Original research

The relationship between serum anion levels and mortality of hypertensive patients; a retrospective cohort

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Abstract:

Background: There is still controversy regarding the role of chloride ion and other serum ions in prediction of mortality in patients with hypertension. Therefore, the present study was planned out with the aim of assessing the relationship of serum levels of chloride, bicarbonate, sodium, and potassium ions with mortality in hypertensive patients.

Methods: The present retrospective cohort was carried out on patients with hypertension presenting to a heart clinic in Tehran, Iran. Data were gathered by an acute care nurse practitioner using patients' medical profiles. Serum levels of chloride, bicarbonate, sodium, and potassium ions were assessed on the first visit and the correlation of these ions with 2-year mortality of the patients was evaluated by reporting hazard ratio (HR) with 95% confidence interval (95%CI).

Results: Finally, data of 893 individuals were assessed (73.91% male; mean age 49.52±15.60 years). During the 2 years of follow up, 67 (7.5%) cases of death was observed. Cox regression analysis showed that compared to normal levels of bicarbonate, decrease in this ion to measures less than 22 mEq/L leads to increased risk of mortality in hypertensive patients (HR=10.31; p<0.0001). This analysis showed that decrease of serum chloride ion to less than 97mEq/L also increases the risk of mortality in patients with high blood pressure (HR=2.89; p=0.001). However, there was no correlation between serum levels of sodium or potassium and incidence of mortality in patients (p>0.05).

Conclusion: For the first time, the findings of the present study showed that serum anion levels play an important role in incidence of mortality among patients with hypertension and can therefore be used for risk stratification of hypertensive patients.

Keyword: Hypertension; Risk Assessment; Serum; Anions

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1. Introduction

Hypertension is a known risk factor for cardiovascular diseases (1, 2) and leads to premature deaths (2, 3). Although most cardiovascular deaths commonly occur in the 5th decade of life onwards, various epidemiologic and physiologic studies have shown that high blood pressure in childhood and youth, are among the roots of hypertension and cardiovascular diseases in older age (4). Hypertension is one of the major causes of mortality in human populations and by timely treatment of this disease, its cardiovascular side effects can be prevented (5). High blood pressure in adulthood is

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accompanied by increased risk of developing cardiovascular diseases, congestive heart failure, and renal dysfunction (3, 6). The importance of high blood pressure is increasing in the east Mediterranean region, like other risk factors of non-communicable diseases. Various studies have expressed that it affects up to 25% of adult individuals in some countries (7).

One of the most important solutions for decreasing the burden caused by hypertension is screening high risk patients to be able to take more effective treatment measures and carry out more accurate follow ups for these patients based on the results. Mortality due to hypertension is the most important outcome that the physicians and medical staff want to minimize. In this regard, using physiologic parameters or scales can be of help in outcome prediction and reducing the burden caused by high blood pressure. Recent studies show that serum chloride level may be a predicting factor for long-term mortality incidence in patients with hypertension (8). These studies express that serum chloride level lower than 100 mEq/L is associated with 48% increase in mortality of hypertensive patients (9). Yet, there is still controversy regarding the role of this ion and other serum ions in prediction of mortality in patients with hypertension. Therefore, the present study was planned out with the aim of assessing the relationship of serum levels of chloride, bicarbonate, sodium, and potassium ions with mortality in hypertensive patients.

2. Method

The present retrospective cohort was carried out on patients with hypertension presenting to a heart clinic in Tehran, Iran. Data were gathered by an acute care nurse practitioner using patients' medical profiles, and recorded in a checklist. The present study was approved by the ethics committee of Tehran University of Medical Sciences. Diagnosis of hypertension was done by a cardiologist based on the definition of having a systolic blood pressure over 140 mmHg or diastolic blood pressure over 90 mmHg in at least 2 blood pressure evaluations during one week.

According to the routine of the clinic in which the study was done, blood pressure was measured using a mercury sphygmomanometer. In each visit, blood pressure of each patient was measured twice in a semi-seated position using a suitable cuff. The details of attaching the cuff and recording blood pressure have been reported in previous studies (10-13). Height of the patients was measured via a standard height-meter in standing position and their weight was recorded with minimum clothing and without shoes using a SECA scale (made in Germany) with 50 gr error. Other evaluated baseline information included baseline cardiovascular disease, chronic kidney disease, drug abuse and smoking.

10 cc venous blood was drawn from each patient on the first visit for biochemical evaluations and chloride, bicarbonate, sodium, and potassium ion levels were assessed. Bicarbonate level was divided into 3 groups of normal (22-28 mEq/L), less than normal (lower than 22 mEq/L), and more than normal (more than 28 mEq/L). Sodium level was also categorized as normal (135-145 mEq/L), hyponatremia (lower than 135 mEq/L), and hypernatremia (more than 145 mEq/L). Additionally, chloride level was grouped as normal (97-106 mEq/L), Hypochloremia (<97 mEq/L), and Hyperchloremia (>106 mEq/L). Serum potassium was also divided into 3 groups of normal (3.5-5.1 mEq/L), hypokalemia (lower than 3.5 mEq/L) and hyperkalemia (more than 5.1 mEq/L). The final outcome of the study was considered to be 2-year mortality of the patients.

Data were entered to STATA 14.0 statistical software and analyzed. Quantitative data were reported as mean and standard deviation (SD) and qualitative ones as frequency and percentage. Sample size determination was designed based on previous studies in which hazard ratio (HR) of normal level of chloride in mortality prediction compared to its level being less than 100 mEq/L was 0.73 (8). Therefore, by considering alpha to be 0.05 and 90% power, minimum sample size required was 425 patients.

Patients were divided into 2 groups of dead and alive based on their final outcome and mean serum levels of the studied ions were compared between the 2 groups. To compare the demographic and baseline variables of the patients, initially univariate analyses (chi square test for qualitative variables and independent t test for quantitative ones) were done. Afterwards, variables that had $p<0.1$ were entered to a multivariate Cox regression model. In this model, various levels of the studied ions based on the classifications done (normal, less and more than normal) as well as age at first visit, sex, body mass index, baseline cardiovascular disease, chronic kidney disease, tobacco smoking, alcohol use, systolic blood pressure, and diastolic blood pressure were entered. Findings were reported as HR with 95% confidence interval (CI). In all analyses, $p<0.05$ was considered as significance level.

3. Result

At the beginning of the study, data of 940 patients was evaluated. 47 patients decided to withdraw from participating in the study and therefore, in the end data of 893 individuals were assessed (73.91% male; mean age 49.52±15.60 years). During the 2 years of follow up, 67 (7.5%) cases of death was observed. Mean age of the patients who died was significantly higher than those who

Table 1: Baseline characteristics of hypertensive patients

Variable	Dead	Alive	Total	P
Age (years)	57.51±18.19	48.79±15.14	49.52±15.60	< 0.0001
Male sex	55 (82.09)	605 (73.24)	660 (73.91)	0.92
BMI (kg/m2)	28.19±5.44	28.62±6.03	28.58±5.98	0.57
SBP (mmHg)	174.49±31.92	170.25±33.09	170.61±32.99	0.31
DBP (mmHg)	101.38±17.42	102.97±16.25	102.84±16.35	0.44
Alcohol (n, %)	4 (5.97)	117 (14.16)	121 (13.55)	0.06
Smoking	11 (16.42)	69 (8.35)	80 (8.96)	0.03
Opium	10 (14.93)	45 (6.16)	55 (6.89)	0.007
CVD	9 (13.43)	39 (4.72)	48 (5.38)	0.002

BMI: body mass index; CVD: history of cardiovascular diseases; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Table 2: Cox regression analysis for the association between serum bicarbonate, sodium, chloride and potassium level and mortality

Serum Electrolytes	Adjusted hazard ratio*	95% confidence interval	P
Bicarbonate			
Normal level	*Ref.*	*Ref.*	---
Lower than 22 mEq/L	10.31	2.51 to 42.37	<0.0001
Higher than 28 mEq/L	0.23	0.02 to 2.51	0.23
Sodium			
Normal	*Ref.*	*Ref.*	---
Hyponatremia (<135 mEq/L)	0.42	0.13 to 1.44	0.17
Hypernatremia (>145 mEq/L)	1.57	0.92 to 2.69	0.10
Chloride			
Normal level	*Ref.*	*Ref.*	---
Hypochloremia (<97 mEq/L)	2.89	1.59 to 5.26	0.001
Hyperchloremia (>106 mEq/L)	0.49	0.14 to 1.72	0.26
Potassium			
Normal level	*Ref.*	*Ref.*	---
Hypokalemia (<3.5 mEq/l)	0.74	0.34 to 1.62	0.45
Hyperkalemia (>5.1 mEq/l)	0.99	0.57 to 1.71	0.96

*, Adjusted for age at first visit, sex, body mass index, baseline cardiovascular disease, chronic kidney disease, tobacco smoking, alcohol use, systolic blood pressure, diastolic blood pressure.

stayed alive (p<0.0001). Additionally, a significant correlation was detected between smoking (p=0.03), opium addiction (p=0.007), and history of cardiovascular diseases (p=0.002) with death (table 1).

Mean serum bicarbonate level in those who died (12.90±3.58) was significantly higher than those who survived (25.73±9.88) (p<0.0001). Serum chloride level in the dead and alive patients was 94.34±3.31 and 100.21±6.09, respectively (p<0.0001). It should be noted that a similar pattern was seen regarding serum sodium level (134.39±3.48 versus 142.68±7.52; p<0.0001). However, potassium level was not different between the dead and alive groups (p=0.75) (figure 1).

Cox regression analysis showed that compared to normal levels of bicarbonate, decrease in this ion to measures less than 22 mEq/L leads to increased risk of mortality in hypertensive patients (HR=10.31; p<0.0001). This analysis showed that decrease of serum chloride ion to less than 97mEq/L also increases the risk of mortality in patients with high blood pressure (HR=2.89; p=0.001). However, there was no correlation between serum levels of sodium or potassium and incidence of mortality in patients (p>0.05) (table 2 and figure 2).

4. Discussion

Findings of the present study showed that serum anion levels play a very important role in predicting the outcome of hypertensive patients. According to the results, decrease of serum bicarbonate and chloride levels lead

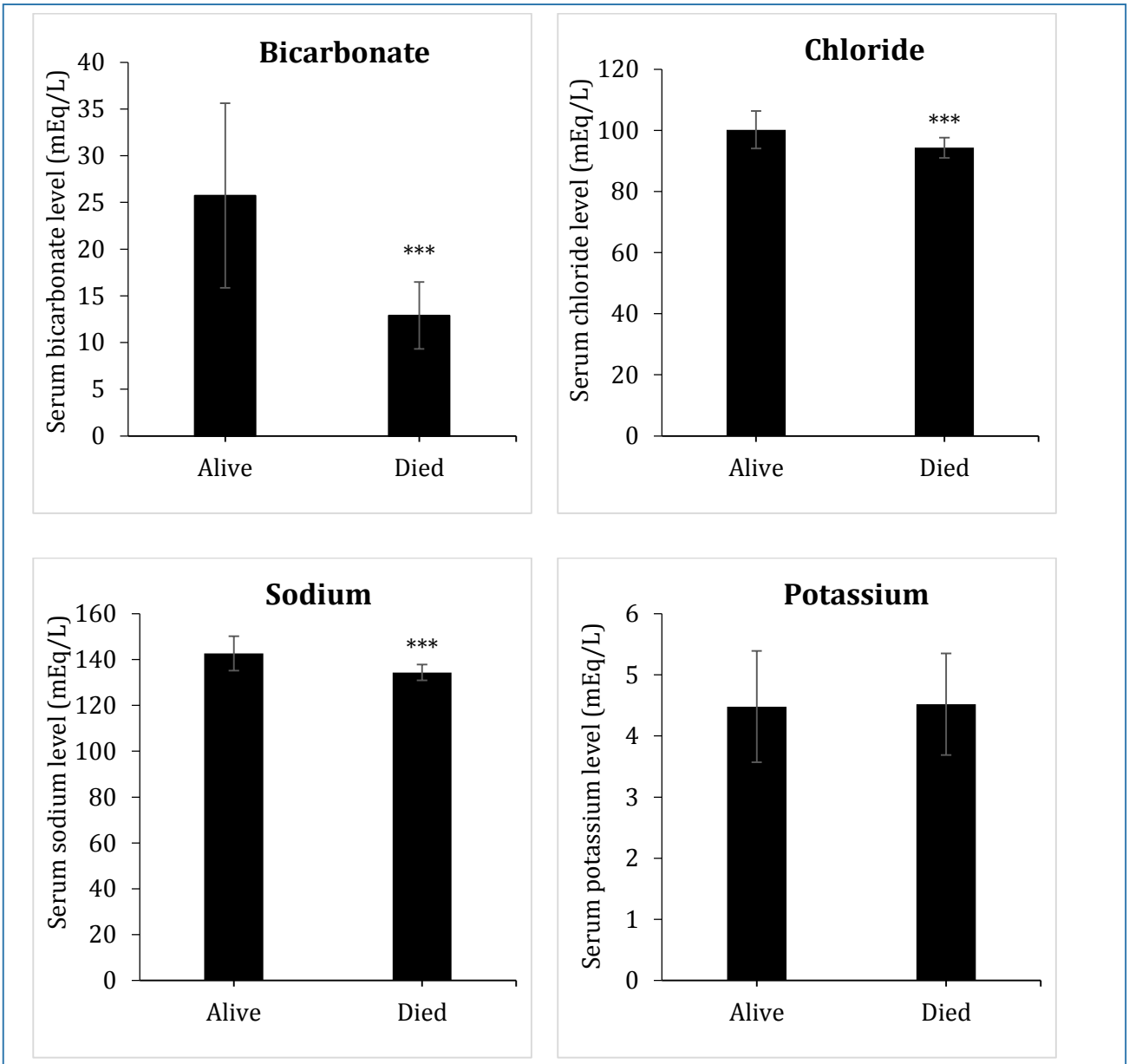

Figure 1: Comparison of serum bicarbonate, chloride, sodium and potassium levels between alive and dead hypertensive patients.

to an increase in the risk of mortality among patients with hypertension. In this 2-year short term cohort it was determined that drop in serum level of bicarbonate to less than 22 mEq/L and serum level of chloride to less than 97mEq/L are important and independent predictive factors for all-cause of mortality in these patients.

The public belief is that the most important ion in predicting the outcome of hypertensive patients is serum sodium ion, yet the findings of the current study showed that serum anions are important predictive factors of mortality in these patients. Although serum chloride level evaluations are routinely done in patients with hypertension, using this ion or serum bicarbonate ion for screening and risk stratification is not common. However, the present study pointed out the importance of considering these ions, which was in line with previous studies. For instance, McCallum et al. in a 35-year cohort showed that chloride ion is a strong predictive factor of mortality among hypertensive patients (8). In addition, by studying Belgian patients for 10 years De Bacquer et al. showed that serum chloride levels less than 100 mEq/L are associated with increased risk of mortality in hypertensive patients (9).

It seems that serum anions play an important role in pathophysiology of hypertension. A possible mechanism for explaining the increase in mortality risk with decrease in anion levels can be that these ions play a role in increasing hyponatremia incidence or cause distortion in acid-alkaline balance. However, analyses have shown that the effects of bicarbonate and chloride are independent from hyponatremia and therefore, further studies are needed to better understand the mechanism

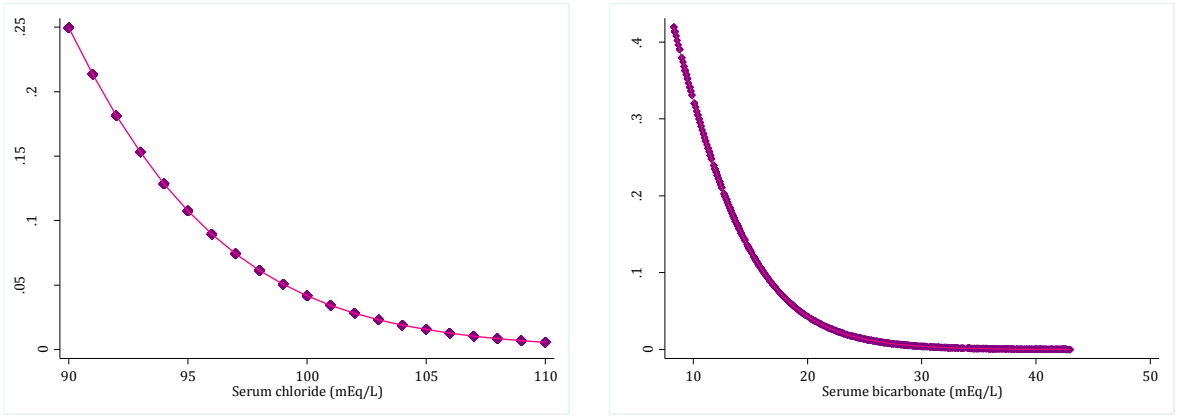

Figure 2: Correlation of serum chloride and bicarbonate levels with probability of death in hypertensive patients.

of action of these anions in incidence of mortality among patients with hypertension.

One of the most important limitations of the present study was not evaluating the amount of diuretics used by the studied patients. Diuretic use may be a confounder for the findings of this study and it is suggested to consider this in future studies.

5. Conclusion:

For the first time, the findings of the present study showed that serum anion levels play an important role in incidence of mortality among patients with hypertension and can therefore be used for risk stratification of hypertensive patients.

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7. Conflict of interest

No conflict of interest was declared.

8. Funding source

None.

9. Author contribution

Conception and design of the work: MY, BN, and MH; data gathering: BA, MY, and SS; data analysis: MH; drafting the work: MH, and SS; critically revised the manuscript: All authors. All authors approved final version of the paper to be published and agreed to be accountable for all aspects of the work.

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