INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2024.57441
Int J Med Biochem 2024;7(2):95–100

Research Article

Creatinine normalization approach to diluted urine samples screened by LC-MS/MS method

Cigdem Karakukcu[1,2], Derya Kocer[3], Veysel Uzen[3], Hatice Saracoglu[1,2]

[1]Department of Medical Biochemistry, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[2]Medical Biochemistry Laboratory, Drug Application and Research Center, Erciyes University, Kayseri, Türkiye
[3]Department of Medical Biochemistry, University of Health Sciences, Kayseri, Türkiye

Abstract

Objectives: Urine is the most used matrix in drug analysis; however, it is susceptible to adulteration or tampering. Urine creatinine is the most important urine integrity parameter used as an indicator of dilution. This study aimed to evaluate the prevalence of diluted urine samples and the change in positivity after creatinine normalization.

Methods: Urine samples screened by the LC-MS/MS method over a 3.5-year period (n=21,927) were included in the study. Positivity rates were evaluated in both total and diluted urine samples. Additionally, the impact of creatinine normalization on samples with substance concentrations above the limit of quantitation (LOQ) and below the cut-off was investigated.

Results: A total of 350,832 tests were conducted on 21,927 urine samples, resulting in an overall positivity rate of 21.2% (n=4652). The ratio of diluted urine was 1.6% (n=343), with 61.5% (n=211) testing negative (<LOQ), 23.3% (n=80) testing positive (at least one substance >cut-off), and 15.2% (n=52) testing above LOQ and below cut-off. After creatinine normalization in diluted urines, the sample positivity rate increased from 23.3% (n=80) to 33.8% (n=116) (p<0.001), and the substance positivity rate increased from 2.3% (n=125) to 3.9% (n=212) (p<0.001).

Conclusion: Precautions should be taken in reporting diluted urine samples to avoid reporting false negative results. The creatinine normalization approach shows promise in laboratories using quantitative screening methods such as LC-MS/MS for samples with substance concentrations above the LOQ and below the cut-off. However, more clinical and laboratory collaboration is needed for its routine application.

Keywords: Creatinine normalization, diluted urine, illicit drug, screening test

How to cite this article: Karakukcu C, Kocer D, Uzen V, Saracoglu H. Creatinine normalization approach to diluted urine samples screened by LC-MS/MS method. Int J Med Biochem 2024;7(2):95–100.

The urine is the most preferred biological sample for toxicology screening analysis. It has some advantages such as easy sampling, availability of sufficient samples, a higher concentration of substances or metabolites than blood, a wider detection window (average 2–3 days), and availability of validated analysis methods [1, 2]. However, the most important disadvantage is that urine is open to manipulation. For this reason, urine integrity tests are necessary to evaluate whether a urine sample has been diluted or tampered with by mixing with any external chemicals to produce a negative result [3, 4].

The Substance Abuse and Mental Health Services Administration (SAMHSA) recommends creatinine, specific gravity (if creatinine is below 20 mg/dL), and pH tests for urine integrity assessment. Additionally, nitrite, oxidants, or glutaraldehyde tests are preferable. A sample is considered not to be urine or has been replaced if its creatinine level is below 5 mg/dL and the specific gravity is below 1.001 kg/L. If the creatinine is between 5–20 mg/dL and/or the specific gravity is between 1.001–1.003 kg/L, it is classified as a "diluted urine sample" according to both SAMHSA guideline (revised 2018) and Australian Standard As/NZS4308:2008 [5, 6].

Address for correspondence: Cigdem Karakukcu, MD. Department of Medical Biochemistry, Erciyes University Faculty of Medicine, Kayseri, Türkiye; Medical Biochemistry Laboratory, Drug Application and Research Center, Erciyes University, Kayseri, Türkiye
Phone: +90 352 207 66 66 - 13854 **E-mail:** ckarakukcu@hotmail.com **ORCID:** 0000-0001-9858-3272
Submitted: March 18, 2024 **Revised:** April 18, 2024 **Accepted:** April 19, 2024 **Available Online:** May 06, 2024

Urine samples can be diluted through external means such as adding water, or internal means such as consuming large volumes of water or ingesting diuretics. Drug test results in diluted urine make it difficult to determine if the participant is using drugs, as they may provide inconclusive results. In diluted urine samples, analyte concentrations can be achieved below the cut-off value. It is known that urine dilution affects the test results of many substances, including marijuana, amphetamines, cocaine, morphine, codeine, and phencyclidine by lowering their concentrations below the cut-off value [7].

There is an ongoing debate regarding whether diluted urine samples should be rejected or tested in the laboratory. However, a more dominant opinion suggests that these samples should be accepted, as some may still yield positive results. In cases of a positive drug result from diluted urine, the laboratory has detected the presence of an illicit substance despite the dilution. Conversely, when a negative result is obtained from a diluted urine sample, it is unclear whether the donor used any drugs or not [1]. Substances that are below the cut-off value are typically reported as negative [7, 8]. For that reason, detecting results for substances above the limit of quantitation (LOQ) and below the cut-off in diluted urine samples can provide valuable data.

Creatinine is a metabolic waste product that is converted from creatine and creatine phosphate in muscle and excreted by the kidneys. Creatinine production depends on muscle mass, age, gender, water consumption, and diet, but the excretion level is maintained within certain limits over 24 hours in healthy subjects [9, 10]. Therefore, urine creatinine concentration is used as an indicator of urine dilution in urine integrity tests [5]. Creatinine normalization is the process of dividing the analyte concentration by the creatinine concentration in the same urine sample and multiplying by the reference creatinine level [11]. The creatinine normalization of urinary drug concentrations is used by athletic organizations and pain management programs to compensate for dehydration, overhydration, and changes in glomerular filtration rate [11–14]. However, similar procedures have not been yet adopted by drug analysis programs.

Immunoassays are frequently used as a substance screening method. However, liquid chromatography-mass spectrometry (LC-MS/MS) is encouraged for screening analysis nowadays, which has many advantages over immunoassay, such as low determination and quantitation limits, analyzing the drug and their metabolites separately, and lack of cross-reactivity, etc. [15].

This study aimed to investigate the frequency of diluted urine samples accepted to the laboratory over 3.5 years, to determine positivity and negativity rates according to cut-off or LOQ values, and the impact of creatinine normalization on the results of these samples.

Materials and Methods

Samples

This retrospective study received approval from the Clinical Research Ethics Committee of Kayseri City Hospital, in compliance with the Declaration of Helsinki, on July 11, 2023 (Decision No: 866).

Data from drug abuse tests conducted on urine samples accepted from psychiatry, the Alcohol and Drug Abuse Treatment Center, and the Probation Clinic between June 2018 and November 2021 were screened from the laboratory information management system (LIMS), in the Medical Biochemistry Laboratory of Kayseri City Hospital, in Türkiye. Diluted urine samples with creatinine levels between 5–20 mg/dL were identified, and the drug screening results, and demographic data of the subjects were collected for these samples.

Chain of custody was applied to all urine samples. Informed consent was obtained from all subjects. Before sample transfer to the laboratory, urine temperature was measured within 4 minutes after sampling and those not between 32–37°C were rejected.

Urine integrity test

Urine integrity tests (creatinine, specific gravity, nitrite, and pH) were performed before drug screening analysis. Urine creatinine levels were measured on Cobas c701 (Roche Diagnostic, Germany) with the compensated Jaffe method. Specific gravity and pH were evaluated with Dirui H10 urinalysis test strips. Nitrite was measured by a colorimetric method with TEST TRUE™ Nitrite Assay kit (Axiom Diagnostics).

The sample was considered a diluted urine sample if the creatinine was 5–20 mg/dL. Acceptable values for specific gravity are 1.003–1.020.

Analysis of drugs

All urine drug screening analyses were performed by LC-MS/MS method using a Restek Allure PFPP 5µm column (length 50 mm, inner diameter 2.1 mm) on AB-SCIEX 4500 Q-TRAP with a validated in-house method (Table 1). The total flow rate was 0.5 mL/min, the oven temperature was 40°C, and the total analysis duration was 18 minutes. Two-level internal control samples were injected in every single run. Samples were prepared by the "dilute and shoot" technique. After dilution with methanol, the internal standard was spiked and injected into the LC-MS/MS system.

The screened substances, their LOQ determined by verification studies, and administratively determined cut-off values were presented in Table 2. The cut-off values were based on SAMHSA LC-MS/MS cut-off concentrations. For opiate group drugs, the optimal cut-off values were determined by our previous published study [16]. Targeted analytes were amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine

Table 1. Method validation results

Substances	Linear range (ng/mL)	Precision (RSD%)	Accuracy (Bias%)
Amphetamine	5–2000	3.97	15.07
Methamphetamine	5–2000	2.4	15.1
MDMA	5–2000	1.91	–3.07
Benzoylecgonine	1–2000	0.33	9.37
THC-COOH	5–200	1.75	–1.25
Morphine	25–2000	1.31	2.1
Codeine	25–2000	0.79	5.39
6-MAM	5–500	0.87	0.35
Diazepam	12.5–500	2.7	–0.92
Clonazepam	25–500	2.25	–0.29
Lorazepam	12.5–500	2.33	1.16
JWH-18	6.25–100	2.23	–11.31

RSD% and bias% values less than 20% were acceptable. RSD: Relative standard deviation; MDMA: 3,4-methylenedioxymethamphetamine; THC-COOH: 11-Nor-9-carboxy-Δ9-tetrahydrocannabinol; 6-MAM: 6-monoacetylmorphine.

(MDMA) for amphetamines; benzoylecgonine for cocaine; 11-Nor-9-carboxy-Δ9-tetrahydrocannabinol (THC-COOH) for cannabinoids; morphine, codeine, and 6-monoacetylmorphine (6-MAM) for opiates; diazepam, clonazepam, and lorazepam for benzodiazepines; AB PINACA, AB FUBINACA, UR-144, AM-2201, and JWH-18 for synthetics. Carbamazepin-d3 and methadone-d3 were used as internal standards.

Creatinine normalization study

Similar to the study conducted by Cone et al. [11], we established our reference creatinine values to ensure suitable adjustments for our specific population. From the mean urinary creatinine concentration of 200 healthy subjects (100 female and 100 male), we determined 97 mg/dL for females and 118 mg/dL for males. For diluted urine samples with drug screening results above the LOQ and below the cut-off, creatinine normalization was applied for each substance using the following formula. Subsequently, the results were re-evaluated in terms of positivity.

$$\text{Substance concentratio after normalized creatinine} = \text{Substance concentration} \times \frac{\text{Reference Creatinine}}{\text{Sample Creatinine}}$$

Study data were analyzed on Analyse-it for Microsoft Excel (Analyse-it Software, Ltd, The Tannery, 91 Kirkstall Road, Leeds, United Kingdom). In addition, positivity rates before and after creatinine normalization were compared using the Pearson Chi-square Test on SPSS 22.0 package program (IBM Corp., Armonk, NY, USA).

Results

Over 3.5 years, a total of 21,927 urine samples were accepted to the laboratory for drug screening, with 350,832 tests (16 parameters for each urine sample) performed. 91% (n=19,958) were men, and the median age was 31 years (min-max, 17–68). The overall positivity rate was 21.2% (n=4,652).

Table 2. Substances screened in drug screening analysis and their LOQ and cut-off values

Substance	LOQ (ng/mL)	Cut-off (ng/mL)*
Amphetamine	1.5	250
Methamphetamine	1.8	250
MDMA	1.32	250
Benzoylecgonine	2.34	150
THC-COOH	1.65	15
Morphine**	11.02	300
Codeine**	4.69	300
6-MAM	2.24	10
Diazepam	2.89	300
Clonazepam	8.13	300
Lorazepam	6.5	300
AB PINACA	1.31	10
AB FUBINACA	1.27	10
UR-144	1.38	10
AM-2201	1.21	10
JWH-18	1.35	10

*: The used cut-off values were taken from "Standard Drug Testing Cut-Off Levels from SAMHSA Certified Labs"; **: For morphine and codeine, the cut-off values were lowered to 300 ng/mL [16]. LOQ: Limit of Quantitation; MDMA: 3,4-methylenedioxymethamphetamine; THC-COOH: 11-Nor-9-carboxy-Δ9-tetrahydrocannabinol; 6-MAM: 6-monoacetylmorphine.

1.6% (n=343) of urine samples were categorized as "diluted". Of these, 84.5% (n=290) were from men, and the median age was 32 years (min-max, 19–68). When the drug screening results were examined, 61.5% (n=211) tested negative for all substances (<LOQ), while 23.3% (n=80) tested positive for at least one substance (>cut-off), and 15.2% (n=52) had substance concentration(s) above LOQ and below cut-off (Table 3). The most frequently detected substances in diluted urine samples were amphetamine and methamphetamine.

After creatinine normalization, the sample positivity rate was achieved from 23.3% (n=80) to 33.8% (n=116) (p<0.001), and the substance positivity rate was increased from 2.3% (n=125) to 3.9% (n=212) (p<0.001) in diluted urine samples (Table 4, Fig. 1). As a result, 69.2% (n=36) of the samples with substance concentrations above the LOQ and below the cut-off became positive.

Discussion

In most drug analysis laboratories, creatinine measurement is a standard component of urine integrity testing. Urine samples with creatinine levels between 5–20 mg/dL are classified as diluted, and it is advisable to report results from these samples [5]. This approach helps to avoid both

Table 3. Positivity and negativity rates of total and diluted urine samples

	Total urine sample		Diluted urine sample	
	n	%	n	%
Sample	21927	100	343	1.6
Negative samples (<cut-off)	17275	78.8	263	76.7
Negative samples (<LOQ)	15112	68.9	211	61.5
Negative samples (>LOQ and <cut-off)	2163	9.9	52	15.2
Positive samples (>cut-off)	4652	21.2	80	23.3
Substance	350832	100	5488	1.6
Negative substances (<cut-off)	339528	96.8	5363	97.7
Negative substances (<LOQ)	304808	86.9	5235	95.4
Negative substances (>LOQ and <cut-off)	34720	9.9	128	2.3
Positive substances (>cut-off)	11304	3.2	125	2.3

LOQ: Limit of Quantitation.

Table 4. The effect of creatinine normalization on positivity rates of diluted urine samples

	Before creatinine normalization		After creatinine normalization		p
	n	%	n	%	
Negative samples (>LOQ and <cut-off)	52	15.2	16	4.7	<0.001
Positive samples (>cut-off)	80	23.3	116	33.8	
Negative substances (>LOQ and <cut-off)	128	2.3	41	0.7	<0.001
Positive substances (>cut-off)	125	2.3	212	3.9	

The positivity rates before and after creatinine normalization were compared with Pearson Chi-square Test. LOQ: Limit of Quantitation.

wasted time and the possibility of missing a positive result with potential forensic implications.

Consuming a large volume of water and using diuretics can dilute urine, providing a simple way to obtain a test result below the cut-off concentration [3]. Attempts to dilute urine before substance analyses are common, even when chain of custody is applied. In this study, despite the chain of custody, the prevalence of diluted urine was 1.6% (n=343). However, despite the number of attempts, cheating on drug tests is not as straightforward as it may seem; most cheaters are apprehended, and, in fact, the majority of diluted urine samples still tested positive [17, 18]. In this study, 23.3% of diluted urine samples tested positive for at least one substance (>cut-off value). However, the presence of substance concentration(s) above the LOQ and below the cut-off was observed in 15.2%. Such a result could be a "true negative" or a "false negative."

One approach to reducing the false negative rate in urine drug analysis programs has used lower screening and confirmation cut-off concentrations (e.g., LOQ) for diluted urine samples instead of administrative cut-offs. In this context, the Correctional Services Canada (CSC) program accepts cut-off values of amphetamine 100 ng/mL, benzoylecgonine 150 ng/mL, opiates 120 ng/mL, and cannabinoids 20 ng/mL for diluted urine samples [19]. Fraser and Zamecnik reported that 25.9% (n=2054) of 7912 diluted urine samples were positive according to SAMHSA cut-off concentrations. When the same samples were evaluated with lower cut-off concentrations defined by CSC, the positivity rate increased to 39.9% (n=3154). This study by Fraser and Zamecnik showed that the false negative screening rate in diluted urine samples can be effectively reduced by using lower cut-off concentrations [19, 20]. However, there is still no worldwide consensus on cut-off values. Therefore, lowering cut-off values for diluted urine samples is challenging.

There are several studies examining the applicability of creatinine normalization for drug analysis in diluted urine samples [11–14]. Athletic organizations and pain management programs employ creatinine normalization of urinary drug concentrations to account for dehydration, overhydration, and variations in glomerular filtration rate. However, similar procedures have not yet been adopted by other drug analysis programs.

In this study, the creatinine normalization procedure was applied and 32 of 52 urine samples with substance concentrations above the LOQ and below the cut-off became pos-

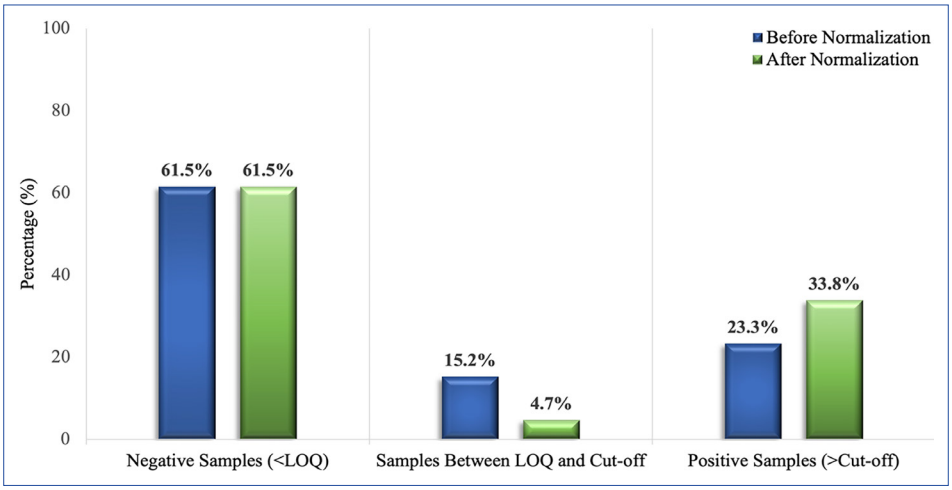

Figure 1. Change in positivity rates of diluted urine samples after creatinine normalization.
LOQ: Limit of Quantitation.

itive. This increased the positivity rate from 23.3% to 33.8%. The creatinine normalization approach seems to be potentially beneficial to decrease the possibility of false-negative results in diluted urine samples. Across diluted positive samples, the highest positivity rate was for methamphetamine and amphetamine. Methamphetamine abuse is growing, and it is the most commonly used substance in the last two years in Middle Anatolia in Türkiye [21].

There are a few points to consider in this application. Urine water content varies according to fluid intake throughout the day. Therefore, the analyte/creatinine ratio is a common approach used to normalize analyte levels in random spot urine samples, as it helps to account for variations in urine concentration (such as urine protein/creatinine, albumin/creatinine, cortisol/creatinine ratios). The use of analyte/creatinine ratios is indeed preferred over absolute analyte concentrations alone [22, 23]. In healthy individuals, the analyte/creatinine ratio is a reasonable way to account for variations in urine concentration. Nevertheless, in the presence of conditions, such as tubular dysfunction, that could potentially alter (decrease or increase) the renal excretion of the substance and/or creatinine, the accuracy of the creatinine normalization approach could be compromised. Therefore, information on "chronic diseases" should be requested for each sample. Furthermore, creatinine normalization is applicable only in laboratories using quantitative screening methods. Semi-quantitative methods, such as immunoassays, do not incorporate this application.

The Jaffe method, widely preferred for creatinine measurement similar to our study, is not specific to creatinine and may be affected by various interferences. Interference from bilirubin, glucose, protein, ketone bodies, and cephalosporins is notable. Bilirubin causes negative interference, while the others cause positive interference, potentially measuring values up to 25% higher than the true value. Although kinetic measurements can largely mitigate this effect, interferences stemming from alpha-ketoacids may persist, particularly affecting low creatinine levels (e.g., diluted urine samples) [24]. Therefore, it will be particularly important to choose more reliable methods for the creatinine normalization approach. Enzymatic-based methods may enhance measurement specificity, while the development of techniques for simultaneous creatinine and substance measurement on LC-MS/MS could offer a promising approach.

We recommend that an approach should be chosen according to the reason for requesting drug screening. A creatinine normalization approach is preferable in cases under follow-up, such as probation. However, even if creatinine normalization is not applied, laboratory specialists should report absolute analyte concentrations together with creatinine values in their reports and interpret the results more carefully. When a negative result is detected in a diluted urine sample, "diluted urine sample" information should be added to the laboratory report, and the interpretation of the analysis result should be left to the authority requesting the test. In addition, these samples should be kept for the legal storage period even if they are negative [21, 25].

The strength of our study is the large number of samples. However, a limitation is that the screening panel had to be restricted to only 16 substances due to the large daily flow of samples, which would be very time-consuming and troublesome if included in a wide variety of drugs/substances.

Conclusion

In conclusion, precautions should be taken to avoid reporting false negative results in diluted urine samples. The creatinine normalization approach, for the samples with substance concentrations between the LOQ and cut-off values, may be applied. However, more laboratory-cooperated studies are needed to enable routine application.

Ethics Committee Approval: The study was approved by The Kayseri City Hospital Clinical Research Ethics Committee (No: 866, Date: 11/07/2023).

Authorship Contributions: Concept – C.K., D.K.; Design – C.K.; Supervision – C.K.; Funding – C.K.; Materials – C.K., D.K., V.U.; Data collection &/or processing – C.K., D.K., V.U.; Analysis and/or interpretation – C.K., H.S.; Literature search – C.K., H.S.; Writing – C.K., H.S.; Critical review – C.K.

Conflict of Interest: The authors declare that there is no conflict of interest.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

References

1. Hadland SE, Levy S. Objective testing: Urine and other drug tests. Child Adolesc Psychiatr Clin N Am 2016;25(3):549–65. [CrossRef]
2. Singh Z. Forensic toxicology: Biological sampling and use of different analytical techniques. Forensic Res Criminol Int J 2017;4(4):117–20. [CrossRef]
3. Mizrak S. Fraudulent methods causing false negatives in urine drug testing. Biomed J Sci Tech Res 2019;14(1):10335–37. [CrossRef]
4. Fu S. Adulterants in urine drug testing. Adv Clin Chem 2016;76:123–63. [CrossRef]
5. SAMHSA guidelines. Substance Abuse and Mental Health Service Administration. Available at: https://www.samhsa.gov/medications-substance-use-disorders/statutes-regulations-guidelines. Accessed Apr 26, 2024.
6. Australian/New Zealand Standard. Procedures for specimen collection and detection and quantitation of drugs of abuse in urine. AS/NZS4308:2008. Standards Australia/Standards New Zealand.
7. Dasgupta A. The effects of adulterants and selected ingested compounds on drugs-of-abuse testing in urine. Am J Clin Pathol 2007;128(3):491–503. [CrossRef]
8. Franz S, Skopp G, Musshoff F. The effect of creatine ingestion on urinary creatinine concentration: Does supplementation mask a heavy dilution? Drug Test Anal 2022;14(1):162–68. [CrossRef]
9. Gounden V, Bhatt H, Jialal I. Renal function tests. Available at: https://www.ncbi.nlm.nih.gov/books/NBK507821/. Accessed Apr 26, 2024.
10. Sallsten G, Barregard L. Variability of urinary creatinine in healthy individuals. Int J Environ Res Public Health 2021;18(6):3166. [CrossRef]
11. Cone EJ, Caplan YH, Moser F, Robert T, Shelby MK, et al. Normalization of urinary drug concentrations with specific gravity and creatinine. J Anal Toxicol 2009;33(1):1–7. [CrossRef]
12. Price JW. Creatinine normalization of workplace urine drug tests: Does it make a difference? J Addict Med 2013;7(2):129–32. [CrossRef]
13. Aydoğdu M, Oral S, Akgür SA. The impact of creatinine reference value: Normalization of urinary drug concentrations. J Forensic Sci 2021;66(5):1855–61. [CrossRef]
14. Sawant PD, Kumar SA, Wankhede S, Rao DD. Creatinine as a normalization factor to estimate the representativeness of urine sample - intra-subject and inter-subject variability studies. Appl Radiat Isot 2018;136:121–26. [CrossRef]
15. Kahl KW, Seither JZ, Reidy LJ. LC-MS-MS vs ELISA: Validation of a comprehensive urine toxicology screen by LC-MS-MS and a comparison of 100 forensic specimens. J Anal Toxicol 2019;43(9):734–45. [CrossRef]
16. Karakukcu C, Cıracı MZ, Kocer D, Serdar MA. Evaluation of optimal urine screening and confirmation cutoff values for opiates, at a national reference laboratory. Turk J Biochem 2021;46(5):593–602. [CrossRef]
17. Standridge JB, Adams SM, Zotos AP. Urine drug screening: A valuable office procedure. Am Fam Physician 2010;81(5):635–40.
18. Cook JD, Caplan YH, LoDico CP, Bush DM. The characterization of human urine for specimen validity determination in workplace drug testing: A review. J Anal Toxicol 2000;24(7):579–88. [CrossRef]
19. Fraser AD, Zamecnik J. Substance abuse monitoring by the Correctional Service of Canada. Ther Drug Monit 2002;24(1):187–91. [CrossRef]
20. Fraser AD, Zamecnik J. Impact of lowering the screening and confirmation cutoff values for urine drug testing based on dilution indicators. Ther Drug Monit 2003;25(6):723–27. [CrossRef]
21. Karakükcü Ç, Çiraci MZ, Koçer D, Zararsız GE, Reyhancan M, Altintop I. Regional drug abuse prevalence depending on laboratory-based urine illicit drug screening results. Alpha Psychiatry 2018;19:169–76. [CrossRef]
22. Abusoglu S, Aydın I, Bakar F, Bekdemir T, Gulbahar O, Islekel H, et al. A short guideline on chronic kidney disease for medical laboratory practice. Turk J Biochem 2016;41(4):292–301. [CrossRef]
23. Kapoor N, Job V, Jayaseelan L, Rajaratnam S. Spot urine cortisol-creatinine ratio - A useful screening test in the diagnosis of Cushing's syndrome. Indian J Endocrinol Metab 2012;16(Suppl 2):376–77. [CrossRef]
24. Lamb EJ, Jones GRD. Kidney function tests. In: Rifai N, Chiu RWK, Young I, Burnham CD, Wittwer CT, editors. Tietz Textbook of Laboratory Medicine. 7th ed. St. Louis: Elsevier; 2023. p. 352.e11-17.
25. Küme T, Karakükcü Ç, Pınar A, Coşkunol H. the scope, quality and safety requirements of drug abuse testing. Türk Psikiyatr Derg [Article in Turkish] 2017;28(3):198–207. [CrossRef]