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Early Detection of Acute Kidney Injury: The Role of a Novel Biomarker Panel in Perioperative Care

Doctoral dissertation in medical and health sciences
in the field of medical sciences

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1. Dedication

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My family and beloved ones for their understanding and continuous support.

I dedicate this work to my junior colleagues who are starting their scientific careers in critical care.

2. Abbreviations list

Abbreviation	Full Term
AKD	Acute Kidney Disease
AKI	Acute Kidney Injury
AUC	Area Under the Curve
CI	Confidence Interval
CKD	Chronic Kidney Disease
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
EVAR	Endovascular Aortic Repair
IGFBP-7	Insulin-Like Growth Factor-Binding Protein-7
KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	Kidney Injury Molecule-1
MEDLINE	Medical Literature Analysis and Retrieval System Online
NTN-1	Netrin-1
PACU	Post-Anaesthesia Care Unit
PENK	Proenkephalin A 119-159
POCT	Point-of-Care Testing
RBP-4	Retinol Binding Protein-4
RRT	Renal Replacement Therapy
sAKI	Subclinical Acute Kidney Injury
SAPS	Simplified Acute Physiology Score II
SCr	Serum Creatinine
SEMA-3A	Semaphorin-3A
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Protocol
TIMP-2	Tissue Inhibitor of Metalloproteinase-2
UOP	Urine Output

3. List of publications constituting the doctoral dissertation

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ANALIZA BIBLIOMETRYCZNA PUBLIKACJI
PANA KONRADA ZUZDY,
WCHODZĄCYCH W SKŁAD CYKLU PUBLIKACJI STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

Lp.	Opis bibliograficzny	Impact Factor	MNiSW	Najwyższy kwartyl*
Artykuły				
1.	Walczak-Wieteska P, **Zuzda K** [aut. koresp.], Małyszko J, Andruszkiewicz P. Proenkephalin A 119–159 as an early biomarker of acute kidney injury in complex endovascular aortic repair: an explorative single-center cross-sectional study with the utilization of two measurement methods. Periopertaive Medicine. 2025;14(1):1-8 [Rodzaj publikacji: praca oryginalna]	2,100	100	Q2
2.	**Zuzda K**, Walczak-Wieteska P, Andruszkiewicz P, Małyszko J. Evaluation of a Novel Biomarker Panel for Acute Kidney Injury Following Endovascular Aortic Repair. International Journal of Molecular Sciences. 2025;26(22):1-18 [Rodzaj publikacji: praca oryginalna]	4,900	140	Q1
3.	**Zuzda K** [aut. koresp.], et al. Acute Kidney Injury Biomarkers in Perioperative Care: A Scoping Review of Clinical Implementation. Diagnostics. 2025;16(1):1-23 [Rodzaj publikacji: praca poglądowa]	3,300	70	Q1
	Łącznie:	**10,300**	**310**	-
Książki				
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* Kwartyl z roku publikacji, według Impact Factor.

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4. Abstract in Polish

Wprowadzenie. Ostre uszkodzenie nerek (AKI, ang. Acute Kidney Injury) jest częstym i klinicznie istotnym powikłaniem endowaskularnego zabiegu naprawy tętniaka aorty brzusznej (EVAR, ang. endovascular aortic repair), szczególnie w przypadku złożonych procedur z fenestracjami i rozgałęzieniami. AKI u pacjentów poddanych EVAR wynika z wielu patofizjologicznych mechanizmów m.in. uszkodzenia w mechanizmie niedotlenienia-reperfuzji, nefrotoksyczności indukowanej kontrastem, zakrzepicy mikronaczyniowej oraz ogólnoustrojowej aktywacji zapalnej. Obecne kryteria diagnostyczne oparte na stężeniu kreatyniny w surowicy i diurezie godzinowej powodują opóźnienie w diagnostyce AKI i nie pozwalają zidentyfikować przyczyny uszkodzenia nerek. Panel biomarkerów integrujący markery pochodzące z wielu lokalizacji nefronu oraz szlaków patofizjologicznych stanowi koncepcyjnie uzasadnioną, jednak klinicznie niezwalidowaną strategię wczesnego wykrywania AKI w populacjach wysokiego ryzyka.

Cel pracy. Celem rozprawy składającej się z serii 3 publikacji było prospektywne zbadanie panelu biomarkerów wczesnego wykrywania AKI w okresie okołooperacyjnym u pacjentów poddawanych zabiegom EVAR, przy wyborze biomarkerów zgodnie z ich mechanizmem oraz lokalizacją uwalniania z nefronu. Celami pracy były również charakteryzacja wydajności proenkefaliny A 119-159 (PENK) jako wczesnego czynnościowego biomarkera AKI oraz osadzenie tychże badań w kontekście systematycznej oceny wdrażania nowych biomarkerów AKI w opiece okołooperacyjnej.

Metodologia. Rozprawa obejmuje trzy powiązane publikacje. Publikacje 1 i 2 bazowały na prospektywnym, jednoośrodkowym, obserwacyjnym badaniu przekrojowym. 68 pacjentów zostało poddanych elektywnym zabiegom EVAR, w przeważającej mierze złożonym procedurom z rozgałęzieniami. Pacjenci zostali zakwalifkikowani do badania i leczeni zgodnie z ustandaryzowanym protokołem okołooperacyjnym pacjentów poddawanym EVAR. Próbki krwi i moczu były pobierane w 4 punktach czasowych, od okresu przedoperacyjnego przez trzy następujące po sobie dni pooperacyjne. Stężenie PENK w krwi mierzono niezwłocznie za pomocą testu przyłóżkowego (POCT, ang. point-of-care testing) w oddziale pooperacyjnym. Następnie przeprowadzono analizę za pomocą testu immunoenzymatycznego (ang. ELISA, enzyme-linked immunosorbent assay): PENK w osoczu, semaforyny-3A w osoczu (SEMA-3A), białka wiążącego retinol-4 w osoczu (RBP-4), cząsteczki uszkodzenia nerek-1 w moczu (KIM-1), netryny-1 w moczu, tkaninowego inhibitora metaloproteinaz-2 (TIMP-2) w moczu i białka wiążącego czynnik wzrostu insulinopodobny-7 (IGFBP-7) w moczu.

AKI definiowano zgodnie z kryteriami Kidney Disease: Improving Global Outcomes (KDIGO) 2012. Monitorowano także przeżywalność pacjentów w ciągu sześciu miesięcy od zabiegu. Publikacja 3 zawierała przegląd literatury nad nowymi biomarkerami AKI w okresie okołooperacyjnym, oparty na systematycznym przeszukaniu baz MEDLINE, Europe PMC i Scopus.

Wyniki. Panel oparty o biomarkery o różnym mechanizmie uwalniania, łączący PENK POCT (marker filtracji kłębuszkowej), SEMA-3A w osoczu (marker niedotlenienia-reperfuzji) i KIM-1 w moczu (marker uszkodzenia proksymalnych kanalików), osiągając pole pod krzywą (AUC, ang. area under the curve) 0,89, z 95% przedziałem ufności (CI, ang. confidence interval: 0,77-1,00, we wczesnym wykrywaniu AKI. Panel ten wykazał lepsze wyniki niż każdy indywidualny biomarker z osobna oraz dostępna komercyjnie kombinacja TIMP-2×IGFBP-7. Alternatywny panel z RBP-4 w osoczu zamiast SEMA-3A wykazał porównywalne wyniki (AUC = 0,81; 95% CI: 0,65-0,99) bez istotnej statystycznie różnicy. Wśród indywidualnie ocenianych biomarkerów SEMA-3A w osoczu wykazała najwyższą zdolność rozróżniającą (AUC = 0,88), a następnie RBP-4 w osoczu (AUC = 0,81). PENK mierzony za pomocą POCT wykazał wysoką czułość (80% w pierwszy dzień po operacji) i konsekwentnie wysoką wartość predykcyjną negatywną, wspierającą jego potencjalną rolę narzędzia wykluczającego, jednak umiarkowaną zgodność z kryteriami KDIGO. Zaawansowany wiek i okołooperacyjne podanie produktów krwi były określone jako czynniki ryzyka AKI. Pooperacyjne AKI było powiązane z istotnie podwyższoną śmiertelnością w ciągu sześciu miesięcy (50% versus 88,1% przeżywalności; p = 0,006). Przegląd literatury potwierdził, że wdrażanie paneli biomarkerów w praktyce klinicznej pozostaje ograniczone heterogenicznością testów, brakiem standaryzowanych wartości granicznych i niepewnością dotyczącą opłacalności.

Wnioski. Oparty na mechanizmach patofizjologicznych panel biomarkerów integrujący PENK POCT, SEMA-3A w osoczu i RBP-4 w moczu może osiągnąć lepsze wczesne wykrycie AKI u pacjentów poddawanych zabiegom EVAR w porównaniu z indywidualnymi biomarkerami i aktualnie zatwierdzonymi dwumarkerowymi kombinacjami. Jednakże niewielka wielkość próby i jednoośrodkowy charakter badania wskazują na potrzebę szerszej walidacji. Wśród indywidualnie ocenianych biomarkerów SEMA-3A i RBP-4 wykazały najwyższą zdolność rozróżniającą przewyższając tradycyjne markery diagnostyczne, sugerując ich potencjał jako nowe biomarkery AKI w zabiegach niekardiochirurgicznych wysokiego ryzyka. PENK mierzony za pomocą POCT wykazał wysoką wartość predykcyjną negatywną i może zapewniać klinicznie użyteczną zdolność wykluczającą przy łóżku pacjenta, jednak jego

umiarkowana swoistość i tendencja do przeszacowania ryzyka AKI uniemożliwiają jego użycie jako samodzielnego markera diagnostycznego. Wyniki te wspierają prospektywną walidację proponowanych paneli w wieloośrodkowych badaniach i uzasadniają rozważenie włączenia monitorowania PENK POCT do ustandaryzowanych pakietów opieki nad pacjentami z AKI w okresie okołooperacyjnym u pacjentów poddawanych złożonym zabiegom EVAR.

5. Abstract in English

Background. Acute Kidney Injury (AKI) is a frequent and clinically challenging complication after endovascular aortic repair (EVAR), particularly in complex fenestrated and branched procedures. The condition results from multiple mechanisms including ischaemia-reperfusion injury, contrast-induced nephrotoxicity, microvascular thrombosis, and systemic inflammatory activation. Current diagnostic criteria based on serum creatinine and urine output are intrinsically delayed and fail to identify the underlying injury phenotype. A biomarker panel that integrates markers from distinct nephron compartments and pathophysiological pathways represents a conceptually sound yet clinically unvalidated strategy for earlier and more precise AKI detection in high-risk populations.

Aims. This 3 publication-cycle dissertation aimed to prospectively evaluate a biomarker panel for early perioperative AKI detection in patients undergoing complex EVAR, with markers selected according to distinct nephron locations and release mechanisms. Secondary aims were to characterise the performance of proenkephalin A 119-159 (PENK) in early AKI detection and to contextualise the findings against existing evidence on AKI biomarker implementation in perioperative settings.

Methods. This dissertation comprises three interrelated publications. Publications 1 and 2 were based on a prospective, single-centre, cross-sectional observational study. 68 patients undergoing elective EVAR, predominantly complex branched procedures, were enrolled under a standardised perioperative protocol. Serial blood and urine samples were collected from the preoperative period through 3 consecutive postoperative days. PENK was measured immediately by point-of-care testing (POCT) in the post-anaesthesia care unit. Concurrent batch enzyme-linked immunosorbent assay (ELISA) analysis was performed of serum PENK, serum semaphorin-3A (SEMA-3A), serum retinol-binding protein-4 (RBP-4), urinary kidney injury molecule-1 (KIM-1), urinary netrin-1, urinary tissue inhibitor of metalloproteinase-2 (TIMP-2), and urinary insulin-like growth factor-binding protein-7 (IGFBP-7). AKI was defined by Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria, and 6-month survival was assessed by structured follow-up. Publication 3 was a scoping review of novel AKI biomarkers implementation in the perioperative setting, based on systematic searches of MEDLINE, Europe PMC, and Scopus.

Results. The primary mechanism-driven biomarker panel combined PENK POCT (glomerular filtration marker), serum SEMA-3A (ischaemia-reperfusion marker), and urinary KIM-1

(proximal tubular injury marker), achieving an area under the curve (AUC) of 0.89 (95% confidence interval [CI]: 0.77-1.00) for early AKI detection. This panel outperformed each constituent biomarker individually and the commercially available TIMP-2×IGFBP-7 combination. An alternative panel substituting serum RBP-4 for SEMA-3A yielded comparable performance (AUC = 0.81; 95% CI: 0.65-0.99), with no statistically significant difference. Amongst individually evaluated biomarkers, serum SEMA-3A achieved the highest discriminatory performance (AUC = 0.88), followed by serum RBP-4 (AUC = 0.81). PENK measured by POCT demonstrated high sensitivity (80% on postoperative day one) and consistently high negative predictive value, supporting its potential role as a bedside rule-out tool, though with moderate KDIGO agreement. Advanced age and perioperative blood product administration were identified as AKI risk factors after EVAR. Postoperative AKI was associated with significantly increased six-month mortality (50% versus 88.1% survival; p = 0.006). The scoping review confirmed that clinical implementation of biomarker panels remains constrained by assay heterogeneity, absence of standardised cut-off values, and uncertain cost-effectiveness.

Conclusions. This dissertation provides prospective evidence that a mechanism-driven biomarker panel integrating PENK POCT, serum SEMA-3A, and urinary KIM-1 may achieve superior early AKI detection in EVAR patients compared with individual biomarkers and currently approved two-marker combinations. However, modest sample size and single-centre design warrant wider validation. Amongst individually evaluated biomarkers, serum SEMA-3A and RBP-4 demonstrated the highest discriminatory performance and substantially outperformed traditional diagnostic markers, suggesting potential as novel AKI discriminators in perioperative, high-risk, non-cardiac surgery settings. PENK POCT demonstrated high negative predictive value and may provide clinically useful bedside rule-out capability, yet its moderate specificity and tendency to overestimate AKI risk preclude its use as a standalone diagnostic marker. These findings support prospective multicentre validation of the proposed panels and warrant consideration for incorporation of PENK monitoring into structured AKI care bundles for perioperative kidney protection in patients undergoing complex EVAR.

Key words: AKI; EVAR; PENK; semaphorin-3A; biomarker panel; perioperative care

6. Introduction

6.1. Definition of AKI: Epidemiology and Clinical Outcomes

Acute Kidney Injury (AKI) is a common, heterogeneous, and multifactorial syndrome encompassing a broad spectrum of kidney dysfunction, from subtle early changes in nephron function to complete organ failure requiring renal replacement therapy [1]. AKI affects approximately 13.3 million people worldwide per year and is responsible for up to 1.7 million deaths annually [2].

The evolution of AKI definitions has been critical to the field. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) established a harmonised definition and staging system that has since become the standard for clinical practice, research, and public health initiatives. The KDIGO criteria, the current gold standard diagnostic framework, define AKI by an increase in serum creatinine (SCr) of 0.3mg/dL or more within 48 hours, a rise to at least 1.5 times the prior baseline within 7 days, or a reduction in urine output (UOP) below 0.5mL/kg/h sustained for 6 hours (Table 1), with three progressive stages of severity [1,3]. This standard approach replaced earlier heterogeneous definitions that had resulted in widely varying estimates of disease prevalence (1-25%) and mortality (15-60%) [4]. AKI represents a substantial global challenge, affecting 10-15% of hospitalised and more than 50% of intensive care unit patients [1]. The KDIGO framework also introduced the concept of acute kidney disease (AKD), encompassing kidney dysfunction lasting up to 3 months, with AKI representing the subset occurring within the first 7 days [1]. Subclinical AKI (sAKI), detected by elevation in kidney damage biomarkers without meeting conventional creatinine or urine output criteria, represents an emerging clinical entity associated with adverse outcomes including mortality and need for renal replacement therapy [5].

The clinical significance of AKI extends far beyond the acute episode. Patients with AKI face substantially elevated risks of both short-term and long-term adverse outcomes. AKI is associated with increased in-hospital mortality, intensive care unit admission, and need for renal replacement therapy (RRT) [6]. The long-term consequences are equally concerning. Meta-analyses demonstrate that AKI survivors have 2.67-fold increased risk of developing chronic kidney disease (CKD), a 4.81-fold increased risk of end-stage kidney disease, and a 1.80-fold increased risk of death compared to matched controls [7]. These risks persist even in patients with the mildest (stage 1) AKI and those with transient episodes lasting less than 3 days [8]. Furthermore, AKI induces systemic effects beyond the kidneys, including cardiovascular events, stroke, infections, and substantially reduced quality of life [1].

Table 1. Classification and staging of acute kidney injury (AKI), including subclinical AKI.

Stage	Serum creatinine criterion	Urine output criterion	Biomarker criterion	Clinical notes
Subclinical AKI	No qualifying change in SCr; does not meet KDIGO Stage 1 threshold.	No qualifying change in UOP; does not meet KDIGO threshold.	Novel biomarker positivity, e.g. PENK ≥ 80 pmol/L, urinary TIMP-2×IGFBP-7 ≥ 0.3 (ng/mL).	Structural or functional kidney injury preceding KDIGO threshold; associated with adverse long-term outcomes.
Stage 1	↑ SCr ≥0.3mg/dL within 48h, OR ↑ SCr ≥1.5-1.9× baseline within 7 days.	UOP <0.5mL/kg/h for 6-12 h.	-	**Mildest** KDIGO stage; reversible in majority; elevated risk of CKD progression.
Stage 2	↑ SCr ≥2.0-2.9 × baseline.	UOP <0.5mL/kg/h for ≥12 h.	-	**Moderate severity**; increased risk of RRT requirement and in-hospital mortality.
Stage 3	↑ SCr ≥3.0× baseline, OR SCr ≥4.0mg/dL, OR initiation of RRT, OR eGFR <35mL/min/1.73m² in patients <18 years.	UOP < 0.3mL/kg/h for ≥ 24 h, OR anuria for ≥ 12 h.	-	**Severe**; high short- and long-term mortality; high RRT dependency.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IGFBP-7, insulin-like growth factor-binding protein-7; KDIGO, Kidney Disease: Improving Global Outcomes; PENK, proenkephalin A 119-159; RRT, renal replacement therapy; SCr, serum creatinine; TIMP-2, tissue inhibitor of metalloproteinase-2; UOP, urine output.
KDIGO Stages 1-3 adapted from [3]. Subclinical AKI defined as novel biomarker positivity in the absence of KDIGO-qualifying changes in serum creatinine or urine output; concept and PENK threshold adapted from [9].

6.2. Pathophysiology and Heterogeneity of AKI after EVAR procedure

The pathophysiology of AKI involves the simultaneous interactions of haemodynamic instability, inflammatory processes, and nephrotoxic insults [1,10]. In the perioperative care setting, acute tubular necrosis commonly arises from renal ischaemia secondary

to hypoperfusion during surgery, bleeding, dehydration, shock, or sepsis, often compounded by toxic interaction from medications, contrast agents, or pigment injury from myoglobin or haemoglobin [4]. Notably, recent evidence challenges traditional concepts by demonstrating that renal blood flow may be normal or even increased in early sepsis-associated AKI, suggesting a dissociation between renal perfusion and kidney function, with microvascular dysfunction and inflammatory injury playing more prominent roles than global hypoperfusion [11].

In a vulnerable population of patients undergoing endovascular aortic repair (EVAR), AKI combines distinct procedure-specific mechanisms with baseline patient vulnerabilities. The incidence of AKI after EVAR ranges from 2.8% to 23%, with higher rates observed in complex EVAR [12]. The predominant mechanism includes renal hypoperfusion due to systemic iatrogenic vasodilatation. Reduced cardiac output, which triggers ischaemia-reperfusion injury, is another key driver of tubular and epithelial cell death via apoptosis and necrosis. Mitochondrial dysfunction and the generation of reactive oxygen species are additional injury pathways [13,14]. Concurrently, systemic inflammatory responses activate endothelial injury pathways, promote microvascular thrombosis, and amplify tubular damage through cytokine-mediated inflammation. In patients undergoing EVAR, these mechanisms are compounded by procedure-specific insults. Aortic clamping or partial occlusion during device deployment transiently reduces renal perfusion pressure, whilst distal embolization of atheromatous debris and thrombus fragments obstruct renal microvasculature [15]. Iodinated contrast media administered intraoperatively induces direct tubulotoxicity and vasoconstriction of afferent arterioles. This mechanism is especially hazardous in patients with pre-existing CKD, diabetes mellitus, or haemodynamic instability [16]. Furthermore, systemic inflammatory activation following aortic manipulation releases vasoactive mediators that impair the autoregulatory capacity of the renal microvasculature [17]. The clinical significance extends beyond the acute episode, as post-EVAR AKI is associated with persistent renal dysfunction that fails to return to the baseline and confers 1.6 to 2.4-fold increased risk of three-year mortality [12].

6.3. Diagnostic Challenges of AKI

The diagnosis of AKI in the perioperative setting is still challenging due to the limitations of conventional diagnostic criteria and the complex interplay of perioperative factors. The standard KDIGO definition relies on changes in SCr and UOP, both of which are nonspecific and may be confounded by various perioperative factors, including

haemodynamic shifts, fluid administration, technique and duration of the procedure, and the effects of anaesthetic drugs [18]. Intraoperative oliguria may occur in the absence of kidney injury, or conversely, AKI may develop with minimal changes in UOP. Additionally, perioperative AKI often develops rapidly, and the lag in SCr rise can delay diagnosis, limiting opportunities for early intervention. In the context of EVAR, renal dysfunction may arise through a convergence of multiple mechanisms that may act synergistically and are not reliably captured by conventional diagnostic criteria [15]. Moreover, postoperative sAKI not fulfilling the KDIGO criteria occurred in approximately one in ten patients undergoing major surgery, and was associated with longer-term adverse outcomes including major adverse kidney events and 30-day mortality [19]. The evolving understanding of AKI as a continuum ranging from subclinical injury preceding KDIGO stage 1 through AKD, CKD and end-stage kidney disease increasingly challenges the biomarkers used to define AKI. These diagnostic limitations highlight the need for sensitive, mechanism-specific biomarkers capable of detecting early stress and structural injury in the perioperative period.

6.4. AKI Novel Biomarkers

Novel AKI biomarkers have expanded diagnostic capabilities beyond traditional KDIGO criteria, particularly in perioperative non-cardiac surgical patients. Kidney Injury Molecule-1 (KIM-1, ~90 kDa) is a transmembrane glycoprotein upregulated in injured proximal tubular cells; proteolytic cleavage releases its ectodomain into urine within 12-24 h of structural damage, making it a sensitive and site-specific marker of proximal tubular injury [20]. Retinol Binding Protein-4 (RBP-4, ~21 kDa) is a low-molecular-weight carrier protein freely filtered at the glomerulus and almost entirely reabsorbed by healthy proximal tubules. When tubular dysfunction occurs, impaired reabsorption of the retinol-free apo-RBP-4 fraction results in urinary spillage that can signal subclinical injury before SCr elevation [20]. Semaphorin-3A (SEMA-3A), a 65 kDa guidance molecule constitutively expressed in podocytes and collecting tubules, becomes detectable in urine within hours of ischaemia-reperfusion injury. It mediates tubular epithelial cell apoptosis and promotes inflammation, and urinary levels have shown early discriminatory value for AKI prediction in several perioperative cohorts [21]. Netrin-1 (NTN-1) is a 72 kDa anti-inflammatory protein predominantly secreted by proximal tubular epithelial cells in response to hypoxic or toxic injury. It redistributes from the peritubular endothelium

to injured tubules during AKI and is detectable in urine at early stages [21]. Proenkephalin A 119-159 (PENK), a 4.5 kDa stable peptide fragment, is freely filtered across the glomerular

membrane and is neither secreted nor reabsorbed by the tubules. Its plasma concentration therefore rises inversely with GFR, independently of muscle mass, providing a functional estimate of GFR [22].

The cell cycle arrest markers Tissue Inhibitor of Metalloproteinases-2 (TIMP-2, ~21 kDa) and Insulin-like Growth Factor Binding Protein-7 (IGFBP-7, ~29 kDa) are constitutively expressed in renal tubular cells, TIMP-2 predominantly in distal tubule cells and IGFBP-7 in proximal tubule cells. They are released into urine through reduced tubular reabsorption and cellular leakage when tubular stress occurs, before frank injury is established [20,22]. Both biomarkers arrest tubular cells in the G1 phase of the cell cycle, a protective response that limits further replicative damage but simultaneously signals active cellular stress. Their combined urinary measurement (TIMP-2xIGFBP-7) is regulator-approved for predicting moderate-to-severe AKI, stages 2-3, within 12-24 h in high-risk surgical and critically ill patients [20,22]. These biomarkers (Table 2), when used in conjunction, improve diagnostic precision, facilitate risk stratification, and may guide perioperative management strategies. However, limitations include assay variability, lack of harmonised cut-offs, and the need for further validation in diverse surgical cohorts [20].

Table 2. *Novel AKI biomarkers included in the dissertation.*

Biomarker	Molecular Weight	Sample	Nephron Location	Category	Detection Window
KIM-1 *Kidney Injury Molecule-1*	~90 kDa	Urine	Proximal tubule	Damage	12-24 h
RBP-4 *Retinol Binding Protein-4*	~21 kDa	Urine, Plasma	Proximal tubule	Injury / Functional	0-72 h
SEMA-3A *Semaphorin-3A*	~65 kDa	Urine, Plasma	Podocytes / Distal tubule	Damage	2-6 h
NTN-1 *Netrin-1*	~72 kDa	Urine	Proximal tubule	Damage	2-6 h
PENK *Proenkephalin A 119-159*	4.5 kDa	Plasma	Glomerulus	Functional / GFR surrogate	2-6 h
TIMP-2 *Tissue Inhibitor of Metalloproteinases-2*	~21 kDa	Urine, Plasma	Distal tubule	Stress (G1 arrest)	4-12 h

Biomarker	Molecular Weight	Sample	Nephron Location	Category	Detection Window
IGFBP-7 *Insulin-like Growth Factor Binding Protein-7*	~29 kDa	Urine	Proximal tubule	Stress (G1 arrest)	4-12 h

Abbreviation: GFR, glomerular filtration rate.

6.5. The Role of Novel AKI Biomarkers, Biomarker Panels and Bundles in Perioperative Care

AKI is increasingly recognised as a pathophysiologically heterogeneous syndrome. This understanding has driven a shift away from single-biomarker diagnostics towards integrated multi-biomarker panels that interrogate distinct nephron compartments and injury mechanisms. Integration of stress and damage biomarkers offers superior phenotypic characterisation compared with either category alone, enabling more individualised therapy [23]. In the perioperative setting, biomarker-guided risk stratification has gained substantial clinical traction through sAKI detection defined as biomarker positivity without KDIGO criteria, which identifies patients at elevated long-term risk who would otherwise escape clinical detection [9].

Biomarker-guided care bundles demonstrate clinical utility beyond diagnosis. In the PrevAKI randomised controlled trial, urinary TIMP-2×IGFBP-7≥0.3 identified high-risk cardiac surgery patients; the KDIGO bundle intervention significantly reduced AKI incidence compared with standard care [24]. These findings extended to non-cardiac populations in the multinational BigpAK-2 trial, in which the KDIGO bundle significantly decreased moderate or severe AKI within 72 hours of major surgery, with consistent effects across intention-to-treat and per-protocol analyses [25].

7. Rationale and Objectives

The aim of this publication-cycle dissertation was to evaluate the clinical utility of novel biomarkers in the early perioperative diagnosis of AKI following EVAR, with particular emphasis on contextualising these findings within the broader landscape of AKI biomarker research in perioperative care.

Publication 1 evaluated PENK as an early AKI biomarker in patients undergoing complex EVAR. It compared point-of-care testing (POCT) and laboratory enzyme-linked immunosorbent assay (ELISA) methods, assessing sensitivity, specificity, and agreement with KDIGO-defined AKI.

Publication 2 investigated whether a mechanism-based biomarker panel could provide superior early AKI detection compared with individual biomarkers in EVAR patients. The proposed panel comprised PENK POCT, serum SEMA-3A or serum RBP-4, and urinary KIM-1, selected according to distinct nephron locations and release mechanisms.
Publication 3 provided a comprehensive review of novel AKI biomarkers in perioperative care. The review synthesised evidence on diagnostic performance, regulatory approval status, and implementation barriers across functional, stress, and damage biomarkers.

7.1.1. Rationale for Selection of Publications for the Publication Cycle

Prior publications examining the utility of novel AKI biomarkers have consistently highlighted the need for further research in specific high-risk surgical populations, particularly those undergoing complex vascular procedures. Investigators have emphasised the absence of validated, early-detection strategies in EVAR.
The rising number of complex endovascular aortic procedures, including fenestrated and branched EVAR, especially in elderly patients with cardiovascular comorbidity and pre-existing renal impairment, provided the rationale for this investigation. Conventional AKI criteria based on SCr and UOP are particularly limited in this population, where contrast exposure, haemodynamic instability, and ischaemia-reperfusion injury confound traditional markers.
The publication cycle was structured to address three interrelated research questions. First, the utility of PENK as an early AKI biomarker following complex EVAR was evaluated in a prospective manner, in a single-centre cohort, with particular attention to the comparative performance of POCT versus ELISA and to the identification of sAKI. Second, the diagnostic potential of a mechanism-driven biomarker panel, comprising PENK, serum SEMA-3A or serum RBP-4, and urinary KIM-1, was evaluated in the same cohort to determine whether a panel approach could outperform individual biomarkers in early AKI detection. Third, a scoping review of novel AKI biomarkers in perioperative care was undertaken to map the existing evidence base, characterise diagnostic and prognostic performance across functional, stress, and damage biomarkers, and identify implementation barriers in perioperative care.
Earlier identification of kidney injury through novel biomarkers or their combinations, compared to conventional criteria, could enable targeted perioperative monitoring, risk stratification, and timely nephroprotection in high-risk surgical populations.

7.1.2. Scientific Achievements Against the Background of Current Knowledge and the Innovative Aspect of the Study

7.1.2.1. Study Design and Methodology

The original investigations employed a prospective, longitudinal design with serial biomarker sampling from the preoperative period through three consecutive postoperative days, enabling assessment of biomarker kinetics in a clinically relevant time window. The work directly compared POCT with the laboratory ELISA method for PENK measurement in the EVAR setting. The biomarker panel study further introduced a mechanism-driven framework, in which biomarkers were chosen according to their nephron location and release mechanism, representing a more physiologically principled approach to panel construction than prior combinatorial strategies.

7.1.2.2. Study Population

The cohort comprised a prospectively enrolled, procedurally homogeneous group from a single high-volume tertiary referral centre, undergoing complex EVAR, predominantly branched, performed by one surgical team under a standardised perioperative protocol. This uniformity minimised confounding by procedure type, operator variability, and postoperative care differences, limitations that have hampered interpretation in prior biomarker studies of mixed surgical cohorts. Inclusion of patients with pre-existing CKD reflected real-world practice and enabled assessment of biomarker performance across a spectrum of baseline renal function.

7.1.2.3. Novel Biomarker Findings

The dissertation demonstrated, for the first time in a dedicated EVAR cohort, that serum SEMA-3A achieved superior individual discriminatory performance for early AKI detection compared with established biomarkers, with an AUC of 0.88. Serum RBP-4 was identified as a significant AKI discriminator in this population, a correlation not previously reported in the perioperative vascular surgery literature. The three-biomarker panel combining PENK POCT, serum SEMA-3A, and urinary KIM-1 achieved an AUC of 0.89, outperforming individual markers. The commercially available TIMP-2×IGFBP-7 panel also demonstrated no significant discriminatory performance in this cohort.

However, these performance estimates derive from an exploratory, single-centre cohort of 68 patients, of whom only 18 (26.5%) developed AKI. The resulting low number of 18 AKI cases substantially limits statistical power and the precision of AUC estimates, as reflected in the wide confidence intervals (Panel 1: 0.77-1.00; Panel 2: 0.65-0.99). Claims of superiority over TIMP-2×IGFBP-7 must therefore be interpreted with considerable caution. The absence of significant discriminatory performance for TIMP-2×IGFBP-7 in this cohort may reflect

a true lack of utility in the EVAR population, a type II error arising from inadequate statistical power, or both. Generalisation of these findings to other centres, surgical teams, or patient populations is premature without external multicentre validation. The panel findings are best characterised as hypothesis-generating rather than definitive.

7.1.2.4. Practical and Clinical Implications

The research in the dissertation demonstrated the feasibility of bedside PENK for early AKI risk stratification in the postoperative setting. High sensitivity and negative predictive value support its primary clinical utility as a rule-out tool for low-risk patients. AKI occurrence was associated with significantly prolonged hospitalisation and markedly reduced six-month survival, reinforcing the clinical importance of early identification. The findings suggest the incorporation of PENK monitoring into structured AKI care bundles for perioperative kidney protection and provide a rationale for prospective validation of the proposed multi-biomarker panels in larger, multicentre cohorts.

7.1.2.5. Synthesis and Critical Appraisal of the Evidence Base

The scoping review provided a comprehensive, structured synthesis of novel AKI biomarker research in perioperative patient settings, categorising markers according to their biological mechanisms as functional, stress, or damage biomarkers. The review critically evaluated clinical implementation barriers, including assay heterogeneity, absence of standardised cutoff values, and uncertain cost-effectiveness, that have historically limited translation from research to routine practice. By consolidating evidence across diverse surgical populations and mapping regulatory approval status, the review established a conceptual framework for the subsequent original investigations and identified the EVAR population as an underrepresented, high-risk group warranting dedicated biomarker research.

7.1.3. Conceptual Foundations and Research Questions

The publication cycle was designed to evaluate the clinical utility of novel biomarkers in the early diagnosis of perioperative AKI following EVAR. The central premise was the pathophysiological heterogeneity of AKI in this high-risk surgical population, encompassing glomerular dysfunction, tubular injury, and ischaemia-reperfusion damage, that cannot be adequately captured by a single biomarker. Accordingly, the dissertation pursued two complementary objectives: first, evaluation of PENK as a candidate early functional biomarker to establish its diagnostic utility and limitations in this cohort; and second, development and assessment of a mechanism-based biomarker panel incorporating markers

selected according to distinct nephron locations and release mechanisms to address deficiencies identified in single-biomarker evaluation.

7.1.3.1. The following research questions were formulated:

1. Did PENK demonstrate clinically meaningful discriminatory performance for early AKI detection in high-risk patients undergoing EVAR? (Publication 1)
2. Did individual novel biomarkers demonstrate clinically meaningful discriminatory performance for early AKI detection in EVAR patients, and which ones offered the most robust agreement with KDIGO-defined AKI? (Publication 1 and 2)
3. Did a mechanism-based biomarker panel, combining PENK POCT, serum SEMA-3A or serum RBP-4, and urinary KIM-1, demonstrate superior discriminatory performance for early AKI detection compared with individual biomarkers alone? (Publication 2)
4. What were the baseline clinical and procedural risk factors independently associated with AKI development in EVAR patients? (Publications 1 and 2)
5. What was the prognostic significance of postoperative AKI in the EVAR population, and were novel biomarker elevations associated with adverse short-term outcomes? (Publications 1 and 2)
6. What was the current evidence base for novel AKI biomarkers in perioperative care, and what diagnostic, regulatory, and implementation barriers exist across functional, stress, and damage biomarkers? (Publication 3)

8. Methods

Publications 1 and 2 were based on the results of a single-centre, prospective, observational, cross-sectional study conducted between April 2022 and June 2024 at the Central Teaching Hospital of the Medical University of Warsaw, Poland. The research project was designed to investigate the clinical applicability of selected novel renal injury biomarkers in a high-risk perioperative population. The study received approval from the Bioethics Committee of the Medical University of Warsaw (KB/79/2021 and KB/100/2021), and written informed consent was obtained from all participants prior to enrolment, in accordance with the Declaration of Helsinki.

Patients undergoing elective EVAR were enrolled. Surgical procedures and postoperative care were conducted in accordance with a uniformly applied standard operating procedure (SOP) by an experienced vascular surgery team, thereby minimising procedural variability across the cohort. Blood and urine samples for biomarker analysis were collected preoperatively and for up to three consecutive postoperative days. Plasma PENK concentration was measured

immediately after sample collection using a POCT device, the IB10 sphingotest® penKid® lateral flow assay (SphingoTec GmbH, Hennigsdorf, Germany), in the post-anaesthesia care unit (PACU). Remaining blood samples were centrifuged and frozen promptly at -80 °C. Following completion of sample collection across the entire cohort, batch analysis of additional biomarkers was performed using ELISA methodology, including PENK, and a panel of urinary and serum biomarkers comprising SEMA-3A, RBP-4, KIM-1, NTN-1, TIMP-2 and IGFBP-7 (Table 3).

Table 3. *Study sampling schedule and data collection points.*

Parameter	Sample 1	Sample 2	Sample 3	Sample 4
	Inclusion (baseline)	**POD 1 (24 h)**	**POD 2 (48 h)**	**POD 3 (72 h)**
Blood Samples (EDTA)				
Biomarkers	SEMA-3A RBP-4 PENK			PENK
Assay method	ELISA; POCT (for PENK only)			POCT
Urine Samples				
Biomarkers	SEMA-3A RBP-4 KIM-1 NTN-1 TIMP-2 IGFBP-7			-
Assay method	ELISA			-

POD, postoperative day; PENK, proenkephalin A 119-159 measured with point-of-care IB10 sphingotest® penKid® assay and with ELISA assay; SEMA-3A, Semaphorin-3A; RBP-4, Retinol-Binding Protein-4; KIM-1, Kidney Injury Molecule-1; NTN-1, Netrin-1; TIMP-2, Tissue Inhibitor of Metalloproteinases-2; IGFBP-7, Insulin-like Growth Factor-Binding Protein-7; SCr, serum creatinine; KDIGO, Kidney Disease: Improving Global Outcomes; EDTA, ethylenediamine tetraacetic acid; POCT, point-of-care test; ELISA, enzyme-linked immunosorbent assay.

Perioperative data were collected for each participant, including demographic and anthropometric characteristics, medical history, current pharmacotherapy, and routine laboratory parameters. AKI was diagnosed in accordance with the current KDIGO criteria, based on changes in SCr over the perioperative period. The risk of in-hospital mortality on the day of surgery was estimated using the Sequential Organ Failure Assessment (SOFA) score and the Simplified Acute Physiology Score II (SAPS). Subclinical AKI was defined

as a PENK concentration exceeding 80 pmol/L in the absence of meeting standard KDIGO diagnostic thresholds.

During the postoperative observation period in the PACU, lasting up to 72 hours following surgery, continuous monitoring of vital signs and serial assessment of laboratory parameters were performed in accordance with standard clinical practice.

Postoperative adverse events recorded during the observation period included: AKI defined by KDIGO criteria, haemodynamic instability, the requirement for vasopressor agents, the administration of blood products, in-hospital mortality, and duration of hospitalisation. As part of the follow-up procedure, a structured telephone interview was conducted with patients or their next of kin at six months following enrolment to ascertain vital status; six-month all-cause mortality served as the primary long-term outcome.

Associations between clinical and demographic variables and AKI occurrence were assessed by univariate analysis, using the Wilcoxon rank-sum test for continuous variables, and Pearson's chi-squared test or Fisher's exact test for categorical variables, as appropriate. Variables demonstrating a statistically significant association with AKI in univariate analysis ($p < 0.05$) were reported as candidate risk factors. Due to the limited number of AKI events ($n = 18$) relative to the number of candidate predictor variables, multivariable logistic regression was not performed, as it would have risked model overfitting and yielded unreliable coefficient estimates. The association between AKI occurrence and short-term outcomes (duration of hospitalisation, in-hospital mortality) and long-term survival was similarly assessed by univariate comparisons.

Publication 3 constituted a scoping review of the existing literature on novel AKI biomarkers in perioperative settings. A systematic search of the EuropePMC, MEDLINE, and Scopus databases was performed independently by two researchers using controlled vocabulary and keywords pertaining to AKI, novel biomarkers, and surgical or perioperative care. Studies were eligible for inclusion if they investigated novel AKI biomarkers in surgical patients; studies focusing exclusively on critically ill non-surgical populations, non-procedural AKI, or preclinical research without clinical translation were excluded. Following duplicate removal, titles and abstracts were screened independently by two reviewers, with full-text review of potentially eligible studies and resolution of disagreements through discussion or third-reviewer consultation. Findings were synthesised narratively, organised by biomarker category: functional, stress, and damage markers, and by thematic areas including diagnostic performance, regulatory approval status, and barriers to clinical implementation.

9. Publications

Walczak-Wieteska *et al.*
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RESEARCH Open Access

Proenkephalin A 119–159 as an early biomarker of acute kidney injury in complex endovascular aortic repair: an explorative single-center cross-sectional study with the utilization of two measurement methods

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Abstract

Background Acute kidney injury (AKI) remains a significant complication following endovascular aneurysm repair (EVAR). Current diagnostic methods often detect kidney damage too late for effective intervention. This study evaluated proenkephalin A 119–159 as an early AKI biomarker after EVAR procedures, comparing point-of-care testing with the ELISA method.

Methods Between April 2022 and June 2024, 68 patients undergoing elective EVAR were enrolled. Blood samples were collected preoperatively and for three consecutive postoperative days.

Results AKI was diagnosed according to the KDIGO criteria, with proenkephalin A 119–159 measured via point-of-care (penKid) testing and laboratory ELISA method. AKI occurred in 18 patients (26.5%). penKid showed a superior diagnostic performance to ELISA, demonstrating moderate agreement with KDIGO criteria (Gwet's $AC1 = 0.52$, $p < .001$). While penKid exhibited high sensitivity (80% day 1), specificity was moderate (51%). AKI patients had significantly higher median penKid levels (96.47 pmol/L vs 63.01 ng/mL, $p = .001$), longer hospital stays (12 vs 9 days, $p = .028$), and lower 6-month survival (50% vs 88.1%, $p = .006$).

Conclusions penKid testing shows promise as an early AKI biomarker following EVAR procedures, particularly for identifying low-risk AKI patients. However, its moderate specificity suggests it should complement existing clinical assessment tools rather than replace them. These findings support incorporating penKid monitoring into structured AKI care bundles for improved perioperative kidney outcomes.

Keywords Proenkephalin, PenKid, Biomarker, AKI, EVAR

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Background

Serum creatinine (SCr) has been the standard parameter for renal function (Losito 2023) for 90 years and has significant limitations. It is still an essential kidney parameter in perioperative and intensive care settings (Ronco et al. 2019; Bellomo et al. 2004). These flaws, including the delayed detection of renal dysfunction, have prompted the search for early biomarkers of acute kidney injury (AKI).

Proenkephalin A 119–159 (PENK) has emerged as a promising biomarker for AKI. This endogenous, monomeric peptide (Khorashadi et al. 2020; Beunders et al. 2017) maintains a stable concentration after collection, has a long in vivo half-life, and is independent of sex or age (Khorashadi et al. 2020). Studies have shown that elevated PENK plasma concentration correlates with the development of AKI in critical settings (Khorashadi et al. 2020; Ibrahim et al. 2022), with PENK preceding SCr increases in septic patients (Lin et al. 2023) and correlating with the severity of AKI (Caironi et al. 2018).

Postoperative AKI often complicates endovascular aneurysm repair (EVAR), with incidence rates up to 50% (Cucuruz et al. 2020; Saratzis et al. 2015; Saratzis et al. 2016). Risk factors include chronic kidney disease, atherosclerotic disease, and limited cardiovascular reserve (Saratzis et al. 2016). While PENK has been studied in various clinical settings, limited research exists (Gombert et al. 2020; Doukas et al. 2024; Walczak-Wieteska et al. 2024) on its use in vascular surgery. Our study is the first to compare the bedside PENK test with the ELISA laboratory method (PENK/ELISA) in EVAR procedures. We aimed to evaluate the PENK's utility as a predictive AKI biomarker in a perioperative setting and the incidence of sAKI in the EVAR population.

Methods

This single-center, prospective, observational, cross-sectional study was conducted between April 2022 and June 2024 at the Central Teaching Hospital, Medical University of Warsaw. We enrolled 68 patients undergoing elective fenestrated or branched EVAR procedures. The study received ethics committee approval (8/KBL/OIL/2019 and 53/KBL/OIL/2022), and all participants provided written informed consent.

Blood samples were collected from arterial lines preoperatively and for three consecutive postoperative days. For PENK/ELISA measurement, plasma was collected in EDTA tubes, centrifuged, and stored at − 80 °C. The generic PENK ELISA kit was used strictly following manufacturer guidelines. The assay sensitivity was 0.041 ng/mL (1.33 pmol/L), range 0.05–10 ng/mL (1.62–324.81 pmol/L), and intra-assay precision < 9%. AKI was diagnosed according to the *Kidney Disease: Improving Global Outcomes* (KDIGO) 2012 criteria (Khwaja 2012). Following analogical studies, we defined subclinical AKI (sAKI) as a condition where penKid concentrations exceeded 80 pmol/L in the absence of an immediate rise in serum creatinine or fall in urine output that would meet standard KDIGO criteria (Dépret et al. 2020; Breidthardt et al. 2018). Point-of-care penKid was measured immediately with IB10 sphingotest®*penKid*® *assay* designed as a lateral flow test by SphingoTec GmbH, Hennigsdorf, Germany. The lowest detection limit of the immunoassay was 50 pmol/L.

We collected perioperative data, including demographics, medical history, and laboratory tests, and calculated the Sequential Organ Failure Assessment (SOFA) and the Simplified Acute Physiology Score (SAPS) scores on surgery day. Patients were monitored for complications, including AKI, hemodynamic instability, the administration of vasopressors and blood products, and mortality through 6-month post-procedure. The current study set a significance level of $\alpha = 0.05$, permitting a 5% likelihood of committing a type I error. Analyses were conducted using the R statistical language (version 4.3.3; R Core Team, 2024) on Windows 11 64 bit (build 22,631), using the publicly available packages (Appendix 1).

Results

The study involved 68 adult patients who underwent elective EVAR procedures. Two patients were excluded due to a single SCr measurement (before and after). The AKI occurrence referred to a cumulative occurrence for 3 days postoperative. Throughout observation, from the preoperative day to the third postoperative day, AKI occurred in 18 patients (26.5%) out of 66 following the AKI KDIGO criteria (Khwaja 2012).

The median age of the overall cohort (Table 1) was 70.5 years (*IQR*: 62.75–75.25). Patients in the AKI group were notably older, with a median age of 74.5 years (69.5–81.0), compared to 69.0 years (61.0–73.0) in the non-AKI group ($p = 0.010$). The cohort included 25 women (36.8%) and 43 men (63.2%). A higher proportion of men (77.8%) was observed in the AKI group compared to the non-AKI group (58.3%), although this difference did not reach statistical significance ($p = 0.144$). Regarding body mass index (BMI), the median BMI for the cohort was 26.08 kg/m^2 (24.31–29.58). There was no statistically significant difference in BMI between the AKI and non-AKI groups. SCr levels at baseline were significantly higher in the AKI group, with a median value of 1.39 mg/dL compared to 1.01 mg/dL in the non-AKI group ($p < 0.001$).

Among the studied severity scores (Table 2), there is a notable distinction between the groups regarding the SAPS and SOFA scores. The SAPS score was elevated in the AKI group (median 6.49 vs. 3.72, $p = 0.008$),

Table 1 Sociodemographic profile of the patient cohort, stratified by AKI occurrence

Characteristic	N	Overall cohort[a]	AKI occurrence		p[c]
			Yes $n_1 = 18$[a]	No $n_2 = 48$[a]	
Age, y	66	70.50 (62.75, 75.25)	74.50 (69.50, 81.00)	69.00 (61.00, 73.00)	.010
Gender	66				0.144[d]
Female		24 (36.36%)[b]	4 (22.22%)[b]	20 (41.67%)[b]	
Male		42 (63.67%)[b]	14 (77.78%)[b]	28 (58.33%)[b]	
BMI, kg/m^2	66	26.08 (24.31, 29.58)	26.25 (24.98, 30.78)	26.27 (24.31, 29.58)	0.751

[a] Median (Q1, Q3)

[b] *n* (%)

[c] Wilcoxon rank-sum test

[d] Pearson's chi-squared test

indicating that patients with AKI exhibited more severe physiological derangements. The SOFA score also differed significantly between the two groups, with a median of 6.40 in the non-AKI group and a much higher interquartile range in the AKI group, peaking at 20.20 ($p = 0.048$). The need for transfusions was also markedly higher in the AKI group, with 83.33% of AKI patients receiving transfusions postoperatively, compared to 33.33% in the non-AKI group ($p < 0.001$).

Regarding clinical outcomes, the duration of hospitalization was significantly longer in the AKI group, with a median of 12.0 days compared to 9.0 days in the non-AKI group ($p = 0.028$). Importantly, inhospital mortality was higher among patients with AKI, with 11.11% of AKI deceased patients during hospitalization compared to no deaths in the non-AKI group. However, this difference did not reach statistical significance ($p = 0.071$). The 6-month survival rate was significantly lower in the AKI group, with only 50.00% surviving at follow-up compared to 88.10% in the non-AKI group ($p = 0.006$).

Table 3 illustrates the longitudinal trends of these markers. It summarizes the mean concentrations of the penKid and PENK for the overall cohort, stratified by AKI occurrence.

The penKid exhibited a highly significant difference between groups, with a median = 96.47 pmol/L (*IQR*: 74.38, 182.54) in the AKI group compared to median = 63.01 pmol/L (54.89, 78.60) in the non-AKI group ($p = 0.001$). In contrast, PENK/ELISA approached significance ($p = 0.057$), suggesting a potentially weaker association with AKI. The correlation between penKid and PENK/ELISA was also assessed with rho = −0.06, indicating little to no association between these two markers.

Table 3 Mean concentrations of penKid and PENK over time for the overall cohort were stratified by AKI occurrence according to KDIGO criteria

Characteristic	*N*	*Overall cohort*	*AKI occurrence*		*p*[b]
			Yes $n_1 = 18$[a]	*No* $n_2 = 48$[a]	
Baseline — postoperative day 3					
penKid, pmol/L	66	69.83 (56.19, 93.55)	96.47 (74.38, 182.54)	63.01 (54.89, 78.60)	.001
PENK/ELISA pmol/L	66	44.50 (34.43, 72.76)	55.54 (40.28, 84.13)	40.93 (32.81, 61.39)	.057

[a] Median (Q1, Q3)

[b] Wilcoxon rank-sum test

Table 2 Characteristics of perioperative critical care and outcome parameters of the study cohort, stratified by AKI occurrence

Characteristic	*N*	*Overall cohort*[a]	*AKI occurrence*		*p*[c]
			Yes $n_1 = 18$[a]	*No* $n_2 = 48$[a]	
SAPS %	66	3.95 (1.74, 5.82)	6.49 (3.13, 8.77)	3.72 (1.69, 4.67)	.008
SOFA %	66	6.40 (6.40, 9.85)	6.40 (6.40, 20.20)	6.40 (4.80, 6.40)	.048
Transfusion	66	31 (45.59%)[b]	15 (83.33%)[b]	16 (33.33%)[b]	<.001[e]
Duration of hospitalization, days	66	9.00 (7.00, 11.25)	12.00 (8.25, 18.25)	9.00 (7.00, 11.00)	.028
Decease during hospitalization	66	2 (2.94%)[b]	2 (11.11%)[b]	0 (0)[b]	.071[d]
Survival, Follow-Up 6 months	56	44 (78.57%)[b]	7 (50.00%)[b]	37 (88.10%)[b]	.006[e]

[a] Median (Q1, Q3)

[b] *n* (%)

[c] Wilcoxon rank-sum test

[d] Fisher's exact test

[e] Pearson's chi-squared test

Table 4 The agreement results between AKI diagnosis by KDIGO criteria and penKid and PENK

AKI biomarker	*Gwet's AC1*	*SE*	*CI 95%*	*p*
penKid	0.52	0.11	0.31–0.73	**<.001**
PENK/ELISA	0.10	0.12	−0.15–0.34	0.428

The results of the agreement between AKI diagnosis by KDIGO criteria and penKid and PENK/ELISA were assessed. Gwet's AC1 provided a more stable estimate than other metrics, particularly in the presence of imbalanced categories. penKid with a Gwet's $AC1 = 0.52$ ($p < 0.001$) with a confidence interval (*CI* 95%: 0.31–0.73) demonstrated moderate agreement with the KDIGO criteria (Table 4). Conversely, PENK/ELISA showed minimal agreement with the KDIGO criteria ($AC1 = 0.10$, $p = 0.428$).

Subclinical AKI criterion

penKid concentrations exceeding 80 pmol/L were interpreted as indicative of sAKI. To further evaluate the agreement between the predicted and observed classifications, Gwet's AC1 was calculated as a chance-corrected measure. McNemar's test determined the difference between cases where the penKid prediction did not match the observed AKI status — at each time point.

Additional metrics included prevalence, defined as the proportion of patients diagnosed with AKI at each postoperative time point based on creatinine levels, and the detection rate, which indicated the proportion of the total sample correctly identified as AKI cases by penKid. The detection prevalence represented the proportion of the total sample predicted to have AKI by proenkephalin, regardless of the diagnosis.

The overall accuracy of penKid for predicting sAKI varied slightly across the postoperative time points (Table 5). On day 1, the accuracy was 0.55 (95% *CI*: 0.43–0.68), increasing marginally to 0.57 (0.42–0.70) on day 2, and then returning to 0.55 (0.36–0.73) on day 3.

However, the no information rate (NIR) was higher than the observed accuracy at each time point, with values of 0.85 on day 1, 0.77 on day 2, and 0.61 on day 3.

The sensitivity of penKid — its ability to correctly identify patients who developed AKI, presented with values of 0.80 on day 1 and 0.75 on days 2 and 3. The specificity was moderate to low, remaining stable at 0.51 on days 1 and 2 and dropping to 0.42 on day 3. The positive predictive value (PPV) reflected the likelihood that a patient predicted to have sAKI develops AKI, with values of 0.23 on day 1, 0.31 on day 2, and 0.45 on day 3.

Gwet's AC1, a chance-corrected measure of agreement, demonstrated low values across all time points, with 0.18 (95% *CI*: −0.08 to 0.45) on day 1, 0.17 (−0.11–0.46) on day 2, and 0.10 (−0.27–0.46) on day 3.

Table 5 Performance metrics and the predictive capability of penKid levels (the predicted variable) for predicting the occurrence of AKI based on creatinine levels (the observed variable) at various postoperative time points

Performance metric	*Postoperative time point*		
	***Day1* (n = *65*)**	***Day 2* (n = *53*)**	***Day 3* (n = *31*)**
Accuracy (*CI 95%*)	0.55 (0.43–0.68)	0.57 (0.42–0.70)	0.55 (0.36–0.73)
No information rate (NIR)	0.85	0.77	0.61
p-value [accuracy > NIR]	1.000	1.000	0.82
Gwet AC1 (*CI 95%*)	0.18 (−0.08–0.45)	0.17 (−0.11–0.46)	0.10 (−0.27–0.46)
McNemar's test *p*-value	< 0.001	< 0.001	0.061
Sensitivity (AKI occurrence as positive class)	0.80	0.75	0.75
Specificity	0.51	0.51	0.42
Positive pred value	0.23	0.31	0.45
Negative prediction value	0.93	0.88	0.73
Prevalence	0.15	0.23	0.39
Detection rate	0.12	0.17	0.29
Detection prevalence	0.54	0.55	0.65
Balanced accuracy	0.65	0.63	0.59

n number of complete pairs of data, *CI 95%* confidence interval 95%

The prevalence of AKI increased as the postoperative period progressed, from 0.15 on day 1 to 0.23 on day 2 and 0.39 on day 3. This trend was consistent with clinical expectations, as AKI often develops in response to perioperative stress and physiological changes. The detection rate, which reflected the proportion of the total sample correctly identified as AKI cases by penKid, followed a similar pattern, increasing from 0.12 on day 1 to 0.17 on day 2 and 0.29 on day 3.

Discussion

Patient's cohort

In this single-center, prospective, cross-sectional, observational study involving a cohort of unselected patients following complex EVAR, the incidence of AKI was observed to be 26.5%. This occurrence was elevated compared to recently published research findings, reporting incidence rates up to 18% (Villa 2024; Finnesgard et al. 2023). These differences were attributed to several factors, including the type of surgery (elective versus emergency) and specific patient characteristics. The sociodemographic profile data suggested that older age may be a significant risk factor for AKI in this patient population (Tallgren et al. 2007; Saratzis et al. 2020). However, this is contrary to previously published data in the EVAR

group (Castagno et al. 2016). BMI did not demonstrate a strong association with the occurrence of AKI.

Patients with AKI had higher SAPS and SOFA scores. These findings reinforce the notion that AKI is associated with greater systemic organ dysfunction in the postoperative period. The patients who developed AKI were more likely to experience significant perioperative blood loss or other complications requiring transfusion, which could have contributed to or exacerbated renal injury due to hemodynamic instability (Statius 2017) or ischemia–reperfusion injury (Tiwari and Kapitsinou 2022). The prolonged hospitalization period reflects the more complicated recovery trajectory for patients with AKI, likely due to the need for advanced monitoring and supportive care. This suggests also that patients who developed AKI were in a more critical condition postoperatively.

PenKid robustness

The significant difference in median penKid concentration between AKI and non-AKI patients suggests that penKid is a robust marker for the early detection of AKI and may have substantial clinical utility in identifying patients developing AKI, especially at low risk. In contrast, PENK/ELISA approached lower significance, suggesting a potentially weaker association with AKI criteria. While this marker may still hold some value, its discriminative ability appears less robust.

Detection of AKI

penKid with a Gwet's $AC1 = 0.52$ demonstrated moderate agreement with the KDIGO criteria, indicating its potential utility as a reliable marker in clinical practice. Its relatively narrow confidence interval (*CI* 95%: 0.31–0.73) further supports its stability as a diagnostic tool for AKI. Conversely, PENK/ELISA showed minimal agreement with the KDIGO criteria with a confidence interval that spans negative values, suggesting that this biomarker may not be a reliable indicator of AKI compared to the KDIGO standard.

The penKid's sensitivity and ability to correctly identify patients who developed AKI were consistently high across all time points. This indicates that penKid was reliable in detecting AKI when it occurred, making it a valuable tool for identifying at-risk patients. However, the specificity was moderate to low, remaining stable at 0.51 on days 1 and 2 but dropping to 0.42 on day 3. This suggests that while penKid is sensitive to AKI occurrence, its ability to correctly identify patients who do not develop AKI is limited, particularly as time progresses. The decline in specificity on day 3 may indicate that penKid levels become less reliable for ruling out AKI in the later stages of the postoperative period.

penKid's was low across all time points (0.23 on day 1 to 0.45 on day 3). This indicates that a proportion of patients with an elevated penKid level may not ultimately develop AKI based on creatinine criteria, highlighting the risk of overestimating risk if the marker is used in isolation. However, the test's clinical strength lies in its consistently high negative predictive value (NPV), which was 0.93 on day 1 and remained high on subsequent days. This high NPV is clinically significant, as it allows for the confident identification of patients at a genuinely low risk of AKI. This feature enables more efficient allocation of postoperative resources, prevents unnecessary interventions, and allows monitoring to be focused on higher-risk patients.

Numerous studies have demonstrated that PENK can detect AKI with sensitivity comparable to or superior to that of other established biomarkers, such as Neutrophil gelatinase-associated lipocalin (NGAL) and Tissue inhibitor of metalloproteinases 2 (TIMP-2) × Insulin-like growth factor-binding protein 7 (IGFBP-7). This makes it a valuable nephron injury biomarker (Marino et al. 2015; Gayat et al. 2018). Research suggests that PENK levels can reflect glomerular dysfunction and predict new-onset AKI, making it a potential game changer in managing kidney-related complications in intensive care (Schulte 2024) and postoperative settings (Gombert et al. 2020).

In critically ill patients, particularly those undergoing continuous renal replacement therapy, penKid levels have been associated with successful dialysis liberation (von Groote et al. 2022; von Groote et al. 2023; Tichy et al. 2024). Furthermore, the fact that hemodialysis calls do not remove PENK (Jakubowska et al. 2024) suggests that penKid serves as a diagnostic tool and may also provide prognostic insights regarding recovery from AKI.

Prediction of AKI

The variation in penKid's accuracy indicates that the predictive performance of penKid remains relatively consistent in the early postoperative period, albeit with moderate accuracy. The higher values of NIR than the observed accuracy at each time point suggest that the prediction of AKI purely based on penKid levels does not exceed the expected performance from random guessing, as reflected in the *p*-values (1.000 for days 1 and 2 and 0.82 for day 3). Therefore, while penKid showed some predictive potential, it did not significantly outperform chance in this cohort.

The low Gwet's AC1 values suggest that the agreement between penKid predictions and the observed AKI status is limited, and that corrections for chance agreement do not significantly improve the interpretation of proenkephalin's predictive ability. Moreover, McNemar's test

yielded statistically significant *p*-values on days 1 and 2 (both < 0.001), indicating substantial differences between the predicted and observed classifications, with a trend toward systematic prediction errors. On day 3, however, McNemar's test *p*-value was 0.061, suggesting that by this time point, the systematic discrepancies between predictions and observed outcomes were less pronounced but still present.

Detection of subclinical AKI

The prevalence and detection rate results suggest that penKid becomes progressively more effective at identifying sAKI cases as the postoperative period advances. However, the detection prevalence (the proportion predicted to have AKI) was higher than the actual prevalence at all time points, reaching 0.65 on day 3, again indicating a potential overestimation of AKI risk by penKid. The balanced accuracy, which accounts for class imbalances by averaging sensitivity and specificity, remained moderate across all time points, with values of 0.65 on day 1, 0.63 on day 2, and 0.59 on day 3. This suggests that while penKid has some predictive value, it does not offer consistently strong performance, particularly as specificity declines over time.

The use of penKid as a biomarker for predicting sAKI in the early postoperative period showed promise, particularly in its high sensitivity and negative predictive value, which made it a valuable tool for identifying patients at low risk for AKI. However, the moderate accuracy, low specificity, and low PPV suggest that penKid should be used cautiously when predicting sAKI occurrence, particularly in light of its tendency to overestimate AKI risk.

Pathophysiological rationale for PENK's diagnostic accuracy

The robust performance of PENK as a biomarker for GFR and AKI is grounded in its physiological characteristics. PENK is a stable fragment derived from the precursor molecule proenkephalin A. Due to its small size and the fact that it is not bound to plasma proteins, PENK is freely and exclusively filtered by the renal glomeruli. Consequently, its plasma concentration is inversely correlated with the GFR. When GFR declines, as in AKI, the filtration of PENK is reduced, leading to its accumulation in the blood (Khorashadi et al. 2020).

The kidneys possess the highest density of delta opioid receptors outside of the central nervous system, and enkephalins, the biologically active peptides for which PENK is a stable surrogate, are thought to have a regulatory effect on renal function, including inducing diuresis and natriuresis. The elevated penKid levels observed during AKI could therefore result from both a decreased glomerular filtration and a simultaneous increase in the production of enkephalins as part of a systemic stress response or a pathophysiological signalling process (Khorashadi et al. 2020).

PenKid as a part of AKI care bundles

While penKid has the potential to facilitate the early detection of AKI, particularly within the first 48 h after surgery, its use should be considered complementary rather than as a standalone solution. AKI care bundles are excellent examples of comprehensive management of this syndrome, using a structured approach and supplemental biomarkers like penKid. Care bundles have proven to reduce moderate to severe AKI (Schaubroeck et al. 2021). Considering penKid's predictive value, its limitations must be acknowledged to avoid overdiagnosis and unnecessary interventions. To evaluate the final penKid's feasibility in perioperative and intensive care settings, an investigation in RCT trials, preferably with a structured AKI bundle, is necessary.

Limitations and strengths of the study

This study has several limitations. First, we acknowledge the relatively small sample size, which is common in studies of highly specialized procedures and limits statistical power. However, the homogeneity of the cohort, with all procedures and perioperative care standardized and performed by a single team, helped to mitigate the limitations. Second, a generic PENK ELISA kit was used as the only standardized one which was available to our team. Our investigation included a possible sampling bias within the investigated population, as we did not measure with both methods. Finally, our diagnostic criteria for AKI did not include urine output. However, a previous study in a smaller EVAR population reported AKI occurrence using precise urine output recording with almost identical incidence (Saratzis et al. 2015).

More importantly, our data suggest that bedside tests such as penKid are reliable tools for identifying patients with low-risk AKI in a perioperative setting. The cohort was homogeneous, and perioperative management followed a uniformly applied standardized operating protocol. Additionally, we confirmed the superiority of bedside tests versus PENK/ELISA in AKI detection. Future studies could further evaluate the prognostic importance of changes in PENK levels in noncardiac surgery settings.

Conclusions

penKid shows promise as an early biomarker for risk stratification following complex EVAR. While its low PPV and moderate overall accuracy suggest it should not be used as a standalone diagnostic test, its high sensitivity and NPV make it a valuable tool for ruling out AKI in low-risk patients. Its primary utility lies in

its potential integration into structured AKI care bundles, where its early signal can complement clinical assessment and guide proactive management. Although penKid does not fundamentally alter AKI treatment, it supports a more personalized and timely approach.

Abbreviations

AC1	Gwet's AC1 agreement coefficient
AKI	Acute kidney injury
BMI	Body mass index
CI	Confidence interval
ELISA	Enzyme-linked immunosorbent assay
EVAR	Endovascular aneurysm repair
IGFBP-7	Insulin-like growth factor-binding protein 7
IQR	Interquartile range
KDIGO	Kidney Disease Improving Global Outcomes
NGAL	Neutrophil gelatinase-associated lipocalin
NIR	No information rate
NPV	Negative predictive value
PENK	Proenkephalin A 119–159
POC	Point of care
PPV	Positive predictive value
RCT	Randomized controlled trial
RRT	Renal replacement therapy
SAPS	Simplified Acute Physiology Score
SCr	Serum creatinine
sAKI	Subclinical acute kidney injury
SOFA	Sequential Organ Failure Assessment
TIMP-2	Tissue inhibitor of metalloproteinases 2

Supplementary Information

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Supplementary Material: Appendix 1. Packages.

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Authors' contributions
Paulina Walczak-Wieteska: Writing – original draft, Writing – review & editing, Investigation, Conceptualisation, Data curation. Konrad Zuzda: Writing – original draft, Writing – review & editing, Conceptualisation, Data curation, Formal analysis. Paweł Andruszkiewicz: Writing – review & editing, Supervision. Jolanta Małyszko: Writing – review & editing, Supervision, Project administration, Conceptualisation.

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Data availability
The complete dataset used in this study has been deposited in the Zenodo repository (https://doi.org/10.5281/zenodo.14827489). This dataset is freely available for research purposes under a CC-BY 4.0 license.

Declarations

Ethics approval and consent to participate
The study received the Bioethics Committee of the Medical University of Warsaw approval (8/KBL/OIL/2019 and 53/KBL/OIL/2022), and all participants provided written informed consent.

Competing interests
The authors declare no competing interests.
Declaration of generative AI and AI-assisted technologies in the writing process
While preparing this work, the authors corrected spelling and grammar using Grammarly service. After using this service, they reviewed and edited the content as needed and took full responsibility for the publication's content.

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Evaluation of a Novel Biomarker Panel for Acute Kidney Injury Following Endovascular Aortic Repair

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Abstract

Acute Kidney Injury (AKI) following endovascular aortic repair (EVAR) is often diagnosed too late using conventional markers, limiting opportunities for timely intervention in this high-risk population. We investigated whether a mechanism-based biomarker panel could provide improved early AKI detection in EVAR patients. This prospective, single-center study enrolled 68 consecutive EVAR patients between April 2022 and June 2024. AKI was diagnosed using KDIGO 2012 criteria. Seven novel biomarkers, including Proenkephalin A 119-159 (penKid), Semaphorin-3A (SEMA-3A), Retinol Binding Protein-4 (RBP-4), Kidney Injury Molecule-1 (KIM-1), Netrin-1, Tissue Inhibitor of Metalloproteinases-2, and Insulin-Like Growth Factor Binding Protein-7, were measured at baseline, immediate postoperative, 24 h, and 48 h time points, and selected based on distinct nephron locations and release mechanisms. AKI occurred in 18 (26.5%) patients. Top-performing individual biomarkers included serum SEMA-3A (AUC 0.88), serum RBP-4 (AUC 0.81), and penKid (AUC 0.76). A three-biomarker panel combining serum penKid, serum SEMA-3A, and urinary KIM-1 achieved robust discriminatory performance (AUC 0.89, 95% CI 0.77–1.00), superior to individual biomarkers. An alternative panel with serum RBP-4 demonstrated comparable performance (AUC 0.81, 95% CI 0.65–0.99). Multi-biomarker panels combining functional, stress, and injury markers demonstrate promising performance for early AKI detection in EVAR patients. External validation in independent, multi-center cohorts is required before clinical implementation.

Keywords: AKI; EVAR; biomarkers; biomarker panel; PENK; penKid; Semaphorin-3A

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1. Introduction

Acute kidney injury (AKI) is a critical and common complication following endovascular aortic repair (EVAR), substantially increasing the risk of mortality and morbidity [1–3]. The incidence of AKI may be as high as 1 in 3 cases following EVAR procedures, particularly in complex cases involving the implantation of branched and fenestrated aortic stent-grafts [2]. The escalation in perioperative AKI risk with increasing procedural complexity is associated with the implantation of stent-grafts extending to the renal arteries, which may precipitate transient reductions in renal perfusion, an effect exacerbated by exposure to iodinated contrast agents. Notable risk factors for AKI in endovascular aortic interventions include the necessity for perioperative blood transfusion, administration of vasopressor agents, and elevated volumes of intravenous contrast media [4]. Identified

patient risk factors encompass female sex, the presence of diabetes mellitus, compromised baseline renal function, and the administration of angiotensin II receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors [5,6]. Current approaches to diagnosing AKI remain inadequate for early detection. The syndrome is characterized by rapid-onset renal dysfunction with various causes and is traditionally diagnosed using serum creatinine (SCr) and urine output (UOP) according to KDIGO criteria [7]. However, these gold-standard markers have significant limitations that hinder timely intervention. SCr, despite being widely accessible and inexpensive, suffers from poor sensitivity and delayed response to kidney injury. Its concentration can be confounded by muscle mass, hepatic function, and volume status, often rising up to 48 h after initial injury. UOP similarly proves unreliable, influenced by hypovolemia, fasting, and diuretics rather than true nephron function [8]. Most importantly, neither marker effectively differentiates injury location within the nephron or underlying etiology, limiting phenotype-specific management [9].

Over 75 years [10] of use, SCr has not been replaced by newer markers for AKI diagnosis. Due to the latency in AKI diagnosis, efforts have been made to identify novel kidney stress or injury biomarkers. Introducing novel AKI biomarkers into clinical practice is expected to enhance early diagnosis, surpassing the capabilities of traditional AKI criteria. In addition, their use will allow a more accurate determination of the location of kidney injury and its underlying etiology. This advancement can improve AKI phenotyping and subclinical AKI (sAKI) detection [11,12], which refers to renal impairment that has not yet reached the threshold defined by AKI KDIGO criteria [9]. In addition to expediting the diagnosis of nephron injury, a significant advantage of novel AKI biomarkers is their minimal susceptibility to confounding variables such as gender, age, muscle mass, or comorbidities [13].

The diversity of pathophysiological mechanisms underlying AKI, including glomerular dysfunction, tubular damage, and thrombotic microangiopathy, demands a more sophisticated diagnostic approach. Moreover, traditional criteria fail to identify patients with histopathological renal damage who meet sAKI definitions based on novel biomarker elevations. Several studies have demonstrated successful perioperative AKI prediction and early diagnosis with novel biomarkers [14,15].

We hypothesized that a biomarker panel, selected based on distinct nephron locations and release mechanisms, would provide superior early AKI detection compared to traditional criteria in EVAR patients. This study aimed to evaluate the discriminatory performance of a mechanism-based panel for timely AKI diagnosis in the perioperative period.

2. Results

The analysis included 68 adult patients with a median age of 70.5 years (IQR: 62.75, 75.25). All patients underwent EVAR procedures performed by an experienced vascular surgery team at a tertiary referral center. The cohort consisted predominantly of branched EVAR (b-EVAR) procedures (n = 60, 88.2%), with fewer standard infrarenal EVAR (n = 7, 10.3%) and fenestrated EVAR (f-EVAR) (n = 1, 1.5%). During the preoperative period to the third postoperative day, AKI was identified in 18 patients (26.5%). The cohort comprised 25 women (36.8%) and 43 men (63.2%). Men represented a higher proportion in the AKI group (77.8%) versus the non-AKI group (58.3%), p = 0.144.

The study cohort exhibited a high burden of cardiovascular comorbidities, reflecting the typical risk profile of patients undergoing EVAR. Median Body Mass Index (BMI) was 26.08 kg/m^2 (24.31, 29.58) for the overall cohort. No significant difference was observed between the AKI group 26.25 kg/m^2 (24.98, 30.78) and the non-AKI group 26.27 kg/m^2 (24.31, 29.58), p = 0.751. Hypertension was highly prevalent across both groups, 44 patients (91.67%) in the non-AKI group vs. 17 (94.44%) in the AKI group, p = 1.0. Diabetes mellitus

affected 13 patients (27.08%) in the non-AKI group vs. 5 (27.78%) in the AKI group, $p = 1.0$. Coronary heart disease was present in 14 (29.17%) non-AKI patients, and in AKI 8 (44.44%) subjects, $p = 0.241$, while chronic obstructive pulmonary disease was present in 5 (27.78%), 4 (8.33%), $p = 0.055$, respectively. While individual comorbidities did not reach statistical significance, associations between specific chronic diseases and AKI occurrence were substantial across the cohort.

Medication profiles revealed several noteworthy associations. The use of low-molecular-weight heparins (LMWH) was significantly higher among patients who developed AKI (16.67% vs. 0%, $p = 0.018$), potentially reflecting patients with more severe vascular disease. Similarly, the preoperative use of alpha-blockers was more prevalent in the AKI group (22.22% vs. 4.17%, $p = 0.043$). Although not reaching statistical significance, a trend toward higher AKI occurrence was observed among patients receiving ARBs (33.33% vs. 12.50%, $p = 0.073$), consistent with the known perioperative risk of renin-angiotensin system blockade. Use of acetylsalicylic acid, ACE inhibitors, beta-blockers, and diuretics showed no significant association with AKI occurrence. The median number of medications taken did not differ between groups ($p = 0.856$), suggesting that polypharmacy alone was not a primary AKI risk factor in this cohort.

Baseline renal function assessed with SCr was significantly elevated in the AKI group, median 1.39 mg/dL, compared to the non-AKI group, median 1.01 mg/dL, $p < 0.001$ (Table 1). Among patients without preexisting chronic kidney disease (CKD), AKI incidence was relatively low, two developed AKI, and 11 did not, $p = 0.488$. However, patients with moderate-to-severe CKD showed markedly elevated AKI risk. Stage 3b CKD was present in 5 (27.78%) of AKI patients compared to only 1 (2.08%) of the non-AKI group ($p = 0.005$). All patients with Stage 4 CKD developed AKI, comprising 16.67% of the AKI group ($p = 0.018$). In contrast, early-stage CKD (Stages 1–2) showed no significant association with AKI occurrence ($p = 0.556$ and $p = 0.174$, respectively).

Table 1. Baseline clinical parameters of the study cohort, with stratification by AKI occurrence.

Characteristic	N	Overall	AKI Occurrence		*p*
			Yes, $n_1 = 18$ [a]	No, $n_2 = 48$ [a]	
SCr [1] mg/dl	66 [f]	1.06 (0.89, 1.21)	1.39 (1.12, 1.83)	1.01 (0.87, 1.15)	<0.001 [c]
CKD [2] stage	66				<0.001 [c]
no CKD		14 (20.59%) [b]	2 (11.11%) [b]	11 (22.92%) [b]	0.488 [e]
Stage 1		3 (4.41%) [b]	0 (0%) [b]	3 (6.25%) [b]	0.556 [e]
Stage 2		31 (45.59%) [b]	6 (33.33%) [b]	24 (50%) [b]	0.174 [d]
Stage 3a		10 (14.71%) [b]	1 (5.56%) [b]	9 (18.75%) [b]	0.264 [e]
Stage 3b		6 (8.82%) [b]	5 (27.78%) [b]	1 (2.08%) [b]	0.005 [e]
Stage 4		3 (4.41%) [b]	3 (16.67%) [b]	0 (0%) [b]	0.018 [e]
Stage 5		1 (1.47%) [b]	1 (5.56%) [b]	0 (0%) [b]	0.272 [e]
Body Mass Index	66	26.08 (24.31, 29.58)	26.25 (24.98, 30.78)	26.27 (24.31, 29.58)	0.751 [c]
Hypertension	66	18 (26.47%) [b]	17 (94.44%) [b]	44 (91.67%) [b]	1.000 [e]
DM [3]	66	23 (33.82%) [b]	5 (27.78%) [b]	13 (27.08%) [b]	1.000 [e]
CHD [4]	66	11 (16.18%) [b]	8 (44.44%) [b]	14 (29.17%) [b]	0.241 [e]
COPD [5]	66	3 (4.41%) [b]	5 (27.78%) [b]	4 (8.33%) [b]	0.055 [e]
ASA [6]	66	24 (35.29%) [b]	6 (33.33%) [b]	18 (37.50%) [b]	0.754 [e]
LMWH [7]	66	3 (4.41%) [b]	3 (16.67%) [b]	0 (0%) [b]	0.018 [e]
ACEI [8]	66	27 (39.71%) [b]	5 (27.78%) [b]	22 (45.83%) [b]	0.184 [e]

Table 1. *Cont.*

Characteristic	N	Overall	AKI Occurrence		*p*
			Yes, $n_1 = 18$ [a]	No, $n_2 = 48$ [a]	
ARB [9]	66	12 (17.65%) [b]	6 (33.33%) [b]	6 (12.50%) [b]	0.073 [e]
β-blocker	66	32 (47.06%) [b]	8 (44.44%) [b]	24 (50%) [b]	0.688 [e]
α-blocker	66	6 (8.82%) [b]	4 (22.22%) [b]	2 (4.17%) [b]	0.043 [e]
Number of medications	66	3.00 (2.00, 5.00)	3.50 (1.25, 5.00)	3.00 (2.00, 5.00)	0.856 [d]

[a] Median (Q1, Q3); [b] *n* (%); [c] Wilcoxon rank sum test; [d] Pearson's Chi-squared test; [e] Fisher's exact test; [f] Two patients from study cohort had not a preoperative SCr measurement; [1] SCr—serum creatinine, [2] Chronic Kidney Disease, [3] Diabetes Mellitus, [4] Coronary Heart Disease, [5] Chronic Obstructive Pulmonary Disease, [6] ASA acetylsalicylic acid, [7] LMWH low molecular weight heparin, [8] ACEI angiotensin-converting enzyme inhibitors, [9] angiotensin II receptor blockers.

Among the evaluated markers, several demonstrated strong potential for distinguishing between patients with and without AKI, while others showed limited discriminatory capacity (Table 2 and Appendix C, Figure A1). The penKid exhibited a highly significant difference between groups, with a median = 2.97 ng/mL (2.29, 5.62) in the AKI group compared to median = 1.94 ng/mL (1.69, 2.42) in the non-AKI group ($p = 0.001$). Similarly, sSEMA-3A showed excellent discriminative performance, with a significantly higher concentration in the AKI group, 137.35 pg/mL (83.25, 232.86), compared to the non-AKI group, 69.43 pg/mL (51.99, 82.25), $p < 0.001$.

Table 2. Mean concentrations of AKI biomarkers over time for the overall cohort, stratified by AKI occurrence according to KDIGO criteria.

Characteristic	N	Overall	AKI Occurrence		*p* [b]
			Yes, $n_1 = 18$ [a]	No, $n_2 = 48$ [a]	
Baseline—postoperative day 3					
penKid [1], ng/mL	67	2.15 (1.73, 2.88)	2.97 (2.29, 5.62)	1.94 (1.69, 2.42)	0.001
PENK/ELISA [2] ng/mL	68	1.37 1.06, 2.24)	1.71 (1.24, 2.59)	1.26 (1.01, 1.89)	0.057
Baseline—postoperative day 2					
sSEMA-3A [3] pg/mL	29	84.63 (70.40, 178.72)	137.35 (83.25, 232.86)	69.43 (51.99, 82.25)	<0.001
uSEMA-3A [4] mL	15	24.32 (19.03, 59.31)	24.60 (18.65, 54.67)	23.88 (23.37, 117.50)	0.594
sRBP-4 [5] ng/mL	29	19.85 (16.95, 25.47)	24.79 (19.13, 28.48)	17.11 (11.92, 19.67)	0.004
uRBP-4 [6] ng/mL	30	196.11 (97.78, 308.83)	289.53 (113.35, 377.49)	165.47 (66.07, 233.61)	0.028
uKIM-1 [7] ng/mL	30	1.98 (1.22, 2.81)	2.20 (1.88, 3.40)	1.69 (0.89, 2.27)	0.113
uNetrin-1 [8] pg/mL	30	210.06 (72.64, 519.96)	259.37 (83.46, 728.89)	168.81 (69.03, 230.09)	0.300
uTIMP-2 [9] ng/mL	30	6.04 (4.23, 9.08)	4.93 (4.16, 10.00)	6.95 (4.71, 8.88)	0.934
uIGFBP-7 [10] ng/mL	30	100.84 (73.13, 151.55)	91.53 (72.33, 139.31)	120.38 (96.64, 172.86)	0.157

[a] Median (Q1, Q3); [b] Wilcoxon rank sum test; [1] penKid Proenkephalin A 119-159's concentration measured with point-of-care IB10 sphingotest® penKid®, [2] PENK/ELISA Proenkephalin A 159-119's concentration measured with ELISA assay, [3] sSEMA-3A serum Semaphorin-3A, [4] uSEMA-3A urinary Semaphorin-3A, [5] sRBP-4 serum Retinol Binding Protein-4, [6] uRBP-4 urinary Retinol Binding Protein-4, [7] uKIM-1 urinary Kidney Injury Molecule-1, [8] uNetrin-1 urinary Netrin-1, [9] uTIMP-2 urinary Tissue Inhibitor of Metalloproteinases-2, [10] uIGFBP-7 urinary Insulin-like Growth Factor-Binding Protein-7.

RBP-4 in both serum and urine also demonstrated significant differences between the two groups. sRBP-4 concentrations were significantly elevated in patients with AKI 24.79 ng/mL (19.13, 28.48) compared to those without AKI 17.11 ng/mL (11.92, 19.67), $p = 0.004$. uRBP-4 levels followed a similar trend, with higher concentrations in the AKI group 289.53 ng/mL (113.35, 377.49) versus the non-AKI group 165.47 ng/mL (66.07, 233.61), $p = 0.028$. PENK/ELISA approached significance ($p = 0.057$), suggesting a potential, albeit weaker, association with AKI. While this marker may still hold some value, its discriminative ability appeared less robust than other markers, such as penKid and SEMA-3A.

Markers such as uKIM-1 ($p = 0.113$), uNetrin-1 ($p = 0.300$), uTIMP-2 ($p = 0.934$), and uIGFBP-7 ($p = 0.157$) did not show statistically significant differences between the AKI and non-AKI groups.

2.1. Estimating Optimal Cut-Points for Individual AKI Markers

We conducted an analysis to determine the optimal cut-points for various AKI biomarkers, allowing for better discrimination between patients with and without AKI.

Each biomarker demonstrated varying degrees of discriminative power, as reflected by their respective accuracy, sensitivity, specificity, and Area Under the Curve (AUC) metrics (Table 3).

Table 3. Results of optimal cut-point estimations for discriminating patients with AKI with corresponding classification metrics.

AKI Biomarker	n_{obs}	Optimal Cutoff Point (AKI Occurrence)	CI [a] 95%	Accuracy	Sensitivity	Specificity	AUC [b]
penKid [1], ng/mL	67	≥2.29	2.03–3.82	0.73	0.78	0.71	0.76
PENK/ELISA [2], ng/mL	68	≥1.16	0.89–2.41	0.56	0.89	0.44	0.65
sSEMA-3A [3] pg/mL	29	≥89.10	74.50–179.00	0.79	0.71	0.92	0.88
uSEMA-3A [4] pg/mL	15	≥24.31	18.30–∞	0.60	0.60	0.60	0.40
sRBP-4 [5] ng/mL	29	≥23.72	13.10–24.80	0.76	0.64	0.92	0.81
uRBP-4 [6] ng/mL	30	≥289.53	71.20–377.00	0.70	0.53	0.92	0.74
uKIM-1 [7] ng/mL	30	≥1.01	1.01–6.40	0.70	0.94	0.38	0.67
uNetrin-1 [8] pg/mL	30	≥706.15	83.50–802.00	0.63	0.35	1.00	0.61
uTIMP-2 [9] ng/mL	30	≥4.65	2.37–7.41	0.60	0.47	0.77	0.51
uIGFBP-7 [10] ng/mL	30	≥101.70	63.2–257.00	0.70	0.71	0.69	0.66

[a] CI Confidence Interval, [b] AUC Area Under the Curve, [1] penKid Proenkephalin A 159-119's concentration measured with point-of-care IB10 sphingotest® penKid®, [2] PENK/ELISA Proenkephalin A 159-119's concentration measured with ELISA assay, [3] sSEMA-3A serum Semaphorin-3A, [4] uSEMA-3A urinary Semaphorin-3A, [5] sRBP-4 serum Retinol Binding Protein-4, [6] uRBP-4 urinary Retinol Binding Protein-4, [7] uKIM-1 urinary Kidney Injury Molecule-1, [8] uNetrin-1 urinary Netrin-1, [9] uTIMP-2 urinary Tissue Inhibitor of Metalloproteinases-2, [10] uIGFBP-7 urinary Insulin-like Growth Factor-Binding Protein-7.

The penKid biomarker emerged as one of the most promising candidates for clinical use, with an optimal cut-point of ≥2.29 ng/mL. It achieved high accuracy (0.73), sensitivity (0.78), and specificity (0.71) alongside a robust AUC = 0.76. sSEMA-3A also demonstrated exceptional utility, with a cut-point of ≥89.10 pg/mL. It exhibited a high accuracy (0.79) and specificity (0.92), with an AUC = 0.88. The performance of sRBP-4 was similarly strong, with a cut-point of ≥23.72 ng/mL, high specificity (0.92), and an AUC = 0.81. uRBP-4 also offered reasonable performance (AUC 0.74).

Markers such as uKIM-1, uNetrin-1, and uIGFBP-7, while possibly applicable, demonstrated more variable performance. uKIM-1 showed high sensitivity (0.94), making it a strong candidate for early detection of AKI, but its low specificity (0.38) suggests that it may produce a high number of false positives. uNetrin-1 demonstrated perfect specificity (1.00), but its low sensitivity (0.35) limited its utility as a standalone marker. uIGFBP-7 showed balanced sensitivity and specificity (around 0.70), making it a moderately valuable marker, but its AUC (0.66) indicates that it may not be as discriminative as other markers.

2.2. Estimating the Agreement Between AKI Diagnosis by KDIGO Criteria and Individual AKI Biomarkers

Agreement between AKI diagnosis by KDIGO criteria and individual biomarker performance was assessed using Gwet's AC1 statistic, which provides stable estimates in imbalanced datasets (Table 4).

Table 4. The agreement results between AKI diagnosis by KDIGO criteria and individual AKI biomarkers.

AKI Biomarker	Gwet's AC1 [a]	SE [b]	CI [c] 95%	*p*
penKid [1]	0.52	0.11	0.31–0.73	<0.001
PENK/ELISA [2]	0.10	0.12	−0.15–0.34	0.428
sSEMA-3A [3]	0.59	0.15	0.28–0.90	<0.001
uSEMA-3A [4]	0.23	0.26	−0.33–0.79	0.392
sRBP-4 [5]	0.52	0.16	0.19–0.84	0.003
uRBP-4 [6]	0.41	0.17	0.06–0.75	0.022
uKIM-1 [7]	0.40	0.17	0.04–0.76	0.031
uNetrin-1 [8]	0.30	0.18	−0.07–0.68	0.104
uTIMP-2 [9]	−0.07	0.20	−0.49–0.34	0.712
uIGFBP-7 [10]	−0.32	0.18	−0.69–0.031	0.072

[a] AC1 Agreement Coefficient, [b] SE Standard Error, [c] CI Confidence Interval, [1] penKid Proenkephalin A 159-119's concentration measured with point-of-care IB10 sphingotest® penKid®, [2] PENK/ELISA Proenkephalin A 159-119's concentration measured with ELISA assay, [3] sSEMA-3A serum Semaphorin-3A, [4] uSEMA-3A urinary Semaphorin-3A, [5] sRBP-4 serum Retinol Binding Protein-4, [6] uRBP-4 urinary Retinol Binding Protein-4, [7] uKIM-1 urinary Kidney Injury Molecule-1, [8] uNetrin-1 urinary Netrin-1, [9] uTIMP-2 urinary Tissue Inhibitor of Metalloproteinases-2, [10] uIGFBP-7 urinary Insulin-like Growth Factor-Binding Protein-7.

PenKid, with a Gwet's AC1 = 0.52 ($p < 0.001$), demonstrated moderate agreement with the KDIGO criteria, indicating its potential utility as a reliable marker in clinical practice. Its relatively narrow confidence interval (CI 95%: 0.31–0.73) further supported its stability as a diagnostic tool for AKI. sSEMA-3A showed a slightly higher level of agreement (AC1 = 0.59, $p < 0.001$), suggesting that this marker could offer even better alignment with KDIGO-defined AKI. Conversely, PENK/ELISA showed minimal agreement with the KDIGO criteria (AC1 = 0.10, $p = 0.428$), with a confidence interval that spans negative values, suggesting that this biomarker may not be a reliable indicator of AKI when compared to the KDIGO standard. Similarly, uSEMA-3A (AC1 = 0.23, $p = 0.392$) and uNetrin-1 (AC1 = 0.30, $p = 0.104$) exhibit weak agreement, indicating their diagnostic value may be limited or context-specific.

RBP-4, both in plasma (AC1 = 0.52, $p = 0.003$) and urine (AC = 0.41, $p = 0.022$), demonstrated moderate agreement with the KDIGO criteria. The u RBP-4 also showed reasonable agreement, although with slightly less precision. uKIM-1, with an AC1 of 0.40 ($p = 0.031$), showed moderate concordance. In contrast, uTIMP-2 and uIGFBP-7 showed no meaningful agreement with the KDIGO criteria, with Gwet's AC1 values of −0.07 and −0.32, respectively.

Correlation analysis between AKI biomarkers was performed to examine their interdependencies (Figure 1). Most biomarker pairs demonstrated weak correlations (coefficients near 0). For instance, penKid and PENK/ELISA showed rho = −0.06, indicating a negligible association. Similar weak correlations were observed between penKid and other biomarkers, including SEMA-3A (plasma and urine), uNetrin-1, and uTIMP-2.

Several biomarker pairs exhibited moderate correlations. uRBP-4 and uKIM-1 demonstrated rho = 0.66 ($p = 0.003$), while uKIM-1 and uTIMP-2. showed rho = 0.63 ($p = 0.008$). The correlation between uTIMP-2 and uIGFBP-7 was rho = 0.53 ($p = 0.104$).

2.3. Evaluation of Discriminatory Performance Using AKI Biomarker Panels

In clinical practice, relying on a single biomarker is unlikely to provide the optimal balance of sensitivity and specificity necessary for accurately detecting AKI across diverse patient populations. A multi-biomarker approach could be recommended to enhance diagnostic accuracy and improve clinical outcomes. A panel consisting of penKid, sSEMA-3A, and uKIM-1 offered a promising strategy and was chosen to evaluate discriminatory performance. This combination harnessed the strengths of each biomarker: penKid, which

provides balanced sensitivity (0.78) and specificity (0.71); uKIM-1, which showed exceptionally high sensitivity (0.94) for detecting early kidney injury despite modest individual discriminative performance (AUC 0.64); and sSEMA-3A, which exhibited high specificity (0.92) and excellent individual performance (AUC 0.88), collectively enhancing the diagnostic precision of the panel to achieve an AUC of 0.89 (referred to as Panel 1). The inclusion of uKIM-1, despite its lower individual AUC, was based on its complementary role within the multi-marker context.

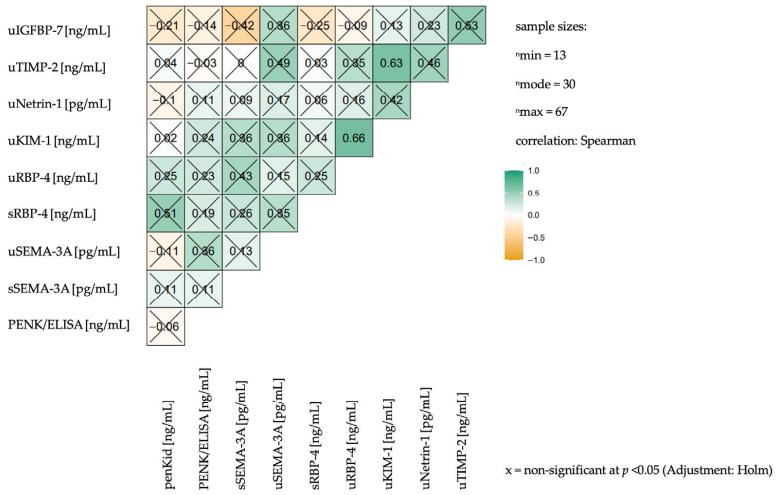

Figure 1. Correlation matrix displaying the relationships between the mean concentrations of AKI markers over the observed period.

As a variation (Panel 2) of the panel above, sRBP-4 was considered an alternative to uSEMA-3A in the biomarker panel for AKI detection, forming a second panel for evaluation. RBP-4 offered a similar diagnostic value, particularly due to its specificity, which enhanced the overall performance of the panel but lowered the agreement rate.

The PENK/ELISA demonstrated poor agreement with AKI diagnosis based on KDIGO criteria, indicating a potential limitation in its diagnostic utility.

The composition of the biomarker panels was limited by the sample size (n = 29). As a result, the effect values of the individual panel components were not further adjusted for potential confounding variables. The fitted generalized linear models assessed the effect of both biomarker panels on AKI occurrence and demonstrated moderate coefficients of determination, with R^2 Tjur values of 0.438 and 0.263, respectively.

The receiver operating characteristic (ROC) for Panel 1, comprising penKid, sSEMA-3A, and uKIM-1, demonstrated robust discriminative performance with an ROC of 0.89 (95% CI: 0.77–1.00). In comparison, Panel 2, which included penKid, sRBP4, and uKIM-1, exhibited a slightly lower ROC of 0.81 (95% CI: 0.65–0.99). Despite this difference in AUC, the DeLong test indicated no statistically significant difference between the two ROC curves (Z = 0.68, 95% CI: −0.13–0.27, p = 0.494), suggesting that both panels perform similarly regarding AKI detection (Figure 2).

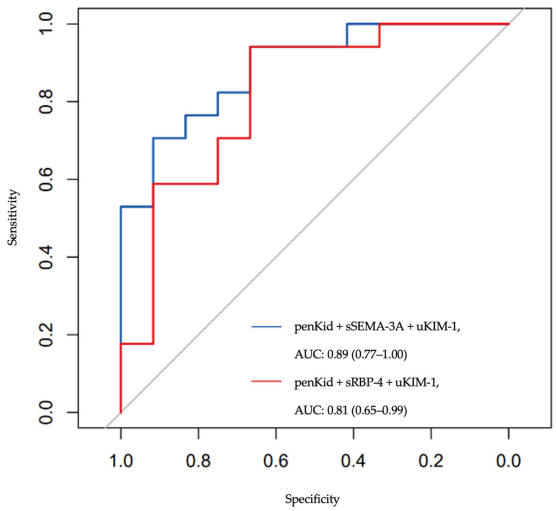

Figure 2. ROC curves for proposed panels of AKI biomarkers.

3. Discussion

The pathophysiology of AKI is widely described as diverse, encompassing numerous mechanisms including glomerular and tubular damage, and thrombotic microangiopathy [16]. The diagnosis of AKI, as determined by traditional biomarkers, does not provide differentiation based on the underlying pathomechanism. Moreover, KDIGO criteria fail to identify all patients who have histopathological evidence of kidney damage [17]. This particular population has been classified into the sAKI group based on variations in levels of novel biomarkers [18]. To identify the most accurate biomarker panel for early AKI detection, this study evaluated selected ones categorized according to their nephron location and underlying release mechanisms. A biomarker panel consisting of penKid, sSEMA-3A, and uKIM-1 demonstrated promise for early AKI detection and was selected to assess discriminatory performance. This combination harnessed the unique strengths of each biomarker: penKid, which provided balanced sensitivity and specificity; uKIM-1, which showed high sensitivity in detecting early kidney injury; and sSEMA-3A, which exhibited high specificity, collectively enhancing the diagnostic precision of the panel (referred to as Panel 1). As an alternative configuration (Panel 2), sRBP-4 was evaluated as a substitute for sSEMA-3A within the multi-biomarker panel. While sRBP-4 offered comparable diagnostic value due to its specificity, its lower agreement rate influenced overall panel performance.

Studies suggested that SEMA-3A has many functions, such as regulating angiogenesis and organogenesis, but it has also been found in adult podocytes and collecting tubules [19]. SEMA-3A is undetectable in the urine of healthy subjects but can be identified within hours of reperfusion-ischemia injury, and its inactivation suppresses this process [20]. This finding suggests that uSEMA-3A may serve as a marker of renal hypoxic injury [21]. In contrast, the higher sensitivity and specificity of serum rather than urine SEMA-3A were confirmed in our patient cohort. We concluded that urine SEMA-3A may have limited or context-specific diagnostic value. This finding supports the utility of this serum biomarker in perioperative patients at high surgical risk for the reperfusion-ischemic AKI phenotype.

Results from serial measurements of penKid, a commercial set of the functional biomarker PENK, indicate its high utility in the perioperative setting. Our findings are consistent with previous studies [22–24]. The function of PENK in the kidney is not fully

understood, with possible regulation of diuresis and natriuresis [25,26]. As a functional biomarker, PENK is recognized as a superior option compared to other biomarkers due to its association with glomerular filtration and its minimal tubular influence [26]. Consequently, PENK demonstrates a robust correlation with actual GFR as assessed by the gold standard iohexol method [27].

Both panels, which combined multiple biomarkers, demonstrated relatively high ROC values, reaffirming the value of a multi-biomarker approach over-reliance on a single biomarker. This finding supported the notion that combining biomarkers with diverse strengths, such as sensitivity, specificity, and representation of different biological pathways, enabled a more comprehensive and accurate assessment of kidney function and early AKI detection.

The lack of a statistically significant difference between the two panels, despite the slightly higher ROC for Panel 1 (penKid + sSEMA-3A + uKIM-1) compared to Panel 2 (penKid + sRBP-4 + uKIM-1), suggested that both panels offered comparable diagnostic performance. This indicated that clinicians could choose either panel based on factors such as biomarker availability, cost, sample material, or specific patient characteristics without compromising diagnostic accuracy for AKI detection. The high discriminatory power of both panels (with ROC values exceeding 0.80) highlighted their potential utility in clinical settings to identify AKI at an earlier stage, enabling timely interventions such as fluid management or medication adjustments to mitigate progression to more severe kidney injury.

Additionally, the finding that sRBP-4 could serve as an alternative to sSEMA-3A without significantly affecting the panel's overall performance provided added flexibility. RBP-4 was significantly elevated in the AKI group but had a lower predictive value than penKid and SEMA-3A. This correlation has not been observed in previous studies [28,29]. In contrast, no significant correlation was found in the cohort for uTIMP-2 and uIGFBP-7, which are reported to be released into the urine shortly after injury [30].

While our biomarker panels demonstrated promising discriminative performance, several factors warrant cautious interpretation. The relatively wide confidence intervals (CIs) for both panels (Panel 1: 0.77–1.00; Panel 2: 0.65–0.99) reflect the limited sample size for panel fitting (n = 29) and indicate substantial uncertainty in the point estimates. Additionally, biomarkers commonly experience 5–15 point AUC decreases when validated in independent cohorts, as observed with neutrophil gelatinase-associated lipocalin (NGAL) and TIMP-2×IGFBP-7 biomarker in AKI prediction studies [31,32]. Applying these benchmarks to our results suggests Panel 1 may achieve external validation performance in the range of 0.74–0.84, while Panel 2 may validate at 0.68–0.77. Importantly, the lower confidence bounds of our panels (0.77 and 0.65, respectively) likely provide more realistic estimates of external performance than the point estimates.

The problem of developing an early biomarker panel for perioperative AKI is still in the early research phase [33]. Currently, a commercially available panel of two biomarkers, TIMP-2×IGFBP-7, did not show statistically significant efficacy in our and recent studies [14,34,35]. Adler et al. assessed the feasibility of uTIMP-2×uIGFBP-7 to predict early AKI after out-of-hospital cardiac arrest with promising results [30]. In our cohort, both uTIMP-2 and uIGFBP-7 demonstrated no significant differences between AKI and non-AKI groups (p = 0.934 and p = 0.157, respectively) and showed negative agreement with KDIGO criteria (AC1 = −0.07 and AC1 = −0.32, respectively), leading to their exclusion from the final panel. In the selection of representative biomarkers for the panels, it was posited that the early diagnosis of perioperative AKI should prioritize well-established injury and functional biomarkers. The biomarker panels proposed in this study were chosen based on the distinct mechanisms influencing the secretion of each biomarker, their varying locations

within the nephron, their complementary performance characteristics, and their efficacy in detecting AKI. These promising results open the way for further studies on biomarker panels in perioperative AKI.

The baseline comorbidity profile of our cohort reflects the complex background characteristic of EVAR patients, with substantial cardiovascular risk burden. The strong association between advanced CKD (Stages 3b–4) and AKI development ($p \leq 0.018$) is particularly clinically relevant, as it identifies patients with eGFR < 45 mL/min/1.73 m^2 as having severely limited renal reserve and heightened vulnerability to perioperative injury. This finding aligns with established literature demonstrating reduced capacity to compensate for nephrotoxic insults in moderate-to-severe CKD [36]. The significant association between LMWH use and AKI occurrence ($p = 0.018$) warrants careful interpretation; increased bleeding risk compromising renal perfusion, or confounding by indication, whereby patients requiring therapeutic anticoagulation had more severe underlying vascular disease. The trend toward elevated AKI risk with preoperative ARB use ($p = 0.073$) was not consistent with data regarding renin-angiotensin system blockade [37]. These baseline risk factors emphasize the importance of risk stratification and support the clinical utility of our biomarker panels for identifying high-risk patients who may benefit from enhanced monitoring and preventive strategies, considering a 4-fold increase in long-term cardiovascular-specific mortality after vascular surgery [38]. The lack of association between early-stage CKD (Stages 1–2) and AKI suggests that preserved renal function (eGFR $\geq$ 60 mL/min/1.73 m^2) provides adequate reserve for most EVAR patients, though biomarker-guided early detection remains valuable even in this population.

The predominantly homogeneous procedural composition of our cohort (88.2% b-EVAR) represents both a strength and a limitation that merits discussion. As a strength, this uniformity minimizes confounding by procedure type that would complicate interpretation in mixed EVAR cohorts. B-EVAR patients undergo similarly complex procedures involving thoracoabdominal aneurysm repair with comparable technical demands, visceral vessel manipulation, and hemodynamic stress patterns [39], providing a relatively uniform baseline of high procedural complexity against which biomarker discrimination could be evaluated. Critically, despite this uniform high procedural complexity, AKI developed in only 26.5% of patients, and our biomarker panels successfully discriminated between those who developed AKI and those who did not (Panel 1 AUC 0.89). This discrimination within a procedurally homogeneous group suggests the biomarkers detect actual kidney injury rather than merely reflecting procedural stress, as the latter would be expected to affect all branched EVAR patients similarly.

Our findings should be interpreted within the broader context of perioperative AKI biomarker research. The NephroCheck™ test, which combines TIMP-2 and IGFBP-7, demonstrated AUCs of 0.80–0.82 for AKI prediction in the multi-center SAPPHIRE study [32], while meta-analyses of NGAL in surgical populations have shown pooled AUCs ranging from 0.71 to 0.78 [31,40]. Our Panel 1 (penKid/sSEMA-3A/uKIM-1) achieved comparable and superior discrimination (AUC 0.89), though direct comparison is limited by differences in patient populations, surgical contexts, and methodological approaches.

3.1. Study Strengths and Limitations

This study's strengths include its prospective design, focus on a clinically relevant high-risk EVAR population, and the evaluation of novel multi-biomarker panels using robust statistical methods. However, the findings are limited by the single-center nature of the research and a modest overall sample size ($n = 68$, with 18 AKI events), particularly for the biomarker panel subgroup analyses ($n = 29$). The limited sample size resulted in wide confidence intervals for panel AUCs (CI widths 0.23–0.34), which reflect substan-

tial uncertainty in performance estimates and increase the risk of optimistic bias despite internal validation efforts. Furthermore, the biomarker panel evaluations could not be adjusted for all potential confounding variables due to sample size restrictions. The predominantly b-EVAR composition (88.2%), while providing procedural homogeneity that minimizes confounding by procedure type, limits generalizability to less complex EVAR variants. While postoperative parameters served as intraoperative stress in this study and showed expected associations with AKI, they cannot fully replace direct intraoperative measurements. This limitation is shared with many biomarker validation studies, where granular procedural data are often unavailable [31,32], but represents an important consideration for interpretation. All limitations necessitate a cautious interpretation of the results as hypothesis-generating and underscore the need for external validation in larger, multi-center studies.

3.2. Future Research Directions

Future research should prioritize rigorous external validation of these biomarker panels in larger, multi-center surgical cohorts with diverse patient populations and varied clinical practices. Validation studies should assess not only diagnostic accuracy but also clinical impact, including whether early biomarker-guided detection improves patient outcomes and healthcare resource utilization.

4. Methods

This single-center, prospective, observational study enrolled patients undergoing EVAR between April 2022 and June 2024 at the Central Teaching Hospital, Medical University of Warsaw, Poland. The study evaluated whether novel biomarkers could serve as early indicators of kidney dysfunction for timely AKI detection in the post-EVAR period.

4.1. Patients Selection

Patients were eligible for enrollment if they met the following criteria: (1) age $\geq$ 18 years; (2) scheduled for elective endovascular aortic repair; (3) able to provide written informed consent; and (4) available for perioperative follow-up through postoperative day 3.

Patients were excluded if they: (1) required emergency EVAR procedures; (2) had end-stage renal disease requiring chronic dialysis; or (3) were unable to provide adequate urine samples for biomarker analysis. Notably, patients with preexisting CKD or baseline renal impairment were not excluded, as these conditions are prevalent in the EVAR population and reflect real-world clinical practice.

4.2. Biomarker Selection

We have selected biomarkers based on the nephron's location sites and the mechanisms behind their release (Table 5). These include indicators of glomerular filtration, such as Proenkephalin A 119-159 (penKid, PENK) and Retinol Binding Protein-4 (RBP-4), as well as markers associated with tissue damage, mostly with tubular, specifically Kidney Injury Molecule-1 (KIM-1), and Netrin-1, and stress-related markers, including Tissue Inhibitor of Metalloproteinase-2 (TIMP-2), Semaphorin-3A (SEMA-3A), and Insulin-like Growth Factor-Binding Protein-7 (IGFBP-7).

Blood and urine samples were taken perioperatively for up to three consecutive days. Serum and urinary samples were collected simultaneously at each time point (preoperative baseline within 24 h before surgery, during EVAR procedure, 24 h, and 48 h post-procedure), enabling direct temporal comparison of biomarker kinetics across compartments. Plasma for ELISA measurement was collected in ethylenediamine tetraacetic acid (EDTA) tubes, centrifuged at 1300$\times$ g for 15 min, and stored at -80 °C until batch measurement. Blood samples (5 mL) were collected via venipuncture or existing arterial/venous lines into

ethylenediamine tetraacetic acid (EDTA) tubes. Urine samples (10–20 mL) were collected from indwelling catheters. Plasma for ELISA measurement was centrifuged at 1300× *g* for 15 min within 30 min of collection and stored at −80 °C until batch measurement. Not all patients had samples available at every time point due to clinical circumstances, early discharge, catheter removal, or inadequate sample volume.

Table 5. Biomarkers categorized by mechanism of release and nephron location.

Biomarker	Sample Type	Nephron Location	Biomarker Type	Mechanism
RBP-4 [1] [28,29]	Urine, Plasma	Proximal Tubule	Injury, Functional	Proximal tubular dysfunction can cause significant increases in urinary RBP-4 due to impaired reabsorption of retinol-free apo-RBP4 fraction.
KIM-1 [2] [41]	Urine	Proximal Tubule	Injury	KIM-1 is a transmembrane glycoprotein upregulated in injured proximal tubules. Proteolytic cleavage releases its extracellular domain into urine.
TIMP-2 [3] [42]	Urine, Plasma	Distal Tubule	Stress	Both IGFBP-7 and TIMP-2 are constitutively expressed in proximal and distal tubules. Urinary elevations result from reduced tubular reabsorption (due to injury) and leakage from damaged cells.
IGFBP-7 [4] [43]	Urine	Proximal Tubule	Stress	
SEMA-3A [5] [21,44]	Urine, Plasma	Distal Tubule	Damage	In ischemia–reperfusion-induced AKI, SEMA-3A mediates tissue injury by promoting inflammation and tubular epithelial cell apoptosis. Secreted by injured podocytes and distal tubular cells during AKI.
Netrin-1 [45]	Urine	Proximal Tubule	Damage	Typically, expressed in peritubular capillaries and tubular epithelium. AKI causes downregulation in the vascular endothelium and redistribution to injured tubules.
PENK [6] [9,46]	Plasma	Glomerulus	Injury, Functional, Regeneration	PENK accumulates in the plasma in settings of reduced GFR.

[1] RBP-4 Retinol Binding Protein-4, [2] KIM-1 Kidney Injury Molecule-1; [3] TIMP-2 Tissue Inhibitor of Metalloproteinases-2, [4] IGFBP-7 Insulin-like Growth Factor-Binding Protein-7, [5] SEMA-3A Semaphorin-3A, [6] PENK/ELISA Proenkephalin A 119-159.

Serum (sRBP-4, sSEMA-3A) and urine biomarkers (uTIMP-2, uIGFBP-7, uNetrin-1, uKIM-1, uRBP-4) were measured with ELISA kits (R&D Systems, Minneapolis, MN, USA), and PENK was measured with a generic ELISA kit. The assays' sensitivity, range, and intra-assay precision were described in Appendix A (Table A1, Table A2). PenKid was measured immediately with the IB10 sphingotest® assay, designed as a lateral flow test by SphingoTec GmbH, Hennigsdorf, Germany. It utilized specific monoclonal antibodies to detect PENK levels accurately. The lowest detection limit of the immunoassay was 50 pmol/L.

The diagnosis of AKI was established using recognized clinical criteria, reflecting an increase in SCr levels according to the current KDIGO guidelines [7]. Medical data were collected perioperatively, including demographics, history, laboratory tests, and pharmacological treatments. Baseline SCr measurements were unavailable for 2 patients (2.9%). Given the minimal proportion of missing data (<5% threshold), complete case analysis was performed without imputation, which is appropriate according to established guidelines when missingness is minimal and appears random [47]. For analyses involving baseline SCr and CKD staging, 66 patients with complete data were included. All other baseline and outcome variables had complete data across the full cohort (n = 68).

The current study established a significance level of $\alpha = 0.05$, allowing for a 5% chance of a Type I error. We examined the agreement between AKI diagnosis based on KDIGO criteria and the performance of specific AKI biomarkers. Gwet's Agreement Coefficient (AC)1 statistic was used to measure the level of agreement. Receiver operating characteris-

tic (ROC) curves were constructed to evaluate the discriminative performance of individual biomarkers and multi-biomarker panels. Area under the curve (AUC) values with 95% confidence intervals were calculated using the DeLong method for biomarker panels. DeLong tests were used to compare ROC curves between panels. Due to the limited sample size relative to the number of potential confounding variables, univariate comparisons were performed for individual biomarkers, and multivariable logistic regression was not conducted to avoid model overfitting and ensure statistical stability. Analyses were conducted using R Statistical Software (version 4.3.3; R Core Team, Vienna, Austria) on Windows 11 Pro 64-bit, utilizing publicly available packages (see Appendix B). A data analysis and statistical plan was written after the data were accessed. No imputation methods were used, as the missing data were assumed to be missing at random and the statistical methods employed (Wilcoxon rank sum test, ROC analysis) inherently accommodate incomplete cases.

The study was approved by the Ethics Committee of the Medical University of Warsaw (8/KBL/OIL/2019 and 53/KBL/OIL/2022), and all participants provided their written informed consent following the Declaration of Helsinki.

5. Conclusions

Novel biomarker panels incorporating penKid, sSEMA-3A or sRBP-4, and uKIM-1 demonstrated promising performance for early AKI detection post-EVAR in this exploratory study, outperforming individual markers. These panels show potential as tools to complement traditional risk factors and standard diagnostics for identifying high-risk patients who may benefit from enhanced monitoring and timely intervention. External validation in larger, multi-center cohorts is essential to confirm diagnostic accuracy, assess generalizability across diverse populations and clinical settings, and determine whether the promising performance observed in this study translates to improved clinical outcomes.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The complete dataset used in this study has been deposited in the Zenodo repository (https://doi.org/10.5281/zenodo.14827489 (accessed on 5 October 2025)). This dataset is freely available for research purposes under a CC-BY 4.0 license.

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Abbreviations

The following abbreviations are used in this manuscript:

AC1	Agreement Coefficient 1
ACEI	Angiotensin-Converting Enzyme Inhibitors
AKI	Acute Kidney Injury
ARB	Angiotensin II Receptor Blockers
ASA	Acetylsalicylic Acid
AUC	Area Under the Curve
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CV	Coefficient of Variation
DM	Diabetes Mellitus
EDTA	Ethylenediamine Tetraacetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
EVAR	Endovascular Aortic Repair
GFR	Glomerular Filtration Rate
IGFBP-7	Insulin-like Growth Factor-Binding Protein-7
IQR	Interquartile Range
KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	Kidney Injury Molecule-1
LMWH	Low-molecular-Weight Heparin
Netrin-1	Netrin-1
NGAL	Neutrophil Gelatinase-Associated Lipocalin
PENK/ELISA	Proenkephalin A 119-159 (measured with ELISA assay)
penKid	Proenkephalin A 119-159
RBP-4	Retinol Binding Protein-4
ROC	Receiver Operating Characteristic
sAKI	Subclinical Acute Kidney Injury
SCr	Serum Creatinine
SE	Standard Error
SEMA-3A	Semaphorin-3A
TIMP-2	Tissue Inhibitor of Metalloproteinase-2
UOP	Urine Output

Appendix A

IGFBP-7 (DY1334) and SEMA-3A (DY1250): Sensitivity and range data not explicitly stated by the manufacturer.

Table A1. Characteristics of the used ELISA assays, R&D Systems, Minneapolis, MN, USA.

Assay	Catalog Number	Sensitivity	Detection Range	Intra-Assay Precision (CV%)	Inter-Assay Precision (CV%)
KIM-1	DKM100	0.009 ng/mL	0.156–10 ng/mL	4.3–4.4%	6.1–7.8%
Netrin-1	NBP2-76771	18.75 pg/mL	31.25–2000 pg/mL	<10%	<10%
RBP-4	DRB400	0.224 ng/mL	1.56–100 ng/mL	7.0%	5.8–8.6%
TIMP-2	DTM200	0.011 ng/mL	0.156–10 ng/mL	4.2–6.5%	6.2–7.3%

Table A2. Characteristic of the used ELISA assay (generic).

Assay	Catalog Number	Sensitivity	Detection Range	Intra-Assay Precision (CV%)	Inter-Assay Precision (CV%)
PENK	201-12-2342	0.041 ng/mL	0.05–10 ng/mL	<9%	<11%

Appendix B

Analyses were conducted using the R Statistical language (version 4.3.3; R Core Team, Vienna, Austria) on Windows 11 pro 64 bit (build 22631), using the packages rio (version 1.2.1 [48]), doParallel (version 1.0.17 [49]), rngtools (version 1.5.2 [50]), doRNG (version 1.8.6 [51]), irrCAC (version 1.0 [52]), sjPlot (version 2.8.15 [53]), parameters (version 0.22.2 [54]), performance (version 0.12.3 [55]), report (version 0.5.8 [56]), correlation (version 0.8.5 [57]), ggstatsplot (version 0.12.3 [58]), pROC (version 1.18.5 [59]), gtsummary (version 1.7.2 [60]), cutpointr (version 1.1.2 [61]), MASS (version 7.3.60.0.1 [62]), ggplot2 (version 3.5.0 [63]), dplyr (version 1.1.4 [64]).

Appendix C

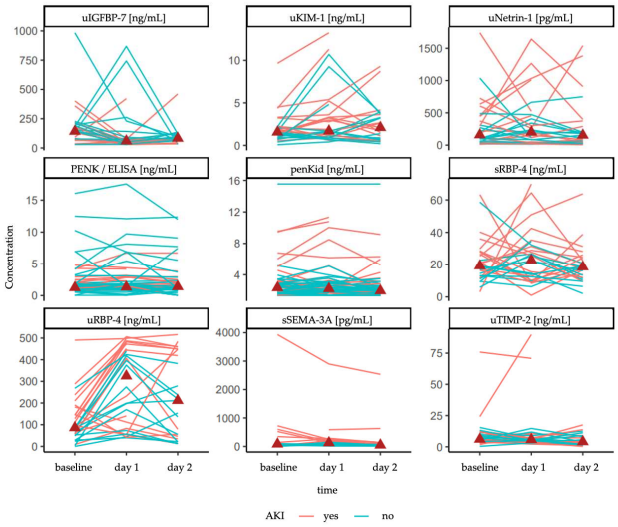

Figure A1. Temporal trends of AKI biomarkers (up to 2 days postoperative) stratified by AKI occurrence according to KDIGO criteria. Red triangles represent the overall median values for the individual time point.

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Review

Acute Kidney Injury Biomarkers in Perioperative Care: A Scoping Review of Clinical Implementation

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Abstract

Background: Acute kidney injury (AKI) remains one of the most common perioperative complications, carrying substantial mortality and healthcare burden. Traditional diagnostic criteria relying on serum creatinine and urine output are limited by delayed detection and inability to characterize the underlying injury phenotype. This scoping review examined the current state of novel AKI biomarker research in perioperative care, evaluated their clinical implementation, and identified knowledge gaps. **Methods**: A systematical search was performed for studies investigating novel AKI biomarkers in surgical settings. Biomarkers were categorized as functional, stress, or damage markers. Data extraction focused on diagnostic performance, clinical outcomes, regulatory approval status, and implementation barriers. A narrative synthesis was organized by biomarker category and thematic areas. **Results**: Several biomarkers demonstrated superior early diagnostic performance compared to traditional ones, including PENK or CCL-14, showing promising accuracy for AKI detection and outcome prediction. TIMP-2*IGFBP-7 and NGAL achieved regulatory approval, and biomarker-guided KDIGO care bundles significantly reduced AKI incidence in surgical populations. However, substantial heterogeneity exists in assays, cutoff values, and clinical validation across different clinical settings. **Conclusions**: Novel AKI biomarkers offer a promise for early detection and risk stratification in perioperative care, yet widespread clinical adoption requires addressing standardization challenges, establishing cost-effectiveness, and validating implementation strategies.

Keywords: AKI; biomarkers; PENK; CCL-14; TIMP-2*IGFBP-7; NGAL; perioperative care

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1. Introduction

Acute kidney injury (AKI) represents a syndrome characterized by rapid deterioration of kidney function. In perioperative care, it is associated with substantial short- and long-term complications, increased mortality [1], and high healthcare utilization, especially in persistent cases [2]. Current Kidney Disease Improving Global Outcomes (KDIGOs) diagnostic criteria (Table 1) for AKI rely on serum creatinine (SCr) and urine output (UOP) [3]. Debate continues regarding the limitations of conventional markers [4,5]. Specifically, they delay kidney injury recognition and show low sensitivity for early tubular injury, potentially missing cases where kidney damage occurs without reaching KDIGO diagnostic criteria [6]. This delayed detection precludes timely intervention during the critical window

when preventive strategies are most effective, directly contributing to progression toward long-term poor kidney outcomes.

Table 1. The KDIGO (Kidney Disease: Improving Global Outcomes) criteria and staging of acute kidney injury.

AKI Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times baseline (7 days) OR ≥0.3 mg/dL increase within 48 h	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/hour for ≥12 h
3	3.0 times baseline OR increase to ≥4.0 mg/dL OR initiation of RRT [1] OR decrease in eGFR [2] to <35 mL/min/1.73 m^2 in patients < 18 years	<0.3 mL/kg/hour for ≥24 h OR anuric for ≥12 h

[1] RRT: renal replacement therapy; [2] eGFR: estimated glomerular filtration rate.

Over the past two decades, advances in biomarker research have identified novel markers that enable earlier AKI detection, better risk stratification, and improved understanding of AKI pathophysiology [7]. These biomarkers can be categorized based on their biological mechanisms: functional markers assessing glomerular filtration, stress markers reflecting cellular response to injury, and damage markers indicating structural injury [8]. Several biomarkers have achieved regulatory approval, including U.S. Food and Drug Administration (FDA) clearance, supporting their clinical translation [9–11]. Importantly, recent clinical trials have demonstrated that biomarker-guided implementation of KDIGO care bundles can significantly reduce AKI incidence and severity in high-risk surgical populations [12,13], establishing proof-of-concept for biomarker-driven precision medicine in perioperative care. Despite these advances, challenges remain in standardizing assays, determining optimal cutoff values, establishing cost-effectiveness, and integrating biomarkers into routine clinical workflows.

This scoping review examines the current state of AKI biomarker research, identifies critical knowledge gaps in clinical implementation, and provides recommendations for future research priorities to advance precision medicine approaches in perioperative AKI management.

2. Materials and Methods

Two researchers independently conducted a systematic search of EuropePMC, MEDLINE, and Scopus databases using controlled vocabulary and keywords related to AKI, novel biomarkers (NGAL, KIM-1, cystatin C, TIMP-2, IGFBP-7, L-FABP, IL-18, CXCL-9, CCL-14, hepcidin, PENK, DKK-3, alpha-1-microglobulin, and CHI3L-1), and surgery or perioperative care. Studies were included if they investigated novel AKI biomarkers in surgical patients, while critically ill populations, non-postprocedural AKI, and preclinical studies without clinical translation were excluded. Following duplicate removal, two independent reviewers screened titles and abstracts, followed by full-text review of potentially eligible studies. Disagreements were resolved through discussion or consultation with a third reviewer.

A narrative synthesis approach organized findings by biomarker category (functional, stress, damage) and thematic areas, including diagnostic performance, regulatory approval,

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and clinical adoption. Knowledge gaps were systematically identified by analyzing inconsistencies in findings, insufficient evidence areas, and discrepancies between preclinical data and clinical translation. Limitations include restriction to English-language publications, absence of formal quality assessment, possible underrepresentation of emerging biomarkers, and substantial methodological heterogeneity precluding quantitative synthesis. Additionally, non-standardized reporting of measurement timing and threshold values hindered direct comparisons, and publication bias may have overestimated biomarker diagnostic accuracy and clinical utility.

3. Current State of AKI Biomarker Research

The classical definition of AKI is primarily based on two key parameters, SCr and UOP. Both measures are well-established and cost-effective; however, they present notable limitations (Table 2) [14]. Moreover, current classification does not accurately differentiate the cause or site of renal injury. SCr is characterized by low sensitivity and specificity and is influenced by factors such as muscle mass, hepatic function, and fluid balance. Furthermore, elevations in SCr often occur 24–36 h after the onset of injury due to increased SCr half-life while eGFR decreases [15]. Similarly, UOP is subject to alterations from hypovolemia, fasting, or the administration of diuretics, which diminishes its reliability for evaluating true renal parenchymal injury during acute perioperative periods. Despite extensive clinical application, SCr has not yet been supplanted by newer biomarkers in the diagnosis of AKI [5]. To overcome the limitations of traditional AKI biomarkers during the perioperative period, extensive research is concentrated on identifying and applying new, early, and effective biomarkers that can better characterize the etiology and severity of renal injury [16] (Table 3). The inherent limitations of SCr in accurately reflecting glomerular filtration rate (GFR) underscore the need to refine the KDIGO definition and incorporate novel biomarkers into GFR estimation formulas. For example, a multicenter study demonstrated that the PENK-Crea equation provides superior accuracy in GFR estimation compared to most traditional and recently developed creatinine-based equations [17].

Table 2. Key limitations of traditional markers of acute kidney injury.

Parameter	Limitations
Serum Creatinine	Low sensitivity for early AKI, requires ~50% loss of renal function before detectable elevation. Delayed rise 24–48 h after acute insult. Poor discrimination between acute and chronic changes. Volume status affects hemoconcentration. Pregnancy-related decrease during gestation. Muscle mass dependent varies with age, sex, body composition, and nutritional status. Influenced by nonrenal factors including dietary creatine, hepatic function, and metabolic rate. Medication interference with tubular secretion inhibitors falsely elevates levels. Non-specific for injury type including glomerular versus tubular. Inadequate for real-time monitoring. Unreliable in extreme body compositions.

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Table 2. *Cont.*

Parameter	Limitations
Urine Output	Transient oliguria occurs with dehydration, stress, or volume depletion. Prone to collection errors even with urinary catheters (incomplete collection, spillage, miscalculation). Reduced output may reflect prerenal factors rather than intrinsic renal damage. Requires accurate hourly measurement and weight-based calculations. Normal or high urine output can occur despite significant renal dysfunction in non-oliguric injury. Requires sustained reduction over hours to meet diagnostic criteria. Influenced by fluid balance, medications, and hemodynamic status.

Table 3. Summary of AKI biomarkers' characteristics in perioperative care.

Biomarker	Name	Sample	Detection Window	Cutoff Value
PENK	Proenkephalin A 119–159	Serum	2–6 h	~57.3 pmol/L
IL-18	Interleukin-18	Urine	4 h	1477 pg/mg creatinine
L-FABP	Liver-Type Fatty Acid–Binding Protein	Urine	4–6 h	~673.1 µg/g creatinine
TIMP-2*IGFBP-7	Tissue Inhibitor of Metalloproteinase-2 * Insulin-Like Growth Factor-Binding Protein-7	Urine	4–12 h	>0.3 $(ng/mL)^2/1000$
CCL-14	C-C Motif Chemokine Ligand-14	Urine	6–24 h	1.3 ng/mL
CXCL-9	C-X-C Motif Chemokine Ligand-9	Urine	Postprocedural	N/S
DKK-3	Dickkopf-related Protein-3	Urine	Preprocedural	>471 pg/mg creatinine
CHI3L-1	Chitinase 3-like Protein-1	Urine	Postprocedural	≥5 ng/mL
KIM-1	Kidney Injury Molecule-1	Urine	12–24 h	19 ng/mL
CysC	Cystatin C	Urine, Serum	6–24 h	>1.33 mg/L (peds) ≥25% increase (adults)
NGAL	Neutrophil Gelatinase-Associated Lipocalin	Urine, Serum	2–6 h	~150–154 ng/mL
α1m	Alpha-1-Microglobulin	Urine	Preprocedural	N/S
Hepcidin-25	Hepcidin-25	Urine, Serum	6–24 h	N/S
GGT	Gamma-Glutamyltransferase	Urine	Postprocedural	N/S
π-GST	π-Glutathione S-Transferase	Urine	3–12 h	16.5 µg/L
IL-9	Interleukin-9	Urine	Postprocedural	N/S
MCP-1	Monocyte Chemoattractant Protein-1	Urine	Post-AKI	N/S
NTN-1	Netrin-1	Urine	2–6 h	~898–2462 pg/mg creatinine
SEMA-3A	Semaphorin-3A	Urine	2–6 h	~390–848 pg/mg creatinine
OPN	Osteopontin	Serum	Postprocedural	N/S
RTECs	Renal Tubular Epithelial Cells	Urine	12–24 h	N/S

Abbreviation: N/S—non-specified.

3.1. Functional Biomarkers and Surrogate Markers of the Glomerular Filtration Rate

3.1.1. PENK

Proenkephalin A 119–159 (PENK), with a molecular weight of 4.5 kDa, is freely filtrated across the glomerular membrane, making its plasma concentration directly proportional to the GFR [18]. The precise role and function of enkephalins in the kidneys remain incompletely understood [19]. However, recent studies have suggested a potential regulatory role

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for enkephalins in the control of diuresis and natriuresis [20]. The importance of PENK in perioperative care has been confirmed by studies in cardiac surgery and contrast-induced (CI)-AKI settings. Elevated preoperative and postoperative PENK levels were associated with increased AKI risk. Changes in PENK serum levels predicted AKI development more rapidly than SCr [21–23] and hospital mortality after AKI [24]. However, there are discrepancies regarding whether PENK levels increase earlier than SCr levels [25]. Most studies have focused on high-risk vascular surgery procedures with small but homogeneous patient groups [19,25–27]. Meta-analytic evidence demonstrated that PENK achieves a pooled sensitivity of 0.69 and specificity of 0.76 for early AKI detection, with an optimal cutoff of approximately 57.3 pmol/L, with moderate sensitivity and specificity [19].

3.1.2. IL-18

Interleukin-18 (IL-18) functions as a potent proinflammatory mediator in both innate and adaptive immune responses. In the context of AKI, IL-18 is produced primarily by proximal tubular epithelial cells following injury. The cytokine plays a direct pathogenic role in kidney injury by stimulating inflammatory pathways and promoting tubular cell apoptosis [28]. The absence of IL-18 has been shown to offer protection against tubular damage [29]. The usefulness of urinary IL-18 as a single-biomarker in clinical trials has not been confirmed despite its physiological basis. A prospective observational cohort study on IL-18 in cardiac surgery patients did not confirm the biomarker's effectiveness as a predictor of AKI but instead linked changes in its concentration to the inflammatory process caused by the use of cardiopulmonary bypass (CBP) [30,31]. A comprehensive meta-analysis evaluating urinary IL-18 across multiple clinical settings found moderate predictive value, with pooled sensitivity of 0.64, specificity of 0.77, and an area under the receiver operating characteristic curve (AUC) of 0.78. In children and adolescents, compared with adults, AUC values were up to 0.78 and diagnostic odds ratios (DORs) were significantly higher than in adult populations [32]. A urinary IL-18 cutoff of 1477 pg/mg creatinine at 4 h postoperatively provided optimal discrimination for AKI in pediatric cardiac surgery [33]. In adults, no standardized numeric cutoff was established; AKI risk can assessed by relative increases or highest quintile values [34].

3.1.3. L-FABP

Liver-type fatty acid-binding protein (L-FABP) is a small 14 kDa cytoplasmic protein expressed in renal proximal tubular epithelial cells and involved in fatty acid metabolism [35]. L-FABP is released in response to ischemic and oxidative stress, and its urinary levels rise within hours of renal insult [36]. In pediatric and adult cardiac surgery, urinary L-FABP levels increase as early as 4–6 h postoperatively in patients who develop AKI, with AUC values ranging from 0.72 to 0.81 for early AKI prediction, outperforming or complementing other biomarkers [36–39]. L-FABP elevation correlated with clinical severity, including longer CBP duration, higher postoperative SCr, and prolonged hospital stay [36,38]. In vascular surgery, L-FABP measured at 6 and 24 h postoperatively was associated with reduced UOP and impaired renal function. The cutoff value for urinary L-FABP in the perioperative AKI was typically in the range of 2226.5 μg/g creatinine at 0 h and 673.1 μg/g creatinine at 2 h postoperatively in adult cardiac surgery, with sensitivity and specificity around 80% for early AKI detection [40]. In pediatric cardiac surgery, a 24-fold increase in urinary L-FABP from baseline at 4 h postoperatively has been associated with AKI, yielding an AUC of 0.81, sensitivity of 71%, and specificity of 68% [37]. Meta-analyses confirmed that urinary L-FABP has moderate sensitivity and specificity for AKI diagnosis across perioperative settings, but performance varies by patient population and timing [41]. L-FABP is most useful as part of a biomarker panel for perioperative AKI risk stratification

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and early intervention, rather than as a standalone test due to lack of standardized assays, cutoff values, and the influence of nonrenal factors [41,42].

3.2. Stress Biomarkers

TIMP-2 and IGFBP-7

Tissue inhibitor of metalloprotease-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7) are two urinary cell cycle arrest markers commercially available. Levels of TIMP-2 and IGFBP-7 increase due to changes in tubular filtration, reduced reabsorption, and leakage. TIMP-2 is mainly secreted by distal tubule cells, while IGFBP-7 is primarily secreted by proximal tubule cells [43]. In high-risk surgical patients, including those undergoing major abdominal, vascular, and cardiac procedures, measurement of urinary TIMP-2*IGFBP-7 within hours after surgery can identify individuals at increased risk for developing moderate-to-severe AKI (stage 2–3) within the next 12–24 h. Diagnostic performance is robust, with AUC values ranging from 0.80 to 0.90 for moderate-to-severe AKI prediction [44–47]. A cutoff of 0.3 $(ng/mL)^2/1000$ is commonly used for early risk identification, while higher values (>2) are associated with greater risk and need for Renal Replacement Therapy (RRT) [45]. However, their diagnostic efficacy still remains unclear, considering the impact of different underlying diseases, various surgical procedures, sampling times, and different cutoff values used for AKI diagnosis [43,48–50]. Moreover, a post hoc analysis of 337 patients from the PrevAKI single-center study revealed that SCr measured at the same time as TIMP-2*IGFBP-7 was superior in predicting AKI development regardless of severity. The AUC for this biomarker panel was 0.60, compared with 0.82 for SCr [51].

3.3. Injury and Damage Biomarkers

3.3.1. C-C Motif Chemokine Ligand-14

Urinary C-C motif chemokine ligand-14 (CCL-14), also known as human C-C chemokines-1, is a small cytokine belonging to the chemokine family, primarily produced by macrophages and monocytes in response to renal injury. CCL-14 is released from injured renal tubular epithelial cells in response to inflammatory mediators and binds to C-C chemokine receptors on monocytes and T cells, driving differentiation into proinflammatory Th1 cells and activating proinflammatory macrophages that initiate downstream inflammatory cascades [52]. Elevated urinary CCL-14 perpetuates renal dysfunction through multiple mechanisms: promoting inflammation and fibrosis via macrophage-mediated pathways, inducing maladaptive repair responses that prevent functional restoration, and potentially triggering apoptosis of renal tubular cells through cell cycle modulation [52,53]. Persistently elevated urinary CCL-14 thus reflects an ongoing inflammatory phenotype characterized by defective renal repair mechanisms and increased risk of progression to prolonged AKI, CKD, and end-stage renal disease [54,55]. The landmark RUBY study [56] demonstrated that elevated urinary CCL-14 levels predict persistent and severe AKI (defined as KDIGO stage 3) with superior discriminative performance compared with other contemporary biomarkers. Subsequent validation studies and meta-analyses have consistently confirmed CCL-14's clinical utility across diverse patient populations, establishing it as one of the most feasible biomarker for persistent AKI prediction [57,58]. A standardized clinical assay for urinary CCL-14 has established two clinically useful cutoff values. A CCL-14 concentration of 1.3 ng/mL achieved 91% sensitivity and identified the vast majority of patients who develop persistent severe AKI, with a negative predictive value of 92%, making it valuable for ruling out disease progression. Conversely, a cutoff of 13 ng/mL achieved 93% specificity and a positive predictive value of 72%, allowing for identification of patients at highest risk of deterioration [54]. Recent meta-analyses evaluating seven

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major AKI biomarkers across 31 studies found that CCL-14 demonstrated superior diagnostic efficacy with an overall AUC of 0.79, outperforming TIMP-2*IGFBP-7, sCysC (AUC 0.70), and NGAL (AUC 0.71). Notably, performance varied substantially by clinical context: in the postoperative population, CCL-14 demonstrated AUC of 0.83–0.93, substantially exceeding other biomarkers [57].

3.3.2. C-X-C Motif Chemokine Ligand-9

C-X-C Motif Chemokine Ligand 9 (CXCL-9) is an interferon-γ (IFN-γ)-induced chemokine involved in lymphocyte chemotaxis with a size of ~14 kDa [59]. Because IFN-γ is crucial for recruiting activated T lymphocytes during interstitial inflammation, CXCL-9 might serve as a specific marker of tubulointerstitial inflammation [60]. CXCL-9 occupies a distinct diagnostic niche, as it was exclusively detected in conditions of ischemia–reperfusion injury, found in 29% of living donor kidney transplant recipients and 63% of donation after circulatory death recipients [61]. Notably, while other biomarkers increase in response to tubular stress and injury regardless of mechanism, CXCL-9 appears to be a marker of inflammatory activation, making it complementary rather than redundant to existing biomarkers [61].

CXCL-9 shows particular promise in acute interstitial nephritis (AIN), a specific form of AKI that has a more treatable etiology than tubular injury [62]. Urinary CXCL9 has demonstrated an AUC of up to 0.94 for AIN diagnosis. More specifically, CXCL-9 levels were 7.6-fold higher in patients with AIN compared with those with other forms of AKI, and notably, 8-fold higher when comparing AIN with acute tubular injury [60]. The combined use of CXCL-9 with tumor necrosis factor-α (TNF-α) and IL-9 demonstrated superior diagnostic performance compared to individual biomarkers alone in AIN detection [60].

3.3.3. Dickkopf-Related Protein-3

Dickkopf-related protein 3 (DKK-3) is a 38 kDa secreted glycoprotein synthesized by stressed renal tubular epithelium. DKK-3 appears to inhibit the protective Wnt/β-catenin signaling pathway, which is transiently activated as a repair mechanism following tubular injury [63]. In a landmark study [64], preoperative urinary DKK-3 concentrations independently predicted the development of postoperative AKI. In this cohort of cardiac surgery patients, urinary DKK-3 concentrations relative to creatinine that exceeded 471 pg/mg were associated with significantly increased AKI risk. In other clinical settings, a prospective study of 490 patients undergoing coronary angiography found that subjects who developed CI-AKI had a 3.8-fold higher urinary DKK-3/creatinine ratio than those without CI-AKI (7.5 pg/mg vs. 2.0 pg/mg, $p = 0.047$). However, the diagnostic accuracy in this setting was more modest compared with cardiac surgery, with an AUC of 0.61. The best cutoff value for DKK3 was 1.7 pg/mg creatinine, achieving 47.4% sensitivity and 72.4% specificity [65].

3.3.4. Chitinase 3-like Protein-1

Chitinase 3-like protein-1 (CHI3L-1) is a 39 kDa protein secreted by various cell types, including macrophages, epithelial cells, fibroblasts, and smooth muscle cells, with macrophages representing a key source of urinary CHI3L-1 during renal stress or injury. CHI3L-1 is considered a "repair phase" protein that becomes elevated in response to structural kidney injury and triggers renoprotective mechanisms through inhibition of apoptosis in renal epithelial cells and suppression of pyroptosis and inflammasome activation in macrophages [66].

In a prospective cohort study [67], which examined 203 cardiac surgery patients, it was found that urinary CHI3L-1 had inadequate predictive value for detecting AKI within 48 h after postoperative admission, with an inability to reliably distinguish patients who developed any stage of AKI. In contrast, SCr measurements obtained at 4 h after surgery

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in a mixed surgical and medical cohort showed superior performance with an AUC of 0.792 for predicting stage 1 or greater AKI, and when combined with baseline SCr changes, achieved an excellent AUC of 0.938 for predicting stage 2 or greater AKI within 12 h. CHI3L-1 demonstrated prognostic significance for AKI progression and mortality too; in a cohort of 249 AKI patients, urine CHI3L-1 concentrations $\geq$ 5 ng/mL were associated with disease progression or in-hospital mortality [68].

3.3.5. Kidney Injury Molecule-1

Kidney Injury Molecule-1 (KIM-1) is a transmembrane glycoprotein with minimal expression in normal kidney tissue but is more abundant in injured proximal tubules. Proteolytic cleavage releases its extracellular domain into urine. KIM-1 has been demonstrated to plays a role in both the process of kidney injury, mostly of ischemic or nephrotoxic drug origin, and the subsequent recovery processes [69]. A systematic review of patient data from various settings, including perioperative ones, reported urinary KIM-1 diagnostic sensitivity and specificity for AKI as 74% and 84%, respectively [70]. In an AKI biomarker prospective study investigating the utility of urinary biomarkers of AKI in major abdominal surgery, the AUC of KIM-1 was statistically significant for stage 1 AKI 0.68, but not for stage 2 [44]. In pediatric cohorts, KIM-1 showed moderate utility in forecasting the need for RRT in pediatric AKI, with an AUC of 0.71 [71]. According to a meta-analysis, a urinary concentration cutoff of 19 ng/for CI-AKI following cardiac catheterization yielded an AUC of 0.88, with sensitivity of 84% and specificity of 78% for predicting AKI [72]. Elevated preoperative KIM-1 levels predicted long-term adverse events, including death, cardiovascular events, and chronic kidney disease (CKD) progression, in cardiac surgery patients [73].

3.3.6. Cystatin C

Cystatin C (CysC) is a 13 kDa, 122 amino acid cysteine protease inhibitor. The molecule is freely filtered at the glomerulus, completely reabsorbed by the proximal tubule, and undergoes full catabolism intracellularly with no return to the bloodstream and no active tubular secretion. CysC concentration is independent of age, gender, muscle mass, and nutritional status, with a relatively constant production rate across populations [74]. Serum CysC (sCysC) serves as a marker of glomerular filtration, while elevated urinary CysC may indicate proximal tubular dysfunction independently of changes in filtration rate [75]. In pediatric cardiac surgery, sCysC peaks early at approximately 8 h postoperatively [76]. Multiple studies demonstrated that sCysC measured within 6 to 24 h postoperatively provides robust predictive capability for subsequent AKI development [77–79]. Systematic review and meta-analysis demonstrated that sCysC exhibits high diagnostic accuracy for postcardiac surgery AKI, with sensitivity of 0.67, specificity of 0.87, and an AUC of 0.86 [79]. A network meta-analysis comparing multiple biomarkers ranked sCysC among the highest performers, with a hierarchical summary receiver operating characteristic value of 0.82 [80]. In contrast, a multicenter study focusing on children [67] utilized urinary CysC to define AKI substages, finding that subclinical AKI (sAKI); CysC-positive without KDIGO AKI occurred in 20.2% of non-AKI patients and was associated with a mortality risk close to that of CysC-negative AKI substage A. Ultimately, this subphenotyping confirmed that CysC-positive AKI substage B patients, representing 50% of traditional AKI cases, were more likely to develop severe AKI (stage 3) and were associated with the highest 30-day risk. In pediatric cardiac surgery context, reported sCysC cutoff for AKI was >1.33 mg/L at 6 h postoperatively [78]. A postoperative increase $\geq$ 25% from baseline also served as a threshold for AKI detection in adults [81]. Despite advantages over SCr for AKI detection, CysC has notable limitations. Glucocorticoids may increase CysC production

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independently of renal function [82]. Thyroid dysfunction [83,84], diabetes, high C-reactive protein and white blood cell counts, and low serum albumin were also associated with higher levels of CysC [85]. This can lead to clinically relevant discrepancies of up to 15.3% difference in mean eGFR [86].

3.3.7. Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a protein expressed by various cells, including neutrophils and renal tubular cells. It exists in monomeric, homodimeric, and heterodimeric forms. NGAL plays a role in iron metabolism and exhibits antimicrobial properties. NGAL concentrations rise in response to epithelial injury and inflammation [87]. In the context of AKI, NGAL levels in blood and urine increase within 2–6 h following kidney injury and peak between 6 and 12 h, significantly earlier than the rise in SCr [88]. The diagnostic performance of NGAL in the postoperative period has been evaluated in several meta-analyses with various surgical procedures, including both noncardiac and cardiac surgery [89–91]. In a study of cardiac surgery patients with postoperative NGAL measurement, analysis demonstrated an AUC of 0.71 with a cutoff of 154 ng/mL, achieving sensitivity of 76% and specificity of 59% [92]. In another study with patients undergoing CPB, NGAL levels greater than 353.5 ng/mL were independently associated with postoperative AKI [93]. In pediatric cardiac surgery patients, plasma NGAL at 2 h after CPB demonstrated discriminative performance with an AUC of 0.96, sensitivity of 0.84, and specificity of 0.94 using a cutoff value of 150 ng/mL [94]. Urine NGAL has been demonstrated to serve as an independent predictor of the development of AKI and the subsequent necessity for RRT in liver transplant patients [91] and mortality after coronary interventions [95]. Nevertheless, the clinical utility of the biomarker is supported by only weak evidence [96].

3.3.8. Alpha-1-Microglobulin

Alpha-1-microglobulin (α1m) represents a marker of proximal tubular damage in the context of acute kidney injury. A low-molecular-weight protein synthesized in liver is freely filtered by the glomerulus and normally reabsorbed and metabolized by the proximal tubule [97]. In the TRIBE-AKI study of 1464 adults undergoing cardiac surgery [98], preoperative urinary α1m was independently associated with postoperative AKI, with each twofold higher preoperative concentration conferring an adjusted odds ratio of 1.36 for AKI development. Furthermore, preoperative α1m successfully identified patients at elevated risk for adverse long-term outcomes, including CKD incidence and progression, cardiovascular events, and all-cause mortality during a median 6.7-year follow-up period [98]. While baseline urinary α1m showed predictive value, postoperative measurements on day 1 did not reliably detect in-hospital AKI [98].

α1m's protective properties derive from its reactive cysteine residue (C34), enabling antioxidant, heme-binding, and radical-scavenging activities. These mechanisms function as "tissue cleaning" processes during oxidative stress and ischemia–reperfusion injury, and α1M further maintains mitochondrial energy balance during cellular injury [99]. RMC-035, a recombinant α1m, has demonstrated early signals of renal protection in a Phase 1 trial [100]. Although a Phase 2 study did not reduce AKI at 72 h, it showed a significant decline in major adverse kidney events (MAKEs) at 90 days, driven primarily by reduced persistent renal dysfunction, warranting further evaluation in ongoing Phase 2b studies [101].

3.3.9. Hepcidin-25

Hepcidin-25 is a low-molecular-weight peptide (2.78 kDa) that is freely filtered by the glomerulus, with approximately 97% reabsorbed by the proximal tubule under physiologi-

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cal conditions. This iron-regulatory peptide hormone possesses antimicrobial properties and is synthesized primarily in the liver, with additional expression in renal tissue [102]. Cardiac surgery with CPB induces hemolysis and tissue injury, releasing free hemoglobin and myoglobin that increase circulating labile iron, which promotes ferroptosis, an iron-dependent form of cell death that damages renal tubular epithelial cells [103]. By sequestering iron intracellularly, hepcidin-25 may limit oxidative stress and ferroptotic injury, providing a renoprotective mechanism in ischemia–reperfusion injury [104].

Early postoperative urinary hepcidin demonstrates significant diagnostic value for predicting AKI protection following coronary interventions [102] and cardiac surgery. In a 100-patient study, urinary hepcidin-25 levels were three to seven times higher in AKI-free patients at 6 and 24 h post-CPB (AUC 0.80–0.88), with creatinine-adjusted hepcidin-25 at 6 h independently predicting AKI avoidance [105]. In a larger prospective cohort of 306 patients, elevated urinary hepcidin-25 on postoperative day 1 inversely predicted AKI development and, when combined with baseline GFR and diabetes status, improved overall AKI prediction (AUC 0.82), outperforming conventional clinical scores [103]. The plasma NGAL/hepcidin-25 ratio has been as a promising marker for predicting MAKE in cardiac surgery patients [106].

3.3.10. Gamma-Glutamyltransferase

Gamma-glutamyltransferase (GGT), also known as gamma-glutamyl transpeptidase, is a membrane-bound enzyme predominantly expressed on proximal tubular epithelial cells of the kidney. In contrast-induced AKI in patients undergoing coronary procedures, GGT showed elevated levels in patients who developed AKI compared to controls, with an odds ratio of 3.21 (95% CI: 1.26–8.15). However, the evidence base demonstrated significant heterogeneity across studies, suggesting variability in GGT's predictive performance depending on clinical context and patient population [107].

3.3.11. π-Glutathione S-Transferase

π-Glutathione S-transferase (π-GST) is a preformed cytoplasmic enzyme that serves as a site-specific marker of distal renal tubular injury. As a constitutive detoxification enzyme, π-GST comprises approximately 2% of soluble protein in renal tubules and is exclusively released into urine when cellular integrity of the distal tubule is compromised. In a multicenter prospective study of 141 cardiovascular surgical patients [108], urinary π-GST demonstrated superior predictive for identifying advanced AKI (stage 2 or 3). π-GST measured at 3 h post-surgery achieved an AUC of 0.784, with an optimal cutoff value of 16.5 μg/L providing 75.0% sensitivity and 68.2% specificity. For predicting the composite outcome of advanced AKI or in-hospital mortality, the optimal cutoff was 14.7 μg/L at 3 h post-surgery, yielding 73.3% sensitivity and 66.7% specificity. Additional studies have confirmed that π-GST performs best during the early postoperative period from 3 to 12 h [109].

3.3.12. Interleukin-9

Interleukin-9 (IL-9) is a cytokine, traditionally associated with allergic and type 2 immune responses. Urine IL-9 is the most extensively characterized biomarker for diagnosing AIN, a form of AKI typically requiring kidney biopsy. In a cohort of 218 patients undergoing biopsy, urine IL-9 demonstrated superior diagnostic accuracy (AUC 0.84) compared to clinical assessment (AUC 0.62), with a high-specificity cutoff yielding a 0.94 post-test probability for AIN and the potential to reduce unnecessary biopsies [110]. IL-9 produced by a subset of CD4+ T helper cells promotes mast cell infiltration and degranulation in AIN, triggering TNF-α release and kidney inflammation, as evidenced by increased TNF-α-positive cells and mast cells in AIN biopsies [110]. In one small observational study

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examining plasma NGAL and IL-9 as predictors of postoperative AKI in 21 coronary artery bypass patients undergoing CPB, neither biomarker achieved statistical significance as an independent predictor, suggesting limited usefulness of IL-9 in other clinical context [111].

3.3.13. Monocyte Chemoattractant Peptide-1

Monocyte chemoattractant protein-1 (MCP-1) is an inflammatory biomarker that serves to predict AKI and long-term kidney outcomes. MCP-1 belongs to the chemokine family and functions as a pivotal mediator of both innate immune responses and tissue inflammation. Stimulation of renal tissue results in a pronounced upregulation of MCP-1 expression, which corelates strongly with the severity of kidney injury [112]. Through the activation of monocytes, MCP-1 contributes to the progression of inflammation and may ultimately lead to renal failure. Moreover, inflammatory cytokines can increase MCP-1 secretion from renal tubular epithelial cells. Follow-up studies on post-AKI patients have demonstrated that elevated MCP-1 is significantly associated with an increased risk of developing CKD [113]. In the TRIBE-AKI study on cardiac surgery patients, elevated urinary MCP-1 was related to an increased incidence of AKI, later development of CKD, and higher mortality. MCP-1 independently demonstrated utility as a reliable biomarker of tubular injury [114,115].

3.3.14. Netrin-1

Netrin-1 (NTN-1) is a large 72 kDa antiinflammatory protein predominantly secreted by proximal tubule epithelial cells in response to hypoxic or toxic injury. NTN-1 contributes to vascular patterning and maturation during renal development, with the kidney exhibiting some of the highest levels of NTN-1 expression. Notably, in animal models of ischemic AKI, NTN-1 was detectable in urine at an early stage following injury [116]. A few human studies involving pediatric patients after cardiac surgery described discrepancies in the effectiveness of NTN-1 as an early biomarker of AKI [116,117]. A 6 h post-CPB urinary NTN-1 concentration of approximately 2462 $\pm$ 370 pg/mg creatinine was observed in AKI cases, compared to lower values in controls, but no specific diagnostic cutoff was defined [117]. In liver transplantation, a 2 h postoperative urinary NTN-1 value of 897.8 $\pm$ 112.4 pg/mg creatinine was associated with AKI [118].

3.3.15. Semaphorin-3A

Semaphorin-3A (SEMA-3A) is a 65 kDa protein that plays roles in the regulation of angiogenesis, organogenesis, and immune responses. It has been identified in adult podocytes and collecting tubules. While undetectable in the urine of healthy individuals, SEMA-3A can be measured within hours following ischemia–reperfusion injury, secreted by injured podocytes and distal tubular cells. Inactivation of SEMA-3A suppresses this secretion [119]. In cases of ischemia–reperfusion AKI, SEMA3A mediates tissue damage by promoting inflammation and apoptosis of tubular epithelial cells. SEMA-3A has been identified as a potential biomarker for the prediction of contrast-induced AKI [120]. A study in patients undergoing percutaneous coronary intervention (PCI) reported SEMA-3A cutoff of 389.5 pg/mg creatinine at 2 h post-insult, with 94% sensitivity and 75% specificity [120]. In liver transplantation, 2 h postoperative mean values of 847.9 $\pm$ 93.3 pg/mg creatinine were associated with AKI development [118]. Pediatric cardiac surgery patients demonstrated peak values of 2596 $\pm$ 591 pg/mg creatinine at 6 h post-CPB, although a specific diagnostic threshold was not established [121].

3.3.16. Osteopontin

Osteopontin (OPN) is phosphorylated 37.7 kDa glycoprotein and is predominantly synthesized in kidney tissue. In the context of ischemia–reperfusion injury, OPN plays a

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complex dual role as both a pathogenic and protective mediator [122]. One study suggested that increased OPN release following AKI is associated with neurocognitive decline [123]. Furthermore, circulating OPN released from the kidneys during AKI has been implicated in the development of remote lung inflammation and subsequent respiratory failure [124]. OPN was also associated with postoperative complications and inflammatory responses after major surgery [125]. In the CASABLANCA AKI Prediction substudy, OPN was evaluated alongside KIM-1, IL-18, and CycC in patients undergoing coronary and peripheral angiography. Incorporating OPN into traditional risk scoring models enhanced prediction of both procedural AKI and long-term cardiorenal outcomes during a median 3.7-year follow-up [126].

3.4. Renal Tubular Epithelial Cells

Oyaert et al. [127] prospectively evaluated automated urinary flow cytometry measurement of renal tubular epithelial cells (RTECs) as an early AKI biomarker in 239 adult cardiac surgery patients. The study found that RTEC counts at 12 and 24 h post-admission demonstrated excellent diagnostic accuracy (AUC 0.946 at 24 h for all AKI up to 7 days), performing comparably to or superior to TIMP-2*IGFBP-7, GGT, and α1m. Notably, RTEC counts correlated with AKI severity, distinguished between rapid reversal and persistent AKI, and showed significantly higher levels in patients requiring RRT [128].

3.5. Factors Affecting Biomarker Specificity: False Positives and False Negatives

Clinical interpretation of novel AKI biomarkers requires awareness of conditions that may confound their diagnostic accuracy. NGAL concentrations are elevated in systemic infections and inflammatory states independently of kidney injury [87], while urinary IL-18 rises in response to CPB-induced inflammation rather than tubular injury specifically [30,31]. CysC levels are affected by glucocorticoid therapy, thyroid dysfunction, diabetes, and hypoalbuminemia [82–85]. TIMP-2 and IGFBP-7 may be elevated in any condition causing cellular stress [43,48–50]. False-negative results may occur when sampling times do not align with biomarker kinetics [129]. These limitations necessitate clinical context-based biomarker interpretation and support adoption of multi-biomarker panels.

4. Biomarker Panel

A multi-biomarker panel for AKI represents a promising approach to enhance the detection of kidney impairment by integrating multiple markers and thereby overcoming the limitations of single-biomarker strategy, including insufficient sensitivity for early AKI detection and inability to distinguish AKI pathophysiology [130]. Different biomarker signatures can characterize distinct AKI subphenotypes with prognostic implications. For instance, combinations of NGAL and IL-18 effectively differentiated acute tubular nephritis from prerenal AKI [131], CXCL-9 with TNF-α and IL-9 demonstrated superior diagnostic performance in AIN diagnosis [60], while CysC combined with NGAL provided predictive information regarding disease progression risk [132]. The FDA-approved TIMP-2*IGFBP-7 panel represents the most clinically implemented combined biomarker strategy, particularly in perioperative and critical care settings. Expert consensus indicated optimal application in patients undergoing major surgery or those with hemodynamic instability [133]. Additionally, a multiplex panel with 21 serum and urinary proteins, including biomarker candidates, demonstrated enhanced discrimination for AKI versus CKD phenotypes and enabled stratification of progression risk [134].

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5. Regulatory Approval and Clinical Adaptation

Regulatory Approval Status

Approval of AKI biomarkers for commercial use is progressing slowly. To date, only a few patents have been granted for clinical use by European or American drug regulatory authorities. KIM-1, OPN, NGAL, and CysC have been approved by the FDA [135] and KIM-1 and CysC by the European Medicines Agency (EMA) for the detection of drug-induced kidney injury during nonclinical and clinical drug trials [136].

The FDA has formally endorsed the utilization of NephroCheck® (TIMP-2*IGFBP-7) as a biomarker for the purpose of predicting the risk of AKI, particularly within critical care settings [137]. ProNephro AKI (NGAL), an immunoassay for the quantitative determination of NGAL in urine that recently received FDA clearance as well [87]. The penKid (PENK) assay has not yet received full approval; however, it has obtained CE-IVD certification for specific diagnostic platforms [138].

A key advancement in AKI diagnostics would be the integration of novel biomarkers into point-of-care testing panels, enabling rapid and bedside evaluation of renal function for early detection and management of AKI. Still, the expense associated with quantifying the concentration of a single-biomarker or biomarker pair considerably exceeds that of conventional biomarker assessments.

6. AKI Care Bundle Implementation and Biomarker Panels

The KDIGO guidelines [3], established in 2012, outline a series of recommendations aimed at reducing the occurrence of AKI. These guidelines emphasize avoiding nephrotoxic agents and discontinuing angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for 48 h before surgical procedures. Moreover, they highlight the importance of closely monitoring classic AKI biomarkers, preventing hypo- and hyperglycemia and radiocontrast-induced nephropathy, and continuously tracking and optimizing hemodynamics. They also advocate for optimization of patient' volume status. These recommendations were mainly based on expert consensus rather than multicenter trial results, and they were developed at a time when new AKI biomarkers were just being introduced into research practice [3]. Since then, several meta-analyses have shown that implementing AKI care bundles in hospitalized patients during routine clinical practice can effectively improve outcomes for those diagnosed with AKI or at risk of developing it [13]. Similar findings were observed in cardiac surgery patients [12]. A meta-analysis of 16,540 patients demonstrated that care bundles incorporating biomarkers had greater impact than bundles without biomarkers, reducing the risk of MAKE, AKI, and the need for RRT, although only urinary TIMP-2·IGFBP-7 and NGAL were evaluated [139]. Biomarker selection for this meta-analysis was likely driven by regulatory clearance and availability of substantial clinical trial data. However, subsequent meta-analysis examining 16 studies with 25,690 patients indicated more modest effects, with AKI incidence reduced only in studies utilizing novel biomarkers, electronic alerts, or risk prediction scores (OR 0.71; 95% CI 0.53–0.96) [13].

PrevAKI [140,141] and BigpAK [142] trials have demonstrated reductions in AKI rates. TIMP-2*IGFBP-7 panel was investigated in the international, randomized controlled, multicenter BigpAK-2 trial [143]. This study tested a biomarker-guided approach with implementation of the KDIGO bundle after major surgery in 1180 patients across 34 European hospitals. Patients in the intervention group received KDIGO-recommended nephroprotective care, while the control group received usual care. The trial demonstrated that moderate or severe AKI occurred in 14.4% of intervention patients versus 22.3% of controls (OR 0.57, 95% CI 0.40–0.79; p = 0.0002), with a number needed to treat of 12 (95% CI 7–33). This decisive study confirmed that applying the KDIGO bundle to high-risk patients identified

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by biomarkers can significantly lower AKI incidence after major surgery without increasing adverse events [144].

Integrating novel biomarkers into AKI bundles may enhance diagnosis (Figure 1), particularly of sAKI, where elevated biomarkers precede traditional criteria yet indicate progression risk. Biomarker-guided implementation of KDIGO guidelines [145] has allowed earlier, targeted interventions. However, adding biomarkers to care bundles has not significantly reduced RRT requirements or mortality [139]. Recent studies using cluster analysis on comprehensive biomarker panels have identified distinct AKI subphenotypes with differing clinical characteristics, treatment responses, and outcomes. Four distinct AKI subphenotypes were identified, with subphenotypes 3 and 4 showing markedly different prognoses and treatment requirements [146,147].

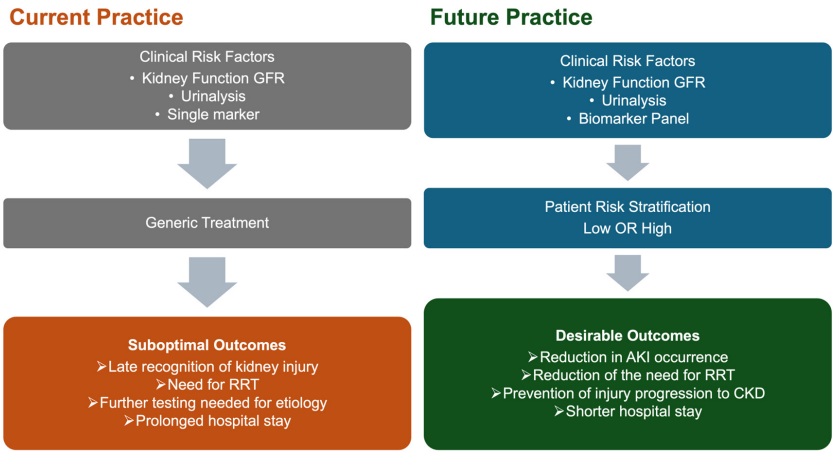

Figure 1. Current and future practice in managing acute kidney injury in perioperative settings. Abbreviations: GFR—glomerular filtration rate, RRT—renal replacement therapy, AKI—acute kidney injury, and CKD—chronic kidney disease.

A modeling study of hospitalized UK adults at risk of AKI assessed the diagnostic accuracy and cost-effectiveness of NephroCheck and NGAL biomarker tests used alongside standard care for AKI detection, compared with standard care alone. The evidence was insufficient to support the cost-effectiveness of widespread biomarker testing [148]. A systematic review and cost-effectiveness analysis by the UK's National Institute for Health and Care Excellence (NICE) examining biomarkers for AKI risk assessment in critically ill conditions reached similar conclusions [149].

7. Conclusions

The expanding repertoire of AKI biomarkers offers opportunities for early detection, risk stratification, and physiological understanding of perioperative kidney injury, with regulatory-approved markers NGAL and TIMP-2*IGFBP-7, along with emerging candidates like CCL-14 or PENK demonstrating clinical utility when integrated into structured care bundles. However, translating biomarker discoveries into routine clinical practice remains challenging due to assay standardization issues, uncertain cost-effectiveness, and the complexity of integrating biomarker panels into time-sensitive perioperative decision-making.

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Abbreviations

The following abbreviations are used in this manuscript:

α1m	Alpha-1-microglobulin
AIN	Acute interstitial nephritis
AKI	Acute kidney injury
AUC	Area under the receiver operating characteristic curve
CBP	Cardiopulmonary bypass
CCL-14	C-C motif chemokine ligand-14
CHI3L-1	Chitinase 3-like protein-1
CI-AKI	Contrast-induced acute kidney injury
CKD	Chronic kidney disease
CysC	Cystatin C
CXCL-9	C-X-C Motif Chemokine Ligand 9
DKK-3	Dickkopf-related protein-3
DOR	Diagnostic odds ratios
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
IGFBP-7	Insulin-like growth factor-binding protein 7
IL-18	Interleukin-18
IL-9	Interleukin-9
KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	Kidney injury molecule-1
L-FABP	Liver-type fatty acid-binding protein
MAKE	Major adverse kidney events
MCP-1	Monocyte chemoattractant protein-1
NGAL	Neutrophil gelatinase-associated lipocalin
NICE	National Institute for Health and Care Excellence
NTN-1	Netrin-1
OPN	Osteopontin
pAKI	Persistent acute kidney injury
PENK	Proenkephalin A 119–159
π-GST	π-Glutathione S-transferase
RRT	Renal replacement therapy
RTECs	Renal tubular epithelial cells
sAKI	Subclinical acute kidney injury

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SCr	Serum creatinine
SEMA-3A	Semaphorin-3A
TIMP-2	Tissue inhibitor of metalloprotease-2
UOP	Urine output

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10. Declaration of Authors' Contributions

Warszawa, 23.03.2026 r.

Oświadczenie

Jako współautor pracy pt. “Proenkephalin A 119–159 as an early biomarker of acute kidney injury in complex endovascular aortic repair: an explorative single-center cross-sectional study with the utilization of two measurement methods” oświadczam, że mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi nadzór merytoryczny. Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

Wkład lek. Konrada Zuzdy w powstawanie publikacji określam jako 30%, obejmował on: opracowanie koncepcji badania, zbieranie i analizę danych, redakcję oraz złożenie manuskryptu. Jednocześnie wyrażam zgodę na wykorzystanie wyżej wymienionej pracy jako część rozprawy doktorskiej lek. Konrada Zuzdy.

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Oświadczenie

Jako współautor pracy pt. “Evaluation of a Novel Biomarker Panel for Acute Kidney Injury Following Endovascular Aortic Repair” oświadczam, że mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi nadzór merytoryczny. Mój udział procentowy w przygotowaniu publikacji określam jako 5%.

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Wkład lek. Konrada Zuzdy w powstawanie publikacji określam jako 30%, obejmował on: opracowanie koncepcji badania, zebranie i analizę danych, redakcję oraz złożenie manuskryptu. Jednocześnie wyrażam zgodę na wykorzystanie wyżej wymienionej pracy jako część rozprawy doktorskiej lek. Konrada Zuzdy.

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Wkład lek. Konrada Zuzdy w powstawanie publikacji określam jako 60%, obejmował on: opracowanie koncepcji przeglądu literatury, projekt manuskryptu, przegląd piśmiennictwa, przygotowanie i redakcja tekst publikacji, koordynacja pracy współautorów. Jednocześnie wyrażam zgodę na wykorzystanie wyżej wymienionej pracy jako część rozprawy doktorskiej lek. Konrad Zuzdy.

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11. Summary

AKI remains a challenging perioperative complication in patients undergoing EVAR. Current diagnostic criteria based on SCr and UOP are limited by delayed detection and inability to characterise the underlying injury phenotype.

This publication series addressed these limitations through three complementary investigations. First, PENK was evaluated as a early functional biomarker, establishing its diagnostic utility and limitations in this cohort. Second, a biomarker panel, comprising markers selected according to distinct nephron locations and release mechanisms, was assessed to determine whether combining complementary pathophysiological signals could overcome the limitations of single-marker strategies. Third, a scoping review of novel AKI biomarker in perioperative care contextualised these findings, identifying key barriers to clinical translation and priorities for future research. The hypothesis, that a panel integrating functional and injury markers would provide earlier AKI detection compared with conventional diagnostic criteria or single-biomarker approaches, was supported across the three publications. Collectively, these findings support a paradigm shift in perioperative AKI surveillance for patients at high risk, from reliance on delayed functional markers towards mechanism-driven, multi-biomarker strategies capable of earlier injury detection. The identification of modifiable risk factors, including perioperative blood product administration, underlines the potential for targeted preventive interventions to reduce AKI incidence and its associated long-term burden in this population.

Future research should prioritise prospective multicentre validation of the proposed biomarker panels across diverse surgical settings, with standardised sampling protocols and pre-specified cut-off values.

12. Conclusions

1. PENK measured by POCT was significantly elevated in patients who developed AKI following complex EVAR and, whilst its moderate specificity precludes standalone diagnostic use, its consistently high negative predictive value supports a reliable bedside rule-out role.
2. Serum SEMA-3A and serum RBP-4 demonstrated the highest individual discriminatory performance for AKI following EVAR, with their distinct nephron localisations, podocytes and distal tubule for SEMA-3A, proximal tubular epithelium for RBP-4, thereby supporting complementary roles within a multi-biomarker panel.
3. A mechanism-driven panel comprising PENK POCT, serum SEMA-3A, and urinary KIM-1 achieved the highest discriminatory performance for early AKI detection, substantially exceeding individual biomarkers, with a comparable alternative panel substituting serum RBP-4 for SEMA-3A.
4. Advanced age and perioperative blood product administration were identified as risk factors for AKI following complex endovascular procedures.
5. Postoperative AKI development was a predictor of adverse long-term outcomes, increasing six-month mortality.
6. A scoping review of novel AKI biomarker research in perioperative care confirmed that, despite a growing evidence base, widespread clinical implementation of biomarker panels remains constrained by heterogeneity in measurement methods, lack of standardised cut-off values, and uncertainty regarding cost-effectiveness.

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14. Bioethics Committee's Opinion

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

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KB/ 100 /2021

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 30 lipca 2021 r. po zapoznaniu się z wnioskiem:

Lek.Konrad Zuzda
Klinika i Katedra Nefrologii,Dializoterapii
i Chorób Wewnętrznych
ul. Banacha 1a, 02-097 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt.:"Nowe panele biomarkerów oraz sztuczna inteligencja we wczesnym wykrywaniu ostrego uszkodzenia nerek."

- Badanie może być prowadzone wyłącznie w okresie obowiązywania polisy ubezpieczeniowej.

wyraża następującą
o p i n i ę

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma-Kozakiewicz

*niepotrzebne skreślić

Komisja wyraża pozytywną opinię w sprawie przeprowadzenia wnioskowanych badań- na warunkach określonych we wniosku oraz dodatkowo zastrzegając:
1/ obowiązek przedstawienia Komisji:

- wszystkich zmian w protokole mających wpływ na przebieg oraz ocenę badania,
- wszystkich przypadków zdarzeń niepożądanych,
- zawiadomienia o przyczynach przedwczesnego zakończenia badania,
- sprawozdania w toku przeprowadzonych badań-za sześć miesięcy,
- raportu końcowego.

strona podpisowa do uchwały Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym nr KB/.....109..... z dnia 30 lipca 2021r.

1. Prof. dr hab. n.med. Magdalena Kuźma –Kozakiewicz .....
2. Dr hab. n. med. Tomasz Grzela .....
3. Dr hab. n. med. Andrea Horvath-Stolarczyk .....
4. Dr hab. n. med. Urszula Ambroziak .....
5. Dr hab. n.med. Maciej Siński .....
6. Dr hab. n. farm. Sylwia Flis .....
7. Prof. dr hab.n.med Tomasz Jakimowicz .....
8. Dr n. med. Leszek Kraj .....
9. Mec. Danuta Lewandowska .....
10. Dr n .farm. Agata Maciejczyk .....
11. Dr hab. n.med. Barbara Grzechocińska .....
12. Dr n. med. Artur Hącia OP .....
13. Mgr Anna Jasińska .....

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KB/ 49 /2021

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 14 czerwca 2021 r. po zapoznaniu się z wnioskiem:

Lek.Konrad Zuzda
Klinika Hepatologii i Chorób Wewnętrznych
Klinika i Katedra Nefrologii,Dializoterapii
I Chorób Wewnętrznych
ul. Banacha 1a, 02-097 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt". Koliste RNA,nowy panel biomarkerów oraz nauczania maszynowe w predykcji ostrego uszkodzenia nerek u dorosłych pacjentów hematoonkologicznych."

- Badanie może być prowadzone wyłącznie w okresie obowiązywania polisy ubezpieczeniowej.

wyraża następującą
o p i n i ę

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma-Kozakiewicz

*niepotrzebne skreślić

Komisja wyraża pozytywną opinię w sprawie przeprowadzenia wnioskowanych badań- na warunkach określonych we wniosku oraz dodatkowo zastrzegając:
1/ obowiązek przedstawienia Komisji:

- wszystkich zmian w protokole mających wpływ na przebieg oraz ocenę badania,
- wszystkich przypadków zdarzeń niepożądanych,
- zawiadomienia o przyczynach przedwczesnego zakończenia badania,
- sprawozdania w toku przeprowadzonych badań-za sześć miesięcy,
- raportu końcowego.

strona podpisowa do uchwały Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym nr KB/.....79..... z dnia 14 czerwca 2021r.

1. Prof. dr hab. n.med. Magdalena Kuźma –Kozakiewicz .....
2. Dr hab. n. med. Tomasz Grzela .....
3. Dr hab. n. med. Andrea Horvath-Stolarczyk .....
4. Dr hab. n. med. Urszula Ambroziak .....
5. Dr hab. n.med. Maciej Siński .....
6. Dr hab. n. farm. Sylwia Flis .....
7. Prof. dr hab.n.med Tomasz Jakimowicz .....
8. Dr n. med. Leszek Kraj .....
9. Mec. Danuta Lewandowska .....
10. Dr n .farm. Agata Maciejczyk .....
11. Dr hab. n.med. Barbara Grzechocińska .....
12. Dr n. med. Artur Hącia OP .....
13. Mgr Anna Jasińska .....

15. Publications Arising from Doctoral Contribution

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BIBLIOTEKA UCZELNIANA

Nr referencyjny
BIBG/Punktacja/183 /2026/KK

Warszawa, 19.03.2026

Sz. Pan
Lek. Konrad Zuzda
Klinika Nefrologii, Dializoterapii
i Chorób Wewnętrznych

ANALIZA BIBLIOMETRYCZNA CAŁOKSZTAŁTU DOROBKU PUBLIKACYJNEGO
PANA KONRADA ZUZDY,
W POSTĘPOWANIU O NADANIE STOPNIA NAUKOWEGO DOKTORA

Lp.	Opis bibliograficzny	Impact Factor	MNiSW	Najwyższy kwartyl[1]
I. Artykuły opublikowane w czasopismach naukowych lub w recenzowanych materiałach z konferencji międzynarodowych ujętych w aktualnym wykazie MNiSW[2]				
1.	Walczak-Wieteska P, **Zuzda K** [aut. koresp.], Małyszko J, Andruszkiewicz P. Proenkephalin A 119–159 as an early biomarker of acute kidney injury in complex endovascular aortic repair: an explorative single-center cross-sectional study with the utilization of two measurement methods. Periopertaive Medicine. 2025;14(1):1-8 [Rodzaj publikacji: praca oryginalna]	2,100	100	Q2
2.	**Zuzda K**, Walczak-Wieteska P, Andruszkiewicz P, Małyszko J. Evaluation of a Novel Biomarker Panel for Acute Kidney Injury Following Endovascular Aortic Repair. International Journal of Molecular Sciences. 2025;26(22):1-18 [Rodzaj publikacji: praca oryginalna]	4,900	140	Q1
3.	**Zuzda K** [aut. koresp.], Walczak-Wieteska P, Andruszkiewicz P, Małyszko J. Acute Kidney Injury Biomarkers in Perioperative Care: A Scoping Review of Clinical Implementation. Diagnostics. 2025;16(1):1-23 [Rodzaj publikacji: praca poglądowa]	3,300	70	Q1
4.	Maksim R, Buczyńska A, Sidorkiewicz I, Mojsak M, Śliwowska-Burzyńska J, **Zuzda K**, Gugnacki P, Krętowski A, Sierko E. Standard of practice imaging vs. PET/MR: a comparative prospective study in rectal cancer staging. International Journal of Colorectal Disease. 2025;40(1):198 [Rodzaj publikacji: praca oryginalna]	2,300	140	Q2

1 Kwartyl z roku publikacji, według Impact Factor.
[2] Wykaz sporządzony zgodnie z przepisami wydanymi na podstawie art. 267 ust. 2 pkt 2 lit. b Ustawy z dnia 20 lipca 2018 r. - Prawo o szkolnictwie wyższym i nauce (Dz. U. z 2022 r., poz. 574 z późn. zm.). Wykaz stanowi załącznik do komunikatu MNiSW z 5 stycznia 2024 r. w sprawie wykazu czasopism naukowych i recenzowanych materiałów z konferencji międzynarodowych.

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5.	Adamczyk K, **Zuzda K** [aut. koresp.], Jankowski M, Świerczyński R, Chudziński K, Czapski B, Szułdrzyński K. Effects of Opioids in Cancer Pain: An Interplay Among Genetic Factors, Immune Response, and Clinical Outcomes - A Scoping Review. Cancers (Basel). 2025;17(5):863 [Rodzaj publikacji: praca poglądowa]	4,400	140	Q2
6.	Walczak-Wieteska P, **Zuzda K**[*], Szczęsna K, Ziętalewicz J, Andruszkiewicz P, Małyszko J. Proenkephalin A 119–159, a Possible Early Biomarker of Acute Kidney Injury in Complex Endovascular Aortic Repair: a Single Centre Observational, Cross Sectional Study. European Journal of Vascular and Endovascular Surgery. 2024;67(6):1023-1024 [*]równorzędny pierwszy autor [Rodzaj publikacji: research letter]	6,800	140	Q1
7.	Walczak-Wieteska P, **Zuzda K** [aut. koresp.], Małyszko J, Andruszkiewicz P. Proenkephalin A 119–159 in Perioperative and Intensive Care - A Promising Biomarker or Merely Another Option? Diagnostics (Basel). 2024;14(21):2364 [Rodzaj publikacji: praca poglądowa]	3,300	70	Q1
8.	**Zuzda K**, Grycuk W, Małyszko J, Małyszko J. Kidney and lipids: novel potential therapeutic targets for dyslipidemia in kidney disease? Expert Opinion on Therapeutic Targets. 2022;26(11):995-1009 [Rodzaj publikacji: praca poglądowa]	5,800	100	Q1
9.	Marcinkowski W, **Zuzda K**[*], Zawierucha J, Prystacki T, Żebrowski P, Małyszko JS, Wojtaszek E, Małyszko J. Vaccination and COVID-19 in Polish Dialysis Patients: Results from the European Clinical Dialysis Database. Vaccines (Basel). 2022;10(9):1565 [*] równorzędny pierwszy autor [Rodzaj publikacji: praca oryginalna]	7,800	140	Q1
10.	Milkowski A, Prystacki T, Marcinkowski W, Dryl-Rydzynska T, Zawierucha J, Malyszko JS, Zebrowski P, **Zuzda K**, Małyszko J. Lack or insufficient predialysis nephrology care worsens the outcomes in dialyzed patients - call for action. Renal Failure. 2022;44(1):946-957 [Rodzaj publikacji: praca oryginalna]	3,000	40	Q2
	Łącznie:	43,700	1080	-
II. Artykuły opublikowane przed 1.01.2019 r. w czasopismach ujętych w wykazie czasopism MNiSW z dnia 25.01.2017 r., o ile czasopismo uzyskało co najmniej 10 pkt.				
	Łącznie:	-	-	-
III. Pozostałe artykuły				
	Łącznie:	-	-	-
	Łącznie (cz. I- III):	**43,700**	**1080**	-

IV. Monografie naukowe/rozdziały w monografiach wydane przez wydawnictwa ujęte w wykazie MNiSW[3] lub jednostki organizacyjne podmiotów, których wydawnictwa są ujęte w tym wykazie
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[3] Wykaz sporządzony zgodnie z przepisami wydanymi na podstawie art. 267 ust. 2 pkt 2 lit. a Ustawy z dnia 20 lipca 2018 r. - Prawo o szkolnictwie wyższym i nauce (Dz. U. z 2022 r., poz. 574 z późn. zm.). Wykaz ogłoszony komunikatem MEiN z dnia 22 lipca 2021 r. w sprawie wykazu wydawnictw publikujących recenzowane monografie naukowe.

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