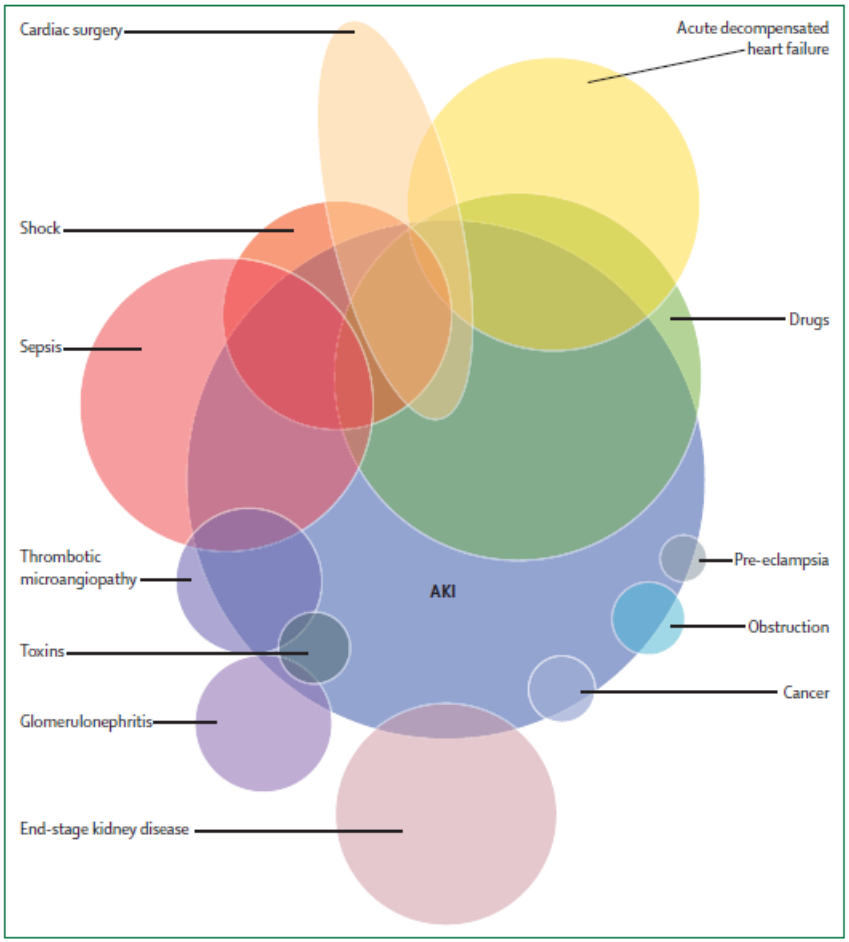
The Clinical Spectrum of AKI Syndrome

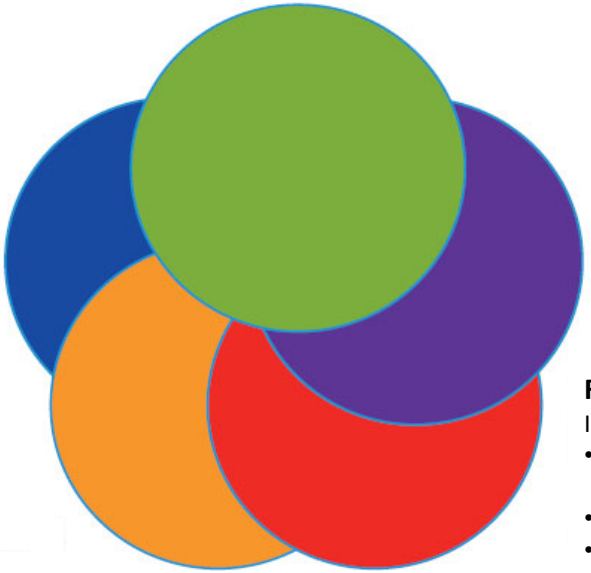


Adapted from Ronco C, Bellomo R, Kellum JA. *Lancet*. 2019;394:1949-64.

The Five R's

Risk
Identifying high-risk individuals for primary prevention of AKI
- Use of risk scores to predict risk of AKI
- Identification of modifiable risk factors

Rehabilitation
Post-discharge care of AKI
- Follow-up of kidney function
- Educational campaigns on the importance of long-term follow-up



Recognition
Prompt diagnosis
- Early and sequential sCr and UO assessment
- Availability of point of care tests and diagnostics tools

Renal support
Renal replacement therapy in AKI
- Timely intervention with RRT
- Education and training of personnel for peritoneal dialysis

Response
Interventions for incipient and established AKI
- Use of protocol-based management of hemodynamic and fluid status
- Avoidance of nephrotoxic drugs
- Appropriate drug dose adjustment for kidney function

Adapted from Macedo E, Garcia-Garcia G, Mehta R, et al. *Ann Nutr Metab*. 2019;74(suppl 3):45-50.

Main Risk Factors for Developing AKI

- Shock
- Infectious diseases
- Cancer
- Transplant

Main Risk Factors for Developing AKI

Nonmodifiable	Modifiable
• Comorbid medical conditions – Chronic kidney disease – Diabetes mellitus – Cancer – Chronic heart disease – Chronic lung disease – Chronic gastrointestinal disease • Demographic factors – Gender – Age	• Dehydration • Hypotension • Intravascular volume depletion • Anemia • Hypoxia • Use of nephrotoxic agents (antibiotics, iodinated contrast, nonsteroidal anti-inflammatory drugs, anticancer drugs, antiretroviral, calcineurin blockers)

Adapted from Macedo E, Garcia-Garcia G, Mehta R, et al. *Ann Nutr Metab*. 2019;74(suppl 3):45-50.

Kidney Stress

- Supply and demand balance
- Kidneys demanding more supply than available
- Parallel to other organ systems

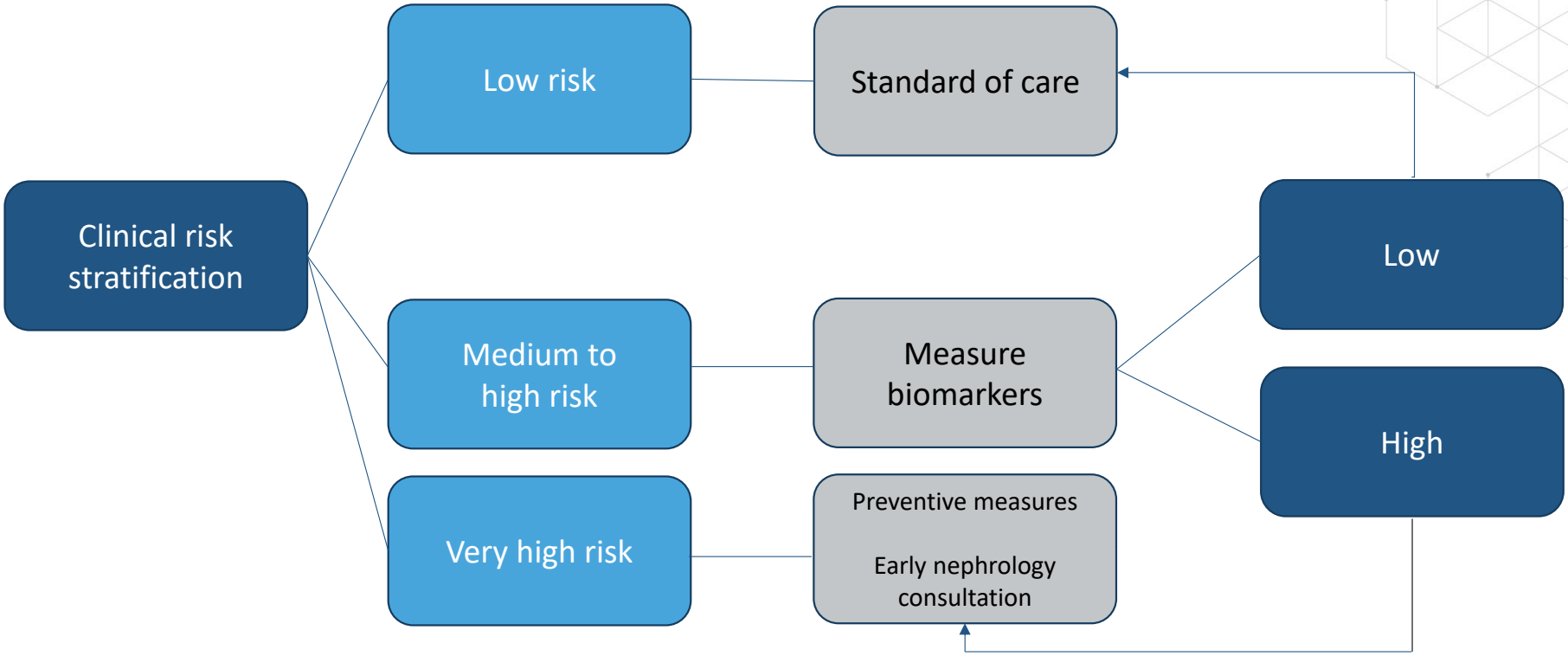
Recently Discovered Biomarkers Include:

Biomarker Category	Example
Functional biomarker	Cystatin C, proenkephalin
Urinary low-molecular-weight protein[a]	α_1-microglobulin, β_2-microglobulin, retinol-binding protein, adenosine deaminase-binding protein, cystatin C
Cellular injury/stress-associated protein	Neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, liver-type fatty-acid-binding protein, tissue inhibitor of metalloproteinase 2, and insulin-like-growth-factor–binding protein 7
Urinary tubular enzyme	Proximal renal tubular epithelial antigen, α-glutathione S-transferase, piglutathione S-transferase, γ-glutamyltranspeptidase, alanine aminopeptidase, lactate dehydrogenase, N-acetyl-beta-glucosaminidase, alkaline phosphatase
Inflammatory mediator[b]	Interleukin-18

[a] Undergoes glomerular filtration and is reabsorbed without secretion.
[b] Released by renal cells.

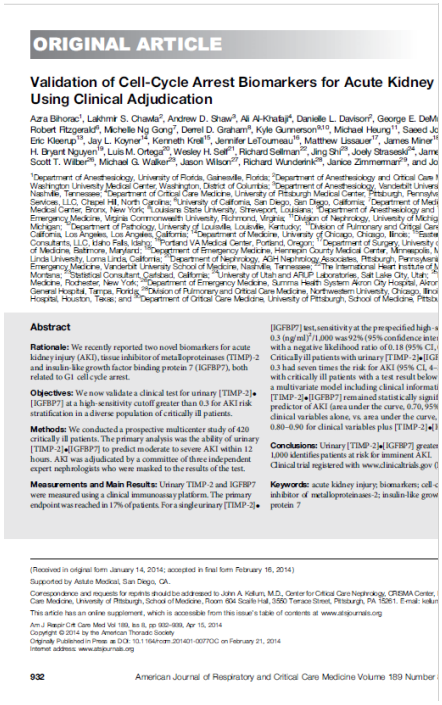
Rizvi MS, Kashani KB. *Journal of Applied Laboratory Medicine*. 2017;2(3):386-399.

Incorporating AKI Biomarkers TIMP-2 and IGFBP7 in Clinical Practice



Rizvi MS, Kashani KB. *Journal of Applied Laboratory Medicine*. 2017;2(3):386-399.

“The biomarkers don't predict anything. The biomarkers identified the damage that we previously were not able to recognize.”



ORIGINAL ARTICLE

Validation of Cell-Cycle Arrest Biomarkers for Acute Kidney Using Clinical Adjudication

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Abstract

Rationale: We recently reported two novel biomarkers for acute kidney injury (AKI), tissue inhibitor of metalloproteinases (TIMP)-2 and insulin-like growth factor binding protein 7 (IGFBP7), both related to G1 cell cycle arrest.

Objectives: We now validate a clinical test for urinary [TIMP-2]• [IGFBP7] at a high-sensitivity cutoff greater than 0.3 for AKI risk stratification in a diverse population of critically ill patients.

Methods: We conducted a prospective multicenter study of 420 critically ill patients. The primary analysis was the ability of urinary [TIMP-2]•[IGFBP7] to predict moderate to severe AKI within 12 hours. AKI was adjudicated by a committee of three independent expert nephrologists who were masked to the results of the test.

Measurements and Main Results: Urinary TIMP-2 and IGFBP7 were measured using a clinical immunoassay platform. The primary endpoint was reached in 17% of patients. For a single urinary [TIMP-2]• [IGFBP7] test, sensitivity at the prespecified high-s
0.3 (ng/ml)²/1,000 was 92% (95% confidence inte
with a negative likelihood ratio of 0.18 (95% CL)
Critically ill patients with urinary [TIMP-2]•[IGF
0.3 had seven times the risk for AKI (95% CI, 4–
with critically ill patients with a test result below
a multivariate model including clinical informati
[TIMP-2]•[IGFBP7] remained statistically signif
predictor of AKI (area under the curve, 0.70, 95%
clinical variables alone, vs. area under the curve,
0.80–0.90 for clinical variables plus [TIMP-2]•[I

Conclusions: Urinary [TIMP-2]•[IGFBP7] greate
1,000 identifies patients at risk for imminent AKI.
Clinical trial registered with www.clinicaltrials.gov (

Keywords: acute kidney injury; biomarkers; cell-c
inhibitor of metalloproteinases-2; insulin-like grow
protein 7

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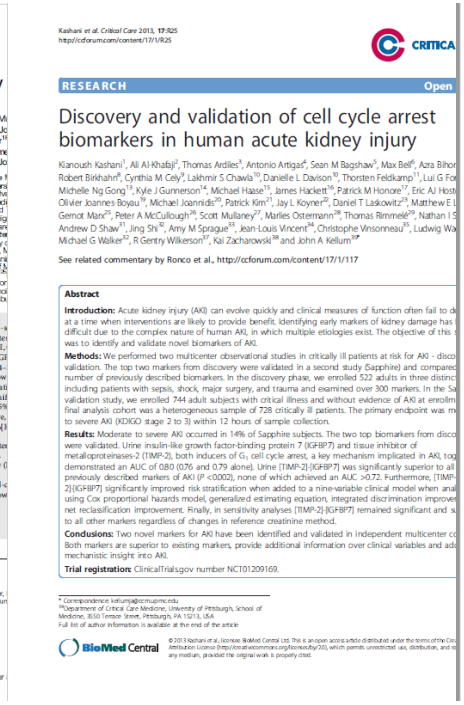

Kashani et al. Critical Care 2013, 17:R25
http://ccforum.com/content/17/1/R25

CRITICA

RESEARCH Open

Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury

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Michelle Ng Gong[13], Kyle J Gunnerson[14], Michael Haase[15], James Hackett[16], Patrick M Honore[17], Eric AJ Host
Olivier Joannes-Boyau[19], Michael Joannidis[20], Patrick Kim[21], Jay L Koyner[22], Daniel T Laskowitz[23], Matthew E L
Gernot Marx[25], Peter A McCullough[26], Scott Mullaney[27], Marlies Ostermann[28], Thomas Rimmele[29], Nathan I S
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See related commentary by Ronco et al., http://ccforum.com/content/17/1/117

Abstract

Introduction: Acute kidney injury (AKI) can evolve quickly and clinical measures of function often fail to d
at a time when interventions are likely to provide benefit. Identifying early markers of kidney damage has
difficult due to the complex nature of human AKI, in which multiple etiologies exist. The objective of this
was to identify and validate novel biomarkers of AKI.

Methods: We performed two multicenter observational studies in critically ill patients at risk for AKI - disco
validation. The top two markers from discovery were validated in a second study (Sapphire) and compared
number of previously described biomarkers. In the discovery phase, we enrolled 522 adults in three distinc
including patients with sepsis, shock, major surgery, and trauma and examined over 300 markers. In the Sa
validation study, we enrolled 744 adult subjects with critical illness and without evidence of AKI at enrollm
final analysis cohort was a heterogeneous sample of 728 critically ill patients. The primary endpoint was m
to severe AKI (KDIGO stage 2 to 3) within 12 hours of sample collection.

Results: Moderate to severe AKI occurred in 14% of Sapphire subjects. The two top biomarkers from disco
were validated. Urine insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of
metalloproteinases-2 (TIMP-2), both inducers of G_1 cell cycle arrest, a key mechanism implicated in AKI, tog
demonstrated an AUC of 0.80 (0.76 and 0.79 alone). Urine [TIMP-2]·[IGFBP7] was significantly superior to all
previously described markers of AKI ($P < 0.002$), none of which achieved an AUC >0.72. Furthermore, [TIMP-
2]·[IGFBP7] significantly improved risk stratification when added to a nine-variable clinical model when anal
using Cox proportional hazards model, generalized estimating equation, integrated discrimination improve
net reclassification improvement. Finally, in sensitivity analyses [TIMP-2]·[IGFBP7] remained significant and s
to all other markers regardless of changes in reference creatinine method.

Conclusions: Two novel markers for AKI have been identified and validated in independent multicenter co
Both markers are superior to existing markers, provide additional information over clinical variables and ad
mechanistic insight into AKI.

Trial registration: ClinicalTrials.gov number NCT01209169.

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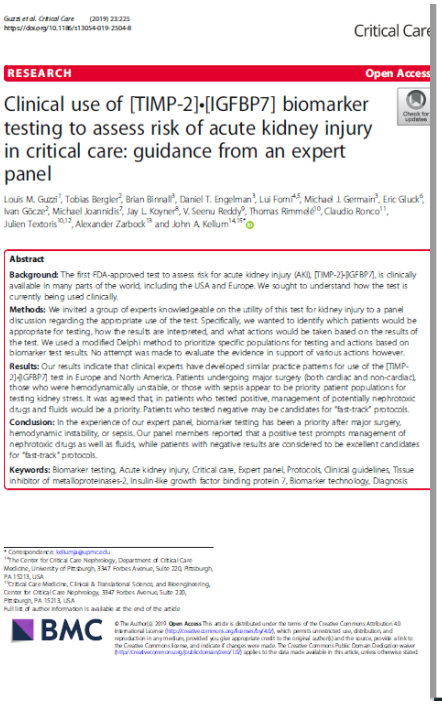

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Critical Care

RESEARCH Open Access

Clinical use of [TIMP-2]•[IGFBP7] biomarker testing to assess risk of acute kidney injury in critical care: guidance from an expert panel

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Abstract

Background: The first FDA-approved test to assess risk for acute kidney injury (AKI), [TIMP-2]•[IGFBP7], is clinically available in many parts of the world, including the USA and Europe. We sought to understand how the test is currently being used clinically.

Methods: We invited a group of experts knowledgeable on the utility of this test for kidney injury to a panel discussion regarding the appropriate use of the test. Specifically, we wanted to identify which patients would be appropriate for testing, how the results are interpreted, and what actions would be taken based on the results of the test. We used a modified Delphi method to prioritize specific populations for testing and actions based on biomarker test results. No attempt was made to evaluate the evidence in support of various actions however.

Results: Our results indicate that clinical experts have developed similar practice patterns for use of the [TIMP-2]•[IGFBP7] test in Europe and North America. Patients undergoing major surgery (both cardiac and non-cardiac), those who were hemodynamically unstable, or those with sepsis appear to be priority patient populations for testing kidney stress. It was agreed that, in patients who tested positive, management of potentially nephrotoxic drugs and fluids would be a priority. Patients who tested negative may be candidates for "fast-track" protocols.

Conclusion: In the experience of our expert panel, biomarker testing has been a priority after major surgery, hemodynamic instability, or sepsis. Our panel members reported that a positive test prompts management of nephrotoxic drugs as well as fluids, while patients with negative results are considered to be excellent candidates for "fast-track" protocols.

Keywords: Biomarker testing, Acute kidney injury, Critical care, Expert panel, Protocols, Clinical guidelines, Tissue inhibitor of metalloproteinases-2, Insulin-like growth factor binding protein 7, Biomarker technology, Diagnosis

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Clinical Review & Education

JAMA Surgery | Special Communication

Guidelines for Perioperative Care in Cardiac Surgery
Enhanced Recovery After Surgery Society Recommendations

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Enhanced Recovery After Surgery (ERAS) evidence-based protocols for perioperative care can lead to improvements in clinical outcomes and cost savings. This article aims to present consensus recommendations for the optimal perioperative management of patients undergoing cardiac surgery. A review of meta-analyses, randomized clinical trials, large nonrandomized studies, and reviews was conducted for each protocol element. The quality of the evidence was graded and used to form consensus recommendations for each topic. Development of these recommendations was endorsed by the Enhanced Recovery After Surgery Society.

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Supplemental content
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Enhanced Recovery After Surgery (ERAS) is a multimodal, transdisciplinary care improvement initiative to promote recovery of patients undergoing surgery throughout their entire perioperative journey.[1] These programs aim to reduce complications and promote an earlier return to normal activities.[2,3] The ERAS protocols have been associated with a reduction in overall complications and length of stay of up to 50% compared with conventional perioperative patient management in populations having noncardiac surgery.[4-6] Evidence-based ERAS protocols have been published across multiple surgical specialties.[3] In early studies, the ERAS approach showed promise in cardiac surgery (CS); however, evidence-based protocols have yet to emerge.[7]

To address the need for evidence-based ERAS protocols, we formed a registered nonprofit organization (ERAS Cardiac Society) to use an evidence-driven process to develop recommendations for pathways to optimize patient care in CS contexts through collaborative discovery, analysis, expert consensus, and best practices. The ERAS Cardiac Society has a formal collaborative agreement with the ERAS Society. This article reports the first expert-consensus review of evidence-based CS ERAS practices.

Methods

We followed the 2011 Institute of Medicine *Standards for Developing Trustworthy Clinical Practice Guidelines*, using a standardized algorithm that included experts, key questions, subject champions, systematic literature reviews, selection and appraisal of evidence quality, and development of clear consensus recommendations.[8] We minimized repetition of existing guidelines and consensus statements and focused on specific information in the framework of ERAS protocols.

As sanctioned by the ERAS Society, we began with a public organizational meeting in 2017 where broad topics of ERAS in CS were discussed, and we solicited public comment regarding appropriate approaches and protocols. A multidisciplinary group of 16 cardiac surgeons, anesthesiologists, and intensivists were identified who demonstrated expertise and experience with ERAS. The group agreed on 22 potential interventions, divided into preoperative, intraoperative, and postoperative phases of recovery.

After selecting topics and assigning group leaders, literature searches were conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure), and this included reviews, guideline documents, and studies that were conducted on humans since 2000, published in English, and retrievable from PubMed, Excerpta Medica (Embase), Cochrane, the Agency for Healthcare Research and Quality, and other selected databases relevant to this consensus.[9] Medical Subject Heading terms were used, as were accompanying entry terms for the patient group, interventions, and outcomes. Two independent reviewers (W.B.A. and 1 nonauthor) screened the abstracts considered for topics. Prospective randomized clinical trials, meta-analyses, and well-designed, nonrandomized studies were given preference. When multiple publications had sample overlap, the most recent report was selected. Controversies were discussed and resolved via in-person meetings, conference calls, and discussions. A minimum of 75% agreement on class and level was required for consensus.[10] Consistent with the Institute of Medicine guidelines, panel members with relevant conflicts of interest (COI) were identified and recused from voting on associated recommendations. The structure of the recommendations was modeled after prior published ERAS guidelines.[8] We used the Society of Thoracic Surgeons/American Association for Thoracic Surgery 2017 updated document "Classification of Recommendations and Level of Evidence," and American College of Cardiology/American

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NINJA:

Nephrotoxic Injury Negated by Just-in-time Action

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