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