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Clinical examination findings as predictors of acute kidney injury in critically ill patients

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Background: Acute Kidney Injury (AKI) in critically ill patients is associated with a markedly increased morbidity and mortality. The aim of this study was to establish the predictive value of clinical examination for AKI in critically ill patients.

Methods: This was a sub-study of the SICS-I, a prospective observational cohort study of critically ill patients acutely admitted to the Intensive Care Unit (ICU). Clinical examination was performed within 24 hours of ICU admission. The occurrence of AKI was determined at day two and three after admission according to the KDIGO definition including serum creatinine and urine output. Multivariable regression modeling was used to assess the value of clinical examination for predicting AKI, adjusted for age, comorbidities and the use of vasopressors.

Results: A total of 1003 of 1075 SICS-I patients (93%) were included in this sub-study. 414 of 1003 patients (41%) fulfilled the criteria for AKI. Increased heart rate (OR 1.12 per 10 beats per minute increase, 98.5% CI 1.04-1.22), subjectively cold extremities (OR 1.52, 98.5% CI 1.07-2.16) and a prolonged capillary refill time on the sternum (OR 1.89, 98.5% CI 1.01-3.55) were associated with AKI. This multivariable analysis yielded an area under the receiver-operating curve (AUROC) of 0.70 (98.5% CI 0.66-0.74). The model performed better when lactate was included (AUROC of 0.72, 95%CI 0.69-0.75), $P = .04$.

Conclusion: Clinical examination findings were able to predict AKI with moderate accuracy in a large cohort of critically ill patients. Findings of clinical examination on ICU admission may trigger further efforts to help predict developing AKI.

1 | INTRODUCTION

Acute kidney injury (AKI) is a frequently occurring complication of critical illness, with severe impact on morbidity and mortality. Incidences up to 60% have been reported, depending on definitions and populations studied.[1,2] Many studies focus on advanced measures, such as biomarkers [3] or imaging [4] for predicting AKI. These techniques are frequently time-consuming, costly, and are not available on a global scale.[5] In contrast, variables obtained by clinical examination are readily available without limitations by settings or costs. Clinical examination signs and symptoms may reflect the underlying disease state and could therefore potentially be used to identify patients at risk for AKI. Clinical examination is always the first diagnostic test in each new patient or each new diagnostic

dilemma. Specifically in the Intensive Care Unit (ICU) clinical examination may differentiate between types of shock, eg sepsis or hypovolemia,[6] which are in itself associated with AKI through various pathophysiological mechanisms including hypoperfusion, immune response, and drug toxicity. Early risk stratification may ultimately accelerate preventive measures to protect renal function in the critically ill.[7-10] The aim of this study was to investigate the predictive value of clinical examination findings as readily available measures for AKI.

Editorial comment

This study assessed the strength of association for different routine clinical bedside physical findings on ICU admission with developing acute kidney injury later on during ICU stay, in a secondary analysis of observations in a large cohort study. Higher heart rates, colder extremities, and prolonged capillary refill were more likely in patients who later during their ICU stay developed acute kidney injury.

2 | METHODS

This was a sub-study of the Simple Intensive Care Studies-I (SICS-I), a single-centre, prospective observational cohort study (NCT02912624).[11]

Ethics: The local institutional review board approved the study (M15.168207).

2.1 | Participants and study size

All patients of 18 years and older who were acutely admitted to the ICU, with an expected ICU stay of at least 24 hours, were eligible for inclusion in the SICS-I. Exclusion criteria were discharge within 24 hours and no informed consent. Patients with known chronic kidney disease before ICU admission (defined by serum creatinine above 177 µmol/L following definition of the Dutch National Intensive Care Evaluation registry[12,13]) were excluded from this analysis.

TABLE 1 Baseline characteristics of included patients

	N = 1003
Age, years (SD)	62 (15)
Gender, male (%)	623 (62)
BMI, kg/m^2 (SD)	26.9 (5.4)
Diabetes mellitus, n (%)	191 (19)
Liver cirrhosis, n (%)	47 (4.7)
Mechanical ventilation at inclusion, n (%)	597 (60)
Use of vasopressors at inclusion, n (%)	499 (50)
Use of RRT during first 3 days, n (%)	50 (5.0)
APACHE IV, score (SD)	74.9 (28.9)

Note: SD, standard deviation, BMI, body mass index, RRT, renal replacement therapy, APACHE IV, acute physiology and chronic health evaluation.

2.2 | Variables

Patient characteristics were registered at admission.[14] All patients underwent clinical examination within 24 hours after ICU admission according to a prespecified protocol. All measurements were conducted by trained researchers who were not involved in patient care and took place as early as possible after ICU admission. Their findings were not revealed to the patients' caregivers. All clinical examinations were standardized and cut-off values for abnormal clinical signs were predefined in the protocol and summarized in E-Table 1 (clinicaltrials.gov; NCT02912624). In the SICS-I, blood pressure data were obtained from both invasive arterial continuous measurement and non-invasive oscillometry. The non-invasive measurements were used when available as this method is more generalizable to other settings than the ICU.

2.3 | Definitions

AKI and its severity were defined according to the KDIGO definition based on serum creatinine, urinary output and RRT (renal replacement therapy) criteria.[15] Indications to start RRT were based on clinical judgment by the treating physician and included metabolic acidosis, hyperkalemia, and anuria or oliguria especially in combination with clinical signs of volume overload. AKI, defined as KDIGO stage I or higher, was determined on day two and day three after ICU admission as the predictive value of clinical examination on day one was investigated. The Modification of Diet in Renal Disease (MDRD) formula was used for estimation of the ideal serum creatinine for each individual at baseline assuming a creatinine clearance of 75 ml/min/1.73m^2.[16,17] Comorbidity data were defined following the Dutch National Intensive Care Evaluation (NICE) registry.[12,13] Capillary refill time (CRT) was the time for skin color to fully return after applying firm pressure at the sternum, index finger, and knee for 15 seconds and considered prolonged if > 4.5 seconds. The difference between central temperature (Tc) measured by a bladder thermistor catheter and peripheral temperature (Tp) measured by a skin probe was the delta temperature (ΔTc–p) and considered abnormal if > 7°C. This was measured for both the foot (ΔTc–pf) and the big toe (ΔTc–pt).[11]

2.4 | Statistical analyses

The overall statistical methods were described in the statistical analysis plan of SICS-I (NCT02912624). Continuous variables were reported as means and standard deviations (SD) or median and interquartile ranges (IQR) for normally distributed and skewed variables respectively. Categorical data were presented in proportions. Associations were calculated as odds ratios (OR) with confidence

intervals (CI). Student's *T*-test, Mann-Whitney *U* test or the Chi-square tests were used as appropriate. No data were imputed for this analysis. Associations between clinical examination and AKI, and comorbidities and AKI were first explored by univariate analysis. We used univariate associations with $P < .1$ for entrance of a variable into the multivariable model, which was decided a priori to be adjusted for age and vasopressor use regardless of their univariate association. The final model was based on logistic regression analysis to identify variables which were independently associated with AKI. Discrimination of the final model was evaluated with receiver operating characteristic (ROC)-curves. Calibration of the multivariable model was checked with the Hosmer-Lemeshow (H-L) Goodness of Fit (GoF) test and by plotting observed AKI proportions against predicted risks of 10 equally sized groups. Analyses were performed using Stata version 15 (StataCorp, College Station, TX, USA).

2.5 | Sensitivity analysis

Two sensitivity analyses were performed. The first sensitivity analysis included lactate as variable in the model since lactate may be readily available as point of care assessment in some ICU's.[18] We assessed whether lactate as a potentially readily available variable would improve the model. We recorded the serum lactate closest to clinical examination. Second, since all variables included in the final multivariable model reflect symptoms of circulatory shock, we also tested whether the presence of shock only performed similar compared to the primary model. This model included age, comorbidities, and the need for vasopressors (as proxy for shock).

2.6 | Statistical significance

The SICS-I was designed to address multiple hypotheses on six different outcomes and, therefore, the acute kidney injury outcome was adjusted for multiple hypothesis testing.[14] We refer to our SAP for more details, but in short, a *P*-value of 0.015 indicated statistical significance and p-values between 0.015 and 0.05 indicated suggestive significance with an increased family-wise error rate.[19,20] For our sensitivity analyses, a *P*-value below 0.05 indicated statistical significance due to the hypothesis-generating purpose. Accordingly, primary analyses are presented with 98.5% CIs and sensitivity analyses with 95% CIs.

3 | RESULTS

Between 27 March 2015 and 22 July 22 2017, 1075 patients were included in the SICS-I. Of these, 72 (7%) suffered (known) chronic kidney disease before admission and were, therefore, excluded from this analysis. Table 1 presents the baseline characteristics of the patients included in the cohort. The observed clinical signs are shown in Table 2. The median time from ICU admission to inclusion was 15 hours (IQR 8-20 h).

From the 1003 included patients, 414 patients (41%) fulfilled the criteria for any stage of AKI on day two or three after ICU admission. The severity of AKI was stage 1, stage 2 and stage 3 in 148 (15%), 122 (12%), and 144 (14%) patients respectively (Figure 1). In total, 153 patients had AKI based on creatinine, 146 patients based on urine output and 115 patients based on both or the use of RRT. Heart rate, per 10 beats per minute for convenient clinical implementation, appeared to have a linear relationship with AKI (E-Figure 1). Low blood pressure, prolonged CRT, abnormal ΔTc–p, and subjectively cold temperature were all associated with AKI in univariate analysis (E-Table 2). Collinearity was observed between the systolic-, diastolic- and mean arterial blood pressure variables, between ΔTc–p on the dorsum of the foot and the big toe measurements and the CRT measured on the finger, sternum, and knee. Only the variables with the strongest univariable association from the variables that showed collinearity were included in the final analyses. The comorbidities cardiovascular insufficiency,

TABLE 2 Observed clinical signs

No.		N = 1003
Central circulation		
1	Respiratory rate, >22 pm	729 (72.7%)
2	Heart rate,> 100 bpm	290 (28.9%)
3	Atrial fibrillation, present	73 (7.3%)
4	Systolic blood pressure, <90 mmHg	98 (9.8%)
5	Diastolic blood pressure, <45 mmHg	80 (8.0%)
6	Mean arterial pressure, <65 mmHg	150 (15.0%)
7	Cardiac murmurs	84 (9.3%)
8	Crepitations	134 (13.5%)
Organ perfusion		
9	Consciousness	
	Alert	736 (73.4%)
	Reacting to voice	161 (16.1%)
	Reacting to pain	38 (3.8%)
	Unresponsive	68 (6.8%)
10	High ΔTc-p, foot	543 (54.1%)
11	High ΔTc-p, big toe	690 (68.8%)
12	Subjectively cold	619 (62.1%)
13	Prolonged CRT sternum	79 (7.9%)
14	Prolonged CRT finger	192 (19.1%)
15	Prolonged CRT knee	275 (27.4%)
16	Skin mottling score	
	Mild (0-1)	683 (68.1%)
	Moderate (2-3)	290 (28.9%)
	Severe (4-5)	30 (3.0%)

Note: PM, per minute, BPM, beats per minute, ΔTc-p, Delta temperature central – peripheral, CRT, capillary refill time. ΔTc-p was considered high if above 7°C, CRT was considered prolonged if above 4.5 seconds.

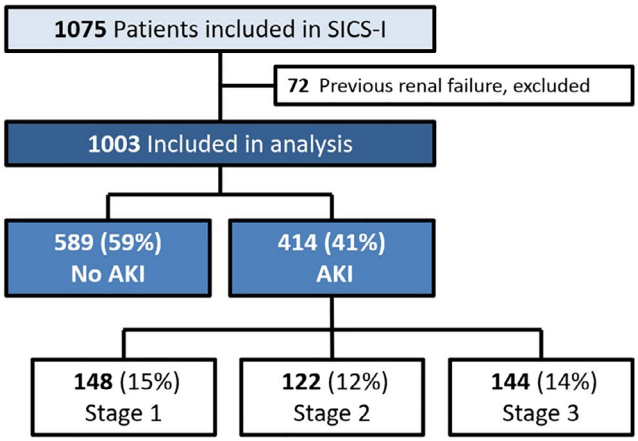

FIGURE 1 Flowchart of patient inclusion and types of AKI

TABLE 3 Admission findings relevant for predicting AKI on day 2 and 3 of ICU admission

	OR	98.5% CI	*P*-value
Age	1.02	1.00-1.03	<0.001
Use of vasopressors	2.28	1.63-3.20	<0.001
Liver cirrhosis	3.15	1.42-7.00	<0.001
Heart rate, per 10 BMP increase	1.12	1.04-1.22	<0.001
Subjectively cold temperature	1.52	1.07-2.16	0.003
Prolonged CRT-sternum	1.89	1.01-3.55	0.013

*Description: model included 997 patients. Pseudo-R2 = 0.09. Hosmer–Lemeshow goodness-of-fit test χ^2 11.58; *P* = .17. AUROC = 0.70 (98.5% CI 0.66-0.74). Abbreviations: BPM, beats per minute, CRT, capillary refill time. CRT was considered prolonged if above 4.5 seconds.

liver failure, and immunosuppression were associated with AKI in univariate analysis and were thus also included in the model. In the final multivariable analyses, increasing heart rate, subjectively cold extremities, and a prolonged CRT on the sternum were associated with AKI (AUROC entire model = 0.70, 98.5% CI 0.66-0.74, H-L GoF 10.67, *P* = .22) (Table 3, E-Figure 1).

3.1 | Sensitivity analyses

First, we evaluated the effect of adding lactate to the model. Adding lactate to the clinical examination findings-based prediction model resulted in a small but statistically significant improvement in the prognostic performance (AUROC entire model = 0.72, 95% CI 0.69-0.75), *P* = .04 (E-Table 3, E-Figure 3). Since all variables included reflect symptoms of circulatory shock, we also tested whether the presence of shock only defined by the need for vasopressors performed similar compared to the primary model, but the model including circulatory shock performed statistically significantly worse (AUROC 0.66 [95% CI 0.66-0.73], *P* < .001, E-Table 4, E-Figure 4).

4 | DISCUSSION

In this retrospective analysis of prospectively collected observational data, we found that clinical examination findings are able to moderately predict the occurrence of AKI. Clinical examination could be used as initial trigger to raise awareness of the critically ill patients at risk for kidney failure and perform additional measures which help predict the occurrence of AKI.

Early detection and possible prevention of further kidney injury is of utmost importance to limit its consequences as still no treatment for AKI exists.[21] Clinical examination consists of readily available signs, can be performed by anyone after training and could assist in early detection of AKI. While many studies included blood pressure and/or comorbidities in their analysis, only few addressed the association between a comprehensive clinical examination and AKI. One study by Lima et al investigated the prognostic value of subjective peripheral perfusion assessment in 50 critically ill patients and observed that patients with signs of abnormal perfusion have a higher SOFA score. Renal function is an important component of the SOFA score, but this study did not explore direct associations of clinical signs with AKI.[22] Argyropoulos et al searched for risk factors which could assist in identifying those at risk for AKI upon ICU admission and created models that could quite accurately predict the occurrence of AKI.[23] This study however only used laboratory data (such as urea and albumin) and defined AKI based on creatinine criteria only.[23] Studying patients with septic AKI, Lara et al found that abnormal CRT in 95 septic patients with hyperlactatemia was associated with the need for RRT.[24] Bourcier et al evaluated temperature gradients as proxy for tissue perfusion and found that it was associated with urine output in 40 critically ill patients with sepsis.[25] Similarly, in our model subjectively cold temperature was associated with AKI. Measured temperature differences were however not associated with AKI in multivariable analysis, which may be explained by the fact that subjective temperature is a more crude measure. Alternatively (subjective assessment of) temperature may be susceptible to measurement error due to its inherent subjective nature. Poukkanen et al described how lower mean arterial pressure and lactate, amongst others, were associated with progression of AKI in patients with severe sepsis. [26] Although we only assessed one-time clinical examination findings, and also included critically ill patients without sepsis, our results were in line with these studies. The recent results of the ANDROMEDA trial suggest that in septic shock patients, targeting (signs of) peripheral perfusion during resuscitation might result in less organ failure, while no reduction in 28-day all-cause mortality was observed.[27]

Recently, Bhatraju et al developed a three variable model to predict severe AKI which performed excellent in a group of 1075 SIRS patients.[3] This model yielded a much higher AUROC compared to our model, possibly explained by differences in AKI stage, and outcome definition. Moreover, the model was developed and validated internally in a highly selected population and includes a biomarker, which may not be available everywhere.[3]

Sensitivity analysis showed a small but significant improvement of the model by including lactate, which is not surprising given that lactate is a well-recognized predictor of severity of illness and AKI.[28,29] We did not include lactate in the primary model since it is likely not widely available as point of care test.[18] Second, assessing circulatory shock as a single predictor was inferior to incorporating clinical examination signs and symptoms as separate predictors. Shock was herein defined as the need for vasopressors, which was a factor also included in the main model. Definitions of shock remain arbitrary, but we suggest that these results suggest that clinical signs individually predict AKI better compared to just the need for vasopressors. In a previous SICS-I analysis, vasopressors were not associated with AKI, however, in that analysis a different subpopulation was included.[30]

Most of the included clinical signs reflect the underlying pathophysiology of shock, for example peripheral vasoconstriction. In patients who have just been admitted and are at an early stage of illness, tachycardia and peripheral vasoconstriction may still be present to maintain sufficient mean arterial pressure and/or for sufficient perfusion of vital organs. Peripheral vasoconstriction results in cold extremities, which was one of the factors predicting AKI in our population. As mentioned, signs and symptoms depend on timing of the clinical examination. Even though there was a delay between ICU admission and our clinical examination, patients present to ICU at a variable moment in their course of illness, which is not necessarily related to ICU admission time. If a patient is examined early during a septic event, the patient can be warm. In a later stage, patients are treated with vasopressors and extremities may become cold. From our results, it seems as if those patients with poor clinical signs, had probably not yet been fully resuscitated at the time of clinical examination.

4.1 | Implications and generalizability

Although clinical examination is operator dependent, the simplicity of the measures performed, and the detailed protocol provide accessible methods for other studies and reliable results. Our results provide information on the value of clinical examination as a free, first-line, and non-invasive reasonable predictor for AKI, applicable in all settings when conducted properly. These observations may inform other studies to include clinical examination when investigating additional variables for the prediction of AKI. This study had a single centre design; collaboration with other centers and external validation should be performed to assess generalizability. We included a heterogenous population of critically ill patients, while investigation of the predictive value of clinical examination in subgroups might yield more specific clues.

4.2 | Limitations

Several limitations must be acknowledged. First, our study was a retrospective analysis of a prospective observational study, which hampers causal inferences by the current analysis. Second, we used the MDRD formula to estimate baseline serum creatinine (ie before illness) since these data were not collected in the main study. Even though this method is widely accepted, this might have led to either an over- or underestimation of AKI incidence.[31] Third, there are more signs of clinical examination that have been suggested to aid in identifying patients at risk of AKI, such as peripheral edema, which we did not evaluate. Including other clinical variables in future studies might improve the predictive performances of clinical examination.[32] Fourth, the highly dynamic nature of the pathophysiologic response to resuscitation and its translation into clinical signs, is probably not fully captured with a single clinical examination, which is why we currently include repeated measures in our follow-up study, the SICS-II.[33] Last, to compare how these readily available variables perform best vs more advanced variables, we should have included some advanced measures such as imaging or biomarkers to compare model performance within a similar cohort.

5 | CONCLUSIONS

Clinical examination findings were able to predict AKI in critically ill patients, albeit with moderate accuracy. Clinical examination may be useful as a fast, free and non-invasive first-line assessment, 'triggering' additional measures that help predict the occurrence of AKI.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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