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Clinical Decision Tool Reviews

# Review of the Acute Interstitial Nephritis (AIN) Risk calculator

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## Abstract

The AIN risk calculator was developed to improve non-invasive diagnostic accuracy for acute interstitial nephritis, an asymptomatic and often poorly recognized but potentially reversible cause of acute kidney injury. The equation was developed in a cohort of adult patients who underwent a kidney biopsy for acute kidney injury and has been validated in multiple kidney biopsy cohorts. The four variable equation requires blood urea nitrogen (BUN), serum creatinine, and two dipstick urinalysis components—urine specific gravity and urine protein grade. This tool has a low positive predictive value and a high negative predictive value. Hence, a low probability score can effectively rule out AIN. The calculator is therefore intended to be used for patients in whom kidney biopsy is being considered but it cannot diagnose AIN or be used to prescribe treatment without biopsy evidence. A kidney biopsy is required to diagnose AIN for those who are at higher than low risk. Urinary biomarkers have been shown to improve the diagnostic accuracy of the calculator and, once clinically available, could further enhance its performance and facilitate non-invasive diagnosis.

## I. HOW TO USE

### When to Use

The AIN risk calculator can be used in the evaluation of patients with acute kidney injury who are being considered for kidney biopsy to evaluate for AIN. It can help decide whether a patient should undergo a kidney biopsy to evaluate for AIN particularly when the pre-test probability is not high.

### Pearls / Pitfalls

- The intended purpose of the AIN risk calculator is to estimate the likelihood that a patient may have AIN.
- Low probability scores can rule out the diagnosis of AIN provided the pre-test probability (i.e., clinical suspicion) is not high.
- Low probability for AIN does not eliminate the need for kidney biopsy to investigate other causes of kidney injury such as glomerulonephritis. The tool should not be used in patients who have other indications for biopsy.
- The AIN risk calculator can provide support for the decision to biopsy but still relies on comprehensive clinical evaluation and clinical judgement.
- The AIN risk calculator is a risk predictive tool and therefore does not diagnose AIN.
- While the initial study suggested that adding urinary cytokines IL-9 and TNF-α could improve the performance of the calculator, these are not yet available for clinical use and need further research before being incorporated into the calculator.

### Why Use

The AIN risk calculator can be used to identify patients in whom the probability of AIN is low and to avoid unnecessary kidney biopsy in such patients.

The tool can help improve clinical care by promoting early diagnosis and management of AIN.

## II. NEXT STEPS

### Advice

The following actions are suggested:

- Low probability (< 0.05): AIN is unlikely; evaluate for alternative diagnoses.
- Intermediate probability (0.05-0.29): AIN is possible; further evaluation with a kidney biopsy is warranted.

- High probability (≥0.30): AIN is highly possible; further evaluation with a kidney biopsy is still warranted.

Note: thresholds for the above risk categories have not been specified in the study. The above thresholds are extrapolated from model performance values at arbitrary cutoffs in a subsequent validation study.

Note, all patients with AKI should first undergo comprehensive evaluation for all possible causes of AKI including pre-renal causes such as volume depletion, post-renal causes such as obstruction along the urinary tract and intrinsic causes such as acute tubular injury/necrosis (ATN) and glomerulonephritis which can be diagnosed based on history, imaging or laboratory findings. AIN may also co-occur with other AKI etiologies. The diagnosis of AIN requires clinical suspicion based on the patient's exposures, medical history and exam findings. The calculator is not intended to guide treatment solely based on the score but rather to support decision for biopsy for AIN. Clinical judgement remains critical. This tool is not intended to be used in patients at risk of other etiologies of AKI that might require kidney biopsy. Biopsy should not be avoided if there is high clinical suspicion based on history.

### Management

Before considering AIN, all other potential causes of AKI must be excluded. The evaluation of AKI generally involves identification of: (1) the location of injury – pre-renal, intrinsic, post-renal – and (2) the specific cause of the injury. Identifying the causative agent is particularly important in intrinsic AKI such as AIN. Drugs account for over 75% of AIN cases, with antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) being the most common culprits. With the increasing use of cancer immunotherapy, immune check point inhibitors are also being recognized as frequent causes of AIN. A minority of AIN cases are caused by infections and autoimmune diseases such as sarcoidosis. This tool can be used to exclude the likelihood of AIN in patients at risk of AIN. Pre-renal etiologies and post-renal (obstruction) which are both mostly reversible should first be excluded as sole diagnoses. Patients with scores falling in the intermediate or high probability of AIN should undergo kidney biopsy for definitive diagnosis of AIN. Once AIN is diagnosed on biopsy, the offending agent should be promptly identified and discontinued, or the underlying infection or inflammatory condition treated accordingly. In drug-induced AIN, stopping the causative agent alone may not be sufficient and corticosteroid therapy may be necessary. However, there is no consensus on the benefit, dose or duration of steroids, though early initiation (within 7-10 days) has been associated with higher likelihood of recovery in small non-randomized studies and a quick taper is generally preferred to minimize adverse effects. Reversibility is dependent on the time to diagnosis and management and on the extent of fibrosis on biopsy. Initiation of steroids without biopsy evidence of AIN should be avoided as much as possible as the diagnosis itself often has therapeutic implications on the condition being treated by the culprit. For patients highly suspected to have AIN who are deemed at high bleeding risk for biopsy, empiric steroids may be considered on a case-by-case basis considering risks such as infection and hyperglycemia. In such patients, management should be individualized through multidisciplinary discussion regarding alternative therapeutic options when discontinuing suspected culprit drug(s) (particularly when dealing with essential life-saving drugs), as well as the safety of empiric corticosteroids, which should be reserved for persistent AKI despite withdrawal of the suspected culprit. Novel biomarkers improve diagnostic accuracy and may allow non-invasive diagnosis and treatment response monitoring once they become available for clinical use.

### Critical Actions

If all other types of AKI have been excluded as primary drivers of AKI and the clinical suspicion remains high, biopsy remains the gold standard for AIN diagnosis. The most common causes of AIN are drugs and hence, the first step should be uncovering the causative agent and immediate discontinuation. AIN is one of few intrinsic AKI diagnoses that is treatable. Delayed diagnosis may lead to irreversible scarring and chronic kidney disease.

## III. EVIDENCE

### Evidence Appraisal

The AIN risk equation was developed in a cohort of adults hospitalized at Yale New Haven Hospital between 2013 and 2018 and underwent a native kidney biopsy for evaluation of acute kidney injury and had laboratory data prior to biopsy. The study excluded patients with positive ANCA (glomerulonephritis) and dsDNA (lupus nephritis). Histologic diagnosis of AIN was adjudicated by pathologists. The study included 393 adults of whom 22% had AIN in the training set, 158 patients (AIN 27%) in the test set, and an external validation cohort of 1118 patients from the Biopsy Biobank Cohort of Indiana who underwent a kidney biopsy between 2002 – 2019 (11% with AIN, significantly younger and significantly higher eGFR at baseline compared to derivation cohort). Model development and selection involved LASSO regularization and Bayesian information criterion. Evaluated features also included urinalysis components, the count and slope of eGFR pre-biopsy, sterile pyuria, blood eosinophil count, medications such as immunotherapy,

PPI, NSAIDs, recent antibiotic exposure such as beta-lactam and fluoroquinolones, count of allergies, among others. The final model included most recent pre-biopsy serum creatinine, blood urea nitrogen: creatinine ratio, urine specific gravity and urine dipstick protein (stratified by 1+ or lower vs 2+ or higher) with respective adjusted odds ratio and 95% confidence intervals of 2.31 [1.42–3.76], 0.40 [0.20 – 0.78], 0.95 [0.91 – 0.99] and 0.39 [0.23 – 0.68].(Table 1) This model had an AUC (95% CI) of 0.73 [0.64 – 0.81] in the test set and similarly 0.74 [ 0.69–0.79] in the external validation cohort. Performance of pre-biopsy clinician suspicion for AIN and addition of AIN-specific biomarkers has been evaluated in 265 biopsied patients from the Yale AIN study (2015-2018). While the model in this calculator does not contain AIN-specific biomarkers, the AUC was improved to 0.84 (95% CI 0.76–0.91) upon addition of urine IL-9 and TNF-α. The equation was further validated in a cohort of individuals who underwent a kidney biopsy at Yale University and Johns Hopkins Hospitals between 2019 to 2023 (n=1982) with AUCs consistent with the initial study, though this was achieved with recalibration with a correction factor accounting for local prevalence differences for the latter site. The AUC for AIN diagnosis when combined with clinician pre-biopsy suspicion for AIN was 0.77 compared to that of clinicians' pre-biopsy gestalt alone (0.67). Model performance characteristics at different cutoffs with and without clinician pre-biopsy suspicion are shown in Table 2. More recently, a more specific non-invasive urinary biomarker of AIN urinary CXCL-9 has been discovered that predicted biopsy AIN diagnosis with an AUC 0.94 and holds strong promise both for non-invasive diagnosis and for guiding treatment response. This was externally validated in two small biopsy cohorts. While this will need further validation in diverse cohorts, it will likely lead to updates on the indication and interpretation of this risk score once available in clinical practice.

## Formula

Sum = (0.8367518 × log(creatinine)) + (-0.9181938 × log(BUN : creatinine ratio)) + (-0.0501203 × 1000 × (urine specific gravity - 1)) + urine dipstick protein* + log(local prevalence of AIN among all biopsies**/ 0.23) + 0.770398

% Probability of AIN = 100 × $e^{sum}$ / (1+ $e^{sum}$)

* 0.9360127 if urine dipstick protein is 1+ or lower, otherwise 0

** If unknown, enter 0.23

## Facts & Figures

**Table 1.** Selected variables and associated risk estimates

| Variables associated with AIN | OR (95% CI) |
|---|---|
| Serum creatinine before biopsy* | 2.31 (1.42–3.76) |
| BUN : creatinine ratio* | 0.40 (0.20–0.78) |
| Absence of proteinuria** | 2.55 (1.45–4.43) |
| Urine specific gravity*** | 0.95 (0.91–0.99) |

* per natural log increase

** (0 and 1+) vs (2+ or higher) with the latter as reference

*** per 0.001 unit increase

**Table 2.** Model performance characteristics (a) and suggested risk categories (b)

(a)

| Cutoff | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| Model probability=0.05 | 0.95 | 0.22 | 0.20 | 0.96 |
| Model probability=0.30 | 0.34 | 0.92 | 0.45 | 0.87 |
| Clinician prebiopsy suspicion | 0.44 | 0.89 | 0.44 | 0.89 |
| Clinician suspicion or model probability=0.05 | 0.95 | 0.22 | 0.20 | 0.96 |
| Clinician suspicion + model probability=0.05 | 0.44 | 0.89 | 0.45 | 0.89 |
| Clinician suspicion or model probability=0.30 | 0.57 | 0.82 | 0.38 | 0.90 |
| Clinician suspicion + model probability=0.30 | 0.22 | 0.99 | 0.76 | 0.86 |

(b)

| Risk category | Model-predicted probability | Proportion of cohort | Estimated observed AIN incidence* |
|---|---|---|---|
| Low | <0.05 | 19% | 4.5% |
| Intermediate | 0.05–<0.30 | 68% | 15.1% |
| High | ≥0.30 | 13% | 46.5% |

*based on site AIN prevalence of 17%. Data from: Moledina DG, et al. External Validation of an Electronic Health Record-Based Diagnostic Model for Histological Acute Tubulointerstitial Nephritis. *J Am Soc Nephrol*. 2025 May 1;36(5):859-868. doi: 10.1681/ASN.0000000556.

## Literature

### *Original Study*

Moledina DG, Eadon MT, Calderon F, Yamamoto Y, Shaw M, Perazella MA, Simonov M, Luciano R, Schwantes-An TH, Moeckel G, Kashgarian M, Kuperman M, Obeid W, Cantley LG, Parikh CR, Wilson FP. Development and external validation of a diagnostic model for biopsy-proven acute interstitial nephritis using electronic health record data. *Nephrol Dial Transplant.* 2022 Oct 19;37(11):2214-2222. doi: 10.1093/ndt/gfab346.

*Validation studies*

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*Other studies*

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