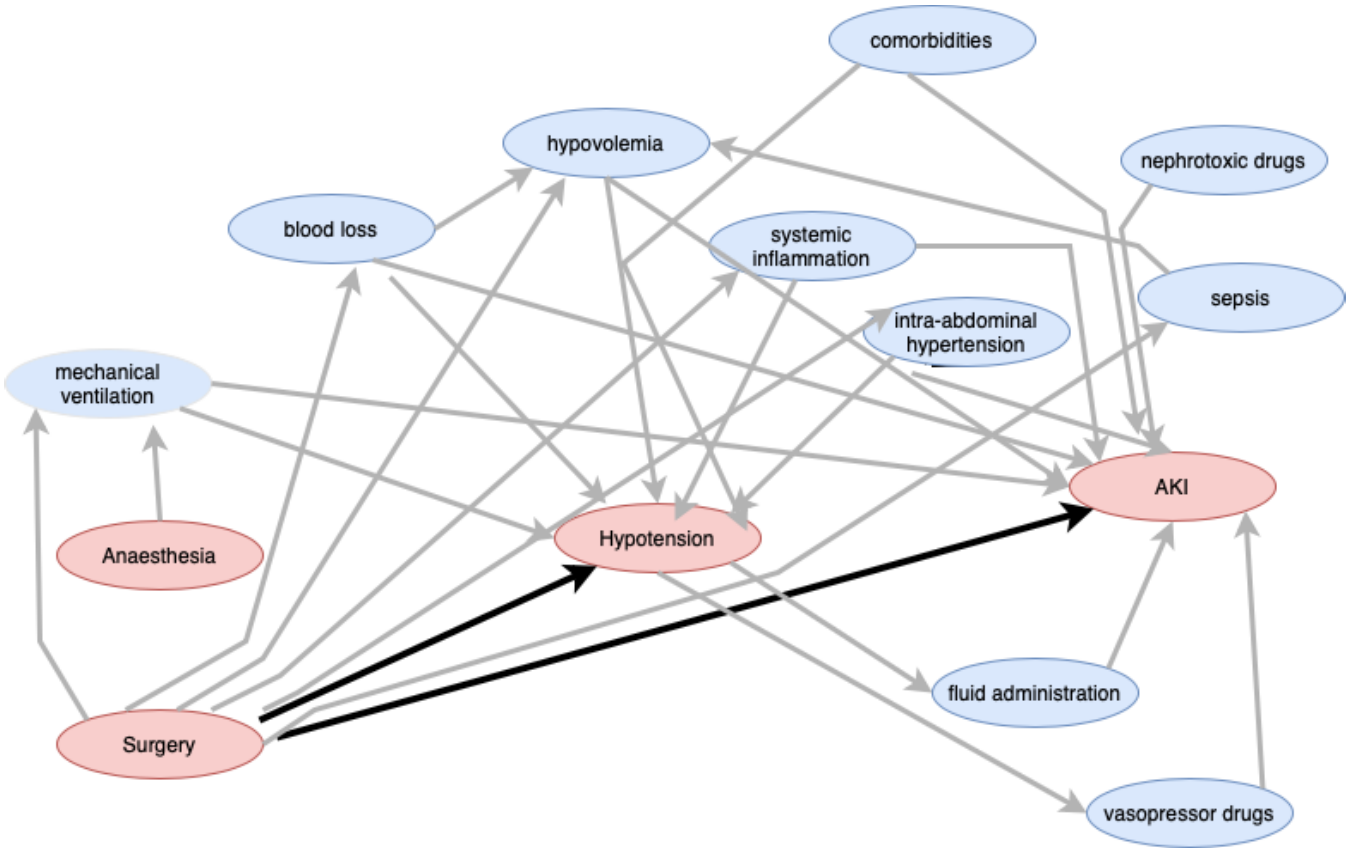
Postrenal causes of AKI are rare (5%). They can be categorised by their anatomic region.
Ureteric obstruction can be caused by external compression due to a tumor or hemorrhage or as a result of an intraluminal blockage. The lower urinary tract is commonly obstructed at the level of the Bladder neck due to calculi or carcinoma, or due to prostate hypertrophy. (35,36)

4.3.3 Postoperative Acute Kidney Injury in Non-Cardiac Surgery

The incidence of AKI in a Post-Anaesthesia Care Unit is up to 7.5%. AKI in hospitalised patients is associated with six times higher odds for death, three times higher odds for increased length of hospital stay, and approximately 7000 US dollars higher cost. Risk factors for postoperative AKI include a higher age, a higher ASA Score, emergency and high-risk surgeries, and ischaemic and congestive heart diseases. (37,42,43)

AKI due to surgery is generally associated with AKI due to hypoperfusion of the kidneys and therefore categorised as a prerenal cause. (35) In injured kidneys, the ability to autoregulate RBF is reduced, therefore, they are more sensitive to hypotension. However, there is uncertainty in scientific knowledge if hypoperfusion of the kidneys during surgery is the cause of postoperative AKI because even severe hypoperfusion alone does not result in lasting AKI in animal models. It seems that microcirculatory mechanisms could be more relevant than RBF. Also, in clinical practice, surgery features a more complex pathophysiology and multiple confounders, as shown in Figure 4. (35,44,45)

Figure 4: The association between surgery, hypotension, AKI, and multiple confounders and interactions adapted from Antonucci et al. (45)



Renal filtration pressure (RFP) results from the difference between MAP and renal backpressure (RBP). RBP correlates with the central venous pressure (CVP) and intrabdominal pressure. However, due to the dominant microcirculatory mechanism inside the kidneys, MAP is only a surrogate parameter for renal perfusion. (45)

Anaesthetic drugs, positive pressure ventilation, blood loss, hypovolemia, systematic inflammation, and intra-abdominal hypertension can reduce RBP due to a decreased MAP. Fluid overload and intra-abdominal pressure can lead to a reduced RFP due to an augmented RBP. Despite the challenges in fully explaining and proving the causal relationship between perioperative hypotension and AKI, it is a scientific consensus that hypotension is associated with AKI, and some interventional studies have also shown a reduced incidence of AKI if hypotension was avoided. (11,45,46)

4.3.4 Diagnosis of AKI

In 2002, the first international consensus for the definition of diagnostic criteria for AKI due to elevated serum creatinine (Scr) and decreased urine output was established by the Acute Dialysis Quality Initiative (ADQI). In 2004, the correlation of Scr or oliguria with the severity of AKI was categorised as risk, injury, and failure, and associated with the adverse outcomes “loss of kidney function” and “end-stage kidney disease”. These findings were published as the RIFLE-criteria by ADQI. In 2007, the Acute Kidney Injury Network (AKIN) published its criteria, associating AKI also with a small rise of Scr in a short period. In 2012, the evidence from AKIN and Rifle Criteria was combined and published as guidelines from a non-profit organisation called “Kidney Disease: Improving Global Outcome”. This progress led to a universal definition for research and a higher sensitivity and specificity in clinical practice and is described in Table 3. (35,47)

Table 3: RIFLE; AKIN and KDIGO criteria in context of definition and severity of AKI due to serum creatinine and urinary output. (35)

Definition of AKI		**RIFLE**	**AKIN**	**KDIGO**
Due to increase of Scr		>50% over <7 days	>0.3 mg/dL or >50% over <48 h	>0.3 mg/dL over <48 h or >50% over <7 days
Due to Urine output		<0.5 mL/kg/h for >6h	<0.5 mL/kg/h for >6h	<0.5 mL/kg/h for >6h
Staging[1]				
1	Increase of Scr	≥ 50%	≥ 0.3 mg/dL or ≥50%	≥0.3 mg/dL or ≥50%
	Urine Output	<0.5 mL/kg/h for >6h	<0.5 mL/kg/h for >6h	<0.5 mL/kg/h for >6h
2	Increase of Scr	≥100%	≥100%	≥100%
	Urine Output	<0.5 mL/kg/h for >12h	<0.5 mL/kg/h for >12h	<0.5 mL/kg/h for >12h
3	Increase of Scr	≥ 200%	≥200%	≥200%
	Urine Output	<0.5 mL/kg/h for >24h or anuria for >12h	<0.5 mL/kg/h for >24h or anuria for >12h	<0.5 mL/kg/h for >24h or anuria for >12h

[1] The Stages 1-3 of AKI in **RIFLE** Criteria are named **r**isk, **i**njury or **f**ailure. Furthermore, the term “**l**oss of kidney function” is used, if renal replacement therapy is needed for >4 weeks. If needed for three months the term “**e**nd-stage-kidney disease” is used. (35)

4.3.4.1 Evaluating the Function of the Kidneys

An increase in GFR is the main parameter to recognise and estimate kidney dysfunction. In clinical practice, GFR is estimated with creatinine clearance. Furthermore, creatinine clearance is estimated with formulas. The most common formulas are Cockcroft-Gault, MDRD (Modification of Diet in Renal Disease), and CDK-EPI (Chronic Kidney Disease Epidemiology Collaboration). (48–51)
To estimate GFR with Scr, a steady state of Scr is required, which is not the case in AKI due to azotemia. Therefore, the rise in serum creatinine and an increased urinary output function as surrogate parameters for kidney dysfunction, with the following limitations: (35)

Creatinine is an amino acid derivative, a waste product from muscle cells without known metabolic effects. Its serum level can rise in malnutrition or due to hard physical exercise. On the other hand, its concentration can decrease in volume depletion. Creatinine is freely filtered in the glomeruli but can also be excreted by proximal tubular cells. Its elimination decreases with advancing age and is lower in females. Despite all the influencing factors, the level of creatinine in blood correlates with GFR, especially in healthy people. But if GFR decreases, the level of creatinine in the blood rises slowly. This results in a blind space until the GFR is decreased by approximately 50%. Even then, it can take 24-48 hours to detect a significant rise. Due to the delay, a rise in creatinine indicates only, that an injury has already happened and has less of a prognostic value. (49,50)

Urea carries the metabolic waste product nitrogen. Blood urea nitrogen (BUN) rises if the GFR decreases. In prerenal AKI, RAAS activation leads to a higher reabsorption of sodium, water, and urea, while in intrinsic AKI urea and creatinine elimination are more parallel. Therefore, the BUN-Scr-ratio would be over 20:1 in prerenal AKI and approximately 10:1 in intrinsic AKI. (35)

4.3.4.2 Novel Biomarkers

There is a high demand for biomarkers that detect AKI sooner, estimate kidney damage, and have a prognostic value (35). Cystatin C and Liver Fatty-Acid - binding Protein are freely filtered in the glomerulus and reabsorbed in the proximal tubule. Neutrophil Gelatinase-Associated Lipocalin and Kidney injury molecule 1 are secreted by tubular epithelial cells in AKI. Their serum levels rise sooner than creatinine, and if detected in urine, they indicate tubular injury. (35,52–54)

4.3.5 Therapy of AKI

The management of AKI depends on its cause. As there is no evidence-based pharmacological agent to inhibit the pathophysiological processes in AKI, the focus of clinical intervention is to prevent further kidney injury and to provide supportive care regarding the complications of AKI: derangement of fluid-, electrolyte-, and acid-base homeostasis and further nutritional, gastrointestinal and infectious complications. (35)

4.3.5.1 Non-Dialytic Supportive Management

In patients suffering from AKI, nephrotoxic medication should be avoided, while drugs which are eliminated by kidneys should be reevaluated. Nutritional demand should be met, and salt and water intake should match the losses. (35)
Fluid overload can be managed by fluid restriction and diuretics. Hyperkalemia can be reduced by intake restriction or through polystyrene resins and loop diuretics. Insulin and beta receptor agonists can cause a potassium flow into the cells, while calcium can stabilise membrane potential to protect the heart from arrhythmias. Metabolic acidosis can be managed with bicarbonate. In severe anaemia, a blood transfusion is required. In hypotension due to vasodilation norepinephrine can improve mortality (35,36,55)

4.3.5.2 Renal Replacement therapy

Hemodialysis is the dissolution of fluid, electrolytes, and toxins from the blood. Absolute indications for hemodialysis are: (35)

- Therapy refractory volume overload
- Persistent hyperkalemia (>5 mmol/L)
- Severe metabolic acidosis (pH < 7.35)
- Overt uremic symptoms

In end-stage kidney disease, it should be administered continuously.
In AKI with persistent azotemia and oliguria in critically ill patients, it remains unclear when to start hemodialysis (35).

4.3.5.3 Fluid Administration

Especially in prerenal AKI the depletion of intravascular volume is recommended. The caveat is given to recognise fluid nonresponsive patients. Also, there are different opinions on which kind of fluid should be given, as presented in the following pages. (56)

4.4 Perioperative Volume Therapy

4.4.1 Physiology of Fluid Balance

The fluid inside the human body is distributed into two main compartments: intracellular and extracellular volume. Extracellular fluid can be further subdivided into intravascular or interstitial volumes. These three compartments differ in the composition of their solution. Outside the cell is an increased sodium concentration and a decreased potassium concentration. Inside the cell it is the other way around. The plasma in the vessels and the cells contains negatively charged proteins, while there are none in the interstitium. The water is mainly in the interstitium and moves passively along the osmotic gradient. (1,57)

Osmolality describes the number of osmotic active agents inside a solution. Osmosis is the ability of a molecule to attract water. The mechanism of proteins attracting water inside the vessel is called oncotic or colloid pressure. Effective osmolality refers to the new steady state, after the admission of a solution into the body. Therefore, isotonic means that after the administration of a fluid into fluid compartments, the new steady state will be the same regarding osmolality. While hypotonic refers to dilution and hypertonic to a rise in osmolality. (1)

The direction and the rate of water flux between the compartments are influenced by their osmotic state, the hydrostatic pressure, and the permeability of the dividing membrane. As the cellular membrane is not rigid, hydrostatic pressure does not matter for the flux between the interstitium and intracellular milieu. Inside the cell membrane, there are multiple transport proteins, above all, the sodium-potassium-ATPase. Therefore, the cell defends itself against shrinking or bursting, while the endothelial surface with its glycocalyx layer and its tight junctions define the permeability of the vessels. (1)

To modulate circulating volume, the sodium concentration is regulated by sodium reabsorption in the kidney. Due to RAAS, angiotensin II activates sodium transport proteins in the proximal tubular cells, while aldosterone stimulates sodium transport proteins in the distal convoluted tubules, increasing sodium reabsorption. Due to sympathetic activation, norepinephrine leads to vasoconstriction and decreases sodium reabsorption due to reduced GFR. Antidiuretic Hormone (ADH) promotes the incorporation of aquaporins into the cellular membrane in the collecting duct system of the kidneys, thereby facilitating the reabsorption of water. (1)

4.4.2 Objectives of Preoperative Fluid Administration

Initially, the main reason for fluid administration in critically ill patients is to treat or prevent hypotension due to hypovolaemia. The physiological background is explained by the Frank-Starling mechanism, which dictates that the inotropy of the heart rises with the amount of preload (until a certain level). In the further course,

fluids are given to maintain or replace total body water and electrolytes, and as carriers for medications and parenteral nutrition.
The daily demand for water in physiologic circumstances is approximately 30 ml/kg, while the requirement for sodium and potassium is about 1mmol/kg/day, to match sensible (urine, stool, sweat) and insensible losses (respiratory evaporation). (58,59)

Fluids can be categorised into crystalloid or colloid solutions. Crystalloid fluids like saline, half-saline, 5% glucose, and Lactated Ringer's contain osmotic agents that can pass through the endothelium. Colloid fluids contain osmotic agents like albumin that cannot pass through a functional endothelium. In healthy humans, only 10% of 5% glucose (solute-free water), 30% of the isotonic fluid, and approximately 100% of albumin-containing fluid remain in the vessel one hour after fluid administration. (1,56–58)

To evaluate the volume status in patients, the following should be assessed: history of volume losses, lost or gained weight, heart rate and blood pressure, respiratory rate, urinary output, and evaluation of the skin and mucosae. Furthermore, tests to evaluate patients' fluid responsiveness measure changes in SBP, central venous pressure, or heart rate after a passive leg raise, change of positioning, or fluid administration. Although fluid is the most commonly prescribed drug, today hypovolaemia and response to fluid can only be suspected in patients with a degree of uncertainty. (56,58)

Normal saline is criticised for its possibility to cause hyperchloremic acidosis, while colloid fluids can worsen the fluid situation in critically ill patients if the (colloid) osmotic agents pass the capillaries and attract fluid into the interstitium. Therefore, the most recommended fluids are balanced crystalloids. (56)

4.4.3 Complications of Fluid Administration

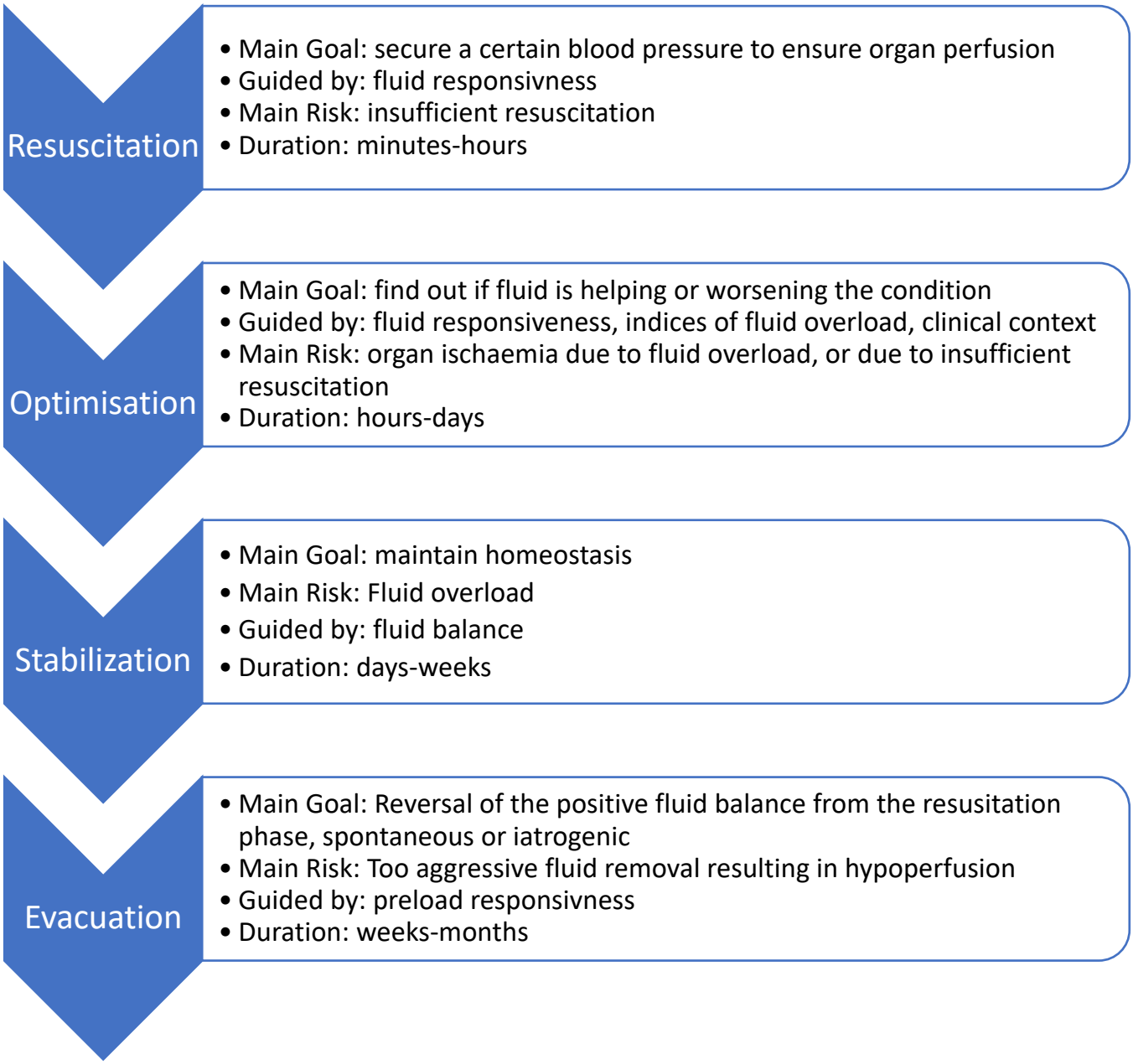
In critically ill patients, the permeability of the endothelium is affected, therefore water shifts easily into the interstitium, causing symptoms of fluid overload: (56)

- Impaired cognition due to cerebral oedema and therefore reduced cerebral perfusion pressure
- Impaired contractility (when the Frank-Starling mechanism is exceeded)
- Reduced renal blood flow and reduced GFR due to renal interstitial oedema
- Poor wound healing due to tissue oedema
- Ascites, Malabsorption, hepatic congestion
- Respiratory distress due to pulmonary oedema and pleural effusion

Therefore, fluid administration can worsen the clinical situation, particularly in the critically ill. Also, a high intravenous fluid administration rate can further damage the vessels' already-affected permeability. (56)

To regulate fluid administration in the critically ill, especially in septic shock, there is a concept of four phases, in which the patients have different needs for fluid therapy, shown in Figure 5. (56)

*Figure 5: The "**ROSE**" principle of fluid management in critically ill patients.* (56)



4.5 Research Question

Perioperative hypotension is strongly associated with adverse events like AKI. The severity and duration of hypotension correlate with augmented OR for AKI. AKI is again associated with increased morbidity and mortality. (33,60)
The pathophysiology of hypotension and AKI is complex, but preoperative fluid administration may reduce post-induction hypotension and further adverse events. The use of crystalloid solutions is common practice to maintain intravascular volume and intraoperative blood pressure. However, excessive fluid administration could result in fluid overload and impaired kidney function. (1,35)
Therefore, this study aims to evaluate the impact of preoperative crystalloid bolus on the incidence of postoperative AKI in patients undergoing general anaesthesia for non-cardiac surgery compared to the standard of care.

5 Material and Methods

5.1 Study Design

5.1.1 Main Study

The main study is a prospective randomised intervention study, which primarily deals with the effect of preoperative administration of crystalloid fluids on the time-weighted average of the mean arterial blood pressure after the induction phase with the title "Effect of Pre-operative Intravenous Crystalloids on Post-Induction Blood Pressure" (ClinicalTrials.gov Identifier NCT05079269).
In the main study, patients were randomly assigned to either the intervention group or the control group. Depending on body weight, the intervention group received a balanced, isotonic crystalloid solution within 60 (+/-15) minutes before induction of anaesthesia. Patients with a body weight of <90 kg received 500 ml, and patients with ≥90 kg received 1000 ml of fluid. The main study was fully funded by the Austrian Science Fund (FWF) [10.55776/1097-B] with 260,000 euros for both study sites (Graz and Vienna).

The following inclusion and exclusion criteria were applied:

Inclusion criteria:

1. Minimum age of 45 years
2. Major non-cardiac surgery must be planned
3. With general anaesthesia
4. ASA score > 2 (from mild to severe systemic disease that poses an ongoing threat to life)
5. Patients have at least one of the following risk factors:

a. Age > 65 years
b. History of peripheral artery surgery
c. History of coronary heart disease
d. History of stroke or transient ischaemic attack
e. Serum creatinine > 175 µmol/L (>2.0 mg/dl)
f. Diabetes mellitus treated with medication
g. Active smoking or at least 15 pack years in the medical history
h. Preoperative high-sensitivity troponin T >14 ng/L or troponin I equivalent, defined as ≥15 ng/L (Abbott assay), 19 ng/L (Siemens assay, [Borges, unpublished]), or 25% of the 99% percentile for other assays
i. B-type natriuretic protein (BNP) ≥ 80 ng/L or N-terminal B-type natriuretic protein (NT-ProBNP) ≥ 200 ng/L
j. History of atrial fibrillation
k. Chronic use of at least one antihypertensive medication

Exclusion criteria:

1. Planned Surgery on the carotid artery
2. Planned Intracranial operations
3. Planned pheochromocytoma surgery
4. Patients who require preoperative intravenous vasoactive medication
5. Acute decompensated heart failure (documented ejection fraction (EF) < 30%)
6. Chronic kidney disease (eGFR < 30 mL/min)
7. History of organ transplantation
8. Rectal surgical interventions
9. Patients receiving preoperative bowel preparation
10. Severe pulmonary edema

The main study was conducted from 02.11.2021 until 19.06.2024, at the “Landeskrankenhaus Universitätsklinikum Graz” (LKH) and at the “Allgemeines Krankenhaus” in Vienna.

5.1.2 This Substudy

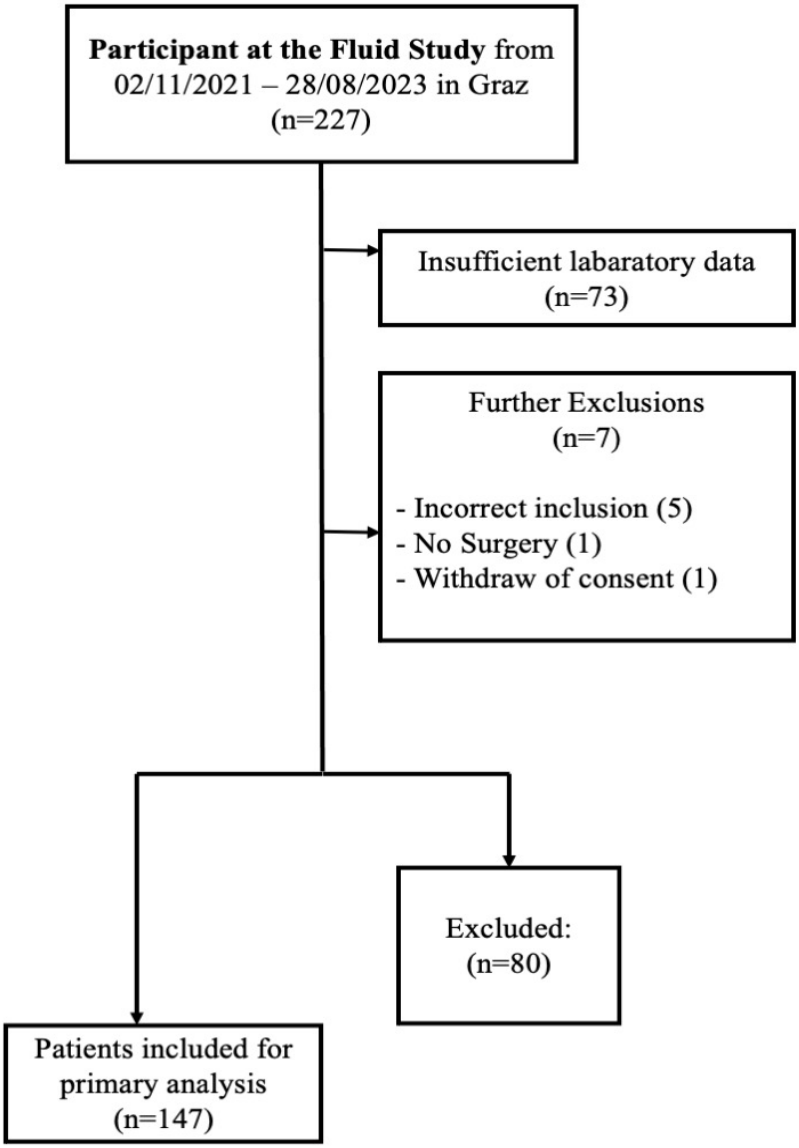
This substudy with the title "The Impact of Preoperative Crystalloid Bolus on Acute Kidney Injury in Non-Cardiac Surgery: A Retrospective Study" is a sub-analysis with preliminary data from the main study.
The primary outcome of this study is to analyse if there is a difference between the control and the intervention group from the main study regarding the incidence of the laboratory AKI criterion after non-cardiac surgery.
Secondary outcomes include the need for renal replacement therapy, length of hospital stay, and mortality. Also, subgroup analyses are performed according to the type of surgery and patient comorbidities.
Therefore, the data for this study will be obtained retrospectively from the previously conducted prospective study and analysed in a post-hoc analysis. This thesis includes only the data collected at the study site in Graz from 02.11.2021 until 28.08.2023, according to the possible data access and the scope of a diploma thesis. The recruitment of the study population is summarised in Figure 6.

5.1.2.1 Definitions

The primary endpoint (incidence of AKI) was reached when there was an increase in the patient’s serum creatinine level of more than 0.3 mg/dL within 48 h of surgery, compared to the most recent laboratory values before surgery. Therefore, the KDIGO Criteria were applied but limited to the collection of serum creatinine values, as urinary output is rarely measured outside the intensive care unit and cannot be reliably assessed retrospectively. Furthermore, a limit of 48 hours was set to maintain a temporal connection between surgery and AKI and reduce possible confounders. Also, inflammatory parameters were tracked.
The following patients were excluded from this study:

- Lack of laboratory values within 5 days prior to surgery
- Lack of laboratory values in the post-surgical period
- If the surgery was cancelled
- Regional instead of general anaesthesia was administered
- Withdrawal of patient consent after enrolment

Figure 6: The study population summarised in a flowchart.



5.2 Hypotheses of this Study

The primary null hypothesis (H0) assumes that the administration of a balanced crystalloid solution within 60 (±15) minutes before induction of anaesthesia or until surgical incision – whichever occurs first - is not associated with a reduction in the incidence of AKI in the following 48 hours after surgery. The alternative hypothesis (H1) assumes that the administration of intravenous fluid shortly before surgery reduces the incidence of postoperative AKI.

5.3 Ethics

For the execution and data analysis of the randomised intervention study, an ethics application was required at both medical universities (Graz and Vienna). The application from Graz was assessed as positive by the ethics committee for the first time on 16 September 2021 (33-520 ex 20/21) and has since been successfully extended annually until the end of the study. For this sub-study, a vote from the Ethics Committee of the Medical University of Graz was obtained. The application was submitted on 05.05.2023 and assigned the number 35-369 ex 22/23. Further documents were submitted on 22.06.2023 and 30.08.2023. In the following expedited review, no objections to the conduct of the study were noted, most recently on 06.08.2024.

5.4 Data

5.4.1 Data Collection

The following Data were used from the main study:

- Age
- Sex
- Treatment Group
- Fluid planned/received
- Time of fluid administration
- Nothing by Mouth Time
- Height
- Weight
- Body Mass Index (BMI)
- ASA-Score
- Ethnicity
- Field of Surgery

The additionally collected data from the local electronic medical records (openMEDOCS) are shown in Table 4.

Table 4: Data collected from the local electronic medical records "openMEDOCS" with their units or classification.

Laboratory values	Unit or classification	Data collected during surgery	Unit or classification	Post surgery
Leukocyte	x*10^9/L	Amount of fluid given	ml	Days at intensive care unit
Haemoglobin	g/dl	Blood loss	ml	Need for renal replacement therapy (yes/no)
Haematocrit	%	Urine production	ml	Mortality 30 days after surgery (yes/no)
CRP	mg/L	Ephedrine	mg	Length of hospital stay (days)
Potassium	mmol/L	Biorphen	ug	
Haemolysis	yes / no	Arteronol	mg	
Serum creatinine	mg/dL	Novalgin	mg	
Urea	mg/dL	Diclofenac	mg	
Uric acid	Mg/dL			
eGFR	ml/min			
Serum osmolality	mosm/kg			
Albumin	g/dL			
Procalcitonin	ng/mL			

5.4.2 Data Management

The same data management and safety measures of the main study will be applied to this analysis.

During the data collection using hospital records, a full identification was inevitable.
All stored data were pseudonymised via case numbers. The data was stored on the servers of the Medical University of Graz via the software “Nextcloud”. The data was managed using Microsoft Excel.

5.4.3 Data Analysis

Continuous variables such as length of hospital stay will be compared using a t-test if normally distributed or a Mann-Whitney U test if not. The requirement for renal replacement therapy and mortality will be compared using a chi-squared test. A p-value less than 0.05 will be considered statistically significant.

Logistic regression analysis will be used to determine the adjusted odds ratio for the impact of preoperative crystalloid bolus on the occurrence of AKI.
A regression analysis is a method for modelling the relationship between variables. Regression analysis can be used to calculate the probability that a dependent variable (also called outcome) is met, when different independent variables (also called predictors) are present. Linear regression is used when the dependent variable is scaled metric. For a dichotomous variable, such as the presence of AKI, logistic regression is the preferred method.

The significance of a regression model is indicated by the calculated p-value, in this case confirmed if $p < 0.005$. A further p-value is used to confirm the significance of the predictor. If $p < 0.005$, the effect of the predictor is considered significant.

All statistical analyses will be performed using appropriate statistical software such as R or IBM SPSS Statistics 29.

6 Results

6.1 The Study Population

A total of 147 patients from the main study population were included in this retrospective cohort study. 65 people from the intervention group and 82 from the control group were included. Table 5 compares the two cohorts in terms of the clinical characteristics of age, sex, BMI and ASA classification.

In terms of sex distribution, 43 out of 65 (66.2%) patients in the intervention group were of male sex. In the control group, 56 out of 82 (68.3%) patients were male. The similar distribution of approximately two-thirds of patients with male sex reflects the main study's population.
The mean age in the intervention group can be quantified as 68.84 years with a standard deviation (SD) of 9.614 years, while the mean age of the control group put as 69.88 years with a SD of 8.395 years. The average BMI in the intervention group was calculated as 28.09 kg/m² (SD: 5,5), compared to a mean BMI of 27.4 kg/m² (SD: 4.93) in the control group.
Most patients were classified with ASA 3, resulting in a mean ASA of 2.81 in the intervention group and a mean ASA of 2.75 in the control group.

Table 5: Demographic data compared between the fluid intervention and the control group.

	INTERVENTION/FLUID	CONTROL/SOC
PARTICIPANTS, N (%)	65 (44.22%)	82 (55.78%)
MALE, N (%)	43 (66.2%)	53 (64.6%)
AGE, YEARS **MEAN +/- SD**	69.20 ± 9.454	70.02 ± 8.389
BMI **MEAN +/- SD**	28.22 ± 5.66	27.40 ± 5.02
ASA **MEAN +/- SD**	2.78 ± 0.573	2.77 ± 0.594
ASA, N (%)		
2	19 (29%)	26 (32%)
3	41 (63%)	49 (60%)
4	5 (8%)	7 (8%)

SOC: Standard of care management; SD: Standard deviation; ASA: American Society of Anesthesiology score; BMI: body mass index

6.2 Primary Endpoint

Incidence of AKI

After formulating the above hypotheses H0 and H1, it was investigated whether the administration of fluid in the intervention group resulted in a reduction in the incidence of AKI. For this purpose, a contingency table was created, which showed that:

- of the 147 patients, 18 (12.2%) reached the primary endpoint of laboratory-detected AKI within 48 hours after surgery

- in the control group, 13 patients (15.9%) reached the primary endpoint
- in the fluid group, 5 patients (8%) reached the primary endpoint

The results are shown in Table 6 and Figure 7.
Since reaching the endpoint AKI is a qualitative, dichotomous variable measured in yes or no, and the two samples are independent, the values were analysed using a chi-squared test.
Therefore, to make a statement about the stochastic independence of fluid administration and the incidence of AKI, the expected frequencies are compared with the observed frequencies. Hereby the null hypothesis assumes that the variables are independent of each other and is favoured over the H1 hypothesis if the chi squared (χ^2) approximates 0 with a p-value under 0.05.
The chi-squared test comparing fluid administration and incidence of AKI resulted in $\chi^2 = 2.248$ with a p-value of 0.134.

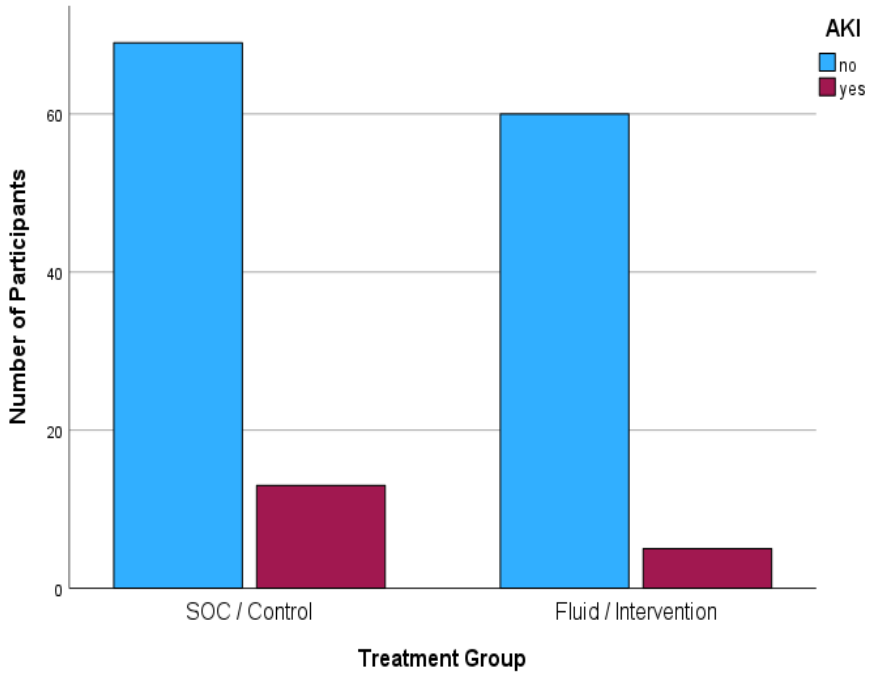
Therefore, no statistically significant difference in the incidence of AKI between the intervention group and the control group was found. The H1 hypothesis must therefore be rejected in favour of the H0 hypothesis.

Table 6: The incidence of AKI and mortality in the control- and intervention group shown as a contingency table.

	AKI		**Mortality**	
	no	yes	no	yes
Control/ SOC Number	69	13	81	1
Expected frequency	72	10	80.9	0.6
Intervention / Fluid Number	60	5	65	0

Expected frequency	57	8	64.6	0.4

Figure 7: The incidence of AKI in the control- and intervention group shown as a bar chart.



6.3 Secondary Endpoints

6.3.1 Mortality

To find out whether there is a significant difference between the intervention and control group regarding the 30-day mortality after surgery, a contingency table was created, and the observed frequencies were compared with the expected frequencies. As the expected frequencies of mortality were below five, and it is a comparison of two dichotomous variables, Fisher's exact test was used to test the following hypotheses:

H0: No difference in incidence of mortality between the groups.

H1: A significant difference in mortality between the groups.

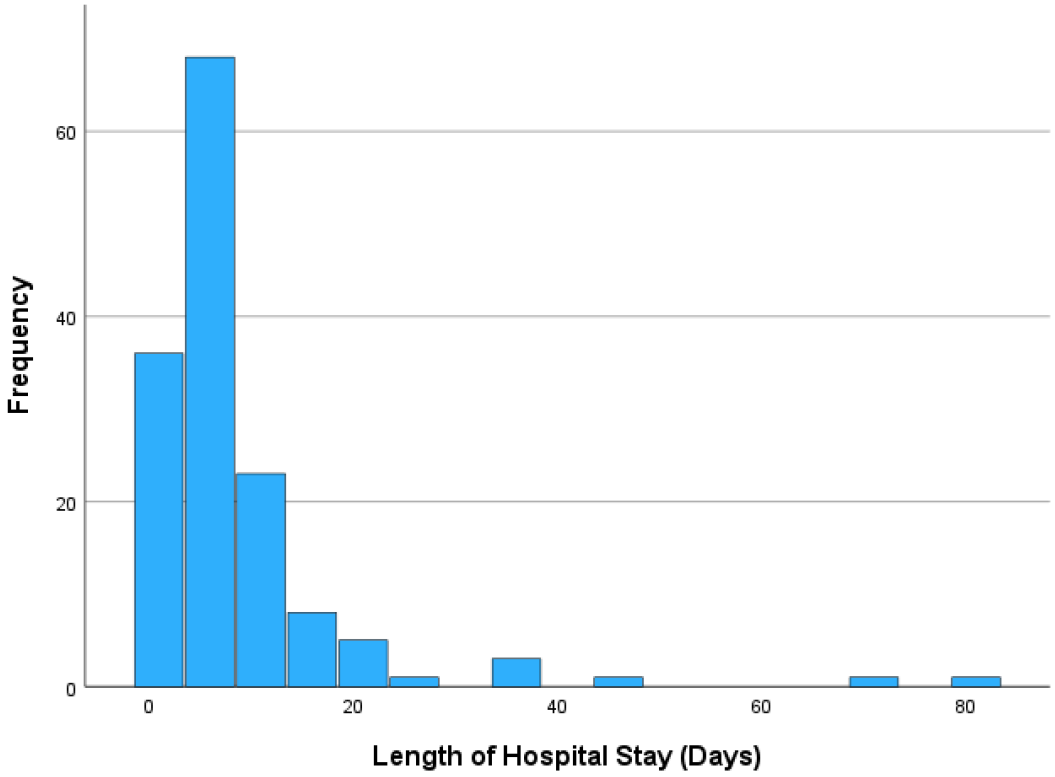
If the p-value is less than 0.05, the null hypothesis would be rejected. The results are shown in Table 6. Out of 147 patients, two died within 30 days of surgery. Both were part of the control group.
A two-side Fisher's exact test results in a p-value of 0.558, showing no significant difference between the groups.

6.3.2 Length of Hospital Stay

To find out whether the fluid administration in the intervention group has a significant influence on the length of hospital stay, the following two hypotheses were formulated:
H0 = No significant difference in length of hospital stay between the groups.
H1 = A significant difference in length of hospital stay between the groups.

With the length of hospital stay in days, a quantitative variable was analysed between two independent groups. Due to the size of the group, the Shapiro-Wilk test was used to test the length of hospital stay for normal distribution with the null hypothesis which claims that the data is normally distributed. A p-value less than 0.05 would result in the rejection of the null hypothesis. The Shapiro-Wilk test resulted in a p-value of less than 0.001. The length of hospital stay is not normally distributed, as shown in Figure 8. Therefore, the Mann-Whitney U test is used to test for a significant difference between the intervention and the control group. The test showed no statistically significant difference in length of hospital stay between both groups, $U = 2239.500$, $Z = -1.668$ and $p = 0.095$

Figure 8: A histogram showing the distribution of the length of hospital stay in days.



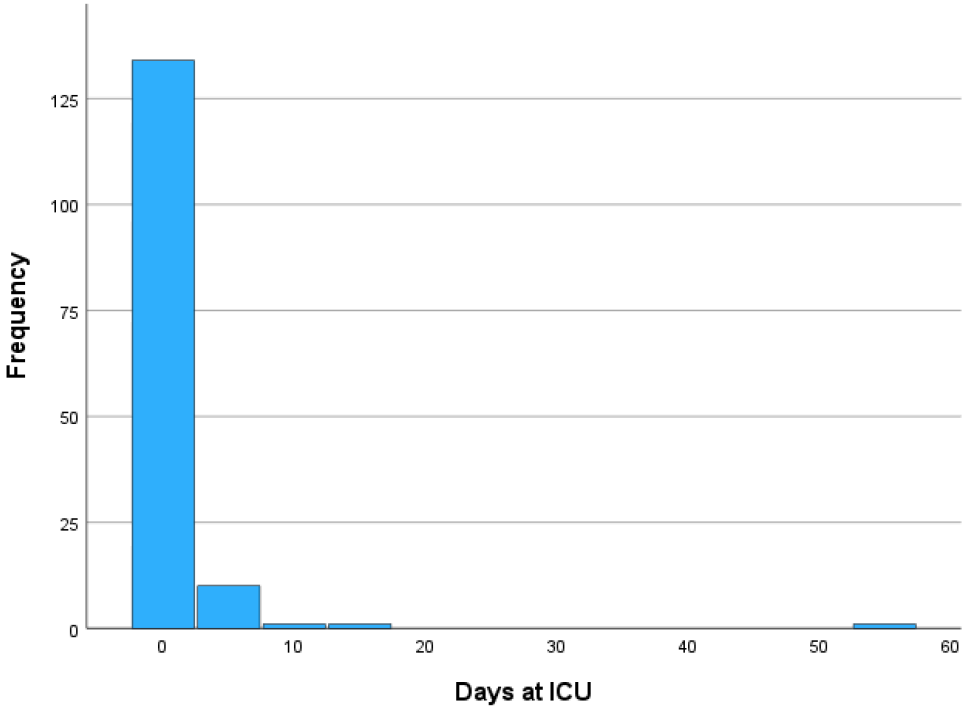
6.3.3 Days in Intensive Care Unit

To find out whether the fluid administration in the intervention group has a significant influence on the days patients had to spend at the intensive care unit (ICU), the following hypotheses were formulated:

H0 = No significant difference in days at ICU
H1= A significant difference in days at ICU

Figure 9 shows that the days at the intensive care unit are not normally distributed. The Shapiro-Wilk test came to a p-value of less than 0.001 and the Mann-Whitney U test results in no significant difference between both groups, U = 2439, Z: 0.892, p = 0.372.

Figure 9: A histogram showing the days spent at the intensive care unit.



6.3.4 Requirement for Renal Replacement Therapy

None of the 147 included patients required renal replacement therapy.

6.3.5 Subgroup Analyses

The influence of the factors age, sex and comorbidities on the incidence of AKI was analysed using logistic regression. The comorbidities were represented using BMI and ASA.

The calculated binomial logistic regression model was not statistically significant ($p = 0.993$; Nagelkerke's $R^2 = 1$).

The regression analysis for the predictors:

- Age
- Sex
- BMI
- ASA

are all resulting, with $p = 1$, in a non-significant influence on the incidence of AKI.

7 Discussion

7.1 Primary Endpoint

In this retrospective study, which investigated whether preoperative fluid administration influences the incidence of AKI, no statistically significant result was found. A presumed association between fluid administration and the incidence of AKI could therefore not be confirmed.

The intervention and control groups analysed showed no relevant differences regarding the distribution of age, gender, BMI and ASA score. This can be attributed to the randomisation that was carried out in the main prospective study. However, the control group is larger, consisting of 55.78% of participants. This is partly due to the fact that patients from the intervention group who did not receive preoperative fluids were included in the control group.
It's also noticeable that overall, there are more men than women, as on average two-thirds of the participants in both groups are of male sex. This could be attributed to the fact that more urological operations were performed than gynecological ones.

The incidence of AKI in this study was 12.24% and is therefore higher than in a study performed by Walsh et al., where the incidence of postoperative AKI in 33,330 perioperative patients was 7.4%. However, in the literature, a variable incidence of postoperative AKI is stated, with a range from 1.8-39.9% in retrospective data for abdominal procedures. Zarbock et al. investigated the incidence of AKI in 10,568 patients in 30 countries in a prospective observational study with 16% for non-cardiac surgery. (37,61)

In this context, it is also important which time period is still considered postoperative. Zarbock et al. investigated a period of 72 hours, while Walsh et al. included seven days post-surgery. Both studies compared post-surgery serum creatinine levels, with the last one measured closest to the surgery (37,61). This could lead to possible confounders. For example, a postoperative infection could

lead to sepsis, which may cause an AKI that has no direct relation to the intraoperative perfusion of the kidneys or the fluid management. On the other hand, an intraoperatively damaged kidney could be more susceptible to a septic state. Therefore, it can be assumed that the definition of the time period influences the sensitivity. But due to the not fully elucidated and multifactorial pathophysiology of AKI, as well as the delayed increase in serum creatinine in the presence of renal damage, the influence on sensitivity and consequently the definition of an exact time period is unclear.
In this study, we used a shortened version of the KDIGO criteria as we wanted to maximise the temporal correlation between the occurrence of AKI and surgery. Also, we included only patients with a serum creatinine level measured five days or less before surgery. As urine production is rarely measured on a normal ward and due to the retrospective design of this subanalysis, urinary output data were not available. Therefore, the presence of AKI was only defined by an increase in serum creatinine of 0.3 in 48 hours after surgery. This raises the possibility that we may have missed some patients with AKI.

The differences in the incidence of AKI depending on the parameter considered (serum creatinine versus urine output) were analysed by Malbrain et al. in a systematic review of 50 clinical studies. The incidence of AKI was compared depending on whether only serum creatinine, only urine output, or both were considered. The incidence of AKI with a KDGIO stage 1 was observed with a median 14% when based solely on an increased serum creatinine level, 15 % assessed by a decreased urine output alone, and 19% when both criteria were considered. A difference of 1-4% could be derived from this. However, a diagnostic error rate up to 20% is quoted from a previous study by Kellum et al. and a further subgroup analysis showed a difference of over 40% in patients older than 60 years. It is unclear whether the results from a broad hospital population can be transferred to the specific post-surgery population in this study. In our study population, however, it is important that the increase in serum creatinine is influenced by hemodilution, e.g. by fluid administration. The dilution effect in post-surgical fluid accumulation is specifically mentioned by Malbrain et al. In this context, it is noted that, in the study performed by Malbrain et al., the time to diagnosis of AKI is delayed by 2.4-46 hours when serum creatinine alone was

observed. These results would strongly affect the post-operative observation period of 48 hours in this study. (62,63)

72% of all AKI cases were in the control group, and the actual incidence of AKI was higher than the calculated, expected frequency in the chi-square test, and vice versa in the intervention group. This suggests that there may be a clinically relevant difference that was not statistically shown in the chi-square test due to the small overall group size.

Another point of consideration is the pathophysiological reasoning behind the study hypothesis. We assume that the administration of fluid shortly before surgery counteracts the blood pressure decrease after induction of anaesthesia and could consequently reduce the incidence of postoperative AKI. The blood pressure data were recorded electronically pre- and intraoperatively and processed in Vienna using the time weighted average and can only be analysed as part of the main study to maintain blinding. Therefore, the extent to which fluid administration influences blood pressure and the extent to which intraoperative hypotension influences the incidence of AKI remains a further question.
Saotome et al. induced hypoperfusion of the kidneys in animal studies and showed that not all animals (merino ewes) with severe hypotension developed AKI. They concluded that severe hypotension alone is insufficient to induce persistent AKI. (44)
The studies of Wesselink et al. and Scott et al. point out the association between hypotension and increased odds for adverse events like AKI and show that not all patients who are exposed to severe hypotension develop AKI (24,33). In the study by Saugel et al., 80% of all patients had perioperative hypotension, but only 3.4% had an AKI (64).

This suggests that there are unexplained pathophysiological mechanisms by which hypoxia caused by reduced perfusion sometimes triggers AKI and sometimes does not. While one size does not fit all describes this circumstance for interventions, we could argue that one harm does not hurt all when it comes to finding the cause of postoperative AKI.

Furthermore, we could not find a corresponding association for the hypothesis that additional fluid administration could, for example, due to fluid overload, increase the incidence of AKI.

Finally, it must be emphasised that the above-mentioned recognitions are only the findings of a retrospective study, so we did not prove the absence of a causal relationship, we only found no association between fluid administration and the incidence of AKI. However, this study can contribute to the planning of further prospective studies involving fluid administration.

Prospective studies with an appropriate study design and a correspondingly large number of cases are required to answer the questions that remain open.
Legrand et al. performed a multicenter, cluster-randomised, crossover pilot study regarding norepinephrine versus phenylephrine to treat perioperative hypotension. 3626 patients were enrolled, concluding in the feasibility of this type of study.(64,65)

7.2 Secondary Endpoints

There was also no significant difference between the two groups in terms of mortality. Overall, one person died within 30 days after surgery. In the study by Saugel et al., of 1457 patients who developed AKI within 7 days of surgery, 2% died. Zarbock et al. investigated hospital mortality (up to 90 days) and described a variable range from North American countries (4,5%) to African countries (23,9%), including only patients with the need for a high dependency unit or ICU after cardiac and non-cardiac surgery. In total, they describe a higher mortality of 8,6% (versus 1,4%) in postoperative AKI patients. (61,64)
Our findings can be attributed to the aspects that:

- the majority of study participants were not critically ill / or did not receive a major surgery with the need for intensive care (only a fifth needed care at an ICU)
- the mortality after surgery is low in modern countries

- we investigated only the 30 days post-surgery.

Also, none of the participants needed renal replacement therapy. This could be explained by the circumstance that the need for renal replacement therapy is a rare adverse event (61). However, it could be possible that there were patients in need of dialysis shortly after their surgery during our observation period, but the patients were excluded from the main interventional study to whose dataset this refers. To investigate if fluid administration influences the need for renal replacement therapy, a large number of cases would be required.

In Zarbocks et al.'s observational multicentre study, only 1.6% of all patients required renal replacement therapy. While in patients with postoperative AKI, 8.6% needed renal replacement therapy at the ICU, and even 9.5% during their hospital stay. An important consideration is that these numbers include all patients and all surgeries, while in this study only non-cardiac surgeries were included, and the above-mentioned exclusion criteria were applied. (61)

In this study, out of 18 AKI patients, two were classified as stage 2 according to KDIGO criteria, and the remaining 16 were classified as stage 1. However, French et al. showed that even an AKI at KDIGO stage 1 is associated with higher mortality and morbidity (66). In order to investigate whether an intervention changes the mortality rate, a large-scale study with correspondingly long follow-up would also be necessary.

No statistical difference was found between the intervention and control group regarding the length of hospital stay. In this context, the length of hospitalization could also be seen as a surrogate parameter for costs in the healthcare system. This finding could also be related to the fact that none of the patients required renal replacement therapy, which would prolong hospitalization. However, this finding also speaks in favor of the intervention of fluid administration regarding safety concerns.

7.3 Subgroup Analysis

In this study, no significant result was shown regarding the possible influence of age, sex, body mass index, and ASA classification on the incidence of AKI. However, it was found that 13 out of 18 AKI patients (73%) were male. While in a study performed by Saugel et al., of 1457 patients with AKI only 51.1% were male. The median age of these patients was 66 years, and they had a median BMI of 26.6 kg/m². (64)

In this study, only 8.8% of the patients had an ASA classification of 4 assigned to them, subsequently 11% of AKI patients. In the study by Saugel et al., only 2.6% of the patients were assigned an ASA classification of 4, but these represent 14.8% of patients with AKI. One can, therefore, see a tendency for the incidence of AKI to increase as the ASA score rises, even if this study cannot show a significant result. Another finding is that patients with an assigned ASA classification of 2 and 3 are also likely to develop AKI. AKI is therefore a perioperative complication that does not only occur in critically ill patients. (64)

7.4 Limitations

This retrospective cohort study benefits from the fact that it refers to the data set of a randomised prospective study. It was therefore not possible to ensure that all options for diagnosing AKI, i.e., serum creatinine, urine production, and also new markers, were utilised and observed over a larger period of time. Furthermore, the case number was too low to confirm a possible statistical significance despite a clinical trend. This leads to the fact that the incidence of rare outcomes like mortality or the need for renal replacement therapy could not be sufficiently recorded to be meaningfully statistically analysed.

A further limitation of this study is that the connection between the investigated outcome (AKI) and the actual intervention (fluid administration) could not be established via the possible perioperative change in blood pressure, as the perioperative blood pressure values were automatically processed in Vienna and

were not available due to the blinding of the ongoing main study. One pathophysiological consideration of the main study is to counteract possible hypovolemia due to preoperative fasting with fluid administration shortly before the induction period. This was not reflected in the data of this substudy. However, further findings on the association between fluid administration and the incidence of postoperative AKI in the entire study population from Graz and Vienna will be obtained from the main study.

Another potential limitation is possible confounders that were not considered in this study. For example, the use of nephrotoxic drugs, or the choice and extent of vasopressors, the blood loss during surgery and the type of procedure may be associated or causally related to the incidence of AKI.
Without exception, all study participants were of Caucasian origin, resulting in a selection / racial bias. Furthermore, the results only refer to patients of the LKH-Graz, which means that differences between different centers or countries are not taken into account.

7.5 Conclusion

To investigate whether the preoperative administration of fluid has an influence on the incidence of perioperative hypotension, the main study randomised patients into the intervention and control groups. In this retrospective cohort substudy, we included 147 patients from the main study to investigate the influence of preoperative fluid administration on the incidence of AKI. The clinical characteristics of gender, age, BMI and ASA of the patients (shown in Table 5) were equally distributed between the two cohorts. The measured serum creatinine values up to 48 hours after surgery were compared to preoperative values up to 5 days prior to surgery. According to the KDIGO criteria a rise of 0.3 mg/dl confirmed the endpoint. AKI was detected in 18 patients, which corresponds to an incidence of 12.25%. In the control group, 13 of 82 patients (15.85%) developed an AKI, which represents 72% of all AKI cases. In the intervention group, only 5 of 65 patients (7.69%) developed an AKI. The clinically increased incidence was not shown to be significant in a chi-square test. Also, for the secondary endpoints (mortality, need for renal replacement therapy, and length of hospital stay), no

significant result was found. In a logistic regression analysis, no correlation could be established between age, sex, BMI and ASA classification and the incidence of AKI. The small number of cases in this study is the main limitation for the interpretation of the results.

The most important findings of this study can be summarised as follows:

- The incidence of postoperative AKI in non-cardiac surgeries was 12.25%.
- There is a recognizable but not statistically significant association between preoperative fluid administration and reduced incidence of AKI.
- The 30-day mortality in this study population was 0.6%.
- The incidence of AKI was statistically independent of age, sex, BMI and ASA.

The conducted study aimed to investigate a possible association between preoperative fluid administration and the incidence of AKI. A clinical trend towards a reduction of AKI is visible, but not statistically significant. To investigate a possible causal relationship between the administration of fluid and the incidence of AKI, a randomised, multicentre study with an appropriate design is needed. Therefore, the findings of this study can help to optimise the planning of prospective studies in the future.

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The following tools were used to optimise the language of the text:

1. ChatGPT (Version 4.0)
    - Publisher/Provider: Open AI
    - Date the content was generated: 13.04.2025
    - Uniform Resource Locator (URL): https://chat.openai.com
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    - Uniform Resource Locator (URL): https://www.deepl.com