Original article

Could Urine pH be a New Parameter for Mortality?

Ayşe ŞahinTutak[1], Hüseyin Avni Fındıklı[2]

[1]Department of Internal Medicine, Adıyaman University School of Medicine, Adıyaman, Turkey; [2]Department of Internal-Medicine, NecipFazıl Research and Training Hospital, Kahramanmaraş, Turkey

Summary. *Background:* Full urineanalysis is a simple and in expensive test that can be easily performed in almost all laboratories and provides extremely useful information. This study aimed to examine whether urinary pH has any prognostic role in respect of mortality in intensive care unit (ICU) patients. *Methods:*In this study, a retrospective examination of patients hospitalized in the Internal Diseases Intensive Care Unit between 2017-2018 at theInvestigators' Hospital was performed. A total of 2100 patients were excluded, of which 563 met at least one of the exclusion criteria. *Results:* Age, the total length of hospital stay (TLSH), and mortality were significantly higher in the pH ≤ 5.5 group (p<0.001). In the multivariate logistic regression analysis, the age (p < 0001, OR = 0.978), TLSH (p < 0001, OR = 0.932), and urinary pH (p < 0.05, OR = 0.718) levels were determined as independent risk factors associated with mortality. *Conclusion:* The pHvalue in general ICU patients was evaluated in respect of mortality could be an independent risk factor for morbidity and mortality.

Key words: Intensive care unit, mortality, urinary pH

Introduction

Full urine analysis is a simple and inexpensive test that can be easily performed in almost all laboratories and provides extremely useful information. Full urine analysis can be applied in dipstick form or with microscopic and chemical methods, and test results are obtained in a very short time. Full urine analysis provides important information about the presence and activity of renal disease and is an important adjuvant test in the diagnosis of urinary infection. Urine pH shows the ability of the kidney to express normal hydrogenion concentration in the plasma and extracellular fluid. Normal urine pH varies between 4.5 and 8, and is generally 6. Very few studies have been conducted related to the changes in urine pH, and those published in the literature have shown variations in pH according to infections, metabolic syndrome,diet, exercise and gender (1-5). However, to our knowledge, there has been no previous study that has examined urine pH according to mortality.

Assuming that it is necessary to have urine pH in the normal range for a body working in normal physiology, it can be expected that the urine pH of patients in the Intensive Care Unit (ICU) will be deteriorated secondary to the pathology. The aim of the researchers; It is a simple and expensive test that can be easily performed in almost any laboratory with complete urine analysis and provides extremely useful information. This study aimed to examine whether urine pH has any prognostic role in terms of mortality in intensive care unit patients.

Materials and Methods

Approval for the study was granted by the Local Ethics Committee. A retrospective examination was made of patients in the Internal Medicine ICU in our hospital between 2017 and 2018. Exclusion criteria were the absence of laboratory and/or clinical data, less than 24 hours of hospitalization, and acute or chronic renal failure. A total of 2100 patients were re-

viewed, and 563 patients were excluded from the study by applying exclusion criteria,and 1537 patients were included in the study (Fig. 1). All laboratory data and clinical results were obtained from patient records in our hospital database.

Statistical Analysis

Statistical analyses of the data obtained in the study were made using SPSS v. 22.0 software (Statistical PackageforSocialSciences) and R soft ware (V.3.2.0, R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org/). Variables were stated as mean ± standard deviation (SD), and categorical variables as number (n) and percentage (%). The patients were categorized according to the urinary pH levels as Low pH for those with ≤5.5 and High pH for thos ewith>5.5, taking 5.5 as the reference value of the 50 th percentile of urinary pH. In the comparison between the groups of continuous variables, the Student's t-test or the Mann Whitney U-test was applied according to whether the distribution was normal or not. In the comparison of categorical variables between groups, the Chi-square test was applied. To determine the independent predictive variables of mortality, forward step wise multivariate logistic regression analysis was applied, including all of the variables determined as p<0.1 in the univariate analysis and the results were presented showing the OddsRatio (OR) and Confidence Interval (CI). For all the tests, a value of p<0.05 was accepted as statistically significant.

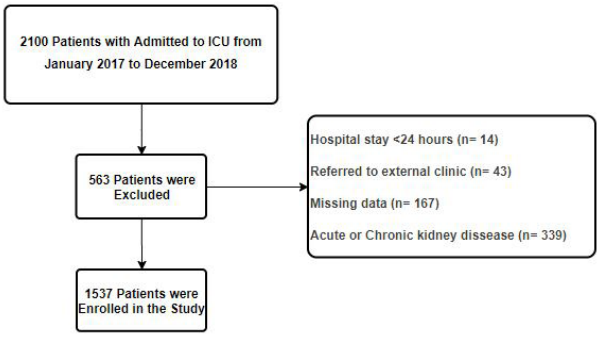

Figure1. Flow chart of patient selection

Results

In our tudy, the pH ≤ 5.5 group contained 911 patients, and the pH> 5.5 group contained 626 patients. Eight-hundred-two (52.2%) of the patients were male,and 735 (47.8%) were women. The mean age was calculated as 67.5 ± 18.4. There was no difference between both groups in terms of gender (p>0.05). Age, length of hospital stay, and mortality were significantly higher in the pH ≤ 5.5 group (p<0.001). The basal demographic, clinical characteristics of both groups are shown in Table 1 and Figure 2. In the sub-group

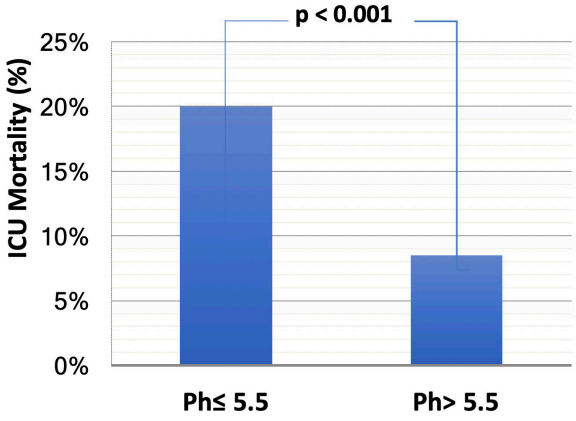

Fig 2. Comparisons of ICU mortality rate among patients with different urinary Ph level

Table 1. Comparison of demographic and clinical variables between urinary pH range

Variables Total	Total (n=1537)	pH ≤5.5(n=911)	pH >5.5(n=626)	P
Sex (male, %)	802(52.2)	471(30.6)	331(21.5)	0.651
Age (years)	73(18-111)	75(18–111)	64.21(18–98)	**<0.001**
TLSH (Day)	5(1–90)	10.5(1–90)	6.7(1–86)	**<0.001**
Non-survivors (%)	439(28.6)	308(20)	131(8.5)	**<0.001**

TLSH: Total length of stay

analysis for urinary pH and mortality, mortality rates decreased between the 5 and 7 urinary pH levels in the form of a trend (Fig. 3).

The results of the univariate analysis applied to determine the predictors of mortality are shown in Table 2. With the aim of determining in dependent predictors of mortality, an analysis was made of an advanced stage risk model including these variables. In the multivariate logistic regression analysis, age (p <0.0001, OR = 0.978), TLSH (p <0.0001, OR = 0.932) and urinary pH (p<0.05, OR= 0.718) levels were determined as independent risk factors associated with mortality.

Discussion

The chemical properties and amount of urine are important in showing the normal physiological functioning of the body and in showing renal perfusion. These properties of urineare affected by the parameters that affect renal perfusion, which include arterial blood pressure, changes in blood pH, hypoxia,and hypercapnia (6).

For the cellular functions of the body to be able to have an optimal course, the pH of the body fluids must be kept within a certain range. The normal range of urine pH is 4.5–8, with a pH<6 indicating acidic urine, and pH ≥ 7 indicating alkaline urine (7). Although urine pH and serum pH are controlled by similar mechanisms, the pH of urine through out 24 h is approximately 6 (8).

In the current study, there was no gender difference relative to the urine pH groups, but a previous study that compared genders reported that the urine pH of females was higher than that of males, and although the difference could not be attributed to differences in diet, it was suggested that it could be related

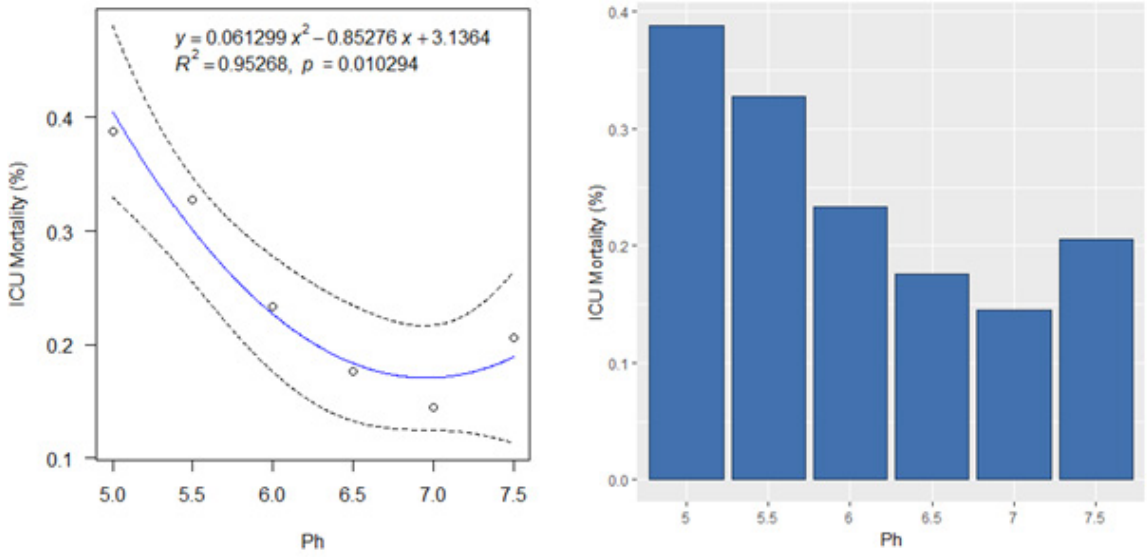

Figure 3. The sub-group analysis for urinary pH and mortality rate

Table 2. Univariate odds ratios of variables for predicting ICU mortality and independent predictors of ICU mortality by multivariate logistic regression analysis

	Univariate odds ratios			Multivariate odds ratios		
Variables	**Oddsratio**	**95% CI**	**P**	**Oddsratio**	**95% CI**	**P**
Sex (male)	0.974	0,780-1,215	0,815	-	-	-
Age (years)	0.973	0.966-0,980	**<0,001**	0.978	0.970-0.986	**<0,001**
TLSH (Day)	0,924	0,912-0,937	**<0,001**	0,932	0,919-0,944	**<0,001**
Urinary Ph	0,518	0,409-0.656	**<0,001**	0.718	0.556-0.927	**0.011**

TLSH = Total length of stay

to the different absorption of nutrient anions in males and females (9).

Acidic urine is known to have an irritation effect on the uroepithelium(10). A previous study that monitored symptoms of the urinary tract showed a regression of symptoms following alkalization of the urine with oral sodium bicarbonate (11), but in another study, it was reported that a change in pH did not greatly change the symptom score (1).

There has been a recent increase in studies related to urine pH and metabolic syndrome. It is well-known that insulin resistance has a fundamental role in all of the diseases (dyslipidemia, hyperglycemia, hypertension, obesity) that metabolic syndrome (MS). By accelerating endothelial dysfunction and the atherosclerosis process, these diseases and insulin resistance can cause that progress to high mortality, such as coronary artery disease, stroke, and peripheral vascular disease. In a study in Korea, a relationship between low urine and MS was confirmed in a Korean population(2). Similarly, in Japan, a relationship between low urine pH and MS has been recorded,and it has also been shown that with an increase in MS characteristics, there was a progressive decrease in pH. Thus, it was concluded that the examination of fasting urine pH could be a practical screening tool for MS (12-13).

In these large studies that have correlated MS with low urine pH, MS is included among the indications for admittance of the majority of patientsto ICU, with atherosclerotic disease and diagnoses associated with complications of these diseases. As this group of patients constitutes the vast majority of ICU patients, the finding of patients in the current study determined with low urine pH could shedlight on there being a low pH before admittance to the ICU.

Accordingto a 2004 study, GFR <60 ml/min/1.73m^2 is accepted as an independent risk factor for hospitalization and cardiovascular events (14), and in a study in 2012, grade 3 chronic renal disease was foundto be higher in patients with fasting urine pH of 5.0–5.5 compared to those with pH of 6.5–7.0 over a mean 7-year follow-up (15). In another study, low urine pH was reported to be a useful marker in predicting the onset of renovascular deterioration in diabetic patients and the view that it was strongly correlated with intrarenal oxidative stress supported this result (16). From the results of these two large studies, it can be concluded that low urine pH increases the risk of chronic renal failure and, secondary to this, increases length of stay in hospital and the rate of cardiovascular events.

Limitations

As a result of the fact that there were few studies on urine pH and no publications associated with intensive care unit mortality in literature, reference chapter of this study was limited as we had to refer to past publications.

Conclusions

As a result of the study, several previous studies have shown a relationship between low urine pH and MS, chronic renal failure, and there foreall atherosclerotic diseases (cerebral events, cardiovascular events). In this study, the urine pH values of all patients in the Internal Diseases Intensive Care Unit ICU were evaluated regardless of the diagnosis of presentation, and the finding of significantly higher TLSH and mortality rates in patients with low urine pH suggested that this may be an independent risk.

References

1. Brumfitt W, Hamilton-Miller JM, Cooper J, Raeburn A. Relationship of urinary pH to symptoms of 'cystitis'. Postgrad Med J. 1990:66;779:727-9.
2. Cho YH, Lee SY, Jeong DW, Choi EJ, Nam KJ, Kim YJ et al. The association between a low urine pH and the components of metabolic syndrome in the Korean population: Findings based on the 2010 Korea National health and nutrition examination survey. J Res Med Sci. 2014;19:599-604.
3. Kanbara A, Miura Y, Hyogo H, Chayama K, Seyama I. Effect of urine pH changed by dietary intervention on uric acid clearance mechanism of pH-dependent excretion of urinary uric acid. Nutr J. 2012:7;11:39.
4. D. Wright Wilson, W. L. Long, H. C. Thompson, Sylva Thurlow . Changes in the composition of the urine after muscular exercise. Biol Chem 1925;65:755-771.
5. Worcester EM, Bergsland KJ, Gillen DL, Coe FL. Mechanism for higher urine pH in normal women compared with

men. Am J Physiol Renal Physiol. 2018:1;314:623-629.
6. Anderson RJ, Pluss RG, Pluss WT, Bell J, Zerbe GG. Effect of hypoxia and hypercapnic acidosis on renal autoregulation in the dog: role of renal nerves. Clin Sci. 1983;65:533-538.
7. Kobayashi H, Yoshiyama M, Zakoji H, Takeda M, Araki I. Sex differences in the expression profile of acid-sensing ion channels in the mouse urinary bladder: a possible involvement in irritative bladder symptoms. BJU Int. 2009;104:1746-51.
8. Seldin and Giebisch's The Kidney (Physiology & Pathophysiology 1-2 Book.5 th Edition.2013
9. Worcester EM, Bergsland KJ, Gillen DL, Coe FL. Mechanism for higher urine pH in normal women compared with men. Am J Physiol Renal Physiol. 2018 ;314:623-629.
10. Sánchez-Freire V, Blanchard MG, Burkhard FC, Kessler TM, Kellenberger S,Monastyrskaya K. Acid-sensing channels in human bladder: expression, function and alterations during bladder pain syndrome. J Urol. 2011;186:1509-16.
11. Sönmez MG, Göğer YE, Ecer G, Atıcı A, Özkent MS, Öztürk A. Effects of urine alkalinization with sodium bicarbonate orally on lower urinary tract symptoms in female patients: a pilot study. Int Urogynecol J. 2018;29:1029-1033.
12. Shimodaira M, Okaniwa S, Nakayama T. Fasting Single-Spot Urine pH Is Associated with Metabolic Syndrome in the Japanese Population. Med Princ Pract.2017;26:433-437.
13. Hara S, Tsuji H, Ohmoto Y, Amakawa K, Hsieh SD, Arase Y, Nakajima H. High serum uric acid level and low urine pH as predictors of metabolic syndrome: a retrospective cohort study in a Japanese urban population. Metabolism. 2012;612:281-8.
14. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–1305.
15. Nakanishi N, Fukui M, Tanaka M, Toda H, Imai S, Yamazaki M et al. Low urine pH Is a predictor of chronic kidney disease. Kidney Blood Press Res. 2012;35:77-81.
16. Ogawa S, Nako K, Okamura M, et al. Lower urinary pH is useful for predicting renovascular disorder onset in patients with diabetes BMJ Open Diabetes Research and Care 2015;3:e000097.

Correspondence:
Dr Ayşe ŞahinTutak, MD, Specialist
Department of InternalMedicine, Adıyaman University School of Medicine,Adıyaman, Turkey
Siteler, Atatürk Blv. No: 411, 02200 Adıyaman Merkez, Adıyaman, Turkey
Phone: +9(0) 4162161015
Email: aysesahintutak@hotmail.com