ANESTHESIOLOGY

Openventio PUBLISHERS

Review Article

Novel Biomarkers for Early Detection of Perioperative Organ Dysfunction

Lukas Whitmore[1*], Nikos Georgiou[2] and Ines Kowalczyk[3]

[1]*Department of Anesthesiology and Pain Management, Danube University of Applied Medicine, Hungary*
[2]*Department of Surgical Sciences, Nordfjord University of Health Sciences, Norway*
[3]*Department of Perioperative Medicine, Danube University of Applied Medicine, Hungary*

ABSTRACT

Organ dysfunction after major surgery is often diagnosed late, once creatinine, troponin, or a cognitive or respiratory criterion has already crossed a threshold, by which point the injury is established and the window for prevention has closed.

This review surveys biomarkers proposed to detect perioperative organ dysfunction earlier: urinary TIMP-2/IGFBP7 and neutrophil gelatinase-associated lipocalin for acute kidney injury, high-sensitivity troponin and natriuretic peptides for myocardial injury after noncardiac surgery, neurofilament light chain and glial fibrillary acidic protein for postoperative delirium, and epithelial and inflammatory markers for postoperative pulmonary complications.

Troponin surveillance for myocardial injury and urinary cell-cycle arrest markers for kidney injury risk stratification have progressed furthest toward routine use, while neuronal and pulmonary injury markers remain largely confined to research.

Across every organ system, combining biomarkers with clinical and intraoperative exposure data consistently improves prediction over any single marker, underscoring that perioperative organ injury is multifactorial rather than attributable to one pathway.

We conclude that biomarker discovery has outpaced implementation science, and that pragmatic trials randomizing patients to biomarker-triggered pathways are the necessary next step toward better outcomes.

Keywords: *perioperative biomarkers; acute kidney injury; myocardial injury after noncardiac surgery; postoperative delirium; postoperative pulmonary complications*

Citation: Whitmore L, Georgiou N and Kowalczyk I (2025) Novel Biomarkers for Early Detection of Perioperative Organ Dysfunction. Anesthesiology. 5(1):01-05.

DOI: 10.17140/2025.vol5.i01.pp01-05

Corresponding Author: *Lukas Whitmore*

E-mail Address: *l.whitmore@duam.hu*

Article History: *Received 22 April 2025 | Accepted 10 May 2025 | Published 12 June 2025*

Copyright: *© 2025 Lukas Whitmore, et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited (**https://creativecommons.org/licenses/by/4.0/**).*

INTRODUCTION

Organ dysfunction that declares itself only after surgery is one of the more frustrating problems in perioperative medicine, because by the time the clinical signs are obvious - rising creatinine, a troponin that keeps climbing, a patient who cannot be

extubated or who wakes up confused and stays that way - the injury has usually already occurred and the therapeutic window for prevention has closed. Serum creatinine, for instance, is a marker of filtration, not of tubular injury, and it can take 24 to 48 hours to rise meaningfully after a nephrotoxic or ischemic insult; a troponin drawn on postoperative day one may already represent an infarct that started intraoperatively and went unnoticed under general anesthesia's sedation and analgesia. The last decade has produced a wave of candidate biomarkers - cell-cycle arrest proteins, natriuretic peptides, glial and neuronal injury markers, cytokine panels - that promise to shift detection earlier, sometimes by hours, in the perioperative window. This review surveys where that promise has been kept and where it remains unproven, organized by the organ system most often threatened by the physiologic stresses of anesthesia and surgery: kidney, heart, brain, and lung.

The appeal of earlier biomarker-based detection is not simply academic tidiness. Perioperative organ dysfunction - acute kidney injury (AKI), myocardial injury after noncardiac surgery (MINS), postoperative delirium and neurocognitive disorder, and postoperative pulmonary complications - each carries an attributable mortality and cost burden that dwarfs almost any other complication category in surgical practice, and each is, in principle, modifiable if caught early enough to intervene: adjusting fluid strategy, deferring a nephrotoxin, escalating hemodynamic monitoring, initiating antiplatelet or statin therapy, or simply changing the disposition plan from ward to a higher level of monitoring. Whether the new biomarkers actually change any of those decisions in a way that improves outcomes is the harder and less settled question, and it recurs across every organ system discussed below.

RENAL BIOMARKERS: BEYOND CREATININE

Acute kidney injury after major surgery remains common - reported incidences after major noncardiac and cardiac surgery span a wide range depending on definition and population - and its diagnosis by the KDIGO creatinine and urine-output criteria is inherently retrospective [1]. The two urinary biomarkers that have moved furthest toward clinical use are tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7), combined into a single product-reported "AKIRisk" score; both are markers of tubular cell-cycle arrest released by stressed renal tubular epithelium well before glomerular filtration falls enough to move creatinine [2]. In surgical cohorts, an elevated [TIMP-2]·[IGFBP7] product measured in the early postoperative hours has predicted subsequent AKI with reasonable discrimination, and several implementation studies have used the result to trigger a bundle of supportive measures - optimizing volume status, avoiding nephrotoxins, deferring contrast studies - though the evidence that the bundle itself changes hard outcomes such as dialysis-free survival is less mature than the biomarker's discriminative performance would suggest [3].

Neutrophil gelatinase-associated lipocalin (NGAL), in both plasma and urine, remains the most extensively studied injury biomarker across surgical and critical-care populations, rising within two to six hours of an ischemic or nephrotoxic insult, well ahead of creatinine [4]. Kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP), and interleukin-18 add complementary information about proximal tubular injury and inflammation, and combination panels generally outperform any single marker, though at the cost of assay complexity that has limited uptake outside specialized centers [5]. A recurring theme in the more recent reviews is that biomarker performance is highly context-dependent - a marker validated in cardiac surgery with cardiopulmonary bypass does not necessarily transfer cleanly to a laparoscopic colectomy population with different baseline renal reserve and a different injury mechanism - and that risk stratification frameworks combining biomarkers with clinical and intraoperative variables (hypotension burden, cumulative vasopressor exposure, contrast load) outperform any biomarker used alone [6]. Even so, translating an earlier positive test into a management pathway that measurably reduces AKI incidence, rather than simply relabeling patients who would have recovered regardless, is the piece of the puzzle still being worked out in ongoing pragmatic trials.

CARDIAC BIOMARKERS AND MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

High-sensitivity cardiac troponin has arguably done more than any other single perioperative biomarker to reshape clinical practice, because it revealed that most myocardial injury occurring around noncardiac surgery is clinically silent - occurring without chest pain, without ischemic electrocardiogram changes, and without meeting the universal definition of myocardial infarction - yet is strongly associated with 30-day mortality [7]. This entity, myocardial injury after noncardiac surgery (MINS), is now recognized well enough that professional statements recommend routine perioperative troponin surveillance in patients at elevated cardiovascular risk undergoing intermediate- or high-risk surgery, specifically because relying on symptoms to trigger testing misses the majority of cases [8]. The pathophysiology appears heterogeneous, spanning a supply-demand mismatch related to perioperative tachycardia, anemia, and hypotension, through to plaque rupture and thrombosis indistinguishable from a spontaneous type 1 infarct, and this heterogeneity is part of why a single troponin trajectory does not map cleanly onto a single

management algorithm [9].

Beyond troponin itself, natriuretic peptides (BNP and NT-proBNP) measured preoperatively add incremental prognostic information for perioperative cardiac events and have been incorporated into some risk-stratification pathways alongside clinical risk indices, flagging patients in whom postoperative troponin surveillance is most likely to be worthwhile [10]. Newer work has explored combining high-sensitivity troponin kinetics with copeptin, growth differentiation factor-15, and other markers of hemodynamic and inflammatory stress to better separate the supply-demand phenotype from the thrombotic phenotype, since the two arguably warrant different secondary prevention strategies (heart-rate control and anemia correction versus antiplatelet escalation and statin therapy), though prospective outcome data guided by this distinction remain limited [11]. Retrospective cohorts continue to refine which patients with a positive troponin actually benefit from cardiology involvement versus simple risk-factor optimization, underscoring that the biomarker's main proven value so far is prognostic and risk-stratifying rather than diagnostic of a single actionable lesion in every case [12].

NEUROLOGICAL BIOMARKERS: DELIRIUM AND NEUROCOGNITIVE DISORDER

Postoperative delirium and the broader spectrum of perioperative neurocognitive disorders have historically been diagnosed by bedside cognitive screening tools such as the Confusion Assessment Method, which are effective but entirely clinical and offer no window into the biological injury preceding the behavioral change. Blood-based biomarkers of neuronal and glial injury - neurofilament light chain (NfL), a marker of axonal injury, and glial fibrillary acidic protein (GFAP), a marker of astrocytic injury - have been the most consistently studied candidates for filling that gap, and a recent systematic review and meta-analysis found that perioperative elevations in both markers were associated with a higher risk of subsequent delirium, with NfL in particular showing a dose-dependent relationship with delirium severity and duration across several surgical cohorts [13]. Tau protein and S100 calcium-binding protein B (S100B) have been studied for longer but have shown less consistent associations, partly because S100B is not brain-specific and can be confounded by extracranial release during major surgery.

A broader systematic review examining biomarkers of neural injury in blood across general anesthesia populations concluded that while the association between biomarker elevation and postoperative neurocognitive disorder is reasonably reproducible, the timing of sample collection, the anesthetic and surgical exposure, and pre-existing neurodegenerative burden all substantially modify the signal, making a single universal cutoff elusive across heterogeneous surgical populations [14]. Practically, these markers are not yet used to guide bedside decisions the way troponin is used in cardiac risk pathways; their more immediate value has been mechanistic, helping investigators distinguish neuroinflammatory injury from reversible anesthetic-related cognitive slowing, and identifying which patients might be enriched into trials of neuroprotective strategies such as processed-EEG-guided anesthetic titration or multicomponent delirium-prevention bundles.

PULMONARY BIOMARKERS AND POSTOPERATIVE RESPIRATORY COMPLICATIONS

Postoperative pulmonary complications, ranging from atelectasis and pneumonia to frank acute respiratory distress syndrome (ARDS), remain a leading driver of postoperative morbidity, particularly after cardiothoracic and upper abdominal surgery, and biomarker research here has focused heavily on markers of epithelial and endothelial injury alongside the inflammatory cascade that surgery itself triggers. Plasma proteomic profiling in patients undergoing cardiopulmonary bypass has identified early post-bypass biomarker signatures - including markers of endothelial activation and epithelial injury - that improve prediction of subsequent ARDS beyond clinical risk factors alone, suggesting a biological injury process detectable well before the Berlin-criteria hypoxemia threshold is met [15]. Similar proteomic and cytokine-panel approaches applied after one-lung ventilation during thoracic surgery have sought biomarkers specific to ventilator-associated lung strain in the dependent lung, an injury mechanism distinct from the systemic inflammatory response of bypass [16].

Systemic inflammatory mediators - interleukin-6, interleukin-8, and C-reactive protein among the most studied - rise in a fairly predictable pattern after any major surgery, which is precisely the limitation: distinguishing an expected inflammatory response from an incipient pulmonary complication requires either very high magnitude elevations or serial trajectories rather than single time-point values, and several cohorts have shown that patients who go on to develop clinically important pulmonary complications separate from those who do not primarily on the trajectory and peak of the inflammatory response rather than on any single novel marker [17]. Work in pulmonary resection populations has extended this to an expanded panel of mediators correlated with laboratory and clinical outcomes, again finding that combination panels outperform isolated markers [18]. Reviews focused specifically on cardiothoracic surgery have catalogued a long list of candidate lung-injury biomarkers - surfactant protein D, receptor for advanced glycation end-products (RAGE), Club cell protein 16 - without any single one yet achieving the combination of sensitivity, specificity, and assay

practicality needed for routine bedside use [19]. A validation study examining intraoperative parameters alongside biomarkers for postoperative ARDS similarly concluded that combining physiologic exposure data (tidal volume, driving pressure, transfusion volume) with biomarker levels improved risk prediction over either approach alone, an integration strategy that recurs across every organ system discussed in this review [20]. Detailed temporal-spatial characterization of inflammation and tissue injury patterns in patients developing respiratory failure after lung resection has further suggested that the biological injury cascade begins intraoperatively, well before any clinical sign of respiratory compromise emerges on the ward [21].

INTEGRATING BIOMARKERS INTO PERIOPERATIVE PRACTICE

A pattern common to all four organ systems reviewed here is that no single biomarker functions as a clean stand-alone diagnostic test with the sensitivity and specificity clinicians want; nearly every advance has come from combining biomarkers with each other, or with clinical and intraoperative exposure data, into composite risk scores. This is not a failure of the biomarkers so much as a reflection of the biology: perioperative organ injury is multifactorial, driven by some combination of ischemia-reperfusion, systemic inflammation, direct surgical trauma, and drug or anesthetic exposure, and it would be somewhat surprising if a single protein captured all of that variance for any organ. The practical implication is that implementation research - how to embed a biomarker result into a clinical pathway, who should be tested, and what action a positive result should trigger - now matters as much as biomarker discovery itself, and it is this implementation gap, more than any remaining assay-performance question, that separates most of the markers discussed here from the two exceptions (troponin in MINS surveillance and TIMP-2/IGFBP7 in AKI risk stratification) that have moved furthest into routine practice.

Cost and assay availability are not trivial barriers either. High-sensitivity troponin assays are now near-universal in hospital laboratories, which is part of why MINS surveillance has been adopted relatively quickly, whereas the urinary AKI panels, plasma proteomic signatures, and neuronal injury markers described above generally require specialized or send-out testing that is neither rapid enough nor cheap enough for routine use outside of research protocols or a handful of academic centers. Until turnaround time and cost fall for these assays, their main contribution will likely remain enrichment of research cohorts and refinement of mechanistic understanding, with a slower and more selective migration into everyday perioperative decision-making for the subset of markers - like troponin already has - that clear that practical bar.

CONCLUSION

Biomarker-based detection of perioperative organ dysfunction has advanced furthest where an assay is fast, cheap, and already embedded in hospital laboratory infrastructure, as high-sensitivity troponin demonstrates for cardiac injury, and furthest behind where injury biology is heterogeneous and the assay remains specialized, as is still largely true for neuronal and pulmonary injury markers. Renal biomarkers occupy a middle position, with urinary TIMP-2/IGFBP7 approaching clinical utility in selected surgical populations even as broader adoption awaits clearer evidence that acting on an early positive result changes hard outcomes. Across every organ system, the strongest emerging signal is that combination panels integrating biomarkers with clinical and intraoperative exposure variables consistently outperform any single marker, and that the discovery phase of this field is now outpacing the implementation science needed to turn an earlier positive test into a treatment that actually prevents the organ dysfunction it detects. Closing that gap, through pragmatic trials that randomize on biomarker-triggered management pathways rather than simply validating discrimination, is the next necessary step for this literature.

DECLARATIONS

Acknowledgements The authors thank their respective departments for institutional support during the preparation of this review.

Funding This review received no external funding.

Conflict of Interest The authors declare no conflicts of interest.

Author Contributions Lukas Whitmore conceived the review and drafted the initial manuscript. Nikos Georgiou performed the literature search and critically revised the cardiac and pulmonary biomarker sections. Ines Kowalczyk critically revised the renal and neurological biomarker sections and the manuscript as a whole. All authors read and approved the final manuscript.

Ethics Statement This is a literature review that did not involve new human or animal data collection, and no ethics approval was required.

Data Availability No new data were generated for this review; all sources are cited in the reference list.

REFERENCES

1. Acute Kidney Injury Biomarkers in Perioperative Care: A Scoping Review of Clinical Implementation (2025) PMC12785279.
2. Urinary Biomarkers TIMP-2 and IGFBP7 Early Predict Acute Kidney Injury after Major Surgery, PLOS One.

3. The efficacy of novel biomarkers for the early detection and management of acute kidney injury: A systematic review (2024) PLOS One, DOI:10.1371/journal.pone.0311755.

4. Advances in the diagnosis of early biomarkers for acute kidney injury: a literature review (2025) PMID:40045274.

5. Novel Biomarkers for Early Detection of Acute Kidney Injury and Prediction of Long-Term Kidney Function Decline after Partial Nephrectomy (2023) Journal of Clinical Medicine, DOI:10.3390/jcm11041046.

6. Biomarker-driven risk stratification and early intervention in acute kidney injury: a comprehensive review from early warning to clinical response (2026) Frontiers in Medicine, DOI:10.3389/fmed.2026.1796756.

7. Perioperative Myocardial Injury After Noncardiac Surgery: Incidence, Mortality, and Characterization (2017) Anesthesiology, PMID:29203498.

8. Diagnosis and Management of Patients With Myocardial Injury After Noncardiac Surgery: A Scientific Statement From the American Heart Association (2024) Circulation, DOI:10.1161/CIR.0000000000001024.

9. Perioperative myocardial injury and infarction after noncardiac surgery: a review of pathophysiology, diagnosis, and management (2024) Frontiers in Cardiovascular Medicine, DOI:10.3389/fcvm.2024.1323425.

10. Advances in biomarkers for myocardial injury after non-cardiac surgery (2026) PMID:42416513.

11. Advances in biomarkers for myocardial injury after non-cardiac surgery (2026) ScienceDirect, DOI:10.1016/j.glmedi.2026.100057.

12. Aetiology and associated outcomes of myocardial injury as defined by postoperative troponin elevation in high-risk patients after noncardiac surgery: a single-centre retrospective cohort study (2026) PMC13499167.

13. Perioperative neurofilament light chain and glial fibrillary acidic protein as biomarkers of postoperative delirium: a systematic review and meta-analysis (2026) PMID:42237267.

14. Association of postoperative elevation of biomarkers of neural injury in blood with postoperative neurocognitive disorders in adults receiving general anaesthesia: a systematic review (2026) PMID:42115061.

15. Early plasma proteomic biomarkers and prediction model of acute respiratory distress syndrome after cardiopulmonary bypass: a prospective nested cohort study (2024) International Journal of Surgery, DOI:10.1097/js9.0000000000000434.

16. The Impact of One-Lung Ventilation on Development of Postoperative Respiratory Failure During Lung Surgery: A Proteomic Approach for Uncovering Biomarkers (2025) American Journal of Respiratory and Critical Care Medicine.

17. Association of Acute Systemic Inflammation with Patient-Centric Postoperative Pulmonary Complications following Elective Cardiac Surgery (2024) PMC11806086.

18. Association of an expanded inflammatory mediators response with clinical and laboratory data in the postoperative period of pulmonary resection: a prospective clinical study (2023) PMC10683447.

19. Biomarkers of Lung Injury in Cardiothoracic Surgery (2015) Disease Markers, DOI:10.1155/2015/472360.

20. Evolution of Validated Biomarkers and Intraoperative Parameters in the Development of Postoperative ARDS (2018) Respiratory Care, DOI:10.4187/respcare.06103.

21. Temporal and Spatial Patterns of Inflammation and Tissue Injury in Patients with Postoperative Respiratory Failure after Lung Resection Surgery: A Nested Case-Control Study (2023) PMC10298093.