Enhanced Creatinine and Estimated Glomerular Filtration Rate Reporting to Facilitate Detection of Acute Kidney Injury

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Key Words: Acute kidney injury (AKI); Creatinine; Estimated glomerular filtration rate (eGFR); Diagnostic error

ABSTRACT

Objectives: While acute kidney injury (AKI) can be diagnosed based on specified increases in a patient’s plasma creatinine level, standard creatinine reporting methods typically only flag creatinine results as abnormal when outside the reference range and often fail to identify rising creatinine values indicative of AKI. Here, we evaluate the impact of this limitation in standard creatinine reporting and develop and implement an enhanced creatinine reporting algorithm.

Methods: We evaluated 59,712 plasma creatinine results collected over approximately 3 months, using computational simulations and statistical analyses.

Results: Our analyses demonstrated that 29% of creatinine results substantially increased over the patient’s baseline and concerning for AKI remained within the normal reference range. These concerning results would not be flagged as abnormal using standard reporting. Likewise, we found that simple delta checks are also insensitive at AKI detection. To improve creatinine reporting, we developed and implemented an algorithm within our laboratory information system to alert clinicians to rising creatinine results, which we describe in this report.

Conclusion: While both creatinine reference limits and simple delta checks are insensitive for AKI identification, a simple algorithm can be implemented within a common laboratory information system to enhance AKI identification.

Upon completion of this activity you will be able to:
• list criteria for laboratory diagnosis of acute kidney injury (AKI).
• recognize and discuss the limitations of standard laboratory reference ranges in diagnosing certain conditions, including AKI.
• outline strategies to enhance the value of clinical laboratory testing by applying electronic clinical decision support for result interpretation.

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Acute kidney injury (AKI) is a common problem in hospitalized patients.1 AKI is defined as a substantial decline in renal function occurring over hours to days and is associated with a variety of risk factors in hospitalized patients. In addition, AKI is frequently iatrogenic, with radiocontrast and antimicrobial agents being commonly implicated. While morbidity and mortality vary with AKI severity, even mild AKI has been associated with substantial mortality.1,2 Early AKI typically is recognized based on an increase in a patient’s creatinine level from the patient’s baseline or a decrease in urine output.

Despite the importance of creatinine in diagnosing AKI, standard creatinine reporting is more suitable for the identification of chronic kidney disease (CKD) than AKI. For example, the reporting of creatinine reference ranges only serves to compare the current creatinine result with the creatinine values observed in a healthy reference population. In contrast, for AKI detection, each patient’s creatinine must
be compared with the patient’s individual baseline, not to a reference population. In the present study, we show that creatinine results indicative of AKI frequently remain within the reference range.

To facilitate the detection of CKD, most US laboratories now calculate and report an estimated glomerular filtration rate (eGFR). The Modification of Diet in Renal Disease (MDRD) formula is currently the most commonly used eGFR formula, although several recent studies suggest the CKD–Epidemiology Collaboration (EPI) formula may provide improved clinical utility. Both the MDRD and CKD-EPI formulas help control creatinine results for age, race, and sex. However, the standard eGFR formulas assume creatinine is in steady state, and thus in the setting of rising creatinine levels, the calculated eGFR will overestimate the true glomerular filtration rate (GFR). eGFR overestimates may be particularly dangerous if they are inappropriately used to guide medication dosing.

Laboratories generally only report creatinine results with an abnormal flag if the result is outside the reference range. Accordingly, rising creatinine results indicative of AKI may be “abnormal” for the patient but appear normal on the laboratory report. As a result, failure to carefully trend creatinine values can lead to an overlooked diagnosis of AKI and a delay in addressing the underlying causes. Renal injury may progress during such delays in AKI diagnosis and may be worsened by clinical actions such as administration of intravenous contrast or nephrotoxic antimicrobial agents. Indeed, a recent study identified AKI (“acute renal failure”) as the most commonly overlooked diagnosis in a large Veterans Administration primary care facility. More generally, a comprehensive analysis of 583 malpractice cases identified laboratory testing, including clinician follow-up and interpretation of test results, as a common source of errors resulting in malpractice claims.

Nonetheless, AKI can be diagnosed using objective, quantitative criteria. Several AKI diagnostic guidelines have been published, including the RIFLE (risk, injury, failure and loss), AKIN (Acute Kidney Injury Network), and KDIGO (Kidney Disease Improving Global Outcomes) criteria. For example, RIFLE criteria divide AKI into three categories: risk, injury, and failure. RIFLE defines risk as an increase in plasma creatinine over baseline of 1.5- to 2-fold, injury an increase of 2- to 3-fold, and failure an increase of 3-fold or more. RIFLE failure criteria can also be met by an acute increase in plasma creatinine of 0.5 mg/dL or more or a level of 4 mg/dL or more. RIFLE also includes urine output and GFR-based criteria that can be used to diagnose AKI.

Since AKI can be diagnosed using objective, quantitative criteria, one strategy to improve the identification of AKI and reduce the misinterpretation of reported eGFR values would be to electronically alert clinicians to rising creatinine results meeting AKI criteria. However, given the limitations of typical laboratory information systems (LIS), providing this type of clinical decision support is challenging. Delta checks comparing the current creatinine result with the patient’s most recent prior creatinine result are an important consideration because delta check functionality is supported in most LIS, and delta checks were recently shown to be a useful strategy for detecting AKI in a study performed at a hospital in the United Kingdom. However, in the current report, we demonstrate that delta checks alone are relatively insensitive for the detection of AKI. To overcome the insensitivity of delta checks, we developed an alternative algorithmic approach for identifying creatinine values suggestive of AKI. In this study, we demonstrate the efficacy of our approach for the identification of AKI and provide the details of our clinical implementation.

Materials and Methods

Setting and Creatinine Measurement

The study took place at the Massachusetts General Hospital, a 983-bed tertiary care teaching hospital in Boston, Massachusetts. Plasma creatinine is measured in our hospital’s central laboratory using Roche/Cobas c501 automated analyzers (Roche Diagnostics, Indianapolis, IN) and the Roche/Cobas CREJ2 assay, which is based on the Jaffe method. The intermediate imprecision (coefficient of variation) of this assay ranges from 2.4% to 5%. The central laboratory uses Sunquest, version 7.1 (Sunquest Information Systems, Tucson, AZ) as its LIS. Study procedures were reviewed and approved by the institutional review board.

RIFLE AKI Criteria

For the purposes of assessing the sensitivity and specificity of various AKI identification strategies, key elements of the RIFLE classification criteria were used to determine the “true” AKI status for each patient. In particular, except as otherwise noted, patients whose creatinine results had increased by 1.5-fold or more over their 72-hour minimum creatinine value were classified as having “risk”-level AKI. Patients with creatinine results increased by 3-fold or more were classified as having “failure”-level AKI. Although 72 hours represents a different baseline period than most established AKI criteria, we selected this period for our flagging rules (described below) in consultation with our hospital’s nephrology service (see Discussion for additional explanation). Likewise, we used 72-hour baselines when evaluating RIFLE and KDIGO criteria for consistency. Sensitivity was defined as the proportion...
of patients meeting these AKI criteria (risk or failure as specified) who were classified as having a “substantial creatinine increase” by a particular flagging rule. Specificity was defined as the proportion not meeting these AKI criteria who were not identified by a flagging rule as having a substantial creatinine increase.

Delta Checks and Tracked Minimums

Delta check rules were based on the absolute increase in creatinine from the patient’s most recent prior result (within 72 hours). Creatinine results associated with deltas exceeding specified thresholds were classified as “significantly increased” according to the delta check rules.

The tracked minimum is a single value stored for each patient, evaluated each time the patient has new creatinine reported. Specifically, the tracked minimum is set to the current creatinine if either or both of the following conditions are met:

1. More than 72 hours had elapsed since the tracked minimum was last updated (including if no prior creatinines have been resulted in the past 72 hours)
2. The new creatinine is less than or equal to the prior tracked minimum

If neither of these conditions is met, the tracked minimum is not updated. Tracked minimums that have not been updated for more than 72 hours (“expired tracked minimums”) were not used in the tracked minimum rules. Patients were classified as “significantly increased” according to the “tracked minimum with delta check” rules if their current creatinine exceeded either their tracked minimum creatinine or their most recent prior creatinine (within 72 hours) by more than a specified threshold.

Calculation of eGFR and Kinetic eGFR Values

eGFR values were calculated according the MDRD formula, \(^4\) the same formula used by our laboratory to calculate reported eGFR values. No adjustment was made for race, since this is often unknown to the laboratory, and our laboratory’s calculation includes a comment regarding adjustment for race. Kinetic eGFR (KeGFR) values were calculated according to an adaptation of the formula described by Chen. \(^7\) In calculating KeGFR, we took the MDRD-calculated eGFR as the creatinine clearance, 1.5 mg/dL as the maximum daily creatinine change, the 72-hour minimum creatinine as the steady-state creatinine, the mean of the current and most recent prior creatinine as the mean creatinine, and the change from the most recent prior creatinine as the delta creatinine.

Data and Data Set Generation

Creatinine results and accompanying patient demographic data were extracted from our LIS. As shown in Figure 1, two main data sets were created for this analysis: data sets A and B. Data set A was designed to represent the overall pool of creatinine values (given study inclusion criteria noted above) seen by the laboratory. However, because recognition of AKI at first presentation is a key goal, data set B was developed. Data set B employed a case-control approach, in which cases included only creatinine results from patients meeting AKI criteria for the first time. For data set B, cases included creatinine results from data set A that met AKI criteria in patients who had not previously met AKI criteria. Controls were composed of one randomly selected creatinine result from each patient not meeting AKI criteria at any time during the study period.

As shown in Figure 1, all inpatient and emergency department (ED) patient results during a 100-day period were extracted from our LIS with the latter 90 days included in primary analysis (the first 10 days were used only to calculate AKI status and baseline creatinines). Patients younger than 18 years or older than 100 years at any time during the study period were excluded, because the eGFR is only reported on patients between 18 and 99 years of age. Creatinine results not preceded by a prior result on the same patient within the prior 72 hours were excluded, since no baseline could be calculated.

Data Analysis and Statistics

Data were processed and flagging rules were simulated using Microsoft Access (Microsoft, Redmond, WA) and the R statistical scripting language (R Core Team, Vienna, Austria). \(^4\) Confidence intervals for proportions were calculated using the R binom package \(^5\) and the Wilson method. Receiver operating characteristic (ROC) curve data were generated using the R pROC package. \(^6\) Confidence intervals for areas under the curves for ROC curves, confidence intervals for sensitivities, and \(P\) values comparing ROC curves were computed using the bootstrap method as implemented in the pROC package (2,500 bootstrap repetitions). Figures (including plots of ROC data) were generated in R using the Ggplots2 package. \(^7\) Flagging rule sensitivity was calculated as the proportion of results meeting specified AKI criteria correctly identified, and specificity was calculated as the proportion of results not meeting AKI criteria correctly classified.

Results

Data Sets

As shown in Figure 1, data set A was composed of all creatinine values meeting inclusion criteria and contained 59,712 individual results. In addition, to evaluate the ability
of our flagging rules to identify AKI at the first opportunity, we created data set B using a case-control approach. Data set B comprised 8,186 results (one result per patient). In total, 965 of the results were from patients with AKI (first AKI result for that patient), and the remaining 7,221 results were controls and comprised one randomly selected result from each non-AKI patient.

**AKI and Creatinine Values Within the Reference Range**

Of the creatinine results included in our analysis (data set A), 6.6% were increased from the patient’s baseline by at least 1.5-fold, paralleling RIFLE risk-level AKI criteria (Figure 1). Creatinine results within the reference range may still be diagnostic of AKI, since AKI is diagnosed primarily based on creatinine values relative to an individual patient’s baseline rather than values relative to a healthy reference population. As shown, 29% of the creatinine results meeting AKI criteria were below the upper limit of the creatinine reference range of 1.5 mg/dL. In addition to a proportional increase in creatinine, KDIGO criteria also permit a diagnosis of AKI (stage I) to be made based on an absolute increase in creatinine of 0.3 mg/dL. Results that increased by 0.3 mg/dL but not meeting RIFLE AKI criteria are depicted in the horizontal line representing a 1.5-fold increase. When this additional criterion is included, 12% of the creatinine results meet AKI criteria, with 24% of these results falling below the upper limit of the reference range.

Because optimal clinical management requires identification of AKI at the first opportunity, we also analyzed creatinine results diagnostic of AKI (risk or higher) in patients who had not previously met AKI criteria (data set B). For these patients meeting AKI criteria for the first time (n = 965), 52% (95% CI, 49%-55%) were below the upper limit of the reference range. Taken together, these data indicate that reliance on the reference range alone to identify patients at risk for AKI has the potential for a significant number of patients with AKI to be overlooked.

**Reported eGFRs Can Be Misleading**

In the setting of rising creatinine results (such as in AKI), calculated eGFR values are inaccurate and potentially provide dangerous and misleading overestimates of the true GFR. Since standard eGFR calculations are based on single creatinine measurements and assume steady state, we wished to determine how often the eGFR is potentially inaccurate due to acute creatinine increases. We applied a KeGFR formula to the 66% of creatinine results in data set A that corresponded
to normal eGFR values (eGFR >60 mL/min/1.73 m²). Nearly 8% of normal eGFR results were calculated to be abnormal (<60 mL/min/1.73 m²) when creatinine change was taken into account using the KeGFR formula. Although the KeGFR formula has not been thoroughly validated for clinical use, our results provide an indication that calculated eGFRs in some instances may overestimate the true GFR and may be misleading. Since eGFR values are commonly used for drug dosing, the reporting of inaccurate eGFR values could potentially lead to erroneous drug dosing.

Tracked Minimum-Based Rules Can Improve AKI Detection

To reduce the potential for harm associated with both unnoticed increases in creatinine and inaccurate eGFR values, we sought to highlight creatinine values substantially elevated over the patient’s baseline to permit the earlier diagnosis of AKI as well as prevent errors in medication dosing. We evaluated three flagging strategies that could be implemented within our LIS:

1. Flagging creatinine results exceeding a specified threshold (eg, standard abnormal results flagging based on the current result only)
2. Flagging creatinine results increased by more than a specified threshold (absolute increase) from the patient’s most recent prior result (eg, delta checks)
3. Flagging creatinine results increased by more than a specified threshold from the lesser of the tracked minimum or single most recent prior value (“tracked minimum with delta check”)

Figure 3 shows ROC curves comparing the sensitivity and specificity of the three flagging strategies across a range of specified flagging thresholds. As shown, tracked minimum-based rules in combinations with delta checks were significantly more powerful than delta checks alone or individual creatinine results evaluated in isolation.

Summary statistics for a variety of flagging rules simulated in data sets A and B are shown in Table 1. Note that at a specificity of 95%, tracked minimum rules are 87% sensitive compared with 67% for delta checks (data set A).
**Discussion**

Herein, we demonstrate that more than one-quarter of inpatient and ED creatinine results indicative of AKI are below the upper reference limit and would appear normal with standard creatinine reporting. Moreover, we estimate that approximately 8% of eGFR reported within the normal range occur in patients with evidence of compromised glomerular function. While clinicians can and should trend all creatinine results, actual practice is often time pressured, and trends can easily be overlooked. We estimate that our hospital sees more than 2,000 creatinine results per year that are indicative of AKI but remain within the reference range. Work is currently under way to evaluate the clinical impacts of our flagging rule.

The tracked minimum flagging rules we implemented provide a solution to reduce both overlooked cases of AKI and the misuse of falsely reassuring eGFRs. We demonstrate that these tracked minimum rules can be implemented in a commonly used LIS and provide a high level of sensitivity and specificity for AKI detection. While a recent study from Leeds General Infirmary in the United Kingdom found delta checks to be effective in AKI detection, our data demonstrate that delta checks are suboptimal in our patient population. One factor that may substantially limit the efficacy of delta checks in our patients is the frequency that creatinine is tested. Creatinine elevations in our patients are indicative of AKI but remain within the reference range. Work is currently under way to evaluate the clinical impacts of our flagging rule.

### Rule Selection and Implementation

After reviewing the simulated performance of various rules, we implemented flagging based on tracked minimums at our institution. We stratified flagging thresholds on whether the baseline creatinine was less than or equal to 2.0 mg/dL. We decided to use the following thresholds given our goals, data, and the desire to parallel established criteria: we flagged creatinine results increased by 0.3 mg/dL or more over baseline (lesser of tracked minimum or prior result) when the baseline was less than or equal to 2.0 mg/dL and flagged results increased by 0.5 mg/dL when the baseline was greater than 2.0 mg/dL. We selected these specific flagging thresholds based on a combination of simulation results and the qualitative judgment of nephrologists at our hospital regarding the most effective strategy to alert clinicians to those creatinine results that are clinically concerning and most at risk for becoming overlooked.

**Figure 4** shows a screenshot of a flagged result displayed in our hospital’s electronic medical record. We decided to include the calculated eGFR in the comment provided with each flagged creatinine result since some clinicians may find utility of this value as the upper bound of the true GFR. We had considered strategies to exclude patients receiving dialysis from this flagging rule, since creatinine is expected to vary widely in these patients. However, because our LIS has no direct information regarding which patients are receiving dialysis, we determined that this would be impractical. In addition, because patients receiving dialysis would generally be closely monitored by a nephrologist and have well-understood renal status, we did not anticipate the flags causing confusion or harm in these patients.

<table>
<thead>
<tr>
<th>Data Set</th>
<th>Points Included</th>
<th>AKI Level</th>
<th>Sensitivity at 95% Specificity, Median (95% CI)</th>
<th>Area Under the ROC Curve (95% CI)</th>
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<tbody>
<tr>
<td></td>
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<td>Delta Check</td>
<td>Tracked Minimum</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>All</td>
<td>Risk</td>
<td>0.67 (0.66-0.69)</td>
<td>0.87 (0.85-0.87)</td>
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<tr>
<td>A</td>
<td>BL Cr ≤2 mg/dL</td>
<td>Failure</td>
<td>0.81 (0.78-0.84)</td>
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<td>BL Cr &gt;2 mg/dL</td>
<td>Risk</td>
<td>0.63 (0.61-0.65)</td>
<td>0.90 (0.9-0.9)</td>
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<tr>
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<td>0.84 (0.82-0.87)</td>
<td>0.94 (0.92-0.94)</td>
</tr>
<tr>
<td>B</td>
<td>BL Cr ≤2 mg/dL</td>
<td>Failure</td>
<td>0.97 (0.87-1)</td>
<td>0.97 (0.83-0.97)</td>
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<tr>
<td>B</td>
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AKI, acute kidney injury; AUC, area under the curve; BL, baseline (prior result for delta check–based rules or the lesser of the prior result and the tracked minimum for tracked minimum with delta check–based rules); Cr, creatinine; ROC, receiver operating characteristic.

*In reference to upon specified RIFLE criteria (creatinine increase of 1.5-fold = risk; 3-fold = failure).*

Likewise, in detecting first-time patients with AKI (data set B), at a 95% specificity, tracked minimum rules are 94% sensitive compared with the 84% sensitivity observed for delta checks.

### Table 1

Comparison of Delta Checks to Track Minimum Checks

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to optimize detection of clinically concerning creatinine elevations in typical inpatients at our hospital. Because creatinine testing is not necessarily performed at regular and precise time intervals, we felt that strict 48-hour baselines could miss acute creatinine elevations, even when these occur over less than 48 hours. For example, not all patients have creatinine measurements spaced 48 hours apart, and thus the specific rise over 48 hours is often unknown; using a longer time period improves the sensitivity of the flagging rules. Likewise, we felt that 7 days did not coincide well with the time course of creatinine increases seen during typical inpatient hospitalizations (which are most often shorter than 7 days).

Our decision to use the 72-hour timeframe may highlight a broader consideration related to laboratory clinical decision support. Appropriate clinical practice requires clinicians to make patient-specific clinical judgments for when to order tests or perform other diagnostic evaluations. Thus, unlike in a controlled research setting, in routine clinical practice, some patients will inevitably be “missing” results (eg, creatinine testing at specified time points) that might otherwise be applied to a particular decision support rule. Accordingly, rule developers should consider adding flexibility into decision support rules to accommodate the more limited data that may be available on certain patients. Likewise, utilization management strategies must strike the proper balance between appropriate controls on overutilization and the potential loss of clinically relevant information that could result from underutilization (eg, not checking creatinine frequently enough to identify an important trend).

A limitation of our study is that it is focused on a single hospital. While we expect our patient population to be representative of those at other large tertiary care general hospitals in the United States, results may vary between institutions. In addition, hospitals using other methods for creatinine measurement may find that method imprecision affects specific results. Likewise, the strategy used to calculate baseline creatinine values has been shown to substantially affect AKI identification. We chose to calculate baseline creatinine values according to the tracked minimum with delta checks rules, largely because these rules were clinically reasonable and could be implemented within our LIS. As LIS advance, it may become possible to implement flagging rules using more sophisticated strategies, which may potentially enhance the clinical utility of the flags. Future work may also be useful to evaluate more sophisticated flagging strategies, such as ones that incorporate creatinine results long before admission into patient baselines.

Our hospital’s upper reference limit for creatinine (1.5 mg/dL) is higher than the upper limit of normal used at some other hospital laboratories. Laboratories with more restrictive creatinine reference ranges might expect fewer AKI results to fall within the reference range. Nonetheless, as shown in Figure 3, individual creatinine results serve as a relatively poor indicator of AKI, and there is no creatinine cutoff that is both optimally sensitive and specific for AKI. Thus, altering the reference range will not fundamentally address the limitations of standard creatinine reporting.

This study highlights a broader issue regarding reference ranges. For a number of laboratory tests, “normal” values depend on multiple, patient-specific factors. With some analytes, such as creatinine and most tumor markers, baseline values are among the key interpretive factors. For example, a prothrombin time within the reference range would be concerning in a patient taking warfarin. However, current practice typically involves development of reference ranges based solely on the use of a normal reference population. It may be more optimal to stratify reference ranges for certain tests in a more granular fashion, taking into account the clinical status of the patient. For example, a strategy has recently been proposed to define distinct reference ranges based on genomic data. Increased use of structured clinical data may also facilitate such efforts to stratify reference ranges.
Our study also highlights the need for LIS manufacturers to develop more comprehensive calculation functionalities. Had our LIS been capable of calculating true minimum results, actual creatinine-based RIFLE, AKIN, or KDIGO creatinine criteria could have been used in place of the tracked minimum. Future advances in LIS and electronic health record infrastructure and the improved use of structured data may permit the implementation of improved flagging rules that could exclude patients receiving dialysis or take into account other clinical factors.

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References


