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RENAL DOPPLER RESISTIVE INDEX: APPLICATIONS IN PERIOPERATIVE AND CRITICAL CARE

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Renal Doppler resistive index: applications in perioperative and critical care

Thesis for Doctoral Degree (Ph.D.)

By

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To my amazing fan club at home:

Sara, Selma, and Ines.

"As long as you believe, then it is possible."
Le Professeur on his Invincibles

Popular science summary of the thesis

Renal dysfunction poses a threat to patients undergoing surgery or admitted to intensive care units, and negatively impacts survival of those affected. Early identification of these patients, or of patients at an increased risk of future renal dysfunction, is crucial to be able to optimize treatment and improve prognosis. This thesis, comprising of four scientific studies, explored the potential of a rapid ultrasound examination of the renal blood flow, known as the renal resistive index (RRI), for early detection of patients at risk of renal dysfunction after surgery or during intensive care. Additionally, the occurrence and risk factors for long-lasting renal dysfunction, or chronic kidney disease, after surgery in Sweden were investigated.

In the first study, the RRI method was used on volunteers by two non-experts and one expert. We demonstrated that the method was easy for the non-experts to learn, and therefore has the potential to be widely implemented in healthcare. In the second study, the RRI method was used on around 50 patients admitted to intensive care with COVID-19 during the first wave of the pandemic in Sweden. We discovered a link between high RRI values and acute renal dysfunction, indicating altered renal blood flow, and that the RRI method promptly could identify these patients at the bedside. In the third study, we investigated data from Swedish nationwide public authority and quality registers including almost 240 000 patients that had undergone surgery. Pronounced chronic kidney disease within the first year after surgery affected less than 1%, but we identified several important risk factors that could help recognize these patients at an early stage. Notably, those who developed renal dysfunction in the nearby period after surgery exhibited an increased risk of chronic kidney disease. In the fourth study, the RRI method was used on almost 100 patients undergoing cardiac surgery. We discovered a link between an elevated RRI value before surgery and long-lasting renal dysfunction, as well as other serious conditions such as heart attack, heart failure, and stroke, up to five years after surgery.

Overall, this thesis suggests that most physicians working with patients undergoing surgery or in intensive care effectively can learn the RRI method. RRI holds promise in identifying certain patients with acute renal dysfunction, as well as patients at an increased risk of developing chronic kidney disease after surgery. In this way, RRI may help pinpoint patients in need of extended measures aimed at minimizing the negative effects of renal dysfunction.

Abstract

Doppler-derived renal resistive index (RRI) has emerged as a promising bedside tool for assessing renal hemodynamics, and elevated values ≥0.70 have been associated with adverse outcomes in various clinical settings. This thesis explored new aspects of RRI within perioperative and critical care, as well as the epidemiology of long-term renal outcomes after surgery in Sweden.

In **study I**, we assessed the feasibility of RRI as a point-of-care ultrasound (POCUS) method. After a focused teaching session, an intermediate (resident) and a novice sonographer (medical student) performed RRI measurements in 23 volunteers, and the results were compared to measurements by an expert. Measurements by both non-experts were reliable, accurate and showed clinically acceptable precision.

In **study II**, RRI was measured in 51 patients with Coronavirus disease 2019 during the first wave of the pandemic in six intensive care units at two sites of the Karolinska University Hospital. In these patients, RRI was generally elevated, associated with acute kidney injury, and seemed to decrease dynamically with renal recovery.

In **study III**, perioperative data from 23 Swedish hospitals were matched with extensive national public authority and quality registries. Among 237 124 patients without preoperative renal dysfunction undergoing non-cardiac surgery, 0.67% developed advanced chronic kidney disease, and 7.1% developed major adverse kidney events (advanced chronic kidney disease, kidney failure, or all-cause death) within the first postoperative year. We identified several perioperative risk factors for these outcomes, including advanced acute kidney disease within 90 days after surgery.

In **study IV**, associations of preoperative RRI with long-term renal and cardiovascular outcomes were investigated in 96 patients who had undergone on-pump cardiac surgery at the Karolinska University Hospital. RRI ≥0.70 was associated with persistent renal dysfunction, major adverse kidney events (persistent renal dysfunction, renal replacement therapy, or all-cause death), and major adverse cardiovascular events (myocardial infarction, unstable angina, decompensated heart failure, stroke, or cardiovascular death) within 5 years after surgery.

In conclusion, this thesis suggests that RRI can be used as a POCUS method with implications for assessing renal outcomes in perioperative and critical care, both in the short and long term. Further, this thesis sheds light on the epidemiology and important risk factors for postoperative long-term renal outcomes. RRI may have a role as a bedside measure to identify patients with an elevated risk for such outcomes.

List of scientific papers

I. **Feasibility of renal resistive index measurements performed by an intermediate and novice sonographer in a volunteer population**
Renberg M, Kilhamn N, Lund K, Hertzberg D, Rimes-Stigare C, Bell M
Ultrasound J. 2020 May 20;12(1):28

II. **Renal resistive index is associated with acute kidney injury in COVID-19 patients treated in the intensive care unit**
Renberg M, Jonmarker O, Kilhamn N, Rimes-Stigare C, Bell M, Hertzberg D
Ultrasound J. 2021 Feb 5;13(1):3

III. **Advanced Chronic Kidney Disease after Surgery and the Contribution of Acute Kidney Disease: A National Observational Cohort Study**
Renberg M, Hertzberg D, Rimes-Stigare C, Hallqvist L, Bell M
Manuscript accepted in Br J Anaesth, 2024 Feb *(in press)*

IV. **Association of Preoperative Renal-Resistive Index With Long-term Renal and Cardiovascular Outcomes After Cardiac Surgery**
Renberg M, Sartipy U, Bell M, Hertzberg D
J Cardiothorac Vasc Anesth. 2024 Jan;38(1):101-108

Contents

List of abbreviations

ACEi	Angiotensin converting enzyme inhibitor
AKD	Acute kidney disease
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
ASA score	American Society of Anesthesiologists physical status classification
ATC	Anatomic Therapeutic Chemical classification
AUC	Area under the receiver operator characteristics curve
B mode	Brightness-modulated mode
BMI	Body mass index
CEUS	Contrast-enhanced ultrasonography
CI	Confidence interval
CKD	Chronic kidney diease
COVID-19	Coronavirus disease 2019
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
HR	Hazard ratio
ICC	Intraclass correlation coefficient
ICD-10	International Classification of Diseases, Tenth Revision
ICU	Intensive care unit
IQR	Interquartile range
KDIGO	Kidney Disease: Improving Global Outcomes
LoA	Limits of agreement
MACE	Major adverse cardiovascular events
MAKE	Major adverse kidney events
NPV	Negative predictive value
OR	Odds ratio
POCUS	Point-of-care ultrasound
PPV	Positive predictive value
PW Doppler	Pulsed-wave Doppler
RBF	Renal blood flow
RCWP	Renal capillary wedge pressure
RPP	Renal perfusion pressure
RRI	Renal resistive index
RRT	Renal replacement therapy
RVR	Renal vascular resistance
SARS-CoV-2	Severe acute respiratory coronavirus 2
SCr	Serum creatinine concentration
SD	Standard deviation
SHR	Subdistribution hazard ratio
VExUS	Venous excess ultrasound

1 Introduction

"If you don´t look, you don´t know!"
Josh Zimmerman, POCUS ninja

Point-of-care ultrasound (POCUS) refers to ultrasonography performed and interpreted at the bedside by the treating clinician[1]. The POCUS exam typically is rapid and goal-oriented, and its result can be instantly integrated into clinical decision-making. POCUS has emerged as an integral component of the physical examination and ultrasound imaging, or insonation, has gained recognition as the fifth pillar of bedside assessment together with inspection, palpation, percussion, and auscultation[2].

With growing interest, training opportunities, and accessibility, the basic ultrasound level of clinicians is steadily rising. POCUS protocols for clinicians working with the sickest and most fragile patients have evolved from fundamental assessments of circulatory and respiratory failure to involve a multi-organ approach, utilizing increasingly advanced ultrasound techniques[3, 4]. Given the significant consequences of renal dysfunction in perioperative and critical care, renal POCUS incorporating some of these advanced techniques has emerged as a promising tool[5]. However, challenges arise concerning the reliability of ultrasonography performed by non-expert sonographers in these settings, and the clinical utility of renal POCUS for assessing outcomes, both in the short and long term, is not established.

This thesis investigated the role of bedside quantification of renal perfusion using Doppler ultrasound for assessing renal outcomes in perioperative and critical care. Specifically, we studied the renal resistive index (RRI) and its feasibility as a POCUS tool, its association with short-term renal outcomes in patients with critical Coronavirus disease 2019 (COVID-19), and its association with long-term renal and cardiovascular outcomes in surgical patients. Additionally, this thesis explored the nationwide epidemiology of postoperative long-term renal outcomes in Sweden.

2 Literature review

2.1 Renal dysfunction

Renal dysfunction is characterized by loss of the many regulatory functions of the kidneys, which leads to retention of metabolism waste products and impaired volume, electrolyte, and acid-base homeostasis[6, 7]. Symptoms and clinical course depend on severity, duration, and underlying cause of the dysfunction. Regardless of the setting, renal dysfunction is associated with adverse patient outcomes.

Definitions

Historically, the absence of uniform definitions has impeded coordination of research and clinical practice concerning renal dysfunction. The first consensus definition for acute renal dysfunction was published two decades ago and has since then undergone periodic updates[8, 9]. As of 2012, renal dysfunction is defined based on its onset and duration using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (*Table 1*) [10-12].

Table 1. Definitions of renal dysfunction.

	Functional criteria	**Structural criteria**	**Duration**
AKI	Increase in SCr by ≥50% within 7 days, or Increase in SCr by ≥26.5 μmol/l (0.3 mg/dl) within 48 hours, or Oliguria <0.5 ml/kg/h for ≥6 hours	Not defined	≤7 days
AKD	AKI, or GFR <60 ml/min/1.73 m^2, or Decrease in GFR by ≥35%, or Increase in SCr by >50%	Marker of kidney damage (commonly albuminuria, hematuria, or pyuria)	≤3 months
CKD	GFR <60 ml/min/1.73 m^2 (in absence of structural criteria)	Marker of kidney damage (commonly albuminuria)	>3 months

Acute kidney injury (AKI) is the most acute form of renal dysfunction, and is defined as an increase in serum creatinine concentration (SCr) or a decrease in urine output[10]. It is diagnosed solely based on these functional criteria, without requiring evidence of structural kidney damage. Severity is categorized from stage 1 to 3, and is determined by SCr thresholds or the duration of oliguria. Patients treated with renal replacement therapy (RRT) are classified as having AKI stage 3. Transient AKI recovers within 48 hours, whereas AKI lasting beyond this timeframe is considered persistent[13].

Acute kidney disease (AKD) extends beyond 7 days but remains shorter than 3 months, with its definition recently updated in 2021[11]. AKD may start as an AKI episode, but also includes more subtle renal function abnormalities developed over a longer period. Diagnosis is based on functional criteria or evidence of structural kidney damage, usually albuminuria. A reduced glomerular filtration rate (GFR) may serve as a functional criterion, either estimated using formulas based on SCr or cystatin C (eGFR), or measured directly.

Chronic kidney disease (CKD) is renal dysfunction persisting for more than 3 months with impact on health[12]. Diagnosis is based on decreased GFR or evidence of kidney damage, such as albuminuria, biopsy findings, or abnormalities on imaging. Severity is graded from 1 to 5 based on GFR thresholds. In absence of kidney damage markers, GFR <60 ml/min/1.73 m^2, representing CKD grade 3, is required for diagnosis. CKD grade 4 (GFR <30 ml/min/1.73 m^2) represents advanced CKD, and CKD grade 5 (GFR <15 ml/min/1.73 m^2) represents end-stage renal disease or kidney failure.

In summary, renal dysfunction can be viewed as a continuum of interconnected syndromes spanning from acute to chronic presentations[14]. The AKD definition acknowledges the significant subset of patients with evolving kidney disease who may not fulfil strict criteria for AKI or CKD. Renal recovery is generally defined as the restoration of GFR to within 25% of baseline or to a minimum of 60 ml/min/1.73 m^2 [10, 11].

Epidemiology

Reported incidence of AKI, AKD and transition to CKD in the perioperative and critical care settings vary due to heterogenicity in definitions and patient populations. AKI has received the most attention, and affects over 50% of patients treated in the intensive care unit (ICU)[15]. The major causes are sepsis, accounting for ~50% of cases, and major surgery[16]. Among patients undergoing major surgery, almost 20% develop postoperative AKI with an incidence of over 40% in certain types of cardiac surgery[17]. Recent meta-analyses including over 2 million patients with AKI and over 1 million patients with AKD respectively, demonstrated an elevated risk of long-term development of CKD, kidney failure and mortality across different clinical settings[18, 19]. While the role of AKD for the AKI to CKD transition has been studied in detail in patients undergoing cardiac surgery[20, 21], its impact in non-cardiac surgical settings remains less understood. Additionally, incidence of CKD following surgery or critical care when also considering patients without early evident AKI remains unknown.

In-hospital mortality among ICU patients who do not recover from an AKI episode may be as high as 50%, with 1-year mortality exceeding 20% among those discharged from the hospital[22]. Critically ill patients with AKI who die in the hospital do it mainly from sepsis or cardiovascular events[23], whereas long-term mortality is attributed to cancer and cardiovascular disease[24]. Recognizing CKD, kidney failure, and death as competing outcomes, their composite endpoint termed major adverse kidney events (MAKE) has been proposed as a patient-centered outcome[25], and may affect up to 40% of AKI-survivors within the first year after hospital discharge[26]. The close interplay between renal dysfunction and cardiovascular disease suggests that also composite cardiovascular outcomes, such as major adverse cardiovascular events (MACE), may be pertinent in these patients[27].

Risk factors and pathogenesis

All stages of the AKI to CKD continuum share common risk factors[6, 14]. Non-modifiable risk factors include older age, hypertension, diabetes mellitus and heart failure. In perioperative and ICU settings, additional modifiable risk factors such as anemia, fluid overload, and exposure to nephrotoxins are important[6].

Traditionally, the precipitating mechanisms for the development of AKI have been categorized into prerenal (low renal blood flow [RBF]), renal (intrinsic kidney injury), or postrenal (urinary tract obstruction). However, in clinical practice, multiple overlapping pathophysiological mechanisms coexist such as hypotension, venous congestion, the neuroendocrine response to the underlying disease process or surgery, and renal inflammatory processes[6, 7, 16]. These mechanisms are further influenced by the underlying risk profile of the individual patient, and by the clinical course. The complex

interplay of multiple precipitating factors makes it challenging to identify specific AKI phenotypes at which specific therapeutic interventions can be targeted.

While an adaptive repair process may restore renal structure and function if the initial AKI process is reversed, complete renal recovery is probably uncommon[6, 13]. Instead, each renal insult should be viewed as a "hit" on the kidneys, rendering them more susceptible to future damage. In cases of non-reversal of the AKI process, persistent inflammation leads to tubulointerstitial fibrosis and nephron loss[14]. This maladaptive repair process predisposes renal non-recovery and transition from AKI to AKD and CKD.

Role of renal blood flow

During resting conditions, the kidneys receive ~25% of cardiac output. RBF is autoregulated within physiological blood pressure limits, which maintains a constant net filtration pressure in the glomeruli and stable GFR[28]. According to Ohm's law, RBF is determined by the pressure difference between renal arterial inflow and venous outflow, known as the renal perfusion pressure (RPP), and by the renal vascular resistance (RVR). In clinical practice, RPP is typically calculated as the difference between mean arterial pressure and central venous pressure[16]. Autoregulation of RBF in response to changes in RPP involves two major mechanisms[28]. Firstly, the myogenic response causes instantaneous contraction or dilation of afferent arterioles in response to changes in transmural pressure, thereby adjusting RVR. Secondly, alterations in RBF and GFR lead to changes in tubular delivery of NaCl to the macula densa of the juxtaglomerular apparatus, triggering contraction or dilation of afferent arterioles, again adjusting RVR accordingly. Additionally, RBF and RVR are influenced by numerous hormonal (e.g. angiotensin II, prostaglandins, nitric oxide) and neural signals (e.g. sympathetic nerve activity).

In patients with renal dysfunction, these autoregulatory mechanisms may be impaired, rendering the kidneys vulnerable to fluctuations in RBF, RPP or RVR. Alterations in both renal macro- and microcirculation are considered major pathophysiological contributors to renal dysfunction[16]. RBF may be hindered on a macrocirculatory level from hypotension and low cardiac output states, or from venous congestion causing impaired renal venous outflow. Conversely, in the early stages of sepsis, global RBF may be increased, but microcirculatory disturbances result in periglomerular shunting, leading to impaired blood flow to the renal medulla and risk of medullary hypoxia[29, 30]. Prolonged circulatory alterations may thus contribute to renal vascular remodeling and rarefaction, increased RVR, and the maladaptive renal repair process.

Treatment and prevention

The primary treatment for AKI revolves around addressing the underlying cause and enabling renal recovery by correcting pathophysiological mechanisms. The KDIGO care bundle summarizes these supportive steps and emphasizes the importance of optimizing RPP and volume status while avoiding nephrotoxins[31]. When implemented early in high-risk patients, this bundle has demonstrated efficacy in reducing the incidence and severity of postoperative AKI after cardiac surgery[32, 33] and major abdominal surgery[34]. In cases of AKI accompanied by severe disturbances of homeostasis, RRT may be initiated. Three out of four randomized controlled trials have failed to demonstrate a mortality benefit from early RRT initiation in absence of absolute indications[35-38]. Consequently, a "watch and wait"-strategy is often advocated[39], although delaying RRT beyond a certain point may also be harmful[40].

To enhance renal recovery and prevent progression from AKI and AKD to CKD, systematic follow-up by nephrologists have been advocated[41]. Focus is on early detection and avoidance of new kidney insults, and recognition and optimization of blood pressure and glycemic control. However, patient selection for such follow-up has shown to be challenging[42], and easily accessible measures to identify high-risk patients are warranted. Randomized controlled trials have indicated a slower CKD-progression in patients receiving medications that influence RBF, again suggesting the central role of RBF in determining renal outcomes[43, 44].

Implications for new diagnostic methods

The definitions for renal dysfunction have important limitations, especially when applied to critically ill patients. Firstly, the requirement of knowing the baseline SCr presents a challenge, as this information is often unavailable for patients admitted to the ICU or undergoing emergency surgery, necessitating estimation methods. Secondly, SCr and urine output used in diagnosing AKI serve as imperfect markers of structural kidney injury. Healthy kidneys possess functional reserve capacity which means that SCr is not elevated until there is a 50% decrease in GFR[45], and even then there is a delay of 24-36 hours from kidney injury to steady state of the subsequent SCr increase[46]. Urine output, while a time-sensitive marker of GFR, is influenced by diuretic use and the humoral responses of critical illness and surgery[7, 16]. This means kidney injury is already established by the time AKI is diagnosed. Thirdly, reliable assessment of renal recovery after critical illness is challenging due to factors such as muscle wasting, changes in volume distribution, and compensatory hyperfiltration, which may lower SCr and thus overestimate renal recovery[6]. Altogether, new easily applicable methods for early identification and prognostication of renal dysfunction are warranted. Novel biomarkers of renal cell stress or injury have been extensively studied, but very few have translated into clinical practice. Instead, renal POCUS may offer promise in this regard.

2.2 Ultrasound

Ultrasound principles

Ultrasound constitutes of high-frequency sound waves above the human hearing range and can be used to produce images based on the pulse-echo principle[47]. When an electrical signal is applied to piezoelectric crystals within the ultrasound transducer, the crystals vibrate, generating pulses of mechanical waves that propagate through the tissue as ultrasound. Tissues of varying densities exhibit different acoustic impedances, causing ultrasound waves to travel at different speeds. At tissue interfaces, where acoustic impedance changes occur, some ultrasound waves will be reflected back to the transducer, creating echoes. These echoes are transformed by the piezoelectric crystals to electrical signals, and displayed as an image on the monitor.

Doppler ultrasound

The Doppler effect states that there is a change in the frequency of a sound wave when there is motion relative to the observer[47]. Doppler ultrasound can therefore be used to detect blood flow by analyzing the frequency shifts of the received echoes caused by the movement of red blood cells. Color Doppler displays motion and direction of blood flow. Spectral Doppler displays blood flow velocities over time. It includes pulsed-wave Doppler (PW Doppler), which measures blood flow velocities at specific points, and continuous wave Doppler, which measures the highest blood flow velocity along the insonation line. Importantly, blood flow velocities measured by Doppler ultrasound are dependent on the insonation angle. Therefore, absolute velocities decrease with increasing insonation angle, and obtaining reliable velocities requires minimizing the angle between the Doppler shift signal and the direction of blood flow.

Renal POCUS

Table 2 summarizes commonly used modalities within renal POCUS[5]. Brightness-modulated mode (B mode) and Color Doppler are considered basic POCUS skills, while PW Doppler is suggested to require a higher skill level and additional training[48].

Table 2. Renal POCUS.		
Modality	**Description**	**Clinical question**
B mode	Grayscale image	Kidney size Parenchymal thickness Echogenicity Urinary tract obstruction Masses/cysts/stones
Color Doppler	Motion and direction of blood flow Red = towards the transducer Blue = away from the transducer	Renal perfusion
PW Doppler	Blood flow velocity over time at specific measurement points	Renal arterial flow velocities Renal venous flow profile

2.3 Renal resistive index

RRI represents a quantitative measurement of intraparenchymal renal perfusion. For over three decades, it has been studied in outpatient settings for diagnosing renal disease and prognosticating graft survival in kidney transplant patients[49]. In recent years, its application has gained increased interest in the perioperative and critical care settings.

Technique

The POCUS-technique for obtaining RRI is standardized[50]. The patient is typically examined in a supine or lateral decubitus position, and the kidneys are insonated from a posterolateral approach. A curvilinear low-frequency (2-5 MHz) transducer is used to obtain a B-mode longitudinal axis of the examined kidney. Then Color Doppler is applied to identify interlobar (adjacent to medullary pyramids) or arcuate (at the corticomedullary junction) intrarenal arteries. PW Doppler is applied, and a small Doppler gate (2-5 mm) with low pulse repetition frequency and high gain is used to obtain optimal readings of 3-5 consecutive similar-appearing waveforms of intrarenal blood flow. Peak systolic velocity and end-diastolic velocity is measured, and RRI is simply calculated by using the formula:

$$\text{RRI} = \frac{\text{Peak systolic velocity} - \text{End-diastolic velocity}}{\text{Peak systolic velocity}}$$

To account for regional imbalances in perfusion, RRI should be obtained from the upper, mid, and lower kidney poles. Ultimately, a single mean RRI for both kidneys is calculated.

Normal values

RRI reflects the percentage of velocity reduction of end-diastolic flow in relation to peak systolic flow and can in theory obtain values between 0 and 1. An RRI of 0 would indicate continuous intrarenal blood flow without deceleration throughout the cardiac cycle, while an RRI of 1 would equal totally diminished intrarenal diastolic blood flow.

Normal RRI values fall around 0.60, with 0.70 considered the upper normal threshold in adults[51, 52]. Normal kidneys display a low downstream RVR with significant diastolic flow, resulting in the lowest RRI value observed in the outer regions of the renal parenchyma[53]. Normal side-to-side differences between kidneys is less than 5%[52]. Since the right kidney generally is more accessible due to the beneficial acoustic ultrasound window provided by the adjacent liver, RRI measurements from the right kidney are suggested to be used when repeated assessments are needed[50]. *Figure 1* displays a normal RRI reading.

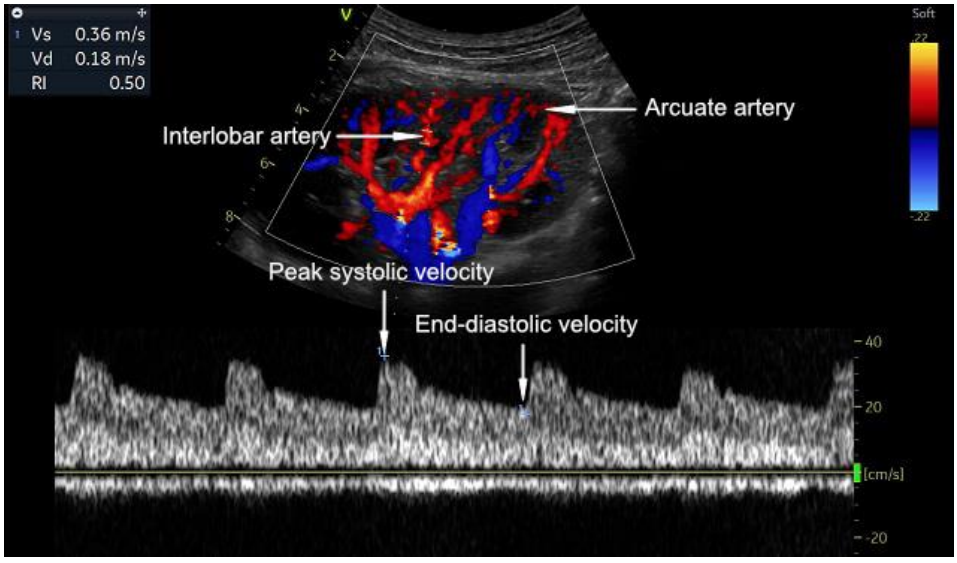

Figure 1. Normal RRI reading of the author's right kidney.

Determinants

Despite its name, RRI is not only a reflection of downstream RVR. Animal studies conducted already 25 years ago demonstrated RRI to be relatively insensitive to increases in RVR[54]. Instead, through in-depth analysis and rearrangement of the RRI formula, a linear association between RRI and systemic pulse pressure has been proposed[55]. Thus, fixed elevated central pulse pressure resulting from decreased systemic vascular compliance is believed to be the major determinant of the RRI elevation observed in patients with older age or atherosclerotic disease[56, 57]. Notably, in patients with transplanted kidneys, RRI is not associated with graft prognosis but rather with the central pulse pressure of the recipient[58]. Heart rate impacts RRI through dynamic pulse pressure alterations. In bradycardia, diastole becomes longer leading to increased pulse pressure and lower end-diastolic intrarenal blood flow velocities, and thereby increased RRI. RRI-formulas corrected for heart rate variabilities exist[59], but are seldom deemed necessary in clinical practice[50]. Although still reflective of renal perfusion, RRI has failed to show a strong association with global RBF in animal and clinical studies[60, 61]. However, RRI seems to increase with increased stroke volume[62].

The major intrarenal factor affecting RRI is the renal capillary wedge pressure (RCWP), which represents a combination of renal interstitial and venous pressures[55, 63]. In AKI, a renal inflammatory state causing downstream vasoconstriction, as well as local edema with increased intracapsular pressure, is suggested to elevate RRI[64]. Additionally, RRI elevation from increased RCWP secondary to venous congestion, has been described in patients with heart failure[65]. Downstream RVR and characteristics of the intrarenal vessels still affect the RRI value, and renal arteriosclerosis seems to be the only histological abnormality independently associated with elevated RRI[66]. In established CKD, RRI elevation may partially depend on elevated RVR from intrarenal vascular rarefaction[67].

In summary, RRI is determined by extrarenal or upstream factors, primarily affected by systemic pulse pressure, as well as intrarenal or downstream factors affecting RVR (*Table 3*). Some of these factors are static while others are dynamic, making interpretation of the final RRI value complex and highly dependent on the clinical situation.

Table 3. Major determinants of RRI.		
Determinants		**Effect on RRI**
Pulse Pressure (upstream factors)	**Systemic vascular compliance (arterial stiffness)**	Reduced in older age or by systemic atherosclerosis → RRI↑
	Heart rate	Bradycardia → RRI↑ Tachycardia → RRI↓
	Stroke volume	RRI↑
	Aortic valve disease	Aortic insufficiency → RRI↑ Aortic stenosis → RRI↓
	Renal artery stenosis	RRI↑, or if severe → RRI↓
Resistance (downstream factors)	**Vasoconstriction**	Increased by vasopressors, local inflammation/AKI, or hypoxia/hypercapnia → RRI↑
	Occlusion	Emboli or thrombotic microangiopathy → RRI↑
	Renal capillary wedge pressure	Increased by local inflammation/edema/AKI, intraabdominal hypertension, or venous congestion → RRI↑
	Renal vascular compliance	Decreased in renal arteriolosclerosis → RRI↑

RRI and AKI

In the perioperative and critical care settings, RRI has been primarily studied for early detection and short-term prognostication of AKI (*Table 4-5*).

Consistently, patients admitted to the ICU who develop severe AKI (stage 2 to 3) within the first days have higher RRI compared to those who develop no or only mild AKI (stage 1)[68-70]. Several single-center studies have suggested that patients progressing to persistent AKI typically present with RRI >0.70-0.80 at admission[71, 72], but recent studies have come to question the clinical utility of these findings. In a French multicenter study on 351 unselected ICU patients, RRI measurements at admission had an area under the receiver operator characteristics curve (AUC) of only 58% for prediction of AKI short-term reversibility[73]. A sub-analysis on 118 patients that did not meet KDIGO-criteria for AKI at the time of measurement showed an equally poor performance of RRI to predict de novo-AKI[74]. Similar conclusions were drawn from a Dutch single-center study on 371 unselected ICU patients[75]. Overall, the ICU community has shifted from enthusiasm to a more cautious stance regarding the role of RRI alone for early prediction of AKI reversibility[76].

In comparison, the perioperative setting may offer a more beneficial environment for researching markers of AKI prediction, as baseline renal function often is known, and the surgical trauma provides a well-defined timepoint for the insult driving the AKI process. RRI elevation >0.70 in the immediate postoperative period has been associated with subsequent AKI development after cardiac[77-79] and non-cardiac surgery[80-82]. Notably, dynamic RRI elevations may serve as the earliest possible warning signal for an ongoing kidney injury process, facilitating the identification of patients requiring urgent clinical review and meticulous supportive care. This monitoring can even be conducted intraoperatively by using transesophageal POCUS[83, 84]. Additionally, patients with elevated preoperative RRI have an increased risk of early postoperative AKI[85]. Recent meta-analyses have concluded that perioperative RRI should be considered a useful marker for early AKI prediction and short-term prognostication in this setting, although heterogeneity among individual studies may weaken generalizability[86, 87].

Table 4. Selected studies of RRI and AKI in the ICU setting.				
Reference	**n**	**Outcome**	**RRI cut-off (AUC, sens, spec)**	**Comment**
Lerolle 2006[68]	35	AKI on day 5	0.74 (0.85, 78, 77)	Septic shock patients
Darmon 2011[71]	51	AKI-duration >3 days	0.79 (0.91, 92, 85)	
Schnell 2012[88]	58	AKI on day 3	0.71 (0.91, NR, NR)	2 centers Better performance than cystatin C
Song 2018[70]	124	AKI within 7 days	0.69 (0.81, 52, 87)	Surgical ICU Better performance in combination with central venous pressure
Haitsma Mulier 2018[69]	99	AKI stage 2-3 within 7 days	0.74 (0.72, 53, 87)	
Darmon 2018[73]	351	AKI-duration >3 days	0.71 (0.58, 50, 68)	8 centers Similar performance for predicting de novo-AKI in sub-analysis on 118 patients[74]
Garnier 2020[72]	100	AKI-duration >3 days	0.69 (0.93, 78, 90)	Confirmed AKI cases. Better performance than TIMP-2 x IGFBP7
Wiersema 2020[75]	371	AKI on day 3	0.74 (0.59, 32, 72)	Similar performance in combination with renal venous Doppler
Abbreviations: n, number of patients; TIMP-2 x IGFBP7, a novel cell cycle arrest kidney biomarker.				

Table 5. Selected studies of RRI and AKI in the perioperative setting.				
Reference	**n**	**Outcome**	**RRI cut-off (AUC, sens, spec)**	**Comment**
Cardiac surgery				
Bossard 2011[77]	65	AKI within 4 days	0.74 (0.91, 85, 94)	
Guinot 2013[78]	82	AKI-duration >3 days	0.73 (0.93, 93, 88)	
Hertzberg 2017[85]	96	AKI within 48 hours	0.70 (NR, 78, 46)	Measured preoperatively
Hermanssen 2021[79]	100	AKI within 4 days	0.73 (0.73, 88, 58)	Better specificity in combination with renal venous Doppler
Kajal 2022[84]	115	AKI within 7 days	0.68 (0.71, 70, 67)	Measured intraoperatively by TEE
Non-cardiac surgery				
Marty 2015[80]	50	AKI within 48 hours	0.71 (0.86, 94, 71)	Hip/knee arthroplasty
Marty 2016[81]	48	AKI within 48 hours	0.71 (0.89, 76, 89)	Hip fracture repair
Valeri 2022[82]	53	AKI within 1 week	7% increase from preop to postop (0.75, 33, 50)	Open aortic surgery
Abbreviations: n, number of patients; TEE, transesophageal echocardiography.				

RRI and resuscitation

By reflecting renal perfusion, and thereby acting as a surrogate marker of systemic perfusion, RRI has the potential of being a quantitative monitoring tool in resuscitative scenarios. In shock states, RRI elevation is suggested to stem from a combination of increased pulse pressure, impaired cardiac function, and increased RCWP[89]. RRI >0.70 has demonstrated good predictive performance as an early warning signal for detecting hemodynamic deterioration in trauma patients[90]. Moreover, the RRI value seems to be a dynamic measure in these situations, rapidly responding to therapeutic interventions[91]. In postoperative fluid responsive patients, RRI decreases with passive leg raising or fluid administration[92, 93]. However, results from the ICU setting regarding RRI changes after fluid administration have been less consistent[94-96]. Several patients included in these studies already had established AKI, suggesting a less predictable response of RRI to interventions when renal dysfunction is already present. Indeed, RRI has shown to correlate with mean arterial pressure in ICU patients without AKI but not in those with AKI[97]. Nevertheless, a decrease in RRI concurrent with an increase in urine output has been described when mean arterial pressure is titrated upwards using vasopressors[98], still indicating the potential utility of RRI as a therapeutic target in acute settings.

RRI and long-term renal outcomes

The role of RRI in predicting the progression of AKI to AKD and CKD is not established. Studies on RRI performed in the perioperative and critical care settings have not provided long-term follow-up data. However, RRI elevation has been associated with renal function decline in patients with traditional risk factors for CKD development such as hypertension[99] and diabetes mellitus[100]. It is plausible that RRI measured during a clinically stable phase reflects these fixed patient-specific risk factors for renal function decline, but this has not been thoroughly investigated across various clinical settings.

In patients with established CKD, RRI is extensively studied and is the ultrasonographic measurement that best correlates with long-term renal prognosis[67]. RRI >0.70 have shown to be a risk factor for accelerated renal function deterioration[101-103] or death[104] independent of baseline GFR or albuminuria. Further, RRI >0.80 has shown associations with progression to both kidney failure and early death in these patients[105]. However, predictive performance of RRI >0.80 as a solitary marker for long-term renal function decline and mortality has recently been questioned, with an AUC of 66% and 67%, respectively, for predicting these outcomes[106].

2.4 Critical COVID-19 and the kidney

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) struck Sweden in April 2020. Critically ill patients with a new form of virus-induced acute respiratory distress syndrome quickly flooded Swedish ICUs. During the first wave, over 40% of patients with COVID-19 admitted to the ICUs at the Karolinska University Hospital also developed AKI, with half of them requiring RRT, placing significant strain on resources[107-109]. The patients presented with severe systemic inflammation and a hypercoagulable state with an increased risk of both arterial and venous thromboses[110]. Early post-mortem findings identified a high grade of endothelial dysfunction and renal microthrombi in those with AKI[111]. Being a new and unfamiliar disease entity, RBF impairment therefore emerged as a potential contributor to renal dysfunction, and international expert groups advocated for research into POCUS assessment of AKI in these patients[112].

2.5 Thesis rationale

Renal hemodynamics play a central role in the progression and recovery of renal dysfunction in perioperative and critical care, and RRI serves as a rapid and non-invasive bedside tool for quantifying renal perfusion. However, several uncertainties persisted leading up to the studies included in this thesis.

Firstly, the feasibility of RRI as a POCUS method had not been established since measurements in previous studies were performed by experienced sonographers[68, 69, 77, 78, 80, 81, 88, 113]. We hypothesized that RRI could be effectively learned and applied also by inexperienced sonographers outside of expert centers.

Secondly, we hypothesized that RRI would be elevated in critical COVID-19 patients with AKI, and that the method could serve as a bedside tool for identifying these patients.

Thirdly, we investigated the occurrence of long-term renal dysfunction after surgery. In this context, we hypothesized that AKD was an important risk factor, and that RRI could serve as a quantifiable risk measure for identifying high-risk patients at an early stage.

3 Research aims

The general aim of this thesis was to investigate the role of RRI in assessing renal outcomes in perioperative and critical care. Specific aims were:

- To study the feasibility of RRI as a POCUS method (study I).
- To study the association of RRI with AKI in critical COVID-19 (study II).
- To study the incidence and risk factors for postoperative advanced CKD and long-term MAKE on a national level in Sweden, and to study the contribution of AKD for these outcomes (study III).
- To study the association of preoperative RRI with postoperative persistent renal dysfunction, and long-term MAKE and MACE (study IV).

4 Materials and methods

Table 6. Summary of methods.				
Study	**I**	**II**	**III**	**IV**
Study design	Validation study	Observational cohort study	Observational register-based cohort study	Observational cohort study
Study population	Volunteers	ICU patients with COVID-19	Patients undergoing non-cardiac surgery	Patients undergoing cardiac surgery
Study period	2019	2020	2007-2013 Follow-up 1 year	2014-2015 Follow-up 5 years
Sample size	23	51	237 124	96
RRI measurements	By 3 operators in every volunteer	During ICU period	None	Before surgery
Outcomes	Interobserver reliability Accuracy Precision	AKI	Advanced CKD Advanced AKD MAKE	Persistent renal dysfunction MAKE MACE
Statistical analysis	Intraclass correlation coefficients Paired t test	Wilcoxon rank-sum test Logistic regression	Fine and Gray competing risks regression Cox proportional hazards regression	Wilcoxon rank-sum test Kaplan-Meier method Cox proportional hazards regression

4.1 RRI measurements

RRI measurements were performed in studies I and II, and had previously been performed on the cohort in study IV. The technique for obtaining RRI adhered to the protocol described earlier[50]. In study I, the same ultrasound device (Vivid S70N, GE Healthcare, Illinois, US) was used in the same volunteers by every operator. In study II, the same ultrasound device was used in all patients on the same site (Vivid S70N, GE Healthcare, Illinois, US on one site, Logiq E10, GE Healthcare, Illinois, US on one site). In study IV, the same ultrasound device (ACUSON Sequoia 512, Siemens Healthineers, Erlangen, Germany) was used in all patients. The operators that performed RRI measurements in patients were not directly involved in patient care.

4.2 Data sources

Medical records

Take Care (CompuGroup Medical, Koblenz, Germany) is the primary electronic health records system utilized by most hospitals and outpatient clinics in the Stockholm Region. It contains medical records, including laboratory data and imaging data obtained during clinical practice. Clinisoft (Centricity Critical Care, GE Healthcare, Illinois, US) is an electronic patient database management system utilized by all adult ICUs at the Karolinska University Hospital. It acquires and stores physiological data alongside ICU-specific monitoring and therapeutic settings. Data extracted from these medical records were used in studies II and IV.

The Orbit Register

Orbit is a surgical planning software and contains data on surgical procedures and perioperative characteristics. Orbit data were used in study III and, at the time of data extraction, covered approximately one-third of units performing surgery in Sweden.

National Board of Health and Welfare Registries

The National Board of Health and Welfare, a Swedish government agency, oversees various health data registries. Data from the following registries were used in study III:

The National Patient Register[114], which contains hospital discharge dates and International Classification of Diseases, Tenth Revision (ICD-10) codes for all diagnoses in hospital and specialized outpatient care. Registrations are 85-95% correct for most diagnoses[115].

The Swedish Prescribed Drug Register[116], which contains dates and Anatomic Therapeutic Chemical classification (ATC) codes for all dispensed drug prescriptions from Swedish pharmacies[117].

The Swedish Cause of Death Register[118], which contains death dates for >99% of Swedish citizens[119].

National Quality Registries

Several national quality registries exist in Sweden, containing data on specific diagnoses and disease states.

The Swedish Renal Register[120] contains data on active uremia care, including patients on hemodialysis and peritoneal dialysis. It covers >97% of patients on chronic dialysis in Sweden[121]. Data from this register were used in study III.

4.3 Statistical analysis

In all studies, data were presented as frequency (n) and percentage (%) for categorical variables, and as median with interquartile range (IQR) or mean with standard deviation (SD) for continuous variables. Between-group comparisons were conducted using the Chi^2, Fischer's exact, or Wilcoxon rank-sum tests, as appropriate. Specific statistical analyses for each study are described separately. For all analyses, 2-sided p-values <0.05 were considered statistically significant. Data were analyzed using Stata version 15.1 (StataCorp, College Station, TX, US).

4.4 Study I

Design

This validation study was conducted at the Karolinska University Hospital including volunteers who were examined by three operators with varying levels of prior ultrasound experience. The intermediate non-expert, a resident in anesthesia and intensive care, regularly used POCUS in clinical practice but had no experience in renal Doppler. The novice non-expert was a medical student with no clinical experience in POCUS. The expert, a specialist in clinical physiology, possessed over 20 years of experience in RRI measurements.

Both non-experts participated in a structured half-day course that included theoretical background and supervised practical training to learn the RRI technique. RRI measurements were then performed consecutively by all operators in each volunteer, the order of operators being random for every volunteer, with the measurements and results blinded to the other operators.

Definitions

Interobserver reliability for mean RRI between non-experts and the expert was assessed using the intraclass correlation coefficient (ICC), categorized as poor if <0.50, moderate if ≥0.50, good if ≥0.75, or excellent if ≥0.90[122]. Accuracy was defined as absence of systematic measurement error (bias). Precision was defined as absence of random measurement error. Clinically acceptable precision for the non-experts was a priori defined as having 95% limits of agreement (LoA) within ±0.06 from the expert, corresponding to a measurement error within ±10% for a normal RRI of 0.60.

Statistical analysis

ICC and 95% confidence intervals (95% CIs) were calculated based on individual measurements, consistency of agreement, using a 2-way mixed effects model[123]. Bias represented the mean difference between paired measurements, and was determined using paired t tests. The 95% LoA were calculated as ±1.96 SDs from the mean difference of paired measurements. Bland-Altman plots were constructed to visualize bias and random measurement errors between operators. To assess progression in the technique of obtaining RRI, analyses were repeated after excluding the first 5 volunteers.

4.5 Study II

Design and study population

This observational cohort study was conducted in six COVID-ICUs at two sites of the Karolinska University Hospital during the first COVID-19 wave in Sweden in 2020. Inclusion criteria were positive SARS-CoV-2, ICU admission, and age ≥18 years. Exclusion criteria were pre-existing kidney failure, palliation, ongoing cardiac arrythmia, or treatment with extracorporeal membrane oxygenation. On specific dates for each ICU, RRI measurements were performed by one of two trained operators on eligible patients.

Definitions

The primary outcome was AKI at the time of RRI measurement, defined according to the SCr criteria of the KDIGO guidelines[10]. AKI severity was categorized based on SCr increase compared to baseline: stage 1 if ≥1.5-fold increase or absolute increase ≥26 μmol/l, stage 2 if ≥2.0-fold increase, stage 3 if ≥3.0-fold increase or absolute increase to >354 μmol/l or initiation of RRT. The highest SCr from ICU admission to the day of RRI measurement was compared to baseline SCr, which was defined as the last known value measured during a disease-free phase before admission or, if unavailable, the SCr at hospital admission. Patients whose SCr had peaked >7 days before RRI measurement and returned to baseline, no longer fulfilling the KDIGO SCr criteria, were classified as having recovered AKI. Oliguria was defined as <0.5 ml/kg/ideal body weight/hour for 24 hours.

Statistical analysis

Median RRI between groups were compared using the Wilcoxon rank-sum test. The association of RRI with AKI was assessed using logistic regression, calculating odds ratios (ORs) and 95% CIs. To adjust for confounding factors, an exploratory multivariable model was constructed using manual forward variable selection based on significance levels ($p < 0.2$) in univariate analyses.

4.6 Study III

Design and study population

This observational cohort study utilized prospectively registered data from 23 Swedish hospitals. Eligible patients were adults undergoing surgery between 2007 and 2013, with follow-up until 2014. Patients with missing data or undergoing cardiac or obstetric surgery had been a priori excluded from the dataset[124]. Exclusion criteria were preoperative renal dysfunction or undergoing kidney surgery.

The study population was identified from Orbit and linked, using the unique Swedish personal identity number, to the National Patient Register, the Swedish Prescribed Drug Register, the Swedish Cause of Death Register, and the Swedish Renal Register. The final dataset thus included information on the surgical procedure, as well as diagnoses, hospital stays, dispensed drug prescriptions, mortality, and chronic dialysis from 5 years before surgery until end of follow-up.

Definitions

Exclusion criteria were defined as described in *Table 7*. The approach of using renal-specific diagnoses, drugs, and procedure codes to exclude patients with renal dysfunction has been shown to correspond to eGFR ≥60 ml/min/1.73 m2 in >90% of the remaining patients when validated against SCr in a Swedish setting[125]. American Society of Anesthesiologists physical status classification (ASA score) was defined as 1: normal healthy patient, 2: patient with mild systemic disease, 3: patient with severe systemic disease, and ≥4: patient with severe systemic disease that is a constant threat to life[126].

The primary outcome was advanced CKD within 1 year after surgery, corresponding to CKD grade 4-5 from postoperative day 91 to 365 (*Table 7*). The approach of using renal-specific diagnoses or drugs to identify patients with renal dysfunction has been shown to correspond to an eGFR <30 ml/min/1.73 m^2 in >93% of cases when validated against SCr[125]. By incorporating registrations from the Swedish Renal Register, >97% of patients on chronic dialysis were covered[121]. Secondary outcomes were advanced AKD within 90 days after surgery, and MAKE within 90 days (MAKE90) and 1 year (MAKE365) after surgery (*Table 7*).

Table 7. Definitions of exclusion criteria and outcomes.	
Exclusion criteria	
Preoperative renal dysfunction (eGFR <60 ml/min/1.73 m^2)	ICD-10: N17, N18, N19, Z49 ATC: V03AE, A02AH, B03XA Procedure code starting with PBL, PBM, PBU, JAK10 Registration in the Swedish Renal Register
ICD-codes registered in any position; for N17 and N19 within 1 year before surgery, for N18 and Z49 within 5 years before surgery. *ATC-codes registered as dispensed drug at least once within 1 year before surgery.* *Registration in the Swedish Renal Register before surgery.*	
Kidney surgery	Procedure code starting with KAC, KAD, KAS
Primary outcome	
Advanced CKD (eGFR <30 ml/min/1.73 m^2)	Within 1 year after surgery (postoperative day 91-365): ICD-10: N18, Z49 ATC: V03AE, A02AH, B03XA Registration in the Swedish Renal Register
ICD-codes registered in any position: for N18 from postoperative day 90, for Z49 as first postoperative registration. *ATC-codes registered as first postoperative drug dispense.* *First postoperative registration in the Swedish Renal Register.* *For all registrations within 90 days after surgery patients were considered to have advanced AKD transitioning to advanced CKD, and the date was set to 3 months after the registration date.*	
Secondary outcomes	
Advanced AKD (eGFR <30 ml/min/1.73 m^2)	Within 90 days after surgery (postoperative day 0-90): ICD-10: N17, N19, Z49 ATC: V03AE, A02AH, B03XA Registration in the Swedish Renal Register
MAKE90 (eGFR <30 ml/min/1.73 m^2, chronic dialysis, all-cause death)	Within 90 days after surgery: ICD-10: N17, N19, Z49 ATC: V03AE, A02AH, B03XA Registration in the Swedish Renal Register Registration in the Swedish Cause of Death Register
MAKE365 (eGFR <30 ml/min/1.73 m^2, chronic dialysis, all-cause death)	Within 1 year after surgery: ICD-10: N18, Z49 ATC: V03AE, A02AH, B03XA Registration in the Swedish Renal Register Registration in the Swedish Cause of Death Register
ICD-codes registered in any position. *ATC-codes registered as first postoperative drug dispense.* *First postoperative registration in the Swedish Renal Register.* *Postoperative registration in the Cause of Death Register.* *For MAKE365: N18 registered from postoperative day 90, Z49 registered as first postoperative registration. For all registrations within 90 days after surgery (except for registrations in the Swedish Cause of Death Register) patients were considered to have advanced AKD transitioning to advanced CKD, and the date was set to 3 months after the registration date.*	
Abbreviations: A02AH, sodium bicarbonate; B03XA, erythropoiesis-stimulating agents; JAK10, laparotomy with placement of peritoneal dialysis catheter; KAC, nephrectomy; KAD, partial nephrectomy; KAS, kidney transplantation; N17, acute renal failure; N18, chronic renal failure; N19, unspecified renal failure; PBL/PBM/PBU, procedures involving arterio-venous fistulas; V03AE, phosphate or kalium binders; Z49, dialysis care.	

Statistical analysis

Associations of perioperative risk factors with the outcomes were assessed using Fine and Gray competing risks regression for renal outcomes[127], and Cox proportional hazards regression for MAKE. The competing outcome was all-cause mortality. Multivariable models were constructed based on variables with $p < 0.1$ in univariate analyses and biological plausibility. For AKD and MAKE90, analyses were performed on all patients. For CKD and MAKE365, analyses were performed on those alive at postoperative day 90 and included also postoperative variables. Subdistribution hazard ratios (SHRs), hazard ratios (HRs) and their 95% CIs were calculated. For advanced CKD, cumulative incidence curves were constructed based on the multivariable Fine and Gray model and stratified by previous episodes of advanced AKD. For CKD, two sensitivity analyses were performed to assess the robustness of the findings.

4.7 Study IV

Design and study population

This observational cohort study was a long-term follow-up of a cohort of cardiac surgery patients[85]. Eligible patients were adults without preoperative kidney failure or kidney transplants, who underwent on-pump cardiac surgery at the Karolinska University Hospital in Solna in 2014 or 2015, and who had undergone RRI measurements the day before surgery. Exclusion criterion was loss to follow-up, which lasted until 5 years after index surgery.

Definitions

Preoperative RRI ≥0.70 was defined as elevated in accordance with clinical practice. The primary outcome was persistent renal dysfunction, defined as a ≥25% decline in eGFR from the preoperative value sustained for a minimum of 3 months[25]. Secondary outcomes were MAKE (incorporating the primary outcome, initiation of RRT, or all-cause death[25]) and MACE (incorporating myocardial infarction, unstable angina, decompensated heart failure, stroke, or cardiovascular death[27]). To calculate eGFR, the 2021 Chronic Kidney Disease Epidemiology Collaboration formula based on sex, age, and SCr was used[128]. Baseline SCr was obtained at the closest time before surgery (generally the day before surgery). Postoperative AKI was defined according to SCr or urine output criteria of the KDIGO guidelines[10].

Statistical analysis

Median RRI between groups was compared using the Wilcoxon rank-sum test. Cumulative incidence curves were constructed using the Kaplan-Meier method, and the log-rank test was used for comparisons of those with and without elevated RRI. The association of elevated RRI with the outcomes was assessed using Cox proportional hazards regression, with calculation of HRs and 95% CIs. Predefined multivariable models were constructed, adjusted for basic patient characteristics (age, sex), physiological parameters at measurement (pulse pressure, heart rate), and clinically important comorbidities (eGFR-level, heart failure). Additionally, exploratory multivariable models were constructed using stepwise forward variable selection based on significance levels ($p < 0.2$) in univariate analyses and biological plausibility. Two sensitivity analyses were performed to assess the robustness of the findings.

Additionally for this thesis, AUC for preoperative RRI ≥0.70 for predicting the primary outcome was calculated together with its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with corresponding 95% CIs. This analysis was performed on patients without preoperative severe aortic insufficiency since this vitium itself may alter the RRI value without necessarily affecting renal prognosis[129].

4.8 Ethical considerations

All studies in this thesis were approved by the Swedish Ethical Review Authority (studies I, II and IV) or by the Regional Ethics Committee, Stockholm, Sweden (study III), and complied with the Declaration of Helsinki.

RRI measurements, conducted in studies I, II and IV, are non-invasive diagnostic ultrasonographic procedures known to be safe for humans[47]. Caution was taken during the measurements to ensure they did not interfere with routine patient care.

Regarding the ethical principles of research – doing good, avoiding harm, justice, and autonomy – the latter warrants further reflection concerning the studies included in this thesis. In studies I and IV, volunteers and patients provided informed consent before enrollment. However, in study II, the Swedish Ethical Authority granted an approach with waived informed consent due to the critical condition of the COVID-19 patients, rendering them incapable of providing consent. Pandemic restrictions during the first wave prevented relatives from being in the hospitals, hindering consent through next of kin. In this context, it can be argued that the imperative need for knowledge about this new and deadly disease, combined with the observational nature of the study and the non-invasive nature of the performed measurements, outweighed the potential violation of autonomy. A written information sheet was provided to patients or next of kin with the opportunity to withdraw participation retrospectively. No included patient withdrew their participation. In study III, which solely relied on registry data, informed consent was waived. All data handled in this study were anonymized, and the key file for identifying individual patients was kept at The National Board of Health and Welfare, which had been responsible for data matching.

Patient data used in all studies were handled according to established confidentiality routines, ensuring the privacy and confidentiality of the individuals involved.

5 Results

5.1 Study I

Volunteers

A total of 23 volunteers were included. Median age was 38 years (IQR, 31-49), 61% were female, and median body mass index (BMI) was 24 kg/m^2 (IQR, 23-26). Median RRI measured by the expert was 0.58 (IQR, 0.52-0.62).

Comparison of RRI between operators

Out of a possible 138 kidney pole measurements, the intermediate operator obtained 136 (99%) acceptable readings, the novice 134 (97%), and the expert 138 (100%). At least two acceptable kidney pole readings were obtained per kidney, and each operator obtained an acceptable mean RRI for every volunteer.

ICC for the intermediate and expert was excellent (0.96 [95% CI, 0.90-0.98]), and for the novice and expert in the range of moderate to excellent (0.85 [95% CI, 0.69-0.94]). Both non-experts exhibited good accuracy with negligible bias (95% CI for mean difference, <±0.02) and clinically acceptable precision (95% LoA, ≤±0.06) (*Figure 2*).

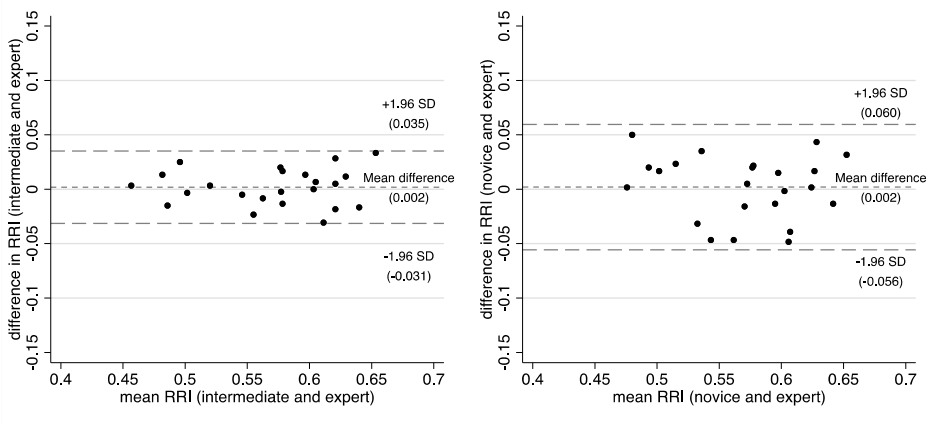

Figure 2. Bland-Altman plots comparing measurements of the intermediate to the expert (left) and the novice to the expert (right). Bias is indicated by the mean difference, and precision is indicated by the 95% LoA (± 1.96 SDs from the mean difference).

After excluding the first 5 volunteers, both non-experts were able to obtain all possible kidney pole measurements. ICC remained excellent for the intermediate and expert, and increased to the range of good to excellent (0.90 [95% CI, 0.75-0.96]) for the novice and expert.

5.2 Study II

Study population

A total of 51 patients were included. Median age was 63 years (IQR, 57-67), 88% were male, and median BMI was 29 kg/m^2 (IQR, 25-31). Hypertension and diabetes mellitus were present in 57% and 20% respectively. During the ICU period, 96% had received mechanical ventilation and vasopressor therapy respectively.

RRI measurements were performed on median ICU day 18 (IQR, 6-29). AKI was present in 23 patients (45%), of which 17 (74%) had AKI stage 3 and 13 (57%) received RRT. The AKI patients had higher BMI, and more often received mechanical ventilation or vasopressors at the time of measurement compared to those without AKI. Among the 28 patients without AKI, 11 (39%) had a previous AKI episode but had recovered.

RRI and AKI

Median RRI for all patients was 0.76 (IQR, 0.69-0.82). RRI was higher in patients with AKI compared to those without (0.80 [IQR, 0.71-0.85] vs 0.72 [IQR, 0.67-0.78], p=0.004), largely driven by the many patients with AKI stage 3 (*Figure 3*). RRI did not differ between patients that never had AKI and those with recovered AKI, but was higher in the AKI group compared to both of these groups (*Figure 3*). RRI was higher in oliguric patients compared to non-oliguric patients (0.84 [IQR, 0.83-0.85] vs 0.74 [IQR, 0.69-0.81], p=0.009).

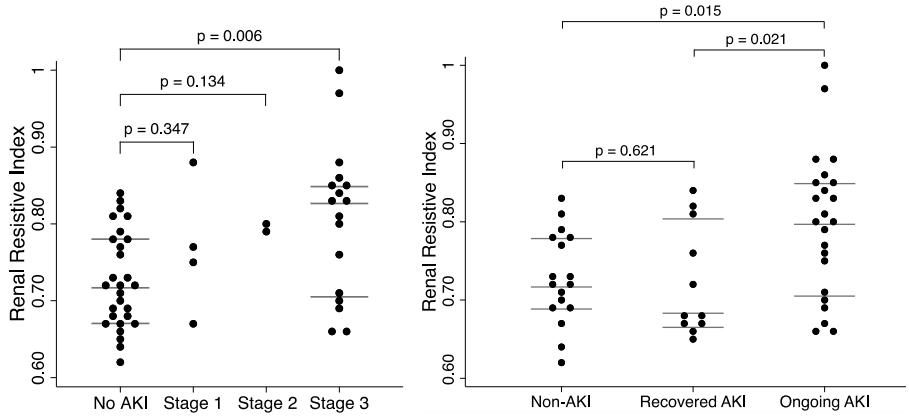

Figure 3. Dot plots of RRI in patients with no AKI and AKI stages 1-3 (left), and of RRI in patients who never developed AKI, who recovered from AKI, or had an ongoing AKI episode at the time of measurement (right). Each dot represents a patient. Horizontal lines represent median, upper, and lower quartiles.

RRI was associated with AKI after adjustment for BMI, CKD, vasopressors, and antiplatelet use (OR, 1.22 [95% CI, 1.07-1.41]).

5.3 Study III

Study population

The final study population consisted of 237 124 patients of which 230 081 (97%) were alive at postoperative day 90. Median age was 63 years (IQR, 47-74) and 56% were female. The most prevalent surgery types were orthopedic (32%), abdominal (19%), and urological (9%), with 30% classified as emergency procedures and 21% performed due to cancer indications. Among all patients, 25% had an ASA score ≥3. Hypertension and diabetes mellitus were present in 19% and 10% respectively.

Long-term outcomes

Overall, 1 597 patients (0.67%) developed advanced CKD within 1 year after surgery and 16 789 (7.1%) developed MAKE365. Advanced AKD within 90 days after surgery and MAKE90 were developed in 1 661 (0.70%) and 8 270 (3.5%) respectively. In general, patients developing any of these outcomes were older, more often male, and had a higher preoperative comorbidity burden compared to those not developing any outcome. *Figure 4* illustrates patient status in relation to renal outcomes and death at postoperative day 90 and 365. Among those alive at postoperative day 90 with advanced AKD, 36% were alive and had developed advanced CKD 1 year after surgery and 51% had developed MAKE365. Among those alive 1 year after surgery with advanced CKD, 33% had a previous episode of advanced AKD within 90 postoperative days.

Perioperative risk factors for long-term outcomes

Multivariable analyses identified several risk factors for the long-term outcomes related to patient characteristics, the surgical procedure, and the postoperative course (*Table 8-9*). Notable risk factors associated with advanced CKD were higher ASA score, undergoing urological surgery, prolonged surgical duration, repeated surgery, and postoperative use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) (*Table 9*). Advanced AKD was associated with advanced CKD (SHR, 44.5 [95% CI, 38.7-51.1]) and MAKE365 (HR, 6.60 [95% CI, 6.07-7.17]). Cumulative incidence of advanced CKD was increased in those with advanced AKD, especially in the first 3 months after which diagnosis was considered (*Figure 5*). Results were consistent in sensitivity analyses.

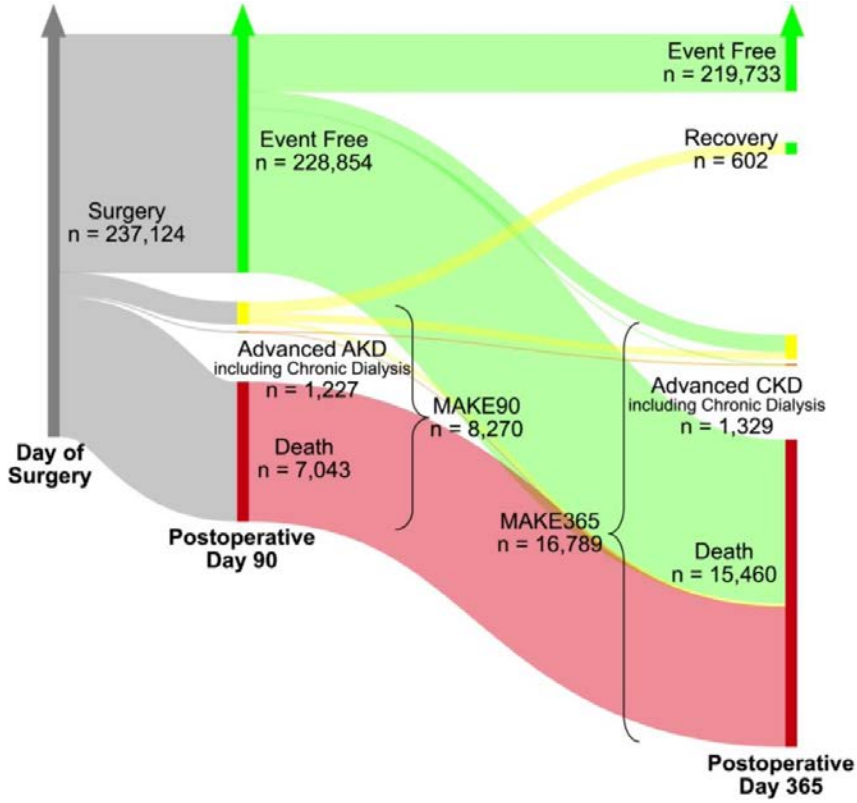

Figure 4. Sankey diagram showing patient status at day 90 and 365 after surgery according to renal outcomes and death. Green flows represent patients that were event-free at postoperative day 90. Yellow flows represent patients with advanced AKD at postoperative day 90, of which orange flows represent patients on chronic dialysis. Recovery corresponds to eGFR ≥60 ml/min/1.73 m^2.

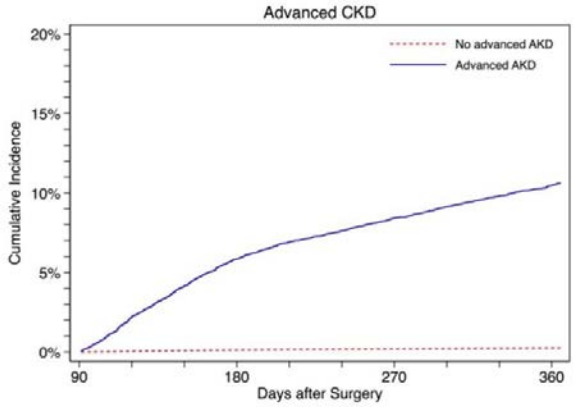

Figure 5. Cumulative incidence function curve for advanced CKD in patients alive at postoperative day 90 according to previous episodes of advanced AKD.

Table 8. Multivariable analyses for development of advanced AKD within 90 days after surgery and MAKE90 in all patients.

	Advanced AKD	MAKE90
Events / total population (%)	1,661 / 237,124 (0.70%)	8,270 / 237,124 (3.5%)
	Adjusted SHR (95% CI)	**Adjusted HR** (95% CI)
Demographics		
Age (years) <65	Reference	Reference
65–69	1.38 (1.17–1.64)*	1.53 (1.40–1.67)*
70–74	1.43 (1.20–1.70)*	1.75 (1.60–1.91)*
75–79	1.65 (1.39–1.97)*	2.23 (2.05–2.43)*
80–84	1.79 (1.50–2.14)*	2.69 (2.48–2.92)*
≥85	1.93 (1.62–2.31)*	4.48 (4.16–4.83)*
Male sex	1.31 (1.17–1.46)*	1.12 (1.07–1.17)*
ASA score 1	Reference	Reference
2	3.87 (2.96–5.06)*	4.17 (3.57–4.86)*
3	8.96 (6.81–11.8)*	12.0 (10.3–14.0)*
≥4	21.5 (15.8–29.4)*	35.1 (29.8–41.2)*
Surgical variables		
University hospital	1.18 (1.06–1.31)*	0.95 (0.91–1.00)
Cancer indication	1.39 (1.23–1.56)*	2.95 (2.79–3.10)*
Emergency procedure	2.08 (1.85–2.34)*	2.96 (2.81–3.11)*
Type, Abdominal	Reference	Reference
Breast	0.13 (0.06–0.28)	0.13 (0.09–0.18)
Endocrine	0.45 (0.27–0.78)	0.39 (0.28–0.54)
Ophthalmic	0.30 (0.14–0.68)	0.35 (0.24–0.53)
Ear Nose and Throat	0.25 (0.13–0.51)	0.29 (0.20–0.42)
Oral and maxillofacial	0.36 (0.21–0.63)	0.44 (0.34–0.57)
Thoracic	1.43 (1.06–1.93)*	1.44 (1.26–1.64)*
Neuro	0.33 (0.25–0.43)	1.02 (0.94–1.11)
Urological	1.77 (1.51–2.08)*	0.72 (0.65–0.78)
Gynecological	0.48 (0.34–0.68)	0.42 (0.36–0.50)
Orthopedic	0.65 (0.57–0.75)	0.87 (0.82–0.93)
Vascular	0.85 (0.68–1.06)	0.76 (0.68–0.85)
Dermatological	1.12 (0.85–1.47)	0.68 (0.59–0.78)
Duration >4 hours	3.81 (3.35–4.33)*	1.65 (1.53–1.78)*

Both models adjusted for preoperative comorbidities (hypertension, diabetes mellitus, ischemic heart disease, heart failure, atrial fibrillation, peripheral arterial disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, anemia) in addition to presented variables.
*Elevated point estimate with p <0.05.

Table 9. Multivariable analyses for development of advanced CKD within 1 year after surgery and MAKE365 in those alive at postoperative day 90.

	Advanced CKD	MAKE365
Events / patients alive at postoperative day 90 (%)	1,562 / 230,081 (0.68%)	9,746 / 230,081 (4.2%)
	Adjusted SHR (95% CI)	**Adjusted HR** (95% CI)
Demographics		
Age (years) <65	Reference	Reference
65–69	0.96 (0.81–1.15)	1.34 (1.24–1.44)*
70–74	1.15 (0.97–1.37)	1.48 (1.37–1.59)*
75–79	1.19 (1.00–1.43)	1.79 (1.66–1.92)*
80–84	1.19 (0.97–1.46)	2.19 (2.04–2.36)*
≥85	1.30 (1.06–1.59)*	3.19 (2.98–3.42)*
Male sex	1.26 (1.11–1.42)*	1.08 (1.03–1.13)*
ASA score 1	Reference	Reference
2	2.75 (2.16–3.50)*	3.13 (2.82–3.47)*
3	4.06 (3.12–5.28)*	5.96 (5.36–6.64)*
≥4	5.47 (3.87–7.73)*	8.85 (7.76–10.1)*
Surgical variables		
University hospital	1.30 (1.15–1.47)*	0.97 (0.92–1.01)
Cancer indication	1.56 (1.36–1.79)*	5.11 (4.86–5.36)*
Emergency procedure	not included	1.68 (1.59–1.76)*
Type, Abdominal	Reference	Reference
Breast	0.35 (0.20–0.61)	0.38 (0.32–0.44)
Endocrine	1.08 (0.73–1.62)	0.75 (0.61–0.94)
Ophthalmic	1.08 (0.62–1.88)	1.24 (0.99–1.56)
Ear Nose and Throat	1.17 (0.77–1.77)	0.78 (0.64–0.96)
Oral and maxillofacial	0.69 (0.42–1.11)	0.93 (0.79–1.09)
Thoracic	1.00 (0.64–1.57)	1.01 (0.87–1.17)
Neuro	0.75 (0.58–0.97)	1.33 (1.23–1.44)*
Urological	2.83 (2.39–3.35)*	1.06 (0.98–1.14)
Gynecological	0.99 (0.73–1.35)	0.69 (0.61–0.77)
Orthopedic	0.85 (0.71–1.01)	1.00 (0.94–1.06)
Vascular	1.13 (0.87–1.46)	1.08 (0.98–1.19)
Dermatological	0.97 (0.67–1.38)	0.89 (0.79–1.00)
Duration >4 hours	1.76 (1.51–2.04)*	0.94 (0.88–1.01)
Postoperative variables		
Advanced AKD	44.5 (38.7–51.1)*	6.60 (6.07–7.17)*
Hospital length of stay >7 days	1.50 (1.30–1.72)*	1.72 (1.64–1.81)*
Repeated surgery within 90 days	2.17 (1.75–2.70)*	1.72 (1.58–1.88)*
Postoperative drugs		
NSAID	0.94 (0.79–1.12)	0.95 (0.89–1.01)
ACEi or ARB	1.28 (1.12–1.45)*	0.82 (0.78–0.86)
Statin	0.92 (0.80–1.06)	0.69 (0.65–0.73)

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug.
Both models adjusted for preoperative comorbidities (hypertension, diabetes mellitus, ischemic heart disease, heart failure, atrial fibrillation, peripheral arterial disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, anemia) in addition to presented variables.
*Elevated point estimate with p <0.05.

5.4 Study IV

Study population

The final study population consisted of 96 patients. Median age was 69 years (IQR, 61-73), 73% were male, and median BMI was 26 kg/m^2 (IQR, 24-29). Median baseline eGFR was 86 ml/min/1.73 m^2 (IQR, 75-96), 59% had hypertension and 21% had diabetes mellitus. Among the surgeries performed, 38% were isolated coronary-artery bypass procedures, 39% were isolated valve procedures, and the remaining 23% were combined or aortic procedures.

RRI and long-term outcomes

In total, 58 patients (60%) had elevated preoperative RRI ≥0.70. These patients were older; more often had preoperative CKD, heart failure, or anemia; and had higher pulse pressure at the time of measurement. During follow-up, 25 patients (26%) developed persistent renal dysfunction, 34 (35%) developed MAKE, and 28 (29%) developed MACE. RRI was higher in patients developing any long-term outcome (*Figure 6*). Among those with elevated RRI and postoperative AKI (n=22, 23%), 45% developed persistent renal dysfunction, 68% developed MAKE, and 59% developed MACE.

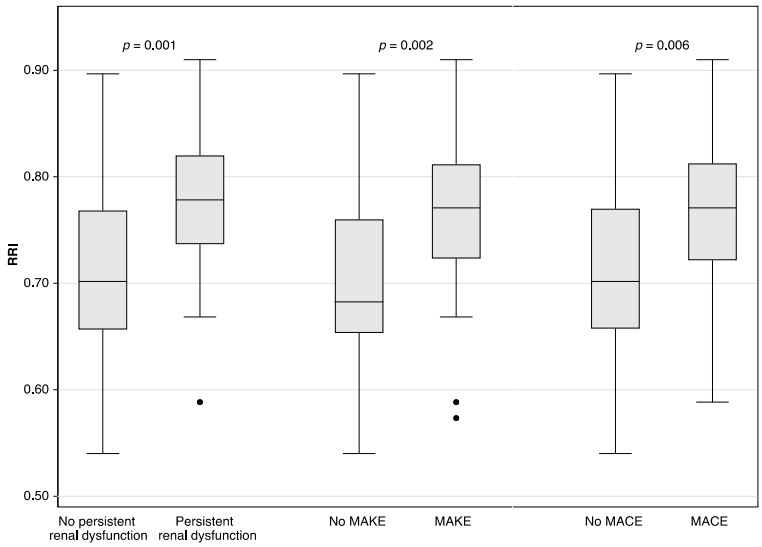

Figure 6. Box plots of preoperative RRI in patients with or without development of long-term outcomes within 5 years after surgery. The central line inside the box represents the median, the ends of the box represent upper and lower quartiles, whiskers represent the upper and lower adjacent values, and dots represent outliers.

Patients with elevated RRI had higher cumulative incidences of all long-term outcomes (*Figure 7*). Elevated RRI was associated with all long-term outcomes across all multivariable models, except for the stepwise forward selection model for MACE (*Table 10*). Results were consistent in sensitivity analyses.

In patients without severe aortic insufficiency at measurement (n=78, 81%), RRI ≥0.70 predicted persistent renal dysfunction during follow-up with an AUC of 0.74 (95% CI, 0.64–0.83), and sensitivity 0.86 (95% CI, 0.65–0.97), specificity 0.61 (95% CI, 0.47–0.74), PPV 0.46 (95% CI, 0.31–0.63), and NPV 0.92 (95% CI, 0.78–0.98).

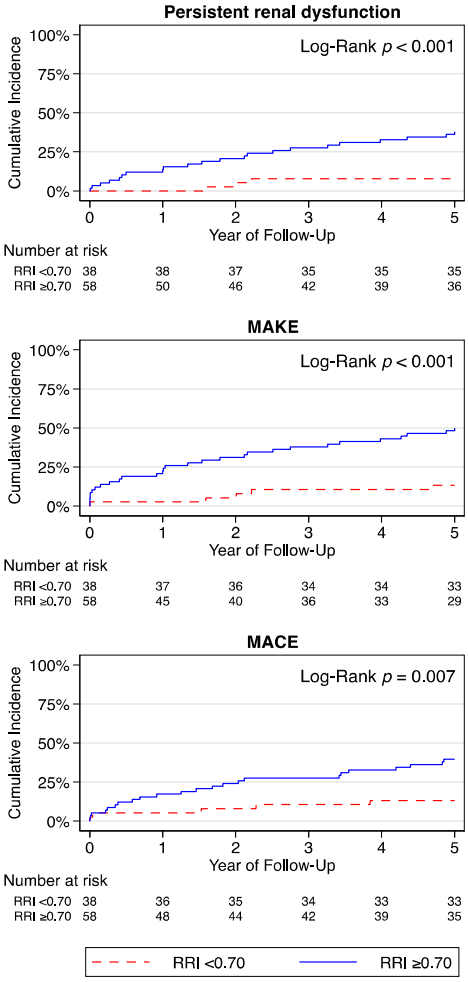

Figure 7. Cumulative incidence curves for long-term outcomes in patients with normal or elevated preoperative RRI.

Table 10. Hazard ratios for long-term outcomes within 5 years in relation to elevated preoperative RRI.

	RRI <0.70	RRI ≥0.70
Persistent renal dysfunction		
Events/patients, n/n (%)	3 / 38 (8%)	22 / 58 (38%)
	Referent	HR (95% CI)
Crude	1.00	6.23 (1.86–20.9)
Adjusted for age, sex	1.00	5.02 (1.48–17.1)
Adjusted for pulse pressure, heart rate	1.00	5.72 (1.63–20.0)
Adjusted for eGFR, heart failure	1.00	5.82 (1.71–19.9)
Stepwise forward selection model[a]	1.00	4.73 (1.37–16.3)
MAKE		
Events/patients, n/n (%)	5 / 38 (13%)	29 / 58 (50%)
	Referent	HR (95% CI)
Crude	1.00	4.91 (1.90–12.7)
Adjusted for age, sex	1.00	3.78 (1.44–9.94)
Adjusted for pulse pressure, heart rate	1.00	5.46 (2.02–14.8)
Adjusted for eGFR, heart failure	1.00	4.21 (1.59–11.1)
Stepwise forward selection model[b]	1.00	2.83 (1.03–7.73)
MACE		
Events/patients, n/n (%)	5 / 38 (13%)	23 / 58 (40%)
	Referent	HR (95% CI)
Crude	1.00	3.50 (1.33–9.21)
Adjusted for age, sex	1.00	2.96 (1.09–8.05)
Adjusted for pulse pressure, heart rate	1.00	3.93 (1.41–11.0)
Adjusted for eGFR, heart failure	1.00	2.81 (1.03–7.65)
Stepwise forward selection model[c]	1.00	2.37 (0.80–7.03)

[a]Final adjustment for age, peripheral vascular disease
[b]Final adjustment for age, anemia, heart failure
[c]Final adjustment for age, anemia, heart failure, stroke

6 Discussion

6.1 Main findings

This thesis explored new perspectives on RRI in perioperative and critical care. Our findings suggest that RRI measurements performed by intermediate and novice sonographers were reliable, accurate, and precise when compared to an expert. Non-experts were able to learn the method after only a half-day training course, and there was a steep learning curve for the technique.

RRI was generally elevated in critically ill COVID-19 patients and was associated with AKI. Patients with an ongoing AKI episode had higher RRI compared to those without AKI or with recovered AKI, indicating dynamic RRI changes in response to renal recovery. All patients with oliguria had RRI ≥0.80.

In patients without preoperative renal dysfunction undergoing surgery, <1% developed advanced CKD while ~7% developed MAKE within the first postoperative year. Advanced AKD was a major risk factor for both outcomes, although most patients developing advanced CKD had not experienced advanced AKD in the near postoperative period. Preoperative RRI ≥0.70 was associated with persistent renal dysfunction, MAKE and MACE within 5 years after cardiac surgery. Up to two-thirds of the patients with elevated RRI and postoperative AKI developed adverse long-term outcomes during follow-up.

6.2 Methodological considerations

All studies in this thesis were observational, investigating associations, and some methodological considerations should be addressed.

Internal validity

Internal validity refers to whether the study findings are accurate and reliable within the studied population[130]. A high level of internal validity indicates absence of systematic errors, including bias and confounding.

Bias

In study I, various measures were undertaken to mitigate bias. Importantly, the three operators performing the RRI measurements were blinded to the examinations and the results of one another. Each operator performed both measurements and calculations of RRI at the bedside, replicating how the method is used within POCUS settings. Examinations were performed consecutively, with minimal time span and random order between operators for every volunteer, to ensure that conditions of paired measurements remained similar. Overall, we believe our meticulous approach rendered reliable results within the study setting.

Study II was susceptible to bias due to several factors. Despite efforts to screen the participating ICUs in a standardized manner, the final study population was essentially a convenience sample of critically ill COVID-19 patients, which may have introduced selection bias. Although the operators performing RRI measurements were not directly engaged in patient care, 25% of the patients had ongoing RRT which prevented blinding to renal function at measurement in these cases. Additionally, there was a risk of misclassification of AKI events and AKI recovery. AKI was defined based on a relative increase in SCr from baseline, and hospital admission SCr was used when representative baseline values were missing (n=7, 14%). This could have led to misclassification of patients with an ongoing AKI process already present at hospital admission as not having AKI, leading to an underestimation of the AKI incidence. Muscle wasting in the most severely ill patients, leading to decreased SCr from lower muscle mass, may have led to misclassification of these patients as having recovered their renal function when in fact renal dysfunction was still present. However, these limitations are well-known pitfalls in AKI research that relies on SCr criteria[11, 131]. The long time from admission to inclusion further meant that the AKI group in fact was a mixture of patients with AKI (duration ≤7 days) and AKD (duration >7 days).

In study III, sensitivity analyses were conducted when the original dataset was cleaned to mitigate the potential impact of selection bias arising from the exclusion of cases with missing data[124]. Consequently, we were able to employ a complete-case approach to missing data. The registry-based approach used for defining renal outcomes in the absence of SCr inevitably introduced the risk of misclassification. However, a validation study conducted in a similar Swedish setting has demonstrated high accuracy for this approach when assessing advanced renal dysfunction with eGFR <30 ml/min/1.73 m^2, strengthening the validity of our findings[125]. Underreporting of less severe events may have led to ascertainment bias with risk of exaggerated point estimates for the associations. We used Fine and Gray competing risks regression for assessing renal outcomes to account for deaths that prevented the occurrence of renal events. Mortality comprised >90% of the MAKE outcome, highlighting the importance of this separate approach to identify risk factors specifically for renal outcomes.

In study IV, preoperative SCr measurements were available in all patients and there was no loss to follow-up, which enhances the validity of our findings. Compared to study III, the larger ratio of renal events relative to deaths (mortality constituted 26% of the MAKE outcome) meant that the issue of competing risks due to death was less prominent, and Cox proportional hazards regression was used for both renal outcomes and MAKE.

Confounding

Confounders are factors that are associated with the outcome, are unevenly distributed between exposure groups, and are not a direct effect of the exposure, thus leading to confusion of effects[130]. While confounders can be eliminated by randomization in experimental studies, they will inherently be present in observational studies and must be handled by other methods.

In studies II, III, and IV, confounding was addressed using multivariable regression analyses. Generally, variables included in these models were established or probable causal factors between the exposure and outcome, of clinical relevance, or had shown an association with the outcome in univariate analyses. In studies II and IV, small sample sizes with few outcome events necessitated careful consideration of the events per variable ratio to avoid overfitting with exaggerated point estimates. The general rule of thumb is to maintain 10 events per variable, although this rule has been challenged and the appropriate ratio probably should be based on the context of the individual study[132]. The final multivariable model in study II had ~5 events per variable, and the results should be interpreted with caution. In study IV, there were 7 to 10 events per variable for the different models with consistent results across all analyses, enhancing the robustness of the findings. In study III, the large sample size allowed for more comprehensive multivariable analyses. However, residual confounding from unmeasured or inaccurately measured variables will never be fully accounted for, and this problem may be more prominent in a registry-based study. Of note, the association of postoperative ACEi or ARB use with advanced CKD may be due to confounding by indication, and is probably better addressed in a clinical trial. Further, point estimates for SHRs, accounting for competing risks, are complex in their interpretation and not directly comparable to HRs. Instead, they should be interpreted more on their directionality than their absolute values[133].

External validity

External validity refers to the extent to which study findings can be generalized to populations beyond those directly studied, thus being applicable to a broader clinical context[130]. Internal validity therefore serves as the foundation for external validity.

In study I, two key considerations should be raised. Firstly, the study was conducted on volunteers predominantly with a normal BMI, and our findings may not be generalized to critically ill or severely obese patients. Nonetheless, our findings should be applicable to many clinical settings, including preoperative measurements as were performed in study IV. Secondly, only one non-expert represented each ultrasound experience level, and it is likely that the non-experts in our study were more motivated than other individuals with similar experience levels.

Study II included only critically ill COVID-19 patients during the first wave of the pandemic in Sweden, resulting in an unusually homogeneous ICU cohort, but also restricting generalizability to this specific patient population. Potential selection bias in the inclusion of patients makes it important to consider the patient characteristics of the final study population when comparing results to other studies. Of note, three out of four patients with AKI at RRI measurements had AKI stage 3, and our findings are therefore primarily applicable to severe AKI cases. RRI measurements were performed late in the clinical course, and the implications on COVID-19 patients in earlier stages of their critical illness are uncertain. While the inclusion of six ICUs at two geographically separated sites enhances generalizability, it is important to note that the presentation of COVID-19 very much has evolved since the first wave, potentially impacting the applicability of our findings to current COVID-19 populations.

In study III, the cohort was large and consisted of patients undergoing various types of non-cardiac surgical procedures at hospitals of diverse levels across all regions of Sweden. Consequently, our findings should be applicable to patients without renal dysfunction undergoing surgery in countries with similar health care systems. The age of the dataset, with follow-up until 2014, however raises the possibility of changes in surgical indications and renal treatment options over time, potentially affecting the relevance of the findings to current surgical cohorts. At the same time, this allows for future comparisons over time.

Study IV was a single-center study including patients undergoing on-pump cardiac surgery. Since this surgery type encompasses an increased risk of postoperative renal complications compared to other surgery types[134], our findings may not be broadly applicable to other surgical contexts. We defined the primary outcome as sustained eGFR-decline ≥25%[25], which was possible due to the utilization of laboratory data with extensive coverage. An alternative approach would have been to use the KDIGO criteria for AKD or CKD, but this would have resulted in fewer events, and we were already limited by the fixed available sample.

Random errors

Random errors will always be present but in contrast to systematic errors, they diminish with increased study power. High precision denotes the absence of random errors and can be assessed using p-values and CIs. Type I errors occur when an association is detected where none exists (falsely rejecting the null hypothesis), while Type II errors occur when a true association is missed (falsely failing to reject the null hypothesis)[135].

Studies II and IV had limited sample sizes, and although main results were statistically significant, the wide CIs suggest that point estimates should be interpreted cautiously. As discussed regarding the multivariable model in study II, there was a risk of a Type I error resulting from a potentially inflated point estimate in the association between RRI and AKI. In study IV, the lack of statistical significance in the exploratory MACE model may instead have been due to the small sample size and a Type II error. The large sample size in study III reduced the likelihood of random errors in this study.

6.3 Clinical perspective

RRI as a POCUS method

There are several reasons RRI is appealing as a POCUS method. Firstly, Doppler readings can be obtained fast (within minutes), and the RRI value can easily be calculated at the bedside. Secondly, RRI is a quantifiable measure that can be monitored repeatably over time. Lastly, by utilizing a ratio of absolute blood flow velocities obtained from the same spectral reading, the final RRI value is independent of the insonation angle. Consequently, operators may acquire different absolute blood velocities due to varying insonation angles while still calculating interchangeable RRI values.

Described as an easy method[50], study I in this thesis was the first to show the feasibility of RRI among non-experts with varying prior ultrasound experience levels. Previous studies have demonstrated low interobserver variability of RRI measurements performed by expert sonographers[97, 136, 137]. One prior validation study was conducted in an ICU setting, involving three French ICUs, which importantly should be seen as expert centers of the RRI method[138]. Non-experts in this study were residents with prior critical care ultrasound training who underwent a comparable training course to that of our study to learn the RRI technique. ICC, when compared to expert sonographers, was in the range of good to excellent (0.89 [95% CI, 0.82-0.93]), which is comparable to the results of both non-experts in our study. However, precision was a concern (95% LoA, >±0.1), raising doubts regarding the clinical utility of RRI measurements by non-experts. In a recent post-hoc analysis of a large multicenter study, the same research group however concluded that clinical findings were robust also after adjustment for operator experience levels[139]. While the volunteer setting in study I may not directly be transferrable to the ICU, it resembled the setting for study IV where measurements were performed on patients in a clinically stable preoperative phase. Further, with the increasing integration of POCUS teaching already into undergraduate medical curricula[140, 141], the outlook for learning advanced POCUS techniques, including RRI, appears promising. It is plausible that the basic ultrasound level today is higher compared to the period of data collection for the mentioned ICU feasibility study over a decade ago[138]. While already recommended as part of POCUS training for nephrologists[142], RRI is however yet to be included in the curriculum for basic critical care ultrasonography outlined by the European Society of Intensive Care Medicine[143].

RRI and AKI

Due to its many determinants, it becomes clear that interpretation of RRI is complex and highly dependent on the clinical context. The disappointing results of RRI to predict short-term AKI prognosis in recent ICU studies may be due to the diverse and heterogenous nature of the included ICU cohorts[73, 75]. In study II, we, for the first time, demonstrated an association of RRI with AKI in ICU patients with critical COVID-19. Pronounced RRI elevations had been suggested from pilot studies including 10 and 15 critically ill COVID-patients respectively[144, 145], and our findings were later confirmed by a single-center study including 65 ICU patients with COVID-19[146]. In the latter study, RRI ≥0.70 was associated with AKI, RRT, and mortality but it was not reported how early or late in the ICU course the measurements had been performed. Eventually, a study employing magnetic resonance tomography to assess RBF in patients with critical COVID-19 displayed reduced global, cortical, and medullary perfusion in those with AKI[147]. Altogether, findings from several studies suggest significantly altered renal hemodynamics in critically ill COVID-19 patients with AKI. Contributing mechanisms may be endothelial injury with activation of complement and coagulation pathways, local inflammation, and thrombotic microangiopathy[148]. During the first wave of the pandemic, the combination of mechanical ventilation with high positive end-expiratory pressures and restrictive fluid management aimed primarily at treating the new form of acute respiratory distress syndrome, may have contributed to a state of relative hypovolemia and further progression of AKI[149, 150]. However, with widespread vaccination programs, advancements in the treatment of COVID-19, and changes in viral variants, the incidence of critical COVID-19 and associated AKI has fortunately decreased significantly[149]. It is uncertain whether these shifts in the disease also are reflected in the RRI of affected patients. Nonetheless, our findings from study II shed light on the feasibility of implementing the RRI method under resource-constrained conditions, also outside expert centers, to enable a rapid bedside assessment of renal function.

Given the dynamic conditions of patients in the ICU, repeated RRI measurements are probably essential to monitor patients over time. Dynamic changes in systemic hemodynamics, dosing of vasoactive drugs, and volume status affecting RCWP, may all influence the RRI value in this setting. In AKI, especially RVR affected by intrarenal vasoconstriction and increased RCWP from local inflammation may contribute to a potentially reversible RRI elevation[64]. Dynamic RRI changes have been reported with progression of AKI in septic ICU patients[136], or in the perioperative period[80-82, 151]. Our findings from study II, showing lower RRI in patients with recovered AKI compared to those with an ongoing AKI episode, suggest that RRI may be dynamic and responsive also to renal recovery. Without repeated measurements, it is challenging to distinguish these dynamic changes from RRI values dependent on more fixed patient-specific factors.

Interestingly, all oliguric patients in our study had an RRI ≥0.80. Therefore, RRI may serve as a bedside tool to identify critically ill AKI patients not capable of managing their fluid balance and thereby assisting clinicians in decisions regarding initiation or discontinuation of RRT. Our cohort comprised of few oliguric patients (n=5, 10%) and further studies are needed to explore the clinical utility of this finding.

Long-term outcomes after surgery

In study III, we investigated the epidemiology of postoperative long-term renal dysfunction, encompassing the characterization of AKD to CKD transition in the perioperative setting. This topic has recently emerged as a prioritized area of research[152]. In the long-term follow-up of the prospective multinational EPIS-AKI study, 10% of patients without preoperative renal dysfunction had an eGFR <60 ml/min/1.73 m^2 when measured at 3 months after surgery[153]. At this time, 1% of patients had advanced AKD or CKD, with eGFR <30 ml/min/1.73 m^2. This incidence is higher compared to our study, but we included a much broader surgical population and not only those undergoing major surgical procedures. We found higher ASA score to be a strong risk factor for both isolated renal outcomes and MAKE, aligning with previous studies on more specific surgery types[154, 155], and highlighting the efficacy of this score in capturing the multifaceted comorbidity burden in surgical patients[156]. Urological surgery was a risk factors for advanced AKD and CKD, while other types of surgery were associated with an increased risk for MAKE. These differences probably stem from the fact that the MAKE outcome was largely driven by mortality. Markers of a complicated postoperative course, such as prolonged hospital stays and repeated surgery, were associated with all long-term outcomes, which is consistent with previous studies[153, 155]. Our study confirms findings from other settings[20, 21, 157], suggesting AKD to be a key driver for the development of advanced CKD and MAKE also after surgery. The primary outcome, advanced CKD, is important since it aligns with the eGFR-threshold of 30 ml/kg/1.73 m^2, at which referral to specialized nephrology care is recommended[12]. This patient group experiences considerable morbidity and mortality[158], and identification of those at risk already in the perioperative period could enable early interventions aimed at improving outcomes.

RRI and long-term outcomes after surgery

In study III, two-thirds of patients with advanced CKD within the first postoperative year had not experienced advanced AKD in the near postoperative period. Instead, most cases had probably transitioned from lighter forms of AKD not captured in our data, or from other triggering events than the surgical procedure. Additional measures, such as RRI, may help identify these high-risk patients at an earlier stage. Elevated RRI measured in a clinically stable phase has shown associations with renal or cardiovascular outcomes in specific out-patient populations[99-101], but our results from study IV was the first to show this association also in a surgical cohort. Interestingly, associations with all long-term outcomes were stronger for RRI than for several traditional risk factors such as hypertension and diabetes mellitus. This indicates that RRI is a sensitive marker for subclinical cardiovascular disease, and it is possible that the elevated RRI observed in these patients represents the systemic atherosclerotic burden, as proposed in previous studies[55-57]. Preoperative RRI may thus serve as an early quantifiable risk measure for long-term postoperative prognosis, reflecting the comprehensive risk profile of the individual patient.

Patients with diminished renal functional reserve capacity, meaning patients whose kidneys lack capacity to further increase GFR, are at the highest risk of renal function decline following a renal insult[45]. Interestingly, RRI has demonstrated to accurately reflect measured renal functional reserve capacity[159, 160], which might explain its promising role in predicting long-term renal outcomes. In our study, preoperative RRI ≥0.70 had an AUC of 74% for prediction of long-term eGFR-decline, which is considered to be in the range of acceptable to good for most prediction models[161]. However, less than half of the patients with elevated RRI developed long-term outcomes during follow-up, as reflected by the PPV of only 46% in our cohort. This suggests that RRI measurements alone are insufficient to rule in high-risk patients and should be combined with other diagnostic measures for better predictive performance. Nevertheless, elevated RRI constitutes a warning signal and could be utilized as a bedside screening tool for an increased risk of CKD, recurrent AKI with progression along the AKI-AKD-CKD continuum, and development of cardiovascular complications in surgical patients. The NPV of 92% in our cohort indicated that a normal RRI effectively ruled out low-risk patients in this setting. However, it is important to note that our study was not primarily designed for prediction purposes. Future properly designed studies are needed to better explore the utility of RRI, as well as determine its optimal cut-offs, for the prediction of long-term outcomes in perioperative and critical care settings.

7 Conclusions

RRI measurements, by quantifying renal hemodynamics and patient-specific risk factors, have a role for the assessment of renal outcomes in perioperative and critical care.

- RRI measurements are feasible within POCUS, and most clinicians can learn the technique following a focused training session.

- RRI was associated with AKI in critically ill COVID-19 patients during the first wave of the pandemic, and the method could effetively be implemented for clinical research during a period of limited resources.

- RRI may be helpful to identify AKI, oliguria, and renal recovery at the bedside.

- Advanced CKD after surgery is a rare but clinically significant outcome. Important perioperative risk factors include a high ASA score and undergoing urological or extensive surgery. Advanced AKD is a key driver for advanced CKD development and MAKE, but clinicians should be vigilant in all high-risk patients undergoing surgery.

- Elevated preoperative RRI is associated with persistent renal dysfunction, and long-term MAKE and MACE after cardiac surgery.

- As a screening tool or in combination with other factors, RRI could serve as a risk measure to help identify high-risk surgical patients requiring intensified clinical care and long-term follow-up.

8 Future perspectives

Renal POCUS, integrating RRI, will certainly play a role as part of the clinical examination for patients treated in the ICU or presenting for surgery in the future (*Table 11*).

In the short-term perioperative and critical care settings, elevated RRI may indicate a very early signal for kidney injury, offering a therapeutic window for interventions. Prospective studies with repeated measurements are needed to determine if RRI is a reasonable therapeutic target in these situations. To enhance predictive performance, RRI measurements should probably be combined with other measures such as resistive indices from other organ systems, or Doppler readings of renal venous outflow. Isolated RRI elevations may suggest an intrarenal cause, while simultaneously elevated resistive indices in arteries of the brain, liver, or spleen may indicate a systemic process[4, 64]. The effective arterial renal perfusion time during the cardiac cycle can easily be evaluated from RRI readings in combination with real-time electrocardiographic tracings, and has shown better diagnostic accuracy for persistent AKI in the ICU compared to RRI alone[162]. Use of the venous excess ultrasound (VExUS) score, which combines venous Doppler readings from kidneys, hepatic veins, and the portal vein, has shown promise as a bedside tool for quantification of fluid overload[163]. With increased congestion, venous flows transition from continuous to more pulsatile, and high VExUS scores have been associated with adverse renal events after cardiac surgery[64, 79] and in mixed ICU patients[164]. The diagnostic accuracy for predicting AKI resulting from fluid overload, congestion, or increased intraabdominal pressure may be best assessed by combining RRI and venous Doppler, thereby assessing the arterio-venous coupling[79, 165]. Contrast-enhanced ultrasonography (CEUS) combines renal ultrasonography with microbubble-based contrast agents and offers a more detailed assessment of renal microperfusion.[166] CEUS has shown to detect regional RBF disturbances in patients with septic AKI[167], but its predictive performance for AKI in the ICU has not shown to be superior to that of RRI[168], while its feasibility as a POCUS method has been questioned[76, 169].

In the long-term perioperative setting, RRI measured in a clinically stable phase could serve as a risk measure to identify high-risk patients. Incorporating RRI into scoring systems for prognostication of short-term complications after specific surgery types has been proposed[170], and our findings suggest this should be explored also for long-term risk assessment in properly designed prediction studies. For prediction of AKI, novel biomarkers have generally not increased the diagnostic accuracy of RRI[72, 171]. However, biomarkers focusing on long-term renal adverse events, in combination with RRI, other POCUS measures, and clinical risk factors, are yet to be investigated.

Furthermore, investigating the role of RRI as a therapeutic target for preventing CKD progression warrants attention. Treatment with sodium-glucose cotransporter-2 inhibitors[172] or angiotensin receptor-neprilysin inhibitors[173] have shown to decrease RRI, and although these drugs have shown to reduce mortality in certain high-risk populations[43, 174, 175], the impact of this RRI decrease on clinical outcomes is not known.

Table 11. Future applications of RRI within POCUS.

Repeated measurements during a dynamic clinical course:	
RRI + RI from brain, liver, spleen + renal venous Doppler + CEUS	Characterization and prognostication of AKI Differentiate intrarenal from systemic causes Asses arterio-venous coupling Assess disturbances of microperfusion
RRI + renal venous Doppler or VExUS	Guide resuscitation (vasopressors, fluids) Assess fluid overload Guide de-resuscitation (diuresis, RRT)
Measurements during a stable clinical course:	
RRI	Prognostication of long-term outcomes (as part of a risk score) Guide preventive therapies (drugs)

There is a need for further studies on the epidemiology of long-term renal outcomes following intensive care and surgery, including also milder forms of the AKI-AKD-CKD continuum. These studies should incorporate high-resolution registries and comprehensive laboratory data to gain a better understanding of long-term renal outcomes of varying severities. Additionally, research exploring MAKE, particularly post-AKI, is warranted as the absence of MAKE at 30, 90 or 365 days in this context should be considered a clinically meaningful measure of renal-disability-free survival.

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