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Emergency medicine pharmacotherapy compromises accuracy of plasma creatinine determination by enzyme-based methods: real-world clinical evidence and implications for clinical practice

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Background: Assessment of kidney function in emergency settings is essential across all medical subspecialties. Daily assessment of patient creatinine results from emergency medical services showed that some deviated from expected values, implying drug-related interference.

Methods: Real-time clinical evaluation of an enzyme method (Roche CREP2) in comparison with the Jaffé gen. 2 method (Roche CREJ2) was performed. During the period of December 2022 and January 2023, we analyzed 8,498 patient samples, where 5,524 were heavily medicated STAT patient specimens, 500 were pediatric specimens, and 2,474 were from a distant general population in a different region using the same methods.

Results: In 109 out of 5,524 hospital specimens (1.97%, $p < 0.001$), the CREP2 value was apparently (25% or more) lower than CREJ2. Suspect interfering medication was found in a sample of 43 out of 46 reviewed patients where medication data were available. This phenomenon was not observed in the general population.

Conclusion: In a polymedicated urgent care hospital population, a creatinine enzyme method produces unreliable results, apparently due to multiple drug-related interferences.

KEYWORDS

creatinine, renal functions, eGFR, urgent care medication, cystatin C

Introduction

Determination of blood creatinine is essential to assess kidney functional status. The first method used for creatinine measurement in clinical specimens was introduced by Jaffé (1). During the past two decades, Jaffé methods have been widely replaced by enzyme-based colorimetric methods employing sarcosine oxidase/peroxidase reaction chemistry (2). It has been shown repeatedly that enzymatic methods are susceptible to negative interference caused by several drugs, such as etamsylate (3), metamizole (4, 5), paracetamol, N-acetyl-p-benzoquinone imine (NAPQUI) (5), acetylcysteine (6), derivatives of salicylic acid (5, 7), high-dose acidum ascorbicum (8), and dobesilate (9). Negative interference by catecholamines at clinically relevant concentrations was also shown to affect these methods (10), and recently, monoclonal immunoglobulins have also been reported to interfere (11, 12). In addition, Roche SmPC for enzymatic creatinine determination (CREP2) states that methyldopa and levodopa cause artificially low results. Etamsylate, acetaminophen (paracetamol), acetylcysteine, and metamizole are also mentioned as potentially interfering substances (13).

Reviewing patient result sign-outs in a large tertiary care hospital performing up to 600 STAT creatinine determinations a day, we observed that approximately 2% of creatinine results deviated from preceding or expected creatinine values in the context of patient history and diagnosis, mode of hospital admission, reference ranges, and/or delta checks. The falls in measured creatinine levels exhibited unpredictable behavior independent of diagnosis—from trauma emergency services through general surgery, urology, and obstetrics to neurology, general internal medicine, and subspecialties such as cardiology, nephrology, and oncology. Of the drugs frequently used in these emergency settings, metamizole, paracetamol, etamsylate, and acetylcysteine represent common medications known to interfere with enzymatic creatinine determination. Observing these inconsistencies, we realized an imminent occurrence of a diagnostic and/or medication error problem, the basis of which may be uncontrollable drug-induced effects leading to falsely low creatinine values by the enzyme method followed by spuriously high eGFR calculated values.

Here, we report on retrospective evaluation of the affected method (CREP2), comparing its performance to a Jaffé generation 2 method (CREJ2) in the context of real-life emergency medicine pharmacotherapy and immediate implementation of corrective measures restoring the accuracy of eGFR determinations. To the best

of our knowledge, this is the first report addressing inaccuracies of enzyme-based creatinine methods relevant to emergency medical services pharmacotherapy and providing immediate, clinically feasible corrective and preventive actions applicable worldwide for hospital emergency laboratory services.

Materials and methods

Survey setting and patient population

The study was performed as an exploratory survey based on pharmacovigilance signals on the potential influence of medications on laboratory tests. The aim was to identify and minimize potential risks from patient medications. The survey was approved by the multicentric IRB of University Hospital Brno under the number 03-091122/EK. Creatinine measurements were performed as a single additional analysis of all accessible clinical specimens covered by legally required informed consent. All methods were applied as described by the manufacturer. All participating laboratories were accredited under the ISO15189 standard. Central and pediatric laboratories of the University Hospital Brno and a Central reference laboratory Spadia lab, a.s. were involved. Altogether, 8,498 paired, real-time patient creatinine measurements were performed. Of those, 5,524 were STAT determinations at the Department of Laboratory Medicine, University Hospital Brno (A), 500 measurements at the Children's Hospital laboratories (B), and 2,474 at Spadia lab a.s. (C).

(A) Hospital adult urgent care population: STAT creatinine determinations were analyzed by both CREP2 and CREJ2 methods summing up to 5,524 measurements from 21 December 2022 to 19 January 2023. This population consisted of 3,449 patients, 45.21% male patients and 54.79% female patients, with an age range of 18–99 years and a median age of 62 years.

(B) Hospital pediatric population: Five hundred STAT creatinine determinations were analyzed using both methods from 15 January 2023 to 9 February 2023. The population at the Children's Hospital is mostly constituted of five intensive care units (neonatal, general pediatric, resuscitation care, infectious diseases, and pediatric oncology/transplantation). This population consisted of 317 patients, 54.9% male patients and 45.1% female patients, with an age range of 0–24 years and a median age of 8 years.

(C) Common adult population: From 5 January 2023 to 31 January 2023, we performed 2,474 measurements in a different geographic region (North Moravia, Czechia) using identical equipment and methods (Roche c702). This dataset served as a “field verification set” performed at the same time in an approximately 200 km distant population assumingly not taking medications used in urgent care hospital settings. This patient population was a general

Abbreviations: STAT, testing performed immediately (“statim”); eGFR, estimated glomerular filtration rate; IRB, institutional review board; SmPC, summary of product characteristics; IDMS, isotope dilution mass spectrometry; LIMS, laboratory information and management system.

regional outpatient population unrelated to a University Hospital Brno referral population. This population consisted of 2,474 patients, 42.3% male patients and 57.7% female patients, with an age range of 1–99 years and a median of 60 years.

Laboratory methods

Creatinine and cystatin C measurements were performed using Roche platforms Cobas 8,000, Pure, or Integra. The CREP2 (enzyme-based) and CREJ2 (rate-blanked and compensated Jaffé gen. 2) methods were installed on the Cobas 8,000 c702 serving as the main measurement device in our hospital. All methods were conducted as described by the manufacturer. Creatinine methods were calibrated using C.f.a.s. Roche IDMS-traceable calibration. Pediatric STAT creatinine determinations were performed at the Children's Hospital using Roche Cobas Integra 400+ instruments as recommended by the manufacturer.

Statistical analysis

The Bland–Altman plot was used to define the limits of agreement between the values of creatinine concentration with a 95% confidence interval. Scatterplots with identity lines were used to visualize log-transformed values of paired measurements. The chi-square test for equality of proportions was used to assess the significance of differences among the populations analyzed. Statistical significance was defined as a value of p of <0.05 . Statistical analyses were performed using R Statistical Software (v4.2.2; R Core Team 2021) (14–16). The datasets generated and analyzed in the current study are not publicly available as they are based on individual patient measurements. The ISO15189-accredited laboratories store the primary data as per the requirement of this document.

Results

Data analysis

We used logarithmic transformation of the rank-ordered creatinine concentrations (x-axis) determined by the CREJ2 method (the lowest value first) and CREP2 methods to present all datapoints for population (A) as shown in Figure 1, Panel A. A substantial portion of CREP2 values deviates from a central tendency set by a blue sigmoid line of increasing CREJ2 concentrations. Panel 1b presents both creatinine methods as log-transformed data. The Panel 1d shows Bland–Altman plots of the full dataset as from Panel A1 visualizing a dispersion of creatinine concentrations. Panel 1e shows the identical dataset but with 25% of outlying values eliminated. Panels 1c and 1f describe the irrelevant general population (C) showing log-transformed values and a Bland–Altman plot showing very good agreement between the two methods. The results for the pediatric population are presented in Figure 2 as full data Bland–Altman plot (2a left panel) and after elimination of outliers greater than 25% (2b right panel). Figure 3 shows ratios of paired creatinine measurements as extracted from the table ranked from the first/s/third event (hospital admission > next morning sampling > next day sampling, etc.)

through the tenth event (i.e., last measurements) as available. Interquartile ranges and medians are shown.

Hospital patient record review

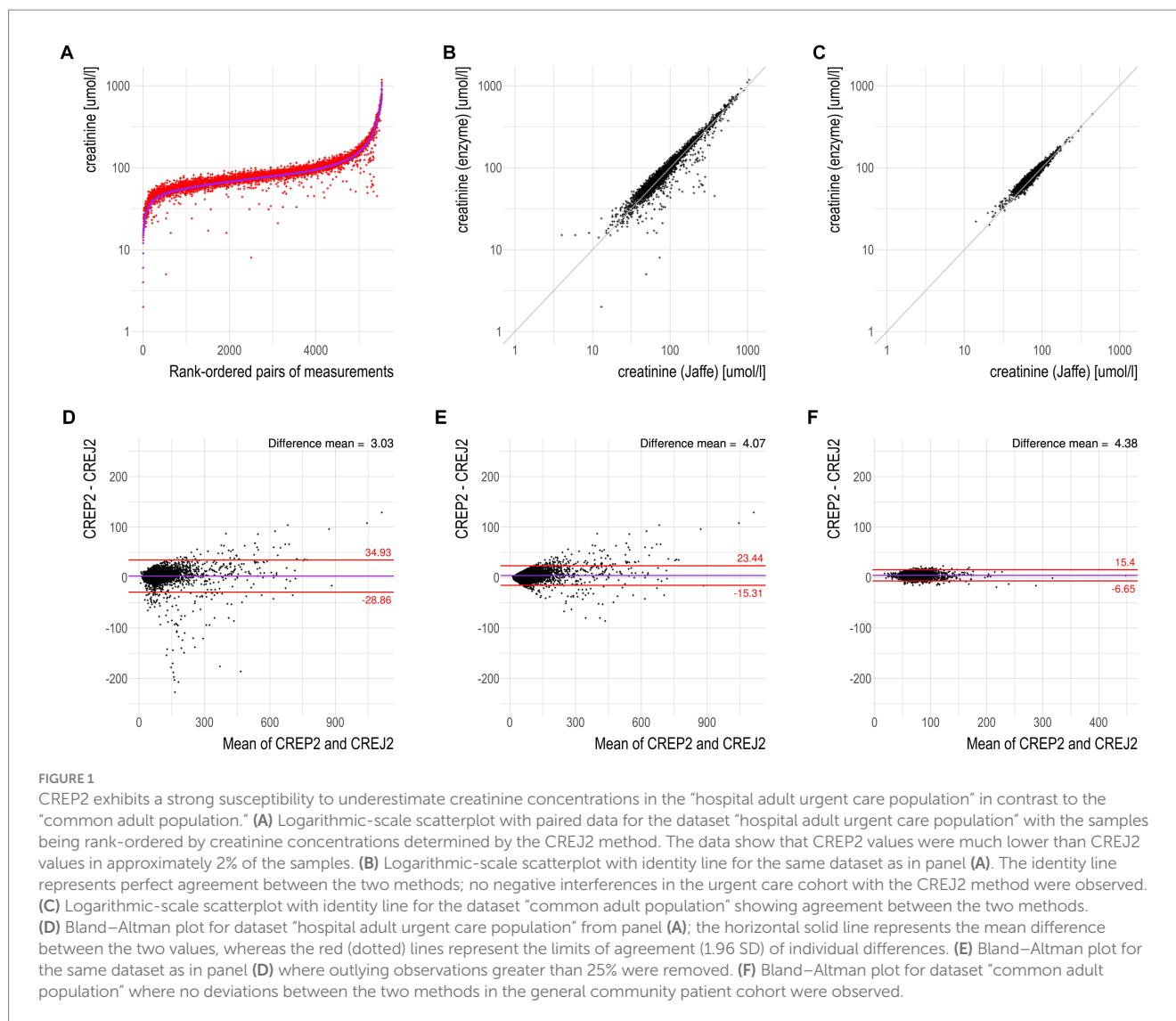
The clinical signal for this observational study was derived retrospectively from daily sign-out reviews. Values of CREP2 discrepant to CREJ2 with preceding measurements higher than 25% by CREP2 were first screened by two clinicians and two clinical pharmacists (MR and DB; KH and SK). We examined the use of etamsylate, metamizole (dipyrone), acetylcysteine, paracetamol, catecholamines, high-dose acidum ascorbicum, and dobesilate during the 72-h period before the time of collection of a sample with a suspiciously low CREP2 value. In urgent care patients, we reviewed drug administration timing in the context of creatinine concentrations that were extracted from daily LIMS results. The criteria were either delta checks and/or inconsistent patient result history. We identified the concerned medication in a sample of 43 of 46 reviewed patients where medication data were available for post-hoc access. All cases identified on the basis of 25% differences between creatinine measurements and selected for review are presented in Table 1. Figure 3 shows the evolution of discrepancies during the hospital stay between the two methods. Creatinine values usually were similar by both methods in the first sample collected after patient entry. With subsequent samples, the enzyme method tended to give low values, presumably because intensive drug treatment had started. With longer treatment, the difference between the methods became smaller, presumably because drug treatment had ended.

Result summary

In the hospital adult urgent care population (A), we found 109 samples (1.97%) where the CREP2 value was 25% or more below the CREJ2 value. There were no such samples in the common adult population (C). The proportions were significantly different ($p < 0.001$) between the population (A) and population (C). We conclude that in a polymedicated urgent care hospital population, the creatinine enzyme method produces unreliable results due to multiple drug-related interferences.

Discussion

Inaccurate clinical inference on renal functions may severely affect diagnostic workup and threaten the safety and effectiveness of treatment. Among a number of putative filtration biomarkers, only cystatin C has been partially adopted in clinical practice, mostly in nephrology specialties, but not in emergency medical services (17). Despite common criticism, blood creatinine remains the only biomarker accessible worldwide. Therefore, the accuracy of its determinations is of paramount importance to reliably calculate eGFR that is predominantly recommended for clinical use (18). Although mentioned in SmPCs of the respective drugs (19–21) and a procedure manual of the affected method (22) as well, real-life urgent care practice often dictates an immediate clinical need for medication and, at the same time, renal function assessment. As we show here, enzyme methods applied on patient STAT specimens with multiple medications do not provide a reliable platform



for creatinine determination. These findings led us to reintroduce the CREJ2 method to clinical practice as the main tool for creatinine determination. The Roche CREJ2 rate-blanked and compensated method has an IDMS-traceable calibration and is therefore suitable for eGFR calculations. Significant improvements in the original Jaffé method have been made, with this generation showing reduced interferences. We kept the CREP2 methods on our instrumentation available as needed, that is, double-checks, patients with muscular wasting, sarcopenia, pediatric population with creatinine less than $20\ \mu\text{mol/L}$, and/or clinical trials with new drugs whose behavior toward creatinine determination is not known.

Clinical practice in our hospitals set new laboratory standards for the evaluation of renal functions. The screening tier in the adult population consists of (i) CREJ2 determination resulting in CKD-EPI eGFR calculation always available as STAT test. The second tier consists of (ii) CREJ2+cystatin C determinations available STAT on a physician’s specific request resulting in a composite CKD-EPI (“DUO”) eGFR calculation—this procedure is intended as a quantitative measure of eGFR covering clinical situations where creatinine may be biologically unreliable, such as muscle wasting processes and extremity amputations. For pediatric populations, the screening tier is (iii) CREJ2 plus patient height resulting in Schwartz-bedside eGFR calculation, and (iv) the

quantitative tier is urea+CREJ2+cystatin C determination and eGFR calculation using the “full” Schwartz equation (23). This practice integrated our findings and general recommendations as well (24, 25).

Conclusion

From a clinical point of view, treatment is always a priority, especially in the emergency setting. Diagnostic laboratories shall use methods suitable for the intended purpose such as in specific patient populations. However, it is the IVD manufacturer’s responsibility to provide such technologies declaring suitability for a given patient setting such as emergency medicine.

Regarding kidney function biomarkers, we think that combining both biological markers, creatinine and cystatin C, reduces the disadvantages associated with each of them separately. This may advance cystatin C usage to urgent care testing in large referral centers as they deal with polymedicated specimens from severely sick patients often with no medical history available. Our new practice greatly improved the reliability of renal function evaluation in our hospitals and the safety of diagnostic procedures and eGFR-based drug dosage as well. Although the

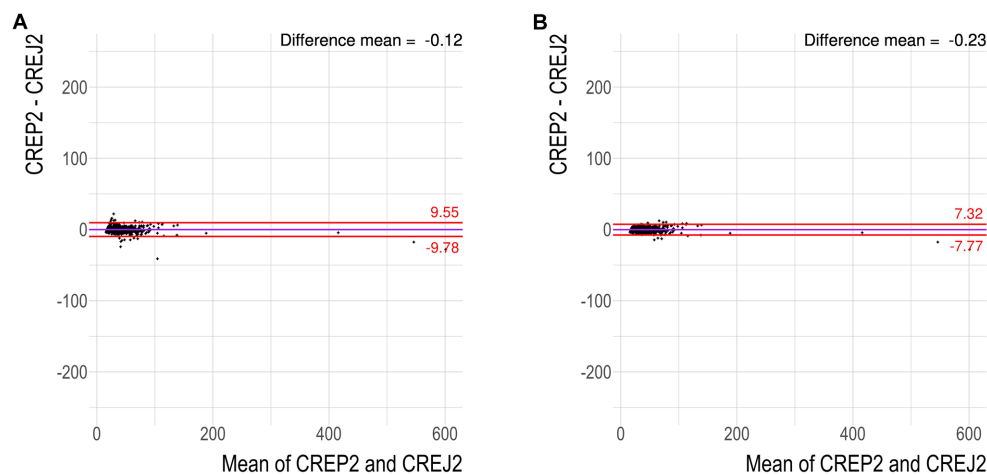


FIGURE 2

Pediatric hospital population does not exhibit susceptibility to underestimate creatinine concentrations by CREP2. (A) Bland–Altman plot for dataset “pediatric hospital population” showing 25 of 500 values greater than 1.96 SD. These cases were then individually screened by a pediatric nephrologist (JS) and a specialist in pediatric laboratory medicine (DV) for suspect medication. (B) Bland–Altman plot for the same dataset with any samples exhibiting the difference between the two methods greater than 25% removed.

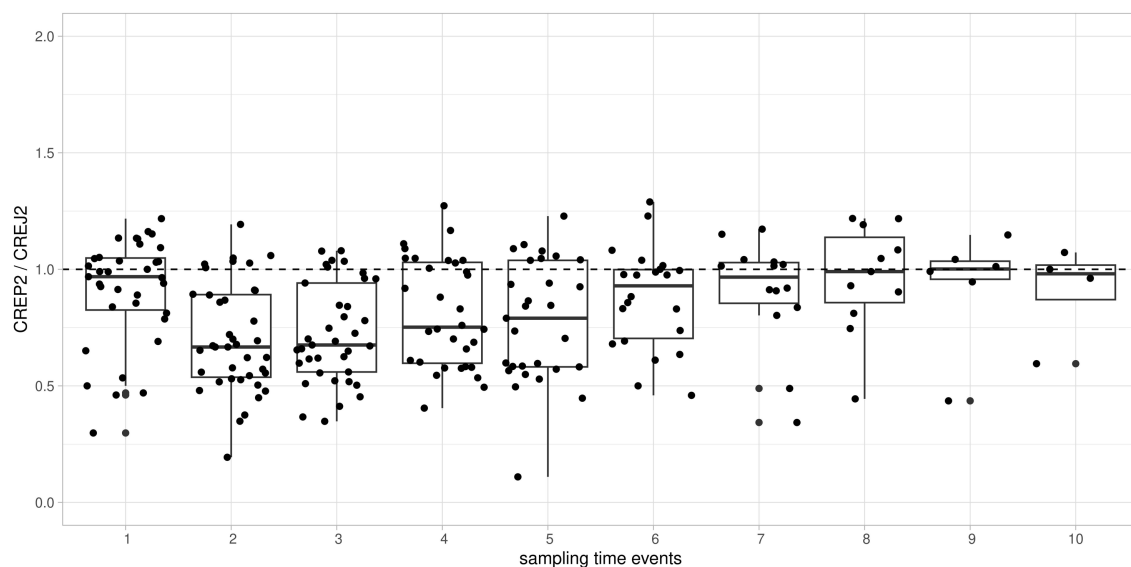


FIGURE 3

Time-dependent individual patient trends of consecutive creatinine measurements expressed as CREP2/CREJ2 ratio and aggregated and ranked to “sampling time events” from the first event through the tenth event. To visualize individual time-dependent trends of ratios of creatinine concentrations, we used relative timescale aggregating measurements as ordinal data. Boxplots of all patients/all measurements showed as “sampling time events 1 through 10” on the x-axis against the ratio of creatinine concentrations by CREP2/CREJ2 are shown. Major deviations from the median line observed among the 2nd through 7th measurement events implying a drug effect present but then returning to result concordance showed as a ratio approximately 1 implying a drug effect being “washed out.”

nature of these drug-related interferences is not fully clear (26), our hypothesis is that drugs and/or drug-related substances with reducing chemical properties may interfere with the hydrogen peroxide/peroxidase step, thus severely affecting the reporter reaction.

Limitations

Our report has several limitations. First, we did not mention which of the two methods produces “true” results. From a laboratory point of

view, the *personalized and often temporary nature* of these abnormalities does not enable their detection by external means such as proficiency testing surveys, where both methods perform satisfactorily, nor by internal means such as delta checks in patients with *no medical record history*. Nevertheless, under our survey design, the CREJ2 method did not produce any false-negative results. Second, the lower limit of quantitation is higher for CREJ2 methods than enzyme methods, which is a limitation in pediatric medicine. Therefore, our pediatric algorithm for specimens $<20 \mu\text{mol/L}$ by CREJ2 implies that both methods are used; notably, in interference-free specimens, the CREP2 method showed

excellent analytical performance, stability, and linearity down to 7 $\mu\text{mol/L}$ (data not shown). Third, it was not technically possible to timely screen all patient records for all possible medications, in part due to the legal inaccessibility of some records.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

Ethics statement

The studies involving humans were approved by the University Hospital Brno, Multicentric Ethics Review Board, approval No. 03-091122/EK. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from a by-product of routine care or industry. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

RD conceived the topic, codesigned methods and pharmacovigilance issues, participated in the result interpretation and writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. SK conceived the topic, codesigned methods, performed medication analysis, participated in result interpretation and writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. MRih conceived the topic, performed interactions with clinical wards with documentation reviews and medication analyses, participated in the result interpretation and writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. DB reviewed patient documentation, performed pediatric analyses with composite eGFR calculations such as Schwartz formulas, participated in the writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. KH reviewed patient documentation, performed medication analyses, participated in the result interpretation and writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. OW performed laboratory workups, participated in conceiving the topic and writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. LB participated in the design of the survey and its conception, performed statistical analyses, participated in the result interpretation and writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. IS surveyed statistical analyses, participated in the writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for

publication. MP performed laboratory analyses, participated in the writing of the manuscript, was confirmed having full access to all the data in the study, and accepted the responsibility to submit for publication. AK performed clinical case analyses, participated in conceiving the manuscript and in result interpretation and writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. AM performed pediatric laboratory analyses, participated in the writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. MB performed laboratory analyses, participated in the writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. JS coordinated laboratory practice for pediatric patients and participated in the writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. MRa coordinated laboratory analyses in an outpatient population, participated in result interpretation and writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. MRic performed laboratory analyses in an outpatient population, participated in the writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. LZ conceived the topic, coordinated working activities, surveyed medication analyses with a focus on antimicrobial therapy, coordinated overall interpretations of findings and writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. DV conceived the topic, coordinated all working activities, surveyed all analyses, coordinated final result interpretation, edited and coordinated the writing of the manuscript, was confirmed to have full access to all the data in the study, and accepted the responsibility to submit for publication. All authors contributed to the article and approved the submitted version.

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DV declares that the study is (i) the own work of the author's team and that (ii) neither the DV nor any of the coauthors have a conflict of interest in regard to this manuscript to declare.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 1 Clinical cases showing blood creatinine concentrations against patient emergency pharmacotherapy timeframe.

Hospital Department, where the adverse event was detected	Patient/date	CREP2 ($\mu\text{mol/l}$)	CREJ2 ($\mu\text{mol/l}$)	Relevant medications (active substances) from patient discharge summaries (dosage unavailable) and/or daily medication cards (dosage available)
	1 (LR)	CREP2	CREJ2	
Department of Surgery	10 January 2023	186	N/A	Paracetamol 1 g orally every 8 h
	12 January 2023	201	N/A	
	14 January 2023	131	N/A	
	15 January 2023	187	325	
	16 January 2023	261	355	
	17 January 2023	304	311	
	18 January 2023	294	288	
	19 January 2023	289	N/A	
	20 January 2023	257	254	
		2 (NN)	CREP2	
Department of Surgery	11 January 2023	81	N/A	Paracetamol 1 g/100 mL i.v. every 8 h (20 min), etamsylate 500 mg i.v. every 8 h
	12 January 2023	92	N/A	
	13 January 2023	34	N/A	
	14 January 2023	61	87	
	15 January 2023	90	86	
	16 January 2023	106	98	
		3 (AE)	CREP2	
Department of Surgery	15 January 2023	124	264	Paracetamol, metamizole, etamsylate 500 mg i.v. every 4h
	16 January 2023	127	220	
	17 January 2023	89	177	
	24 January 2023	135	130	
	4 (KL)	CREP2	CREJ2	
Department of Surgery	13 January 2023	209	N/A	Etamsylate, noradrenalin continuous, paracetamol i.v., metamizole i.v.
	14 January 2023	125	N/A	
	15 January 2023	108	193	
	16 January 2023	124	215	
	17 January 2023	154	264	
	18 January 2023	188	308	
	19 January 2023	243	N/A	
	20 January 2023	305	376	
	21 January 2023	334	353	
	22 January 2023	351	365	
		5 (LN)	CREP2	
Department of Infectious Diseases	15 January 2023	223	330	Metamizole, noradrenalin
	16 January 2023	250	318	
	19 January 2023	232	N/A	
	20 January 2023	220	219	
	21 January 2023	210	227	
		6 (AA)	CREP2	

(Continued)

TABLE 1 (Continued)

Hospital Department, where the adverse event was detected	Patient/date	CREP2 ($\mu\text{mol/l}$)	CREJ2 ($\mu\text{mol/l}$)	Relevant medications (active substances) from patient discharge summaries (dosage unavailable) and/or daily medication cards (dosage available)
Department of Anaesthesiology and Intensive Care Medicine	10 January 2023	117	N/A	Etamsylate 500 mg i.v. every 6 h acetylcysteine inj. 300 mg i.v. every 12 h
	11 January 2023	109	N/A	
	12 January 2023	87	N/A	
	13 January 2023	67	N/A	Noradrenalin 5 mg / 50 mL i.v. paracetamol 1 g i.v. 100 mL (20 min) every 6 h metamizole 1 g/20 mL (30 min)
	14 January 2023	33	N/A	
	15 January 2023	59	80	
	16 January 2023	59	65	
	17 January 2023	67	55	
	18 January 2023	70	61	
		7 (AH)	CREP2	
Department of Pulmonary Diseases and Tuberculosis	11 January 2023	240	N/A	Etamsylate, paracetamol
	13 January 2023	231	N/A	
	15 January 2023	54	131	
	8 (NN)	CREP2	CREJ2	
Department of Internal Medicine and Cardiology	14 January 2023	184	N/A	Metamizole
	15 January 2023	172	248	
	16 January 2023	212	210	
	18 January 2023	133	127	
	21 January 2023	147	170	
	9 (YN)	CREP2	CREJ2	
Referred from another hospital	10 January 2023	307	N/A	Etamsylate administered before patient transportation
	11 January 2023	377	N/A	
	12 January 2023	347	N/A	
	15 January 2023	233	354	
	10 (KI)	CREP2	CREJ2	
Department of Burns and Plastic Surgery	10 January 2023	62	N/A	Etamsylate, noradrenalin, metamizole, paracetamol
	16 January 2023	36	54	
	17 January 2023	39	50	
	22 January 2023	44	53	
	27 January 2023	54	52	
	11 (AVA)	CREP2	CREJ2	
Department of Internal Medicine, Hematology and Oncology	14 January 2023	51	N/A	Metamizole 500 mg orally every 8 h
	15 January 2023	35	45	
	16 January 2023	26	42	
	17 January 2023	35	30	
	19 January 2023	46	N/A	
	23 January 2023	43	35	
	12 (KF)	CREP2	CREJ2	
Department of Neurosurgery	16 January 2023	50	100	Etamsylate
	17 January 2023	73	85	
	18 January 2023	74	77	
	19 January 2023	77	N/A	
	20 January 2023	86	79	
	13 (KRT)	CREP2	CREJ2	

(Continued)

TABLE 1 (Continued)

Hospital Department, where the adverse event was detected	Patient/date	CREP2 ($\mu\text{mol/l}$)	CREJ2 ($\mu\text{mol/l}$)	Relevant medications (active substances) from patient discharge summaries (dosage unavailable) and/or daily medication cards (dosage available)
Department of Anaesthesiology and Intensive Care Medicine	14 January 2023	97	N/A	Etamsylate 500 mg i.v. every 6 h, noradrenalin 5 mg/50 mL i.v., paracetamol 1 g/100 mL i.v. (30 min) as needed
	15 January 2022	100	119	
	16 January 2022	86	161	
	17 January 2023	137	132	
	18 January 2023	130	123	
	19 January 2023	105	N/A	
	14 (KL)	CREP2	CREJ2	
Department of Geriatric Medicine	15 January 2023	159	152	Etamsylate
	16 January 2023	116	209	
	17 January 2023	96	102	
	18 January 2023	157	161	
	20 January 2023	113	92	
	23 January 2023	107	83	
	15 (LN)	CREP2	CREJ2	
Department of Internal Medicine and Cardiology	10 January 2023	343	N/A	Metamizole, tramadol/paracetamol, acetylcysteine
	11 January 2023	386	N/A	
	12 January 2023	430	N/A	
	13 January 2023	467	N/A	
	14 January 2023	419	N/A	
	15 January 2023	396	398	
	16 January 2023	365	397	
	17 January 2023	276	370	
16 (AA)	CREP2	CREJ2		
	10 January 2023	47	N/A	Not accessible
	17 January 2023	41	61	
	24 January 2023	43	54	
17 (KD)	CREP2	CREJ2		
Department of Neurology	14 January 2023	102	N/A	Etamsylate
	17 January 2023	51	82	
18 (ATA)				
Department of Burns and Plastic Surgery	12 January 2023	62	N/A	Not accessible
	12 January 2023	37	N/A	
	14 January 2023	47	N/A	
	17 January 2023	49	45	
	18 January 2023	8	73	
	18 January 2023	36	52	
	19 January 2023	46	N/A	
	23 January 2023	56	47	
	26 January 2023	64	N/A	
19 (OJ)	CREP2	CREJ2		
Department of Neurology	17 January 2023	100	108	Metamizole, paracetamol, etamsylate
	18 January 2023	56	103	
	21 January 2023	48	92	

(Continued)

TABLE 1 (Continued)

Hospital Department, where the adverse event was detected	Patient/date	CREP2 ($\mu\text{mol/l}$)	CREJ2 ($\mu\text{mol/l}$)	Relevant medications (active substances) from patient discharge summaries (dosage unavailable) and/or daily medication cards (dosage available)
	20 (AVA)	CREP2	CREJ2	
Department of Urology	18 January 2023	79	68	Etamsylate, metamizole, paracetamol
	19 January 2023	36	75	
	21 (SI)	CREP2	CREJ2	
Department of Urology	18 January 2023	106	97	Metamizole, etamsylate, paracetamol
	19 January 2023	68	119	
	23 January 2023	90	87	
	23 (IN)	CREP2	CREJ2	
Department of Burns and Plastic Surgery	13 January 2023	45	N/A	
	14 January 2023	60	N/A	
	15 January 2023	54	52	
	17 January 2023	45	49	Not accessible
19 January 2023	28	49		
20 January 2023	36	42		
22 January 2023	22	45		
27 January 2023	45	43		
	24 (YK)	CREP2	CREJ2	
Department of Burns and Plastic Surgery	13 January 2023	68	N/A	Not accessible
	16 January 2023	59	68	
	18 January 2023	52	77	
	19 January 2023	65	N/A	
	20 January 2023	39	69	
	23 January 2023	84	85	
	24 January 2023	69	68	
	25 January 2023	56	46	
	27 January 2023	49	47	
	25 (KL)	CREP2	CREJ2	
Department of Neurosurgery	18 January 2023	95	84	Etamsylate, acetylcysteine, paracetamol
	20 January 2023	77	118	
	21 January 2023	94	98	
	21 January 2023	91	92	
	22 January 2023	102	98	
	23 January 2023	81	83	
	24 January 2023	107	93	
	25 January 2023	91	84	
	26 (LLF)	CREP2	CREJ2	
Department of Internal Medicine and Gastroenterology	18 January 2023	406	358	Etamsylate
	19 January 2023	276	N/A	
	20 January 2023	284	431	
	21 January 2023	273	448	
	22 January 2023	267	448	
	23 January 2023	345	415	
	24 January 2023	391	379	

(Continued)

TABLE 1 (Continued)

Hospital Department, where the adverse event was detected	Patient/date	CREP2 ($\mu\text{mol/l}$)	CREJ2 ($\mu\text{mol/l}$)	Relevant medications (active substances) from patient discharge summaries (dosage unavailable) and/or daily medication cards (dosage available)
	27 (SN)	CREP2	CREJ2	
Department of Internal Medicine and Gastroenterology	18 January 2023	74	81	Polymedication including terlipressin acetate
	19 January 2023	69	N/A	
	20 January 2023	48	78	
	21 January 2023	59	67	
	22 January 2023	38	85	
	23 January 2023	79	81	
	24 January 2023	102	87	
	25 January 2023	102	103	
	26 January 2023	95	N/A	
	27 January 2023	89	83	
	28 (YEL)	CREP2	CREJ2	
Department of Urology	20 January 2023 (11:43)	442	640	
	20 January 2023 (17:05)	362	583	
	21 January 2023	304	587	
	22 January 2023	263	492	
	23 January 2023	228	324	
Department of Surgery	24 January 2023 (5:05)	294	333	Etamsylate 500 mg i.v. every 6 h, metamizole every 8 h
	24 January 2023 (17:08)	317	379	
	25 January 2023	330	355	
	26 January 2023	366	N/A	
	27 January 2023	429	429	
	28 January 2023	462	474	
	29 January 2023	494	496	
	29 (PŘI)	CREP2	CREJ2	
Department of Neurosurgery	20 January 2023	94	100	Metamizole 500 mg every 12 h, etamsylate
	21 January 2023	80	88	
	22 January 2023 (6:07)	42	85	
	22 January 2023 (9:35)	82	113	
	23 January 2023	67	112	
	24 January 2023	49	98	
	25 January 2023	100	96	
	30 (ATA)	CREP2	CREJ2	
Department of Anaesthesiology and Intensive Care Medicine	21 January 2023	78	93	Etamsylate 500 mg i.v. every 4 h
	22 January 2023	32	67	
	23 January 2023	29	64	
	31 (AEL)	CREP2	CREJ2	
Department of Infectious Diseases Department of Urology	16 January 2023	119	105	Etamsylate, paracetamol
	24 January 2023	57	102	
	29 January 2023	108	212	
	30 January 2023	72	178	
	31 January 2023	67	140	
	01 February 2023	92	108	

(Continued)

TABLE 1 (Continued)

Hospital Department, where the adverse event was detected	Patient/date	CREP2 ($\mu\text{mol/l}$)	CREJ2 ($\mu\text{mol/l}$)	Relevant medications (active substances) from patient discharge summaries (dosage unavailable) and/or daily medication cards (dosage available)
	32 (KIR)	CREP2	CREJ2	
Department of Urology	23 January 2023	113	127	Polymedication including: ampicillin/sulbactam, bisoprolol, enoxaparine, methoclopramide, simeticone, omeprazole, itopride, alopurinol, pantoprazole, rosuvastatine, metformin, rivaroxaban, linesolide, bromazepam
	24 January 2023	75	149	
	25 January 2023	149	138	
	27 January 2023	151	147	
	29 January 2023	146	132	
	33 (YAV)	CREP2	CREJ2	
Department of Urology	23 January 2023	42	141	Metamizole, etamsylate, paracetamol
	24 January 2023	75	167	
	25 January 2023	105	168	
	27 January 2023	117	154	
	29 January 2023	111	118	
	34 (LRI)	CREP2	CREJ2	
Department of Urology	16 January 2023	84	69	Metamizole, etamsylate, paracetamol
	23 January 2023	90	87	
	24 January 2023	46	77	
	25 January 2023	66	63	
	27 January 2023	50	86	
	29 January 2023	77	77	
	35 (SAN)	CREP2	CREJ2	
	25 January 2023 (0:35)	54	83	
	25 January 2023 (6:17)	54	75	
Department of Anaesthesiology and Intensive Care Medicine Department of Surgery	25 January 2023 (8:19)	54	77	Etamsylate 500 mg i.v. every 4 h
	26 January 2023	53	N/A	
	27 January 2023	48	57	
	30 January 2023	51	60	
	36 (AAV)	CREP2	CREJ2	
Department of Infectious Diseases	20 January 2023	133	142	Polymedication including: insuline-lispro, insuline-glargin, perindopril-arginine, linezolid, rosuvastatin, pantoprazol
	23 January 2023	137	134	
	25 January 2023	40	115	
	37 (HAN)	CREP2	CREJ2	
Department of Surgery	15 January 2023	142	140	From 21 January 2023: etamsylate 500 mg i.v. every 6 h paracetamol 1 g i.v. every 8 h, noradrenalin continuous
	21 January 2023	345	336	
	22 January 2023	285	337	
	23 January 2023	192	319	
	24 January 2023	157	286	
	25 January 2023	124	270	
	27 January 2023	120	350	
	28 January 2023	151	340	
	29 January 2023	149	342	
	30 January 2023	194	326	

(Continued)

TABLE 1 (Continued)

Hospital Department, where the adverse event was detected	Patient/date	CREP2 ($\mu\text{mol/l}$)	CREJ2 ($\mu\text{mol/l}$)	Relevant medications (active substances) from patient discharge summaries (dosage unavailable) and/or daily medication cards (dosage available)
	38 (KAV)	CREP2	CREJ2	
Department of Anaesthesiology and Intensive Care Medicine	24 January 2023	153	158	Etamsylate 500 mg i.v. every 4 h, noradrenalin continuous 10 mg / 50 ml i.v., paracetamol 1 g i.v. infusion
	25 January 2023	145	207	
	26 January 2023	239	N/A	
	27 January 2023	179	244	
	28 January 2023	145	155	
	29 January 2023	127	125	
	39 (BCH)	CREP2	CREJ2	
Department of Pulmonary Diseases and Tuberculosis	23 January 2023	48	61	Etamsylate
	25 January 2023	42	63	
	30 January 2023	97	95	
	40 (ALA)	CREP2	CREJ2	
Department of Surgery	26 January 2023	147	N/A	27 January 2023: paracetamol 500 mg á every h i.v., etamsylate 500 mg every 4 h
	27 January 2023	70	132	
	29 January 2023	45	81	
	41 (KAV)	CREP2	CREJ2	
Department of Gastroenterology Department of Urology	19 January 2023	103	98	Paracetamol, etamsylate, erdosteine
	23 January 2023	99	83	
	26 January 2023	61	N/A	
	27 January 2023	90	121	
	28 January 2023	131	155	
	29 January 2023	160	154	
	30 January 2023	147	145	
	42 (TIR)	CREP2	CREJ2	
Department of Internal Medicine and Gastroenterology	25 January 2023	455	N/A	
	26 January 2023	541	N/A	
	27 January 2023	410	593	
	28 January 2023	500	673	
	29 January 2023	584	739	Not accessible
30 January 2023	649	782		
31 January 2023	625	685		
01 February 2023	494	531		
02 February 2023	569	572		
	43 (AIM)	CREP2	CREJ2	
Department of Neurosurgery	26.01.2023	73	N/A	Polymedication including: perindopril-erbumin 4 mg tbl. 1-0-0, omeprazole 20 mg tbl. 1-0-1, dexamethasone 4 mg tbl. 1-0-0, escinum tbl. 2-2-2, nadroparine 0.6 ml s.c. 1x daily
	27.01.2023	45	87	
	31.01.2023	69	64	
	44 (LAS)	CREP2	CREJ2	

(Continued)

TABLE 1 (Continued)

Hospital Department, where the adverse event was detected	Patient/date	CREP2 ($\mu\text{mol/l}$)	CREJ2 ($\mu\text{mol/l}$)	Relevant medications (active substances) from patient discharge summaries (dosage unavailable) and/or daily medication cards (dosage available)
Department of Internal Medicine, Geriatrics and Practical Medicine	21 January 2023	187	181	Paracetamol 500 mg 2–2–2 orally as needed, etamsylate 2amp. iv. every 4 hod. 5–9–13 h, noradrenaline
	23 January 2023	146	145	
	26 January 2023	125	N/A	
	27 January 2023 (6:20)	91	157	
	27 January 2023 (8:57)	82	155	
	28 January 2023	106	167	
	29 January 2023	142	177	
	30 January 2023	177	196	
	31 January 2023	218	220	
		45 (KES)	CREP2	
Department of Otorhinolaryngology	18 January 2023	57	57	Not accessible
	19 January 2023	60	N/A	
	21 January 2023	61	62	
	25 January 2023	56	44	
	27 January 2023	31	53	
	01 February 2023	59	68	
		46 (MAV)	CREP2	
Department of Internal Medicine, Geriatrics and Practical Medicine Department of Neurosurgery Department of Infectious Diseases	23 January 2023	129	112	Paracetamol 500 mg orally 1–1–1 as needed, metamizole 1 g intramuscularly 1–0–1
	25 January 2023	134	N/A	
	26 January 2023	102	N/A	
	27 January 2023	74	127	
	30 January 2023	151	140	
	47 (AOJ)	CREP2	CREJ2	
Department of Urology	26 January 2023	179	N/A	Not accessible
	28 January 2023	150	285	
	01 February 2023	106	232	
	48 (AUB)	CREP2	CREJ2	
Department of Trauma Surgery	28 January 2023	102	103	Metamizole, etamsylate, paracetamol
	29 January 2023	31	89	
	49 (AAR)	CREP2	CREJ2	
Department of Trauma Surgery	28 January 2023	94	95	Paracetamol 1 g i.v. every 8 h
	29 January 2023	18	93	
	50 (YAV)	CREP2	CREJ2	
Department of Internal Medicine and Gastroenterology	27 January 2023	305	296	Not accessible
	28 January 2023	317	348	
	29 January 2023 (6:32)	263	402	
	29 January 2023 (16:54)	181	332	
	30 January 2023	175	353	
	31 January 2023	206	303	
	01 February 2023	217	273	
	02 February 2023	263	296	
	51 (KIN)	CREP2	CREJ2	

(Continued)

TABLE 1 (Continued)

Hospital Department, where the adverse event was detected	Patient/date	CREP2 ($\mu\text{mol/l}$)	CREJ2 ($\mu\text{mol/l}$)	Relevant medications (active substances) from patient discharge summaries (dosage unavailable) and/or daily medication cards (dosage available)
Department of Trauma Surgery	29 January 2023	108	112	Etamsylate, paracetamol
	30 January 2023	39	104	
	31 January 2023	33	90	
	52 (LEF)	CREP2	CREJ2	
Department of Pulmonary Diseases and Tuberculosis	28 January 2023	747	721	Etamsylate
	29 January 2023	646	610	
	30 January 2023	151	202	
	31 January 2023	81	73	
	01 February 2023	66	59	
	53 (AAS)	CREP2	CREJ2	
Department of Anaesthesiology and Intensive Care Medicine	28 January 2023	100	117	Noradrenalin 10 mg / 50 mL continuous i.v.
	29 January 2023	97	109	
	30 January 2023	98	146	
	01 February 2023	143	183	
	02 February 2023	151	154	
	54 (KIR)	CREP2	CREJ2	
Department of Internal Medicine and Gastroenterology	23 January 2023	481	434	Paracetamol
	25 January 2023	477	455	
	30 January 2023	407	627	
	31 January 2023	527	767	
	01 February 2023	635	794	
	02 February 2023	732	862	
	55 (YEL)	CREP2	CREJ2	
Department of Urology	30 January 2023	47	102	Metamizole, etamsylate, paracetamol
	31 January 2023	61	90	

Selection of cases was done on the basis of a 25% fall in preceding creatinine concentrations; data were taken as accessible from medical records.