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Alerting to acute kidney injury - Challenges, benefits, and strategies

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A B S T R A C T

Acute Kidney Injury (AKI) is a complex heterogeneous syndrome that often can go unrecognized and is encountered in multiple clinical settings. One strategy for proactive identification of AKI has been through electronic alerts (e-alerts) to improve clinical outcomes. The two traditional criteria for AKI diagnosis and staging have been urinary output and serum creatinine. The latter has dominated in aiding identification and prediction of AKI by alert models. While creatinine can provide information to estimate glomerular filtration rate, the utility to depict real-time change in rapidly declining kidney function is paradoxical. Alerts for AKI have recently been popularized by several studies in the UK showcasing the various use cases for detection and management by simply relying on creatinine changes. Predictive models for real-time alerting to AKI have also gone beyond simple delta checks of creatinine as reviewed here, and hold promise to leverage data contained beyond the laboratory domain. However, laboratory data still remains vital to e-alerts in AKI. Here, we highlight a select number of approaches for real-time alerting to AKI built on traditional consensus definitions, evaluate impact on clinical outcomes from e-alerts, and offer critiques on new and expanded definitions of AKI.

1. Introduction

Acute Kidney Injury (AKI) is a complex heterogeneous syndrome that often can go unrecognized in its early stages. A sudden deterioration in kidney function and structure that is not managed or proactively detected can lead to unfavorable outcomes. These include increased length of stay, on average more than 3.5 days compared to those that do not incur AKI, which further leads to increased likelihood of chronic kidney disease (CKD) and/or death. Adding to the overall burden are also financial considerations in patients that incur AKI [1]. The heterogeneity of AKI enables this syndrome to be encountered in multiple clinical settings, including cancer, sepsis, surgery, critical illness and among others, with use of nephrotoxic medications. However, in many scenarios, AKI is amenable to prevention, early detection and treatment [2–6].

One strategy for proactive identification of AKI has been through e-alerts, which in essence can be thought of as a clinical decision support system (CDSS) that works off databases, such as from the laboratory information system (LIS). A CDSS with meaningful output to help improve health and healthcare decisions and outcomes has been said to deliver the "5 right" elements: The right information about the right patient, in the right format, delivered through the right channel, and at the right point in the workflow [7,8]. From this notion, e-alerts can be valuable as hospital admissions generate vast volumes of laboratory data, that enable opportunities to overlook

Abbreviations: AKI, Acute Kidney Injury; CDSS, Clinical Decision Support System; ADQI, Acute Dialysis Quality Initiative; sCr, serum creatinine; UO, urine output.

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key trends. While data is available from multiple sources such as the pharmacy information systems, CDSS based on predictive models and algorithms for AKI have consistently indicated the importance of laboratory data as having larger weight and impact on overall effectiveness in detecting or anticipating AKI [4,6,9]. This is in part due to the continuous and dynamic nature (time and disease course dependent state) of some laboratory data as opposed to discrete or static data (such as sex and race) [4]. Static data can also be valuable as they may reflect known risk factors for AKI, categorized as exposures and susceptibilities. The latter are generally shared risk factors such as certain demographics and genetic predispositions, whereas exposures include specific patient-related risk factors such as sepsis, cardiac surgery, radiocontrast agents, etc. However, the overall impact of a CDSS or e-alerts for AKI is more likely to be dependent on the relevant laboratory tests [4,6] and frequency of repeat testing [1,10]. Trending laboratory data or identifying meaningful changes according AKI defintions (Table 1) is often helpful. However with information overload in a data centric era, the ease of inattentiveness without e-alerts might result in failure to act promptly before or during treatment [11]. Furthermore, enabling physicians to harness the siloed information from multiple databases (e.g. LIS, pharmacy information system, etc) to aid in integrated decision-making within a favorable time frame is paramount for patient care. Such opportunities can potentially be provided through e-alerts or more involved and complex CDSS that are coupled with care bundles [12].

There are however several limitations with e-alerts and complex CDSS designed for AKI as summarized in Table 2. These include alert fatigue, as reviewed or discussed at lengths elsewhere [13,14], increased inattention to non-alerted patients due to increased reliance on the alert system and unintended consequences when alerting overrides provider's judgment. There are also certain limitations of the alert system, such as potential for false positive alerts, difficulty of direct integration of alerts and potential lack of generalizability of alerts to different care settings [15]. Other challenging factors to consider may include setup and maintenance cost considerations when current evidence is lacking for improving clinical outcomes [16,17], passive or informational nature of some alerts without specific indications for intervention or therapy, and among others, unclear implications of cost-benefit analysis on improving the overall financial burden on the healthcare system due to AKI.

However, e-alerts can be beneficial in some aspects (Table 2) as discussed further in this review and previously [18]. Often alerts may only raise the possibility of the syndrome being present and leave the subsequent management and further actions to the care providers. Even passive reminder alerts have provided compelling evidence in other areas of medicine that has enabled increased delivery of optimal and preventative care. Examples include enabling appropriate laboratory test utilization of cardiac markers [19], improving process of care in medication safety [20], and preventative care reminders for pneumococcal or influenza vaccination [21]. Preventative measures in AKI may require use of shared repositories or databases with relevant laboratory results between hospitals and external laboratories. This can be challenging to set up, but could be useful in establishing an appropriate baseline measure. However, with the growth of regional LIS and shared repositories, continued advances in interoperability of healthcare data, and harmonization efforts of laboratory tests, the thought of a balanced approach to alerting care providers about AKI appears more feasible now than ever.

1.1. The universal definition of AKI

Detection of AKI requires defining the syndrome in a manner that is globally consistent and adopted easily. Historically there has been a wide variation on what constitutes AKI, which made it difficult to compare results across studies, validate new biomarkers, corroborate the impact of e-alerts and overall hampered progress in understanding the syndrome of AKI. Thus, an important progress that has been made are guidelines for defining and staging AKI [22], which some have argued [3,23,24] are not perfect, but nonetheless provide a groundwork for acquiring new knowledge and validating the impact of e-alerts.

The universal adoption of AKI definition as outlined by Kidney Disease Improving Global Outcomes (KDIGO) 2012 guideline, has been important for enabling consistent and familiar recognition of the syndrome by all care providers across institutions (Table 1). This is important for not only potentially predicting and preventing further complications, but also knowing the severity of the disease course. Currently the indications for AKI are based on two diagnostic criteria: 1) Reduction in urinary output (UO) and/or 2) Increase in serum creatinine (sCr) as compared to an established baseline. Either of these criteria can be used to define the 3 stages of AKI (Table 1). Both are regarded as functional markers that have various limitations, but combined together, enable the rule-in of more AKI

Table 1
Universal Definition of AKI.

KDIGO Definition 2012			ADQI Expanded Criteria 2019	
Stage	Serum Creatinine	Urine Output	Stage	Biomarker Status
	-	-	1S	Positive
1	• 1.5x to 1.9x baseline value OR • Delta increase $\geq$ 26.5 μmol/L (0.3 mg/dL)	• $<$ 0.5 mL/kg/hour (6 to 12 hours)	1A 1B	Negative Positive
2	• 2.0x to 2.9x baseline	• $<$ 0.5 mL/kg/hour ($\geq$ 12 hours)	2A 2B	Negative Positive
3	• 3.0x baseline OR • Delta increase $\geq$ 353.6 μmol/L (4.0 mg/dL) OR • Initiation of Kidney Replacement Therapy OR • eGFR $<$ 35 mL/minute/1.73m^2 if $<$18 years of age	• $<$ 0.5 mL/kg/hour ($\geq$ 24 hours) OR • Anuria for $\geq$ 12 hours	3A 3B	Negative Positive

Table 2
Benefits and Challenges with e-alerts for AKI.

Benefits	Challenges
● Enables early detection and opportunities for intervention when uptake and response to alerts is timely. ● Some alerts systems (e.g. relying on simple sCr changes) are unsophisticated and easily deployable than others. ● Complex alert models enable physicians to harness siloed information from multiple databases such as lab and pharmacy for integrated decision making. ● Alerts enables data collection and surveillance of AKI, allowing analysis of alert triggers for the heterogeneous population of AKI. ● Potential for use as a quality metric when alert triggers are known to improve clinical outcomes or show impact on patient management.	● Alert fatigue (increased with lack of specificity or false positives). ● Ensuring assay precision within acceptable limits (i.e. $\leq$ 3.4%). ● Appropriate or necessary baseline measurement of sCr may not be available. ● Ensuring applicability by location specific delivery (e.g. consider dialysis or pregnancy related changes). ● Setup and/or maintenance cost in terms of human capital and other resources. ● Variable approaches to trigger e-alert, leading to lack of standardization in design of algorithms or models. ● Transferability of workflow design and processes across institutions (e.g. due to interoperability or resources). ● Dependence on retesting intervals or frequency of testing necessary biomarkers of interest. ● Some alert models are only informational. Unless tied to specific therapies or subsequent actionable items, this pasive nature may have little or no impact on patient care. ● Unproven clinical benefits or outcome measures in the US when using the KIDGO definition of AKI. ● Financial implications and return on investment after e-alert implementations remains unclear. ● Monitoring dismiss rates or acknowledgement rates may not be feasible with all approaches; However this information could be vital in understanding uptake and improving outcome.

incidents than any one criterion alone [25,26]. In practical terms, the UO criteria enable the detection of oliguria or anuria, whereas the sCr criteria enable the detection of azotemia.

While KIDGO 2012 Criteria for AKI is the most recent guideline to be recognized globally and applied for triggering e-alerts, it should be noted that RIFLE (risk, injury, failure, loss, and end stage renal disease) was the first consensus definition developed by the Acute Quality Dialysis Initiative (AQDI) for classifying acute insult to the kidney by stage and outcome. The RIFLE scheme made use of changes in sCr or estimated glomerular filtration rate (eGFR) for the purpose of classifying the syndrome and made use of the term acute renal failure [27]. In terms of appropriate terminology, the 2019 KDIGO Conference Report has officially recommended against the use of the term “renal”, stemming from the notion that patients and lay public did not widely recognize the term as opposed to “kidney”. The latter was less dependent upon health literacy [28]. To avoid the use of the term ‘renal failure’ and the use of eGFR from the AKI diagnostic criteria (for reasons mentioned in the following section), the RIFLE classification was updated to the Acute Kidney Injury Network (AKIN) scheme [29]. AKIN was subsequently incorporated into KDIGO guidelines published in 2012.

1.1.1. Role of eGFR in AKI

Creatinine based eGFR has traditionally been considered as an overall best index of functioning nephrons and is essential in staging CKD. This functional asssement of the kidney, derived from measured sCr attempts to correct, with some error, the variability in sCr seen across age, sex and muscle mass in the steady state [30,31]. eGFR does not correct for variability of sCr in non-steady state conditions that can present with abrupt decline in kidney function or be amplified further by multiple and concomitant AKI risk exposures (e.g., drugs and surgery). Following a single episode of AKI, one would expect that a true GFR will have an abrupt decline, leading to slow rise in sCr over hours to days before a new steady state is reached. Therefore, eGFR will lag and take days before reflecting the true GFR, which is not easily assessed [32]. Consequently, in the context of hospital acquired AKI with rising sCr, eGFR changes are inaccurate and can overestimate true GFR which can be dangerous, given that eGFR values are used for drug dosing [33].

However, the use of eGFR to assess AKI had been indicated initially by the RIFLE criteria for AKI [27], but studies employing simple and complex CDSS for real time alerts have not relied on eGFR for assessing AKI. This is for good reason as these equations propagate not only measurement error, but amplify clearance rate with large errors often leading to overestimation in non-steady state conditions [30,34–37]. The inherent overestimation is evident for some equations more than others, such as with the modification of diet in renal disease (MDRD) equation where reporting numerical values above >60 mL/min/1.73 m^2 is not recommended [30,38]. Given the lack of steady state, notably in oliguric patients with AKI and in general for those that are critically ill, true GFR can be expected to be low. Specifically, several equations including MDRD or CKD epidemiology collaboration (CKD-Epi) based equations all significantly overestimate true GFR in hospital acquired AKI patients. The discrepancy may decline with increasing length of hospital stay [34], which may be attributable to reaching a new steady state that allows for more accurate estimation. Given these limitations, KDIGO guideline for AKI does not make use of eGFR for staging in adults, but does indicate that eGFR <35 mL/min/1.73 m^2 as stage 3 AKI in pediatrics (<18 years of age) [22].

The inclusion of race specific variables in eGFR based calculations has also added to the eGFR variability. Elimination of the race

variable can impact disease detection and improved drug dosing [39], which in the broader sense could affect the risk factors (CKD and nephrotoxicity) for AKI. Consequently, a new recommendation from the National Kidney Foundation (NKF) and American Society of Nephrology (ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease has recommended implementation of a new equation without the race modifier [40]. While this new proposed equation eliminates some variability, it still does not negate the large uncertainty inherent to eGFR calculations [35] and inapplicability in non-steady state conditions such as hospital acquired AKI.

While direct assessment of eGFR in non-steady state is of little value in AKI, in steady-state, eGFR status (e.g. <60 or >60 mL/mn/1.73 m^2) [41] and decline rates [42] may help inform risk status for screening AKI. For example, risk factors such as diabetes are common and indicate significant risk of AKI in both hospitals acquired AKI and community acquired AKI [43,44]. However active screening for AKI in diabetic patients has not been undertaken, despite higher rates of AKI in patients with diabetes. Notably diabetics who have not progressed to CKD, are 4.7 times more likely to endure an AKI incident than patients without diabetes [42]. For example, Hapca et al. recently analyzed the steepness of the slopes in eGFR in diabetics before AKI, and found that the slope (i.e., the rate of decline) was faster than those without diabetes. And in those without diabetes, the slopes of the trending eGFR values also became steeper after AKI [42]. This finding supports the epidemiological finding based on e-alerts for AKI which showed patients with community acquired AKI sustain more severe AKI than patients with hospital acquired AKI, despite similar risk factors being prevalent in both types of AKI [45]. However, eGFR decline rates based on slope have not been incorporated for further risk characterization or screening and alerting to AKI.

Recognizing the limitation of eGFR lagging behind the true GFR in hospital acquired AKI, an alternative method for use of eGFR to assess AKI include the so called kinetic GFR. This method considers at least two sCr measurements, with one being a steady state sCr (typically obtained before an exposure or an event such as surgery). The underlying principle behind the kinetic GFR method is evaluation of creatinine clearance between two time points, approximating the use of an average sCr change with respect to time and urine output [36,46]. Thus, the kinetic GFR enables the consideration for both azotemia (via sCr) and oliguria (via UO), which together could enable enhanced prediction of AKI in critically ill patients. Similar to kinetic GFR, other related methods include short duration creatinine clearance-based approaches, including the 4hr creatinine clearance [47]. This involves a 4hr urine collection period rather than the standard 24hr collection period in critically ill patients. Evaluating a decrease in 4hr creatinine clearance has been shown to be valuable in identifying AKI when sCr increase was not evident. The value and impact of short duration creatinine clearance is also dependent on the frequency of measurements and the threshold considered as a significant change between the clearance rates. Therefore, comparison to baseline creatinine clearance is still required to identify a declining kidney function, although low creatinine clearance values on entry to ICU could be used for risk stratification of high-risk individuals of AKI [47]. While the performance and indications of the kinetic GFR or short duration creatinine clearance are reportedly better than current steady-state equations as exemplified in small studies [46–48], the adaptation of this model to larger prospective studies for validation remains limited for now. Furthermore, no studies to date have incorporated this approach as part of an automated real-time e-alerts to aid physicians despite some popularity.

2. Urinary output (UO) for diagnosing AKI

In general, lower rates of UO are associated with increased severity of AKI. Oliguria is commonly encountered in critically ill patients and is a sensitive marker of kidney dysfunction [26,49]. While studies have indicated that a change in urine flow rate can be detected earlier with frequent observations than measuring sCr, the UO criteria may only have value in hospitalized patients. However, this diagnostic criterion based on UO is sometimes unreported in studies [44,50], and has wide variation and inconsistency on how one monitors and measures UO [22,51,52]. For example, hourly monitoring performed visually with manual recording can be time consuming for nurses, who may check only when the collection bags need emptying, for example at 6 h [49,51]. Furthermore, it remains unclear how diuretics and other drugs (e.g., angiotensin-converting enzyme inhibitors) affect fluid balance and add to the UO variability [22]. While clinical laboratories are not typically involved in monitoring or measuring UO, the reduction in UO is an important criterion for diagnosis of AKI, and neglecting this marker could potentially delay AKI diagnosis or, even worse, miss it [50]. When there is UO, subsequent biochemical [53–55] or microscopic analysis [56,57] can be performed. However, non-oliguric AKI does not necessarily correlate with renal dysfunction as factors such as diuretics, vasodilators, or aggressive fluid resuscitation can contribute to urine flow [54,58]. Urinary biomarkers and microscopic analysis (with urine dipstick) are therefore valuable but may be limited by concentration effects. It is also important to note that UO also depends on the type of injury (pre-kidney, post-kidney or intrinsic-kidney injury). Notably that pre-kidney injury is associated with oliguria, whereas post-kidney injury is often a result of anuria, and the intrinsic kidney injury being variable [59].

In the context of alerts and CDSS to predict AKI, few studies have prospectively implemented the UO criteria as part of the overall algorithm or as the only entity. For example, a recent approach published by Tomasev et al. using artificial intelligence (AI) to predict AKI [6] with high probability neglected UO. Instead of relying on UO, the AI model-based approach relied on laboratory tests as input parameters, where sCr "was required to label AKI as a ground truth". The authors noted that UO was not recorded digitally at the majority of the sites [6], suggesting that digitization of vital health care information is still not prevalent. Other studies utilizing predictive models have similarly neglected UO for aforementioned reasons while opting for other discrete laboratory parameters beyond sCr (see section on 'Beyond sCr, Predictive Models and Artificial Intelligence') [4]. However, this challenge of preserving digitization and automated detection alerts for AKI by incorporating UO is being tackled and continues to reaffirm the importance of this criterion with potential for improved detection of AKI in the future [50,59].

3. Serum creatinine (sCR) for diagnosing AKI

The sCr criteria for evaluating AKI by e-ealerts is foundational [5,11,60] and remains the most popular approach used with real time detection and prediction models [4,6,61]. This likely stems from sCr having long been subject to digitization, despite sCr being a delayed marker [62] and only recently being subject to assay standardization [63]. Despite the standardization efforts with the availability of the standard reference material 967 (SRM 967) from the National Institute of Standards and Technology (NIST), notable variations between creatine methods are still present. Specifically with Jaffe-based methods where the major contributing factor being lack of specificity, enabling higher imprecision (i.e., coefficient of variation $\geq$4%) than allowed [63]. This would affect alerting to AKI with sCr changes since assay imprecision is of utmost importance for identification of sCr changes. Other limitations of sCr have been highlighted elsewhere [31,32,53,62] and will not be discussed here.

Recently, new guidelines and recommendations for AKI diagnosis have been assembled and expanded (as discussed in section "New and Evolving Definitions of AKI") [53,64]. However, the majority of the studies to predict and/or alert a likely AKI event have come to rely on the universal definition of AKI as outlined by the KDIGO Guidelines published in 2012 [2,22]. Based on this universal definition (Table 1), the laboratory-based measurement of sCr has been positioned as the current marker for predictive and detective alert models. Such alert algorithms based on sCr have led to proactive measures to recognize AKI, improve management and raise awareness about medication contraindicated in kidney failure [9,65].

The increase in sCr criteria has been made evidently important with e-alerts given that significant changes indicative of AKI can occur even when sCr results are within the reference intervals [33]. This is also rationalized by the index of individuality (II), which is the ratio of biological variation of sCr within individuals relative to the biological variation between individuals [66,67]. The II is relatively low for sCr, suggesting marked individuality and therefore implicating the baseline sCr as more important than the population-based reference interval for interpreting a significant sCr change [66,67], as required for AKI.

Although expected sCr changes indicative of AKI evaluation is defined by KDIGO (Table 1), e-alert schemes relying on sCr change alone may not capture all AKI incidents. This is due to the limited specificity of sCr [31], assay interferences [68], and assay imprecision [63,69], which may lead to alert fatigue when reliability of the assay and consequent alerts dependent on sCr changes increase the likelihood of false alarms. Other limitations with e-alerts include establishing appropriate baseline sCr as discussed below.

3.1. Establishing baseline sCr

Given that sCr has a marked index of individuality, baseline sCr is important for determining a change in sCr that is indicative AKI vs a change that is within biological variation. From our survey of literature, there are various approaches to determining baseline value of sCr. In summary, there appears to be 7 general approaches [70–74], as outlined below, and studies have employed one or more of these in establishing an approximate indication of baseline sCr.

1. Imputation of sCr from a 4 variable MDRD based eGFR equation, with assumption that the patient had at least a filtering capacity equal to 75 mL/min/1.73 m^2.
2. Use of admission sCr
3. The lowest sCr value available (e.g., within 7 days)
4. The median sCr values available (e.g., with multiple sCr values spanning more than 7–365 days)
5. Using a reference population estimate of sCr based on age and gender
6. Mean sCr from outpatient visits, spanning prior 7–365 days
7. Using clinical laboratorians such as a clinical chemist to determine the most appropriate baseline sCr

The first approach of imputing baseline sCr with the assumption of eGFR being 75 mL/min/1.73 m^2 is largely inaccurate as it may misclassify stage and overestimates the incidences [70]. This is given, as eGFR is an ideal estimation only when the patients are in steady state (see discussion above on 'Role of eGFR in AKI'). Unfortunately, even advanced models of AKI alerts systems relying on neural networks have been built with this limitation [6]. Relying solely on admission sCr (Approach 2), may be the only option, but may underestimate AKI incidence [70]. Approaches 3 and 4 have been used in combination as part of a national alert algorithm in the UK to maximize sensitivity [71]. Approach 5 is unique and perhaps the most challenging, but is more accurate than Approach 1, when there is no sCr available on admission [72]. Specifically, approach 5 requires a large set of outpatients sCr data (37 000 used by study authors) to generate medians for each year of age by gender. These medians can then be subjected to regression modeling that can be used to estimate a baseline sCr. The authors in their study proved this to be generally more accurate than Approach 1 [72]. Approach 6 relies on previously present sCr obtained during outpatient visits (7–365 days) and has been adjudicated by nephrologists to be the most representative baseline sCr [74]. This approach may lead to lower rates of AKI misclassification [74], reflecting more of a steady-state condition to base subsequent changes in sCr at hospital admission as significant.

The last approach (Approach 7) is to have a manual review of sCr and invoke a clinical laboratory personnel such as a clinical chemist to select the most appropriate sCr. This approach would likely delay delivery of alerts and may not be efficient in high volume laboratories. However, in a study by Selby et al., clinical chemists were the responsible personnel for selection of the appropriate baseline sCr when reverse calculation of eGFR (Approach 1) had to be considered [75]. Other studies similarly invoked manual review by clinical biochemists (analogous to clinical chemists in Canada or US), simply after a delta check that was triggered by an increase in sCr by 26 μmol/L or 50% increase from baseline [10]. Although no imputations were involved for baseline sCr estimation, clinical biochemists appended appropriate comments to results if AKIN criteria were met [76]. Flynn et al. used simple sCr delta checks in their

study, but the responsible clinical biochemist's role involved (twice daily) identifying sCr results >300 μmol/L retrospectively, which were phoned to the necessary care provider [31].

These e-alerts involving clinical chemists for manual interventions are of course not real-time and depending on when the notification occurs can be considered 'near real-time' alerts. The advantage of manual review of baseline sCr is that pathological changes in sCr can be accounted for (e.g., pregnancy), whereas the automated method may neglect such changes without additional configurations or inputs [10]. Overall, the reported benefit of this approach was little cost, with unclear or unproven clinical benefits [10,31].

3.2. Approaches to AKI alerts with sCr - lessons learned

While studies continue to use the changes in sCr as 'ground-truth' indicators of AKI based on KDIGO 2012 criteria [22], earlier study results [11] when sCr assay was less standardized and more imprecise had limited immediate impacts. Furthermore, earlier studies for real-time AKI detection employed changes in sCr that were different from KDIGO 2012 AKI criteria [11]. However, such studies were still valuable and should be recognized for the approach taken, lessons learned, and the hypothesized improvement in patient care that could be realized. For example, an early study by Rind et al. evaluated the effectiveness of real-time computerized alerts by electronic mail to physicians about an increase in sCr by 50% or more (up to 177 μmol/L) for hospitalized patients on various nephrotoxins. Surveying the physicians showed that alerts were reportedly "annoying" to 28% of the physicians whereas 44% found it helpful. While the e-alerts lead to close monitoring of patients receiving nephrotoxic medications, there was no significant impact on length of stay or mortality. However, alerts had some impact on patient care by shortening the time to medication adjustment and enabling risk reduction of subsequent serious kidney impairment by 55% [11]. Unfortunately, the assay type used (Jaffe vs Enzymatic) for sCr is not made evident, which is important given that endogenous materials (e.g. glucose and acetoacetate) and medication are known to interfere with Jaffe methods as well as exhibit high levels of imprecision relative to current standards [63,68,69].

Another AKI prospective study evaluated patients with ≥75% rise in sCr from its previous value, which could have been from any time point from the same day to years back [5]. While this criterion was only used to provide a real-time alert to those patients outside of the Kidney Ward and ICU and not for staging, the effectiveness of such a simple rule brought to light some complications. First, 23% of the alerts were notable in hemodialysis patients with end-stage kidney disease, where a sCr difference between dialysis sessions would generate false alerts [5]. Thus, a question of concern is: what are the impacts of such alerts on dialysis units and are the care providers being notified of expected changes in sCr? Clearly this would enable user desensitization and build alert fatigue (Table 2). To minimize or eliminate such false alarms that can erode actual concern for patient safety, one could enable location-based alerting, but implementation and feasibility by LIS/HIS or other mode of communications may prove challenging. An alternate strategy for reducing alerts in dialysis patients may entail invoking eGFR results as a disqualifier for AKI alert triggers when eGFR values have consistently been indicative of kidney failure (e.g., stage IV CKD, <15 mL/min/1.73 m^2) [77]. However, this latter approach may require other modalities for detecting AKI in acute kidney disease (AKD) and CKD patients.

The first prospective study to evaluate real-time AKI alert based on a consensus definition (rising creatinine and/or UO) was a single center study from Belgium using the RIFLE criteria [60]. To evaluate the effects of such a real-time alert system on therapeutic intervention or progression of AKI, alerts were notified to the intensivists by way of an alpha numeric alert message sent to their cordless telephone, which would display an AKI alert message upon answering the phone. This so-called "AKI Sniffer" system showcased the relevance of an alert system as it significantly increased the timeliness of therapeutic interventions. Consequently, this study was a landmark as it showed that the interventions without delay, improved overall kidney function as evident from a decrease in RIFLE classification. Although not a randomized trial, the beneficial effects of alerts, even if eliciting borderline improvement in the short term, was evident when the alerts were subsequently halted. However, some limitations of this study included imputing baseline sCr (i.e. reverse calculation from eGFR assuming baseline eGFR is 75 mL/min/1.73 m^2) when previous values were not available, lack of digitization of UO, and not clearly distinguishing percentage of the alerts based on sCr vs UO, with the latter being quite variable and manually recorded [60]. Given the variability and lack of digitization of UO, other prospective studies have attempted to focus on purely sCr rise [6,75,78,79].

3.2.1. UK based AKI alert systems

With various approaches for e-alerts in kidney injury, perhaps the most popular and active alert systems are those in the UK, where implementation is mandatory (for example in England and Wales) in secondary care. These alert systems are based on KDIGO 2012 AKI Criteria (with slight modifications) and are employed at a national level to identify AKI in the community and hospital setting through a centralized repository [71,73,79,80]. Such a database allows the Laboratory Information Management System (LIMS) to evaluate changes in real time by comparing measured sCr value (called C1) to previous baseline results in the last 7 days or last 365 days (called RV1 and RV2). Specifically, if previous results within the last year are available, the algorithm evaluates the previous result from the last 7 days and picks the lowest sCr value as baseline reference index value (RV1). If previous results are available from 8 to 365 days, a median sCr value is established as the baseline sCr index (RV2). If both RV1 and RV2 are available, then the ratios are compared to determine if using either baseline value is ≥ 1.5x, which by the KIDGO definition (Table 1) is AKI Stage 1. Further evaluations are sequentially performed if the AKI Stage 2 and Stage 3 criteria for sCr increase (i.e., 2x and 3x increase from baseline) are met. Evident from the algorithmic approach, but not from the KDIGO Definition for staging (Table 1) is also including a check to determine if there is an increase by 3 times the upper limit of the reference interval (ULRI) after meeting the criteria of 1.5x increase from baseline to identify Stage 3 AKI [71]. This step may elicit a sensitivity bias compared to other studies that do not employ this additional rule. For example, 3 times the ULRI in the corresponding author's lab is 330 μmol/L (males) and 294 μmol/L (females), well below the 353.6 μmol/L threshold deemed Stage 3 AKI by KDIGO (Table 1). Although $^1/_3$ of this value is likely to approach the male ULRI for sCr in most

labs, the reason for this step is unclear. If sex specific reference intervals are used, this step could also lead to more classification of Stage 3 AKI in females, who are more susceptible to AKI [22].

Beyond the algorithm for AKI detection, a consistent nationwide alert system seems like a challenge in North America and the studies published from the UK have generally shown to be beneficial from a detection and alerting standpoint [43,65,73,79–81]. Some studies as discussed below have also reported improved clinical outcomes [65,80,81].

3.2.1.1. Impact on primary care. AKI is also commonly encountered by non-specialized healthcare providers and given the lack of association with any specific symptoms; the syndrome of AKI enables evasion of early detection [81]. The popularized UK alert system based on modified KDIGO rules [71], has been extended to primary care in the UK, with the goal to manage community acquired AKI and evaluate impact on patient management and clinical outcome measures [80,81].

An investigation by Barton et al. found that outcomes such as mortality improved significantly after implementing the e-alert system discussed above. In addition, there was also a reduction in the length of stay. Dialysis patients were excluded from the analysis. However, it should be noted that in addition to the e-alerts, there was special handling of AKI stage 2 and 3 by phoning the relevant care provider. After implementing the e-alerts, it was found that hospital admissions increased, a high proportion of patients had sCr repeated within 14 days, and overall, there was a shorter time to hospital admission. Together this enabled the care to be more proactive [81]. While 14 days seems like an appropriate retesting interval for sCr, recommendation from a large cohort-based study found 7 days for repeat sCr as an appropriate response to e-alert from primary care [82]. Subsequently, a study by Aiyegbusi et al. showed that primary care providers were more likely to be responding to e-alerts by requesting repeat sCr within 7 days. Specifically, Aiyegbusi et al. analyzed e-alerts for AKI in primary care retrospectively for a period of 12 months prior to e-alert implementation and compared the results to post-implementation phase for a similar length of period. Implementation of e-alerts was associated with earlier repeat of sCr and increased hospitalization rates within 7 days [80]. This study also suggests that primary care providers are responding earlier, which would enable community acquired AKI to be more optimally managed. Perhaps underappreciated with primary care and e-alerts is also the local education along with a best practice guideline from the "Think Kidneys" campaign [83] that has led to the improved surveillance and response to AKI alerts [80,81].

Table 3
Large Clinical Outcomes Studies Evaluating the Effect of AKI by Real-Time e-alerts Based on KDIGO definition.

Study	N	Study Design	Baseline sCr	Major findings in terms of clinical outcome or patient management
Wilson et al., 2015 [17]	2393 (AKI alert arm = 1201; Usual care, no AKI alert arm = 1192)	Single blind, parallel group randomized trial.	Lowest value within past 7 days.	There were no real benefits to implementing e-alerts in a US healthcare setting, as it did not have significant effect on primary outcomes measured (maximum sCr change, dialysis need, and death at 7 days).
Al-Jaghbeer et al., 2018 [96]	528 108 (Prealert: 181 696; Postalert: 346 412)	Multicenter, observational evaluation of data collected during Prealert vs Postalert period.	Lowest value in the past 12 months. If no baseline available, then baseline was estimated from eGFR based MDRD equation.	The authors found that a small, but sustained decrease was evident in hospital mortality, length of stay and dialysis rate for patients after postalert implementation.
Selby et al., 2019 [65]	20 179 (24 049 AKI episodes; 14 042 episodes in control period; 10 017 episodes in intervention)	Multicenter, stepped-wedge cluster randomized trial.	Lowest value in the past 7 days or a median of values from 8 to 365 days.	Authors evaluated whether a multifaceted intervention that consisted of AKI e-alerts, clinical chemists phoning stage 2 and 3 AKI, coupled with an AKI care bundle and an education program would improve delivery of care and patient outcomes. Evident was the reduction in length of stay and improvement of quality of care. No reduction in 30 day mortality was observed.
Aiyegbusi et al., 2019 [80]	3462 (Prealert: 2257) (Postalert:1205)	Observational evaluation of data collected during pre-alert vs post-alert study.	Lowest value in the past 7 days or a median of values from 8 to 365 days.	AKI alert systems in primary care with the KDIGO modified rules led to higher rates of sCr monitoring and hospitalization rates.
Barton et al., 2020 [81]	2742 (Prealert: 991) (Postalert: 1751)	Observational evaluation of data collected during pre-alert vs post-alert study.	Lowest value in the past 7 days or a median of values from 8 to 365 days.	AKI alert systems in primary care with the KDIGO modified rules in the UK had beneficial impact on patient management and outcome (i.e., follow-up on patients, hospital length of stay and mortality rate).
Wilson et al., 2021 [16]	6030 (AKI alert arm = 3059; Usual care, no AKI alert arm = 2971)	Double blinded, multicenter, parallel, randomized controlled trial.	Lowest value within past 7 days.	There were no recognizable benefits to implementing e-alerts that were informational in nature, as it had no effect on the risk of progression of AKI, dialysis, or death. In non-teaching hospitals, alerts may even be harmful.

3.3. Clinical benefits and outcomes with AKI alerts based on sCr using KDIGO based rules

With the advent of the unifying consensus 2012 KDIGO AKI Criteria, few studies utilizing AKI alerts for real-time reporting have outlined the benefits, challenges and outcomes [9]. Table 3 provides a summary of select large scale studies focusing on the clinical outcomes and impact from implementing e-alerts based on KDIGO definitions of AKI.

The first notable randomized control trial in the US by Wilson et al. showed that there were no real benefits to implementing e-alerts for hospital acquired AKI [17]. In their study, 1201 patients were randomly assigned to an alert group and 1192 patients were assigned to the usual care group. Primary outcomes evaluated between the two groups included maximum sCr change, dialysis need, and death at 7 days following randomization. Beyond the randomized control design, the strength of the study also stems from the heterogeneous patient population with various risk factors for AKI, such as black race, malignancy and nephrotoxin exposure. This enabled the authors to assess any differential effects on various subgroups between the two arms of the trial. For example, patients within both arms who received various medications such as angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker (21%), aminoglycosides (6.1%) and intravenous contrast (6.1%) had no statistically significant difference in how they were managed in the alert group vs the usual care group. Overall, the study was able to conclude that e-alerts may not have a role in improving patient outcomes with the desired end points. And identification of AKI by e-alert does not necessarily lead to meaningful changes in patient management. Importantly, it should be noted that the definition of AKI used in this study was that based on the KDIGO (Table 1; [22]) without modification, whereas alert systems largely employed in the UK studies have used slightly modified versions as discussed above (see "UK Based AKI Alert Systems") [71]. Beyond this difference, this study however had a number of limitations including being a single center with different modes of protocol for alert notification, possibly with only one type of protocol having receipt of notification, and a one-time only page to the responsible care provider. Furthermore, education on appropriate and early response to treatment management following e-alerts may have been lacking. While randomization of the patients were present, care providers could have treated both control and "alert" arm similarly as the trial progressed. This latter limitation is also applicable to a second, but multicenter randomized trial, which was also indicative of no significant improvement in the "alert" arm [16].

In the multicenter randomized trial, similar outcome measures to the previous single center randomized trial were assessed between the alert group and usual care group. At non-teaching hospital sites, alerts appeared to do more harm, which suggests that there are likely inherent differences in implementation, practice, or operational workflow. In the context of nephrotoxic evaluation, alerts were not sent to pharmacists. Despite no proven beneficial outcome that was statistically significant, unclear from review of the study was if alerts were dismissed until kidney function recovery occurred (i.e., sCr declines and alerts no longer continue to pop-up) without acknowledgement of receipt. Thus, dismiss rates or receipt of e-alert rates over the course of the trial (per patient if multiple care providers were involved) and length of time to acknowledgement of e-alert receipts could be valuable in further assessing impact, but remains unclear from the two randomized trials [16,17]. In addition, the potential for Hawthorne Effect is also difficult to rule out in such complex randomized trial designs.

While randomized control studies have indicated negligible or nonsignificant impacts from real time alerts, observational and stepped wedge cluster randomized studies have shown otherwise [9,65] (Table 3). This may stem from differences in how AKI is defined algorithmically. As noted above, in contrast to the randomized trial conducted in the US [16,17], the UK studies employ a modified version of KDIGO (see "UK Based AKI Alert Systems") including use of median sCr baseline measurements prior to 365 days [65]. Other reasons for the differences in finding may include relying purely on e-alerts without telephoning more severe stages, and possibly the difference in informational content associated with alerts (e.g care bundles and subsequent actionable items to pursue).

Despite the differences, the study by Selby et al. [65] has illustrated that alerts reduced the length of hospital stay as found through carefully controlled multicenter study in the UK with 6-month observations before intervention and then intervening with e-alerts and care bundles. The latter included: assessing volume status, treating sepsis, reviewing medications and stopping those contributing to AKI, performing urinalysis and referral (to nephrology or critical care outreach) for AKI stage 3. In addition, an active alert system involving clinical chemists to telephone stage 2 and stage 3 AKI was part of the workflow, in contrast to a more passive and autonomous alert system as part of a pop-up [9,17].

Although a more active alert coupled with a care bundle can be argued as causative reasons for reduction in length of stay, an observational US study by Al-Jaghbeer et al. employed neither of these but observed a notably significant reduction in length of stay, simply from the passive e-alert system. Specifically, the multicenter (14 hospital-based healthcare system) study also found a significant, but subtle and sustained decrease in hospital mortality (0.8%) as well a decrease in dialysis rates (2.7%). These benefits may seem small, but if reproducible, the potential reward can be financially significant (>1.2 billion/year in savings) with more than 17000 lives saved from hospital acquired AKI [9].

3.4. Nephrotoxicity - medication or contrast induced AKI (CI-AKI)

A specific use case for e-alerts for AKI has always been with regards to nephrotoxicity [11]. For example, contrast-induced AKI (CI-AKI) is thought to be increasingly common due to the higher frequency of performed procedures requiring contrast media. Different interventions aiming at the prevention of contrast-induced AKI have been identified and therefore, an accurate and timely alert would be tremendously useful [41,84]. The study by Al-Jaghbeer et al. was also notable in that implementing e-alerts introduced the subtle, but significant effect of reducing (by 45%) intravascular radio contrast agents in patients with AKI [9]. While the effect was not significantly clear for other nephrotoxins, the reduction in CI-AKI may explain the reduced referral for nephrology consult. This large-scale study also confirms the need and intent for having AKI alerts for averting nephrotoxicity, a goal of the initial AKI-alerts systems described in the early 90s by Rind et al. [11]. Recently, Tolan et al. have also shown that intervening with e-alerts

increased the discontinuation of nephrotoxins in a smaller study of outpatients [85]. Together these studies show that e-alerts can modify physician behavior (i.e., adjust medications more rapidly).

An important aspect of CI-AKI is the utility of point of care testing (POCT) for creatinine, either serum or whole blood-based, which improves the turnaround times and workflow efficiency in radiology departments. Cost-effectiveness of such an approach has been also recognized facilitating justification for POCT creatinine use. However, significant progress in utility of POCT creatinine in these clinical settings is hampered by decreased accuracy from available methods, which is an area that warrants further evaluation and research [84,86–88]. For example, an overestimation by POCT creatinine could lead to more false positive rates of CI-AKI and consequent lengthy delays. The new 20/20 AACC AKI Criteria (discussed below) for diagnosing AKI took the bold step of identifying the contributions from analytical variation in creatinine assays, given that such variation can increase false positive rates of AKI. Creatinine methods, including POCT devices, with analytical imprecision >3.4% would not meet the minimum imprecision goals and are not recommended for the purposes of detecting possible AKI [53]. However, as more POCT devices become accepted for evaluating creatinine and subsequent derivation of eGFR for quick assessment of CI-AKI [60], imprecision and allowable error requirements [38, 53,63,69] become more relevant for ruling in kidney dysfunction. Given that most POCT devices typically have larger than ideal imprecisions, adhering to devices that meet the recommended specifications [53,63,69] would enable enhanced reliability and harmonization. POCT creatinine-based methods have also been used to derive eGFR values and were found to be comparable to GFR obtained from using plasma clearance of iohexol as the gold standard [84]. However, the comparability is still questionable given the already large errors that are inherently present in eGFR, as discussed above (see section 'Role of eGFR in AKI').

While eGFR changes are not used as part of e-alerts, an alert system to distinguish high risk patients for CI-AKI based on eGFR status (such as those with eGFR <60 mL/min/1.73 m2) may be useful. For example, in one study, an alert program was developed to notify physicians when ordering contrast-enhanced computed tomography (CT) for patients with eGFR <60 mL/min/1.73 m^2. Once patients were identified based on eGFR status, AKIN criteria were applied [41]. The informational alert recommended prophylactic measures (prehydration, post-hydration, and oral N-acetylcysteine) to ensure acknowledgement that there was a risk of CI-AKI for the patient in question. In the study, 258 adult inpatients with eGFR < 60 mL/min/1.73 m^2 were identified as undergoing contrast enhanced CT before application of the computer alert program and 205 after its application. The comparison between these two cohorts (pre- and post-alerting) showed a 2-fold higher rate of administration of prophylactic measures in patients at risk of CI-AKI. This measure also resulted in fewer hospitalized patients due to CI-AKI after implementation of the computer alert program [41].

Although much has been done to prevent and detect CI-AK, it is also important to note that some authors have questioned the real impact of contrast agents in causing AKI. It has been found that AKI after contrast agent administration has a very low occurrence rate in low-risk patients and is mostly observed in critically ill, at-risk patients. In this latter group, it is likely that other mechanisms play a considerable role in the development of AKI and the contrast agents' role may be less important than previously thought [89]. For example, the scientific re-evaluation of CI-AKI with the aim to determine whether it is a true clinical entity or just a myth has been proposed. The thought of CI-AKI being a mere myth has been supported by the lack of evidence from randomized controlled trials [90].

For medications that are excreted by the kidney, an additional improvement in evaluating nephrotoxicity induced AKI could stem from utilizing different databases, specifically, pharmacy and laboratory repositories with relevant data. Indeed, recent predictive models have capitalized on drug administration data from the pharmacy database paired with kidney function markers from the clinical laboratory database. This enables the improvement of the detection of AKI and development of logistic regressions models for continuous prediction [4].

In hospitalized children with AKI due to nephrotoxins, incorporating both informational databases for alert triggers is perhaps more vital given the differences in pharmacokinetic properties of pediatric patients. Hence, a large, quaternary pediatric institution developed a near real-time automated alerting system for rounding pharmacists who would recommend modifications to medication regimen based on alerts [91]. Specifically, alerts were triggered based on medication exposure (3 or more simultaneous nephrotoxic medications or an intravenous aminoglycoside for 3 days or longer) which would be cross checked against injury triggers. Injury triggers included sCr increase based on pediatric RIFLE criteria and/or if the patient's sCr increased by at least 26.5 μmol/L within a 48-h window. Prior to implementation of such automated alerting, pharmacists were reportedly screening for AKI in a manual fashion by reviewing patient lists and data from electronic health records. Beyond streamlining the workflow, the real benefit was developing the infrastructure for electronic surveillance of nephrotoxicity and consequent AKI [91].

Evident from our review, and highlighted elsewhere [92], there is a great potential for AKI alerts and other types of CDSS [20] to autonomously enable care providers to optimize prescription of medications that are nephrotoxic or excreted by the kidney. While potential benefits have been demonstrated throughout many research studies, practically, AKI alerts have not been implemented at many institutions. For example, in one of our institutions, there are no formal alerting systems for AKI with regards to concerns for nephrotoxicity. However, all pharmacists have a responsibility to review and monitor kidney function for their patients as a core piece of clinical review and identify relevant parameters to monitor for safety and efficacy. They review medication profiles and pay special attention to those patients receiving potentially nephrotoxic agents or where a dose adjustment may be required. The pharmacists can also use a customized LIS report that can be run to highlight patients with sCr levels that fall outside of the acceptable range. Furthermore, they can also use the LIS feature where all recent abnormal test results are listed, which can then assist in highlighting the patients at risk of AKI.

4. New and Evolving Definitions of AKI

4.1. Expanded definition of AKI from ADQI consensus meeting

The recent Acute Dialysis Quality Initiative (ADQI) Consensus statements on assessment, prediction, prevention, and management refined what constitutes AKI beyond sCr and UO. Given the low sensitivity and specificity of these functional markers, vast number of studies as highlighted by the consensus report, have implicated the potential role of various biomarkers beyond sCr and UO. What has been lacking is adoption and universal acceptance of new markers of kidney stress or injury and how such markers would fit into current definitions. Some examples of markers that have gained popularity in North America include NephroCheck (makes use of two markers: tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7), urinary neutrophil gelatinase-associated lipocalin (uNGAL) and cystatin C [55,64]. Consequently, the consensus meeting outlined an expanded criteria for staging AKI, based on the notion that novel biomarkers could be incorporated into the KDIGO 2012 AKI guidelines (Table 1). This led to redefining the stages with biomarkers, as identifying AKI at earlier time points is possible with new markers in comparison to traditional UO or sCr evaluation. This included refining KDIGO Stage 1 AKI into 3 substages and more severe KDIGO stage 2 and stage 3 AKI into two substages [64]. Specifically, Stage 1 AKI would account for new additional biomarkers and break down into AKI Stage 1S, if classical functional markers of sCr and UO were absent, but a proven novel biomarker was positive. However, if classical functional markers of sCr and UO were present, then AKI Stage 1A and AKI Stage 1B could be defined if additional new biomarkers were negative or positive, respectively (Table 1). Similarly, Stage 2 and Stage 3 AKI were further refined into substages depending on positive or negative biomarker status as part of the expanded criteria (Table 1) [64].

Given the heterogeneous syndrome of AKI, this new expanded criteria to incorporate additional biomarkers may enhance detection in a more timely manner, overcoming the limitations of delayed sCr or UO. However, it has been noted that no single biomarker may overcome all of the limitations of sCr in all settings (e.g., subclinical AKI vs acute tubular injury) [3]. Thus, it remains unclear if there is one marker that is useful in all heterogenic situations of AKI or if different biomarkers will have to suit different scenarios and exposures (e.g., nephrotoxicity vs sepsis). Nonetheless, the expanded criteria may enable more increased adoption of various biomarkers beyond the functional indicators of sCr or UO and redefine future studies. In the context of alerts, incorporating these expanded criteria for real-time alerts of AKI with biomarker inclusion await future studies to showcase how management and clinical outcomes could be improved. Despite the limitations of sCr as a delayed marker, and therefore not a depiction of real-time changes in acute kidney function [62], sCr continues to be the most commonly utilized and contributory laboratory marker in alerts models of AKI.

4.2. 20/20 AACC AKI criteria

Recently, a working group for the American Association of Clinical Chemistry (AACC) comprised of nephrologists and clinical laboratorians defined an alternate approach to staging AKI with considerations for analytical and biological variation [53]. The biological variation of sCr within individuals (CV_i) used was 4.5%, which is consistent with the median coefficient of variation (CV) found in the Biological Variation Database hosted by the European Federation of Clinical Chemistry and Laboratory Medicine [93] (confidence interval: 4.2%–5.7%). Using these values, analytical variation as calculated by the approach summarized by Callum Fraser [67] at minimum specification (defined as ¾ of CV_i) was determined to be 3.4%. Therefore, the guidance document noted that intralaboratory variability for sCr should not exceed 3.4% (assuming CV_i of 4.5%). With both biological variation and analytical imprecision in mind, a significant increase in sCr value would typically be greater than 15–18%, as determined by reference change value calculation [66,67]. Rounding to 20% for simplicity, given that analytical and biological variation are not fixed, the working group proposed that a change in sCr could be meaningful if there was an increase in sCr by 20% (when results $>$90 μmol/L) or if sCr increased by 20 μmol/L (when baseline or previous value was $\leq$90 μmol/L). This AKI criteria has been called 20/20 AACC AKI criteria as it can be remembered as the 20 μmol/L or 20% change [53]. While detecting AKI by this change criteria is theoretically reasonable and supported by one study from China [94], further validation is required on the utility and implementation of this approach as an e-alert.

Other limitations of the 20/20 AACC AKI criteria include lack of staging by severity of AKI, which could be valuable in triaging and directing appropriate resources and treatment. Furthermore, while baseline (or previous) values are still required to make meaningful interpretation, the timeframe to observe a 20% increase (or 20 μmol/L increase when baseline value $<$ 90 μmol/L) remains unclear. Although the time between measurements is less significant than observing a meaningful sCr change, the right frequency of ordering sCr or interval between sCr is crucial for early detection, keeping in mind the slow kinetics of sCr. Comparably, the KDIGO 2012 guidelines had noted daily measurements of sCr in context of starting and stopping kidney replacement therapy, but this frequency of sCr order can be variable and often left to the discretion of the care provider [22]. Future improvement to this guidance document will also likely incorporate the removal of the term “renal”, given the most recent consensus report on nomenclature [28]. In addition, while sCr is fairly standardized and traceable to the standard reference material (SRM 967), the relevance of bias is unaccounted for between methods. The goal is to eliminate bias, when possible, but bias between specimens (e.g., whole blood vs serum) or instruments is an important consideration. In addition, if patients travel between hospitals with shared laboratory databases, but with different methodology or even reagent formulation, providing a total error specification beyond allowable imprecision would enhance adoption and harmonization of the appropriate creatinine assays. Further considerations may also need to be made for use of POCT creatinine for general and specific use in CI-AKI. Nonetheless, these minor limitations are overcome with the main strength of 20/20 AACC AKI guidance document, which is an initial account for biological variation and consideration of analytical imprecision of sCr that when overlooked can misinform the indication for AKI.

5. Beyond sCr, Predictive Models and Artificial Intelligence (AI)

While sCr has remained the most relevant indicator for diagnostic staging of AKI, real-time alert using mathematical models [4] and machine learning based [6] approaches have also been developed to enhance the predictive power of an impending AKI incident. One approach supplements the delay in sCr rise by identifying and incorporating additional factors such as other laboratory tests, medications and risk factors as essential clinical data elements that are relevant in the syndrome of AKI [4]. For example, a logistic regression-based model for real-time alerts was developed by Simonov et al. by first doing a retrospective analysis on a large patient data set to identify essential factors as contributory elements in predicting AKI. These included, naturally, sCr changes, but also other lab tests that were found to be relevant, including bicarbonate (second most significant covariate) and electrolytes (sodium, chloride and potassium). Outside of the lab, ICU admission and ventilation were other essential contributing factors in the model. The identified factors were evaluated with a discrete-time logistic regression approach for prediction, with new prediction being generated each time a covariate value was available in the medical record. Notably, a simplified model relying only on time-updated routine laboratory tests performed nearly as well as the complete model (accounting for larger sets of factors outside of the laboratory data, including medications or procedures) in predicting AKI in 24hr. Interestingly, the model using a combination of routine laboratory tests was also more predictive than just sCr changes alone for the outcomes measured. These outcomes included hospital mortality, need for renal replacement therapy and sustained AKI. While the full model is difficult to deploy and maintain as it may draw information from different resources, the model based only on laboratory tests with comparable predictive power could enable more ease of implementation than the full model. Of course, the lab based model is still more challenging to implement than an e-alerts based on sCr changes alone, but the authors show that there is insight to be gained from other laboratory tests for AKI prediction [4].

A more complex approach using machine learning to continuously predict AKI is that taken by the British artificial intelligence (AI) subsidiary, DeepMind Technologies, owned by Google. In this approach, AKI prediction was based on a neural network model trained on a multisite dataset obtained from the US Department of Veterans Affairs with more than 6 billion data entries. The trained model can provide updated estimates of impending AKI in the next 48hrs with an associated uncertainty measure in real time. It was also reported that the model can anticipate increases in seven biochemical tests in 88.5% of AKI cases. Although unclear which seven tests can be predicted for an increase, three of seven are suggested to include sCr, urea nitrogen, and potassium. While sCr increase can be predicted, an annualized median sCr baseline and the minimum 48-h sCr were used as baseline and provided to interpret new sCr as they became available. Ultimately, the result was an incredible accuracy leading to early predictions in 84.3% of cases in which dialysis was required within 30 days, and prediction of 90.2% of cases in which dialysis was scheduled within 90 days of the onset of AKI. When AKI of any severity was considered, the model was able to predict 55.8% of hospital acquired AKI within 48hrs. Such lead times to predict a highly probable AKI event could enable preventative actions to be initiated while being vigilant with closer monitoring by laboratory tests and other assessments [6], which in turn would likely influence and improve the accuracy of the AI model. However, the model is not without limitations, including the use of a heavily male dominated population to train the model and back calculation of sCr using the MDRD formula to estimate baseline sCr. Such imputed baseline sCr has been shown to artificially increase AKI incidence [70] and severity [72]. It remains unclear on how the performance of this temporal model would be without such baseline error or with other improved methods for baseline estimations, such as true reference population-based estimation of sCr [72] that can be obtained retrospectively from this large dataset.

Another approach by Kate et al., using machine learning, but with significantly lower number of patients (n = 44 691) has also enabled continuous prediction of AKI based on changes for a given variable. These variables include prescribing new medication, identifying new co-morbidity, or a new laboratory result that becomes available. Fundamentally clear in this logistic regression model approach are again the value of routine laboratory results, comorbidities based on lab values that can be ruled in (e.g. diabetes, hypercalcemia, hyperlipidemia) and prescription medications that all act as triggers for reevaluating the threshold for probable a AKI [95]. Whereas other machine learning based approaches may assess potential for AKI after 24hr or 48hrs of admission, the uniqueness of this approach is the dynamic nature of the changing trajectory of AKI upon new variable or event change. A variable change such as a a new lab test result that becomes available and/or indication of a prescription for nephrotoxic medication can alter the likelihood of an AKI event. Given that the probability of AKI changes with each new event, the model has an established threshold (0.8) at which an alert is fired. Evident from this approach is that diuretics were the most informative feature that would lead to predicting AKI. However, it remains unclear how this model would perform and function in a prospectively conducted study when integrated into a functioning hospital information system.

6. Conclusion

Today the benefits of e-alerts are largely passive, and remains untackled by many institutions, especially those with limited resources or have no mandate to establish such a system. The benefits highlighted by national alerts systems in the UK [65,73,79] or in specific use case scenarios of nephrotoxic surveillance [41,85,91], or simply AKI surveillance [43], are valuable and provide an example of what is possible. To realize the full potential of AKI alerts, some rule modifications may be necessary in terms of how AKI is defined. This is evident from large studies that have not been consistent with regards to clinical findings on impact and outcomes (Table 3). However, e-alerts impart the benefits of detection, data collection, and in the future the possibility of increased predictive power at much earlier time points in the disease course. There are some downsides to e-alerts and other types of CDSS as summarized in Table 2. Nonetheless, if the rule of “5 right elements” can be followed, these limitations may seem minor. Furthermore, prevention and earlier prediction of AKI are being superseded or improved with additional insights from analytical considerations in assay specifications [53], new markers to fit consensus definitions [64], and compute power and modeling improvements to harness various

informational content for integrated decision making [6]. Thus, the thought of a balanced approach to alerting care providers about AKI appears more feasible now than before and will one day shift from 'alerting to AKI' to automated 'averting of AKI'.

Declaration of competing interest

None.

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