Original Paper

The Influence of Thyroid Function, Inflammation, and Obesity on Risk Prediction of Acute Kidney Injury by Cystatin C in the Emergency Department

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Key Words

Acute kidney injury • Emergency department • Cystatin C • Thyroid function • C-reactive protein • Body mass index

Abstract

Background/Aims: There is a growing role for emergency departments (ED) in assessing acute kidney injury (AKI) for hospital admissions but there are few studies addressing acute kidney injury biomarkers and confounding factors in the ED. Cystatin C (CysC), a newer renal biomarker, is influenced by thyroid function, inflammation and obesity. This study aims to be the first study to address the impact of these parameters in the ED. **Methods:** Admitted patients (n=397) were enrolled in the ED at Robert-Bosch-Hospital, Stuttgart, Germany. Daily serum creatinine (sCr) was recorded for AKI classification by Kidney Diseases Improves Global Outcome (KDIGO) criteria. CysC, thyroid stimulating hormone (TSH), thyroxine (T4), C-reactive protein (CRP) and body mass index (BMI) were registered at enrollment in the ED. Serum samples were collected at enrollment, after 6 hours and in the following mornings (day 1 to day 3). The correlation of CysC and sCr was studied on a two variable logistic regression model. A linear predictor was computed to predict minimal AKI stage and area under the curve (AUC) was calculated. **Results:** Of 397 patients enrolled for classification by KDIGO AKI criteria, n=152 (38%) developed AKI, n=69 (17.4%) reached AKI stage I, n=70 (17.6%) AKI stage II, and n=13 (3%) AKI stage III. Although a correlation between CRP and CysC levels was shown ($\rho=0.376$), this didn't affect the predictive ability for AKI according to our data. We compared receiver operating characteristic (ROC) curves (DeLong test) of CysC to ROC curves of CysC with the additional variables TSH, BMI, and CRP respectively. Our data shows that addition of CRP, TSH, or BMI does not improve prediction of AKI stage beyond prediction

based solely on CysC levels. **Conclusions:** CysC is known to be influenced by thyroid function, inflammation and obesity, but in our large ED population there was no significant impact of these factors on the diagnostic accuracy of CysC to detect AKI in ED patients.

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Introduction

Acute kidney injury (AKI) is a common syndrome, but is still related to increased mortality, heavy burden of illness and high costs [1-5]. The importance of emergency departments (ED) for hospital admissions is rising [6] but few studies address acute kidney injury (AKI) in the ED [7-12]. Recently it was reported that AKI in the ED is more common than previously thought with 25% of unselected ED patients affected [10].

In the last decade, an AKI classification system was proposed by the Acute Dialysis Quality Initiative (ADQI) and validated in large patient cohorts [2]. Now referred to as the Kidney Diseases Improves Global Outcome (KDIGO) criteria, this system classifies AKI into three stages (stage 1-3; mild, moderate, severe) based on increases in serum creatinine (sCr) and a decrease in urinary output, which is an independent indicator of loss of kidney function [13].

Cystatin C (CysC) is one of the most promising renal biomarkers. CysC is freely filtered at the glomerulus, and is neither secreted nor reabsorbed by renal tubules [14]. CysC is produced by all nucleated cells in the human body at a fairly constant rate [15]. This characteristic makes CysC useful for detection of AKI, but there are several known limitations: CysC is influenced by thyroid function, inflammation and obesity [16, 17].

We previously reported on the performance of tissue inhibitor of metalloproteinase-2, insulin-like growth factor binding protein-7 [TIMP-2]·[IGFBP7] for risk assessment of AKI in patients presenting to the ED [18]. In this subanalysis of our ED cohort, we examined the impact of thyroid function, inflammation and obesity on the performance of CysC in a non-intensive care unit (ICU) cohort of patients who presented to the ED.

Materials and Methods

Study Design and Subjects

Patients presenting to the ED of the Robert Bosch Hospital (Stuttgart, Germany) were screened during initial diagnostic workup. Inclusion criteria were age ≥ 18 years, willingness to participate indicated by signing for informed consent, admission to the internal medicine service of the hospital, and hemoglobin ≥ 9.5 g/dl (women) or ≥ 10.5 g/dl (men). Exclusion criteria were: a dialysis requirement (stage 5D of chronic kidney disease according to Kidney Disease Outcomes Quality Initiative, KDOQI), pregnancy, or failure to meet any of the inclusion criteria. Enrolled patients received a physical examination, a medical history and samples for routine laboratory investigation. Urine output, serum samples were collected at enrollment, after 6 hours and in the following mornings. CysC was measured by nephelometry. All relevant clinical data, including patient demographics, health history, reason for hospital admission and baseline sCr were collected in case report forms as anonymized data.

The study was approved by the Ethics Committee of the University of Tuebingen and all subjects provided written informed consent.

Clinical Endpoints

AKI status within 48 hours after enrollment was classified according to the KDIGO consensus guideline. A pre-hospital baseline sCr value was obtained whenever possible from the primary care physician. If a baseline sCr was not available, the lowest sCr from the hospital stay was used as the reference value for

KDIGO staging [19]. The primary endpoint was AKI stage 1-3. Adjudication of AKI was performed by a nephrologist.

Statistical Analysis

Correlations of continuous variables were investigated by scatter plots, by non-parametric scatter plot smoothers, and by Spearman's rank correlation coefficient ρ . If measurements showed a heavily skewed distribution, logarithms of the measurements were taken.

To evaluate the predictive power of a variable, logistic regression models were fitted to the data. Instead of considering models with ordinal outcome (AKI stage with levels "No AKI", "Stage I", "Stage II" and "Stage III") we considered several binary outcomes. Binary logistic regression models supply linear predictors, defined as one and two variables, which may serve as a score to predict AKI stage. For each individual these scores were compared with the observed binary outcome by computing the receiver operating characteristic (ROC) curves and their related area under the curve (AUC). ROC curves based on scores defined as binary variables were finally compared using the method of DeLong et al. [20]. In addition, we report p -values related to each independent variable in the two-variable logistic regression model (Wald's statistic). To compare one- and two-variable logistic regression models, p -values related to the deviance statistic are computed. If p -values do not exceed 0.05, findings are considered to be statistically significant.

We performed the same analysis in an additional subgroup of patients with known chronic kidney disease (CKD).

For all statistical computations and figures the statistical environment R (Vienna, Austria), Version 3.2.2, and several add-on libraries (pROC, RColorBrewer) are used [21].

Results

Baseline Characteristics and AKI Endpoint

We enrolled 400 patients, of whom three refused or withdrew consent. AKI stage within 48 hours was assessed for all 397 patients for classification by KDIGO AKI criteria, and $n=152$ (38%) developed AKI: stage I (risk) $n=69$ (17.4%), stage II (injury) $n=70$ (17.6%) and stage III (failure) $n=13$ (3%) (Fig. 1).

Baseline parameters (Table 1A, and 1B) significantly associated with the primary endpoint (AKI stage 1-3) include enrollment sCr and plasma CysC. The most common comorbidities were hypertension (60%), infectious disease (24%), diabetes (24%), heart failure (23%) and myocardial infarction/acute coronary syndrome (21%). A history of chronic kidney disease was present in 12% of the cohort. Significant differences between patients with or without AKI were shown in admission sCr, admission CysC, and admission urea. Furthermore, significant differences in CRP levels, leukocytes, hemoglobin, hematocrit and chloride were remarkable. In the AKI cohort significantly more patients had comorbid hypertension.

Influence of Thyroid Function, Inflammation and BMI in AKI

First, we examined the correlation between sCr and CysC levels. As expected, a significant correlation was shown between those two kidney markers ($\rho=0.697$), summarized by a scatter plot smoother and Spearman's rank correlation coefficient (Fig. 2).

Second, we analyzed the association of CRP, BMI and TSH measures with CysC (Fig. 3, a-c). Besides BMI, each quantity is displayed on a logarithmic scale. CRP correlates with increasing CysC levels ($\rho=0.376$).

Third, we investigated whether CRP, TSH or BMI levels improve prediction of AKI stage (Table 2 and Fig. 4). The ROC curves using CysC to predict a minimal AKI stage "risk", "injury" or "failure", showed a AUC of 0.7, 0.74 and 0.8 respectively. A significant correlation between the logarithmic CysC and AKI stage was detectable ($p<0.0001$). Log(CRP) levels showed a significant association with AKI stage "risk" and "injury" ($p=0.00073$ and $p=0.011$ respectively), whereas log(TSH) and BMI showed no significant association with any AKI stage ($p>0.05$).

Table 1A. Baseline characteristics; BMI: Body mass index; CysC: Serum Cystatin C; Hb: Hemoglobin; Hct: Hematocrit; ICU: Intensive care unit; IMC: intermediate care unit; IQR: Interquartile range; sCr: Serum Creatinine.

	AKIN 0			AKIN 1-3			p-value	AKIN 1			AKIN 2			AKIN 3			Total n (%)
	n (%)	Median	IQR	n (%)	Median	IQR		n (%)	Median	IQR	n (%)	Median	IQR	n (%)	Median	IQR	
Total	245 (62%)			152 (38%)				69 (17%)			70 (18%)			13 (3%)			397
General ward	186 (76%)			109 (72%)				51 (74%)			48 (69%)			10 (77%)			295 (74%)
IMC	50 (20%)			35 (23%)				16 (23%)			17 (24%)			2 (15%)			85 (22%)
ICU	9 (4%)			8 (5%)				2 (3%)			5 (7%)			1 (8%)			17 (4%)
Age (years)	62.0	23.0		71.0	15.3		<0.0001*	70.0	13.0		71.5	15.8		66.0	39.0		
BMI (kg/m ²)	26.7	6.0		27.7	5.9		0.08	27.7	5.8		27.7	6.1		28.4	5.7		
Admission sCr (mg/dL)	0.9	0.3		1.1	0.7		<0.0001*	1.1	0.6		1.1	0.7		3.5	3.6		
Admission CysC (mg/dL)	0.9	0.3		1.4	0.7		<0.0001*	1.3	0.6		1.3	0.6		2.2	1.8		
Admission Urea (mg/dL)	30.0	16.0		42.0	37.3		<0.0001*	42.0	28.0		40.5	29.0		100.0	52.0		
6h sCr (mg/dL)	0.9	0.3		1.1	0.7		<0.0001*	1.0	0.5		1.0	0.7		2.7	2.3		
Day 1 sCr (mg/dL)	0.9	0.3		1.1	0.7		<0.0001*	1.1	0.6		1.1	0.6		3.0	3.3		
Day 2 sCr (mg/dL)	0.9	0.3		1.2	0.7		<0.0001*	1.2	0.6		1.1	0.4		2.4	3.4		
6h CysC (mg/dL)	1.0	0.3		1.4	0.7		<0.0001*	1.4	0.6		1.4	0.6		2.8	1.4		
Day 1 CysC (mg/dL)	1.0	0.4		1.5	0.9		<0.0001*	1.5	0.6		1.5	0.8		2.8	2.2		
Day 2 CysC (mg/dL)	1.0	0.4		1.5	0.8		<0.0001*	1.4	0.7		1.5	0.8		2.2	1.7		
Urine Output 6h (mL/kg/h)	1.2	0.9		0.5	0.7		<0.0001*	0.7	1.1		0.4	0.5		0.1	0.2		
Urine Output Day 1 (mL/kg/h)	0.8	0.5		0.4	0.4		<0.0001*	0.6	0.5		0.3	0.2		0.3	0.5		
Urine Output Day 2 (mL/kg/h)	0.8	0.5		0.4	0.3		<0.0001*	0.6	0.4		0.3	0.3		0.4	0.1		
TSH (mU/L)	1.2	1.1		1.3	1.1		0.4	1.3	1.1		1.3	1.1		1.7	0.9		
FT3 (pmol/L)	4.6	1.4		4.3	1.3		0.02*	4.3	1.2		3.9	1.2		4.1	1.7		
FT4 (pmol/L)	16.9	4.4		17.8	4.5		0.4	18.2	6.6		17.7	5.2		17.5	3.8		
CRP (mg/dL)	0.3	1.4		1.1	4.1		<0.0001*	0.9	3.6		1.3	4.0		2.4	4.0		
Hemoglobin (g/L)	141.0	20.0		134.0	18.0		0.0003*	135.0	20.0		134.0	16.5		130.0	16.0		
Hematocrit (L/L)	0.41	0.05		0.40	0.06		0.004*	0.40	0.06		0.40	0.05		0.38	0.12		
Platelets (G/L)	220.0	79.0		209.5	104.0		0.06	204.0	100.3		212.0	88.0		219.0	171.0		
Leukocytes (G/L)	7.4	3.3		8.6	4.5		<0.0001*	8.5	4.6		8.6	4.6		10.4	4.9		
Glucose (mg/dL)	118.0	48.0		126.0	44.5		0.2	129.5	44.0		124.5	42.5		115.0	27.0		
Potassium (mmol/L)	4.0	0.4		4.0	0.6		0.9	4.0	0.5		4.0	0.6		4.3	0.8		
Chloride (mmol/L)	103.0	5.0		101.0	6.0		0.0006*	102.0	7.0		100.0	6.0		100.5	6.3		
pH	7.38	0.06		7.38	0.07		0.6	7.38	0.06		7.39	0.06		7.33	0.06		
Bicarbonate (mmol/L)	24.2	2.3		24.5	2.8		0.7	24.7	2.2		24.3	3.0		22.3	5.8		

The ROC curves were each computed using two variables, CysC and an additional variable CRP, TSH or BMI, respectively. Based on a two-variable logistic regression model, a linear predictor was computed, which in turn was used to serve as a score to predict the minimum AKI stage that would occur for each patient. In order to increase the AUC, the CysC, CRP, and TSH are displayed on a logarithmic scale. When comparing ROC curves with an additional variable (CRP, TSH, BMI) to ROC curves with solely CysC, no

Table 1B. Comorbidities; ACS: Acute coronary syndrome; CKD: Chronic kidney disease; MI: Myocardial infarction; PAD: Peripheral artery disease.

	AKIN 0 n (%)	AKIN 1-3 n (%)	p-value	Total n (%)
Comorbidities				
- Infectious	66 (27%)	38 (25%)	0.73	94 (24%)
- Hypertension	127 (52%)	110 (72%)	<0.0001*	237 (60%)
- Heart failure	53 (22%)	39 (26%)	0.39	92 (23%)
- Diabetes	52 (21%)	43 (28%)	0.12	95 (24%)
- Stroke	18 (7%)	10 (7%)	0.84	28 (7%)
- CKD	23 (9%)	23 (15%)	0.11	46 (12%)
- PAD	12 (5%)	10 (7%)	0.50	22 (6%)
- ACS/MI	47 (19%)	37 (24%)	0.26	84 (21%)

Fig. 1. Frequencies of AKI stages (n=397).

Fig. 2. Correlation of sCr and CysC levels, summarized by a scatter plot smoother and Spearman's rank correlation coefficient. The AKI stage is indicated.

Fig. 3. Scatterplots of (a) CRP levels, (b) BMI and (c) TSH levels versus CysC. Besides BMI each quantity is given on a logarithmic scale. The normal range of CysC is indicated by a green bar.

significant correlation was shown ($p > 0.05$), indicating that these factors might not have an influence on risk prediction of AKI.

Influence of Thyroid Function, Inflammation and BMI in chronic kidney disease

In an additional analysis, we investigated if our results are reproducible in the subgroup of patients with known chronic kidney disease (CKD). A correlation of CysC levels with urine albumin-to-creatinine ratio in CKD patients was described previously [22]. Due to a sample

Table 2.

Prediction of AKI stage by cystatin C and the influence of CRP, TSH and BMI levels. Variable 1: correlation between AKI stage and CysC; Variable 2: correlation between AKI-

			Tests and <i>p</i> -values			
Variables			Wald		Deviance	DeLong
Dependent Variable (binary)	Independent Variable 1 (continuous)	Independent Variable 2 (continuous)	LRM(Var1 + Var2)		LRM(Var1) vs LRM(Var1 + Var2)	AUC(Var1) vs AUC(Var1 + Var2)
			Variable 1	Variable 2		
Stage Risk	log(Cystatin C)	log(CRP)	<0.0001	0.00073	0.001	0.3
Stage Risk	log(Cystatin C)	BMI	<0.0001	0.19	0.187	0.74
Stage Risk	log(Cystatin C)	log(TSH)	<0.0001	0.96	0.955	0.75
Stage Injury	log(Cystatin C)	log(CRP)	<0.0001	0.011	0.012	0.1
Stage Injury	log(Cystatin C)	BMI	<0.0001	0.65	0.648	0.64
Stage Injury	log(Cystatin C)	log(TSH)	<0.0001	0.73	0.729	0.62
Stage Failure	log(Cystatin C)	log(CRP)	<0.0001	0.29	0.289	0.13
Stage Failure	log(Cystatin C)	BMI	<0.0001	0.61	0.618	0.38
Stage Failure	log(Cystatin C)	log(TSH)	<0.0001	0.46	0.456	0.97

stage and CRP, TSH and BMI levels respectively. DeLong: comparison of ROC curves using two variables, cystatin C and an additional variable CRP, TSH or BMI, respectively. LRM: Logistic Regression Model

Fig. 4. Prediction of AKI-stage by CysC and the influence of CRP, TSH and BMI levels. The ROC curves were each computed using two variables, CysC and an additional variable CRP, TSH or BMI, respectively. Based on a two-variable logistic regression model, a linear predictor is computed which in turn is used to serve as a score to predict the minimum AKI stage that the patient will undergo. To increase the AUC, CysC, CRP, and TSH are taken on a logarithmic scale. Formulas given in the legends should be interpreted only as a formal description of the model used to set up the predictor. As a result, our data does not suggest that CRP, TSH or BMI improves prediction of AKI stage beyond prediction solely based on CysC levels.

size of $n=1$, AKI stage “F” wasn’t analyzed. No significant association between $\log(\text{CRP})$, BMI and $\log(\text{TSH})$ and AKI stages “risk” and “injury” was remarkable ($p>0.05$) (Table 3 and Fig. 5).

Discussion

CysC is used increasingly in the assessment of AKI [23], is more closely representative of the GFR [24], and because of a putative absence of confounding through sex, age, or muscle mass, this protein is considered superior to sCr as a renal biomarker [25-28].

Detection of AKI in ED is a major problem in clinical practice: For accurate diagnosis of AKI, a change in sCr or decline in urine output is necessary [2], but baseline sCr is mostly not

Table 3. Prediction of AKI stage by cystatin C and the influence of CRP, TSH and BMI levels in the subgroup with chronic kidney disease (n=46). No data for stage “F” are given due to a small sample size (n=1). Variable 1: correlation between AKI stage and CysC; Variable 2: correlation between AKI-stage and CRP, TSH and BMI levels respectively. DeLong: comparison of ROC curves using two variables, cystatin C and an additional variable CRP, TSH or BMI, respectively. LRM: Logistic Regression Model

Subgroup with chronic kidney disease			Tests and <i>p</i> -values			
Dependent Variable (binary)	Independent Variable 1 (continuous)	Independent Variable 2 (continuous)	Wald		Deviance	DeLong
			LRM(Var1 + Var2)		LRM(Var1) vs LRM(Var1 + Var2)	AUC(Var1) vs AUC(Var1 + Var2)
			Variable 1	Variable 2		
Stage Risk	log(Cystatin C)	log(CRP)	0.016	0.13	0.124	0.6
Stage Risk	log(Cystatin C)	BMI	0.01	0.16	0.142	0.98
Stage Risk	log(Cystatin C)	log(TSH)	0.0072	0.1	0.048	0.5
Stage Injury	log(Cystatin C)	log(CRP)	0.038	0.072	0.058	0.2
Stage Injury	log(Cystatin C)	BMI	0.021	0.26	0.254	0.65
Stage Injury	log(Cystatin C)	log(TSH)	0.014	0.12	0.075	1

Fig. 5. Prediction of AKI-stage by CysC and the influence of CRP, TSH and BMI levels in the subgroup with chronic kidney disease (n=46). No ROC curve for stage “F” is given due to a small sample size (n=1).

available at arrival to ED and urinary catheterization for measuring urine output is frequently not indicated. This leads to delay in AKI diagnosis and therapy which results in a poorer outcome and increased mortality rate [29]. Therefore CysC as a novel renal biomarker was examined in AKI: Beyond solely indicating glomerular filtration rate (GFR), CysC also seems to play a role in the prediction of AKI. In different settings, like cardiac surgery, pediatric surgery or critically-ill patients, CysC showed the ability to act as a biomarker for risk prediction of AKI [30-32].

Moreover, in the heterogeneous ED population, a single CysC measurement can give further information on kidney function. Bongiovanni et al. showed an odds ratio of 5.04 for development of AKI at CysC levels >1.44mg/dl at admission [33]. Furthermore, CysC was found to be superior to sCr as an early predictive biomarker of AKI in the ED setting [7].

Shortly after the discovery of CysC, there was growing evidence of a variety of influences on CysC levels like inflammation (expressed as CRP level elevation), body weight and height [17, 34]. Furthermore, we described a significant impact on CysC through thyroid function: CysC levels were significantly lower in hypo- and significantly higher in hyperthyroid patients. By showing an inverse correlation to the measured GFR, we concluded CysC might

be useless in patients with thyroid dysfunction [16], which was confirmed by other groups [35]. Because of this vast number of potential influences, some authors recommended avoidance of CysC for estimation of kidney function [17].

Our goal was to investigate the relevance of these influences and their impact on diagnostic accuracy for detecting AKI in the ED. To our knowledge, so far no study has examined the influences of thyroid function, BMI, and CRP on CysC in the ED setting.

In our ED cohort we proved the known positive correlation of CRP and CysC. Higher CysC levels were found in cases of elevated CRP levels, in accordance with previous studies [17]. But one might wonder if these influences are relevant in clinical practice for risk prediction of AKI, especially in heterogeneous patient populations such as in the ED.

When comparing the ROC curves for prediction of AKI, no significant differences were detected between CysC solely and CysC in combination with BMI, CRP, and TSH respectively (Fig. 4). According to our results, the mentioned influences have no impact on diagnostic accuracy and therefore no relevance in clinical practice for risk prediction of AKI. The same observation was made by Wang et al. in critical ill patients in ICU [36]. Because CysC is a renal filtration marker we tested in an additional analysis these influence in the subgroup of patients with chronic kidney disease and could not find any influence.

Despite a variety of influences on CysC levels, our data suggest that these factors have no impact on ROC curves and the usage of CysC in risk prediction of AKI in ED seems to be appropriate in clinical practice.

Conclusion

In summary, despite several known influences on CysC level, like thyroid function, CRP and BMI, our data indicates that these factors have no impact on diagnostic accuracy for risk prediction of AKI - this implies that no relevant influence is evident on CysC readings in clinical practice. Consequently, it seems appropriate to measure CysC in ED patients for risk prediction of AKI.

Abbreviations

ADQI: Acute dialysis quality initiative; AKI: Acute kidney injury; AUC: Area under the receiver operating characteristics curve; CKD: Chronic kidney disease; CysC: Cystatin C; CRP: C-reactive protein; ED: Emergency department; sCr: Serum creatinine; GFR: Glomerular filtration rate; KDIGO: Kidney Disease: Improving Global Outcomes; KDOQI: Kidney Disease Outcomes Quality Initiative; BMI: Body mass index; TSH: Thyroid stimulating hormone; T3: Triiodothyronine; T4: Thyroxine; TIMP2: TIMP metalloproteinase inhibitor 2; IGFBP7: Insulin-like growth factor-binding protein 7.

Disclosure Statement

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