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BRIEF RESEARCH REPORT

Trauma

Utility of laboratory markers in evaluating for acute compartment syndrome in the emergency department

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Abstract

Background: Acute compartment syndrome is diagnosed by clinical examination with the aid of direct compartmental measurement. Previous work suggested using several laboratory markers that may suggest ongoing acute compartment syndrome in hospitalized patients. Serum creatinine kinase (CK) levels >4000 U/L, chloride (Cl) levels >104 mg/dL, and blood urea nitrogen (BUN) levels <10 mg/dL were found to have 100% association with the diagnosis of acute compartment syndrome. This strategy has not been studied in emergency department (ED) patients.

Methods: A retrospective chart review of all patients diagnosed with acute compartment syndrome of the upper and lower extremity or tibia/fibula fracture was performed from 13 EDs between February 22, 2008 and October 1, 2018. Serum values were collected for each patient: CK, sodium (Na), potassium (K), Cl, bicarbonate (HCO3), glucose, BUN, creatinine (Cr), calcium, lactic acid (LA), and ionized calcium (iCa). A control group composed of patients without acute compartment syndrome who had tibia and/or fibula fractures was analyzed to compare with our cohort.

Results: We identified 930 patients who meet inclusion criteria (389 acute compartment syndrome patients and 541 tibia/fibula fracture patients). Sex and ethnicity were similar in each population. A majority of the patients were evaluated at EDs without a trauma center designation. Using univariate modeling, HCO3, CK, iCa, Cr, BUN, and K values were found to be individual significant predictors of acute compartment syndrome ($P < 0.05$). Multivariate regression models found that HCO3 and Cr were significant predictors of acute compartment syndrome with a C-statistic of 0.77. The Valdez model had a prediction accuracy of 0.52 and a specificity of 99.2% but had a sensitivity of only 2.9%.

Conclusion: Our model demonstrates that use of serum biomarkers in the ED does aid in the diagnosis of acute compartment syndrome in patients in the ED with 99.2% specificity but has a sensitivity of only 2.9%. Further research and prospective evaluation of serum markers are needed.

KEYWORDS

acute compartment syndrome, biomarkers, injury, predictive models, rhabdomyolysis, trauma

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1 | BACKGROUND

Acute compartment syndrome is diagnosed when the clinical examination reveals a tense anatomic compartment.[1] Direct compartmental pressure measurements are made when the clinical examination is equivocal.[2–5] Previous studies show that physicians have a low sensitivity for detecting elevated compartment pressures when relying on physical examination findings alone.[6,7] Bedside compartment pressure measurements can aid in diagnosis; however, these are dependent on technique, the examiner's experience, and type of needle used.[8] Likewise, direct measurement of compartment pressure is an invasive procedure with an increased risk of hemorrhage for those on antiplatelet agents or anticoagulants.[9] Given these diagnostic barriers, a non-invasive method that is sensitive and specific for the diagnosis of acute compartment syndrome on initial presentation would be of great utility.

To assist with the identification of acute compartment syndrome, published literature has suggested using serum markers to diagnose acute compartment syndrome in hospitalized patients[10] with a sensitivity and specificity of 0.85 and 0.87, respectively. Serum creatine phosphokinase (CK) levels >4000 U/L, chloride (Cl) levels >104 mg/dL, and blood urea nitrogen (BUN) levels <10 mg/dL were found to have 100% association with the diagnosis of acute compartment syndrome in hospitalized trauma patients.[10] However, this study used lab values that were obtained during hospitalization and may not be applicable on initial presentation to the emergency department.

To our knowledge, there has yet to be a study evaluating the utility of serum markers in the diagnosis of acute compartment syndrome in the ED. Previous literature does not offer a rationale for the changes in Cl and BUN and their association with acute compartment syndrome. We hypothesized that differences in lactate (LA), bicarbonate (HCO3), and calcium (Ca) may also be significantly different with acute compartment syndrome. We seek to evaluate the utility of serum CK, Cl, HCO3, Ca, and LA in the evaluation of acute compartment syndrome on initial presentation through a retrospective multicenter study of ED patients.

The Bottom Line

Acute compartment syndrome is often difficult to diagnose. This study of 930 patients with upper or lower extremity injuries found that the combination of HCO3, CK, iCa, Cr, BUN, and K was 99.2% specific but only 2.9% sensitive for acute compartment syndrome. This biomarker combination shows promise for ruling in but not ruling out acute compartment syndrome.

2 | METHODS

A multicenter retrospective chart review of all patients diagnosed with either acute compartment syndrome of the upper and lower extremity or tibia/fibula fracture was performed between February 22, 2008 and October 1, 2018 from 13 EDs within an integrated health care organization across Virginia. Our control group included isolated tibia/fibula fractures. The diagnosis of acute compartment syndrome and tibia/fibula fractures was identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and *Tenth Revision* (ICD-10-CM) codes found in Appendix 1. All of the participating hospitals used EPIC for the electronic medical record, which allowed for consistent data collection. Patients who are younger than 18 years of age or without complete laboratory results were excluded. We did not exclude patients with concomitant injuries. If a patient was transferred between hospitals, we used only the data from the first encounter. The initial laboratory results on the day of diagnosis were collected for all patients; including the sodium (Na), potassium (K), Cl, HCO3, glucose, BUN, creatinine (Cr), Ca, LA, ionized calcium (iCa), and CK.

All data extraction and statistical analyses were performed in collaboration with the Eastern Virginia Medical School (EVMS)-Sentara Healthcare Analytics and Delivery Science Institute (HADSI). The authors did not perform the data extraction from the electronic medical record. To test for violations of normalcy, univariate analyses were performed on all continuous variables. Continuous variables with normal distributions were presented as mean ± SD, and non-normal continuous variables were presented as median ± interquartile range. Descriptive statistics of categorical variables were summarized and presented as count (percentage). Parametric *t* test was used to compare the means of normally distributed continuous variables between patient groups and the Wilcoxon Rank Sum test was used to test differences between group medians for non-normally distributed continuous variables. The serum lab values were examined on univariate and multivariate analysis for the ability to predict the outcome of acute compartment syndrome. For the values most strongly associated with acute compartment syndrome based on the concordance statistic (C-statistic), optimal binary cut points to maximize the odds ratio (OR) with acute compartment syndrome were determined using clinical experience and modeling. Multivariate logistic regression analysis was used to determine the best prediction model for acute compartment syndrome. Sensitivity and specificity of each threshold model were determined. All hypothesis testing was carried out at the 95% significance level, with a P value <0.05 accepted as statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Demographics

There were 930 patients who met inclusion criteria, 389 (41.8%) who presented to an ED with acute compartment syndrome and 541 (58.2%) who presented with tibia/fibula fracture (Table 1). The majority of patients in the acute compartment syndrome and tibia/fibula

TABLE 1 Univariate comparison of demographic and patient-level variables on the prediction of acute compartment syndrome

Variable	Acute compartment syndrome (n = 389) n (%)	Tibia/fibula fracture (n = 541) n (%)	χ^2	*P*
Sex				
Male	264 (67.9)	312 (57.7)	9.97	<0.01
Female	125 (32.1)	229 (42.3)		
Ethnicity				
Not Hispanic or Latino	297 (76.4)	442 (81.7)	4.01	0.26
Hispanic or Latino	9 (2.3)	9 (1.7)		
Unknown	83 (21.3)	90 (16.6)		
Emergency department type				
Emergency department with trauma center designation	61 (15.7)	119 (22.0)	5.78	0.02
Community emergency department	328 (84.3)	422 (78.0)		

	Mean (SD)	Mean(SD)	*Z*-statistic	Associated *P*-value	OR (95% CI)	*P***	C-statistic
Age (y)	51.5 (17.6)	51.3 (18.6)	0.54	0.59	1.01 (0.97,1.04)	0.70	0.51
Length of stay (h)	388.3 (317.6)	404.9 (352.2)	−0.25	0.80	1.00 (0.99,1.00)	0.15	0.50
Creatinine kinase (U/L)	2132.8 (7265.3)	813.10 (1349.8)	0.52	0.60	1.00* (1.00,1.00)	<0.01	0.51
Bicarbonate (mmol/L)	23.3 (6.1)	26.6 (5.8)	−6.75	<0.01	0.90** (0.88,0.93)	<0.01	0.64
Ionized calcium (mg/dL)	4.5 (0.4)	4.5 (0.3)	0.97	0.33	0.68 (0.52, 0.89)	0.01	0.52
Calcium (mg/dL)	8.8 (0.8)	8.8 (0.6)	0.77	0.44	0.94 (0.85, 1.05)	0.29	0.49
Chloride (mg/dL)	100.6 (4.7)	100.7 (4.3)	−0.70	0.48	0.94 (0.98, 1.01)	0.41	0.51
Creatinine (mg/dL)	1.2 (1.5)	0.9 (1.1)	3.94	<0.01	1.15 (1.09, 1.21)	<0.01	0.54
Glucose (mg/dL)	121.8 (49.4)	124.1 (41.6)	−5.28	<0.01	0.99 (0.99,1.00)	0.11	0.55
Lactate (mmol/L)	2.7 (4.12)	2.3 (2.29)	2.73	0.01	1.04 (0.99,1.09)	0.06	0.45
Blood urea nitrogen (mg/dL)	17.3 (14.8)	15.0 (10.2)	2.20	0.03	1.02 (1.01, 1.02)	<0.01	0.52
Potassium (mmol/L)	4.1 (0.6)	4.0 (0.5)	3.64	<0.01	1.38 (1.21, 1.56)	<0.01	0.54
Sodium (mmol/L)	138.1 (3.6)	138.2 (3.5)	−0.70	0.49	0.94 (0.97,1.01)	0.45	0.51

*P*** *P* value was computed in univariate logistic regression with continuous predictor and having acute compartment syndrome as outcome.
*Odds ratio was calculated per 500 unit increase in predictor.
**Odds ratio was calculated per 5 unit increase in predictor.
CI, confidence interval; OR, odds ratio; SD, standard deviation.

fracture groups were of non-Hispanic or non-Latino ethnic descent; 297 (76.4%) and 442 (81.7%), respectively. Age distribution among the 2 groups was not significantly different (Z = 0.5397, 0.5894). The majority of patients diagnosed with acute compartment syndrome or tibia/fibula fracture were seen in community EDs.

3.2 | Univariate regression

The serum values for HCO3, CK, iCa, LA, Cr, BUN, and K were all found to be individual significant predictors of acute compartment syndrome using univariate logistic regression ($P < 0.05$) (Table 1). Higher K, BUN, and Cr levels were all significantly associated with an increased likelihood of having acute compartment syndrome.

3.3 | Optimal thresholds

Optimal thresholds were explored univariately in predicting acute compartment syndrome (Table 2). All threshold levels explored were significant; however, the prediction accuracy of the models ranged from c = 0.51 to 0.55. The optimal threshold for LA of >2 mmol/L had

TABLE 2 Univariate models of optimal thresholds for predicting acute compartment syndrome

Threshold	Odds ratio (95% confidence interval)	Sensitivity	Specificity	c	*P*
Blood urea nitrogen (mg/dL)					
>20	1.40 (1.17,1.66)	21.4	83.7	0.53	<0.01
>30	2.00 (1.55,2.57)	10.8	94.3	0.53	<0.01
>40	2.40 (1.74,3.35)	6.7	97.1	0.52	<0.01
>50	2.38 (1.54, 3.67)	3.8	98.4	0.51	<0.01
Lactate (mmol/L)					
>2	0.80 (0.57,1.13)	68.7	36.3	0.53	0.20
>5	2.4 (1.34,4.15)	14.7	93.2	0.54	<0.01
>10	6.1 (2.55,18.26)	9.7	98.3	0.54	<0.01
Creatinine (mg/dL)					
>1	1.50 (1.28,1.74)	28.5	79.0	0.54	<0.01
>1.2	2.24 (1.78,2.82)	12.2	94.2	0.53	<0.01
>1.5	1.90 (1.55,2.32)	15.4	91.2	0.53	<0.01
Creatinine kinase (U/L)					
>2000	2.10 (1.46,3.01)	4.6	87.6	0.51	<0.01
>3000	2.36 (1.55,3.58)	3.5	98.5	0.51	<0.01
>4000	3.52 (2.13,5.99)	4.6	90.8	0.51	<0.01
>5000	5.94 (3.10,12.14)	2.3	99.6	0.51	<0.01
>6000	5.85 (2.52,15.92)	1.9	99.8	0.51	<0.01
Calcium (mg/dL)					
<7.7	2.52 (1.82,3.50)	6.9	97.1	0.52	<0.01
<7.8	2.50 (1.83,3.30)	8.6	96.3	0.53	<0.01
<7.9	2.33 (1.80,3.02)	11.0	95.0	0.53	<0.01
<8.0	2.00 (1.58,2.54)	23.0	81.2	0.52	<0.01
<8.1	1.58 (1.27,1.95)	14.4	90.3	0.52	<0.01
Bicarbonate (mmol/dL)					
10 to 20	2.41 (1.54,3.81)	17.8	91.7	0.55	<0.01

the highest sensitivity (68.7) for predicting acute compartment syndrome. The odds of having acute compartment syndrome increased with increasing CK values. Of the 41 patients with a CK >5000 U/L, 29 had ACS (70.7%) and 12 (29.3%) had a tibia/fibula fracture.

3.4 | Multivariate regression

HCO3, CK, iCa, LA, Cr, BUN, and K were independent variables entered into the stepwise multivariate regression model predicting acute compartment syndrome. After controlling for all predictors, only HCO3 and Cr were found to be significant predictors of acute compartment syndrome (Table 3). C-statistic of the final model is 0.77, indicating good predictability and model fit. After controlling for other predictors, the odds of a patient having acute compartment syndrome are 2.52 times higher for each increase in unit (mg/dL) of Cr (95% confidence interval, 1.399, 4.136).

With the exception of HCO3 and Cr as continuous predictors, none of the other multivariate models with different combinations of predictors and thresholds had a prediction accuracy over 0.56. Evaluating the values used in the Valdez model,[10] using CK >4000 U/L and Cl >104 mmol/L together to predict acute compartment syndrome in the ED patient population had a prediction accuracy of 0.52, a sensitivity of 2.9%, and a specificity of 99.2%. When a BUN <10 mg/dL was added to the model as an additional predictor, the prediction accuracy, sensitivity, and specificity remained the same.

4 | LIMITATIONS

There are several limitations to our study. One limitation is that the time intervals between the onset of injury and when the labs were obtained were unknown because of the retrospective design. Perhaps the models could be adjusted if there is a time-from-injury variable.

TABLE 3 Separate multivariate models with optimal thresholds for predicting acute compartment syndrome

Threshold	OR (95% CI)	Sensitivity	Specificity	c	*P*
Bicarbonate (mmol/dL) (1 unit increase)	0.88 (0.82, 0.94)	51.0	70.0	0.77	<0.01
Cr (mg/dL) (1 unit increase)	2.52 (1.40, 4.14)				
CK (U/L) > 1000	1.97 (1.48, 2.61)	7.4	96.1	0.53	<0.01
Cl (mg/dL) > 100	0.93 (0.81, 1.10)				
BUN (mg/dL) > 7	1.05 (0.90, 1.23)	2.9	99.2	0.52	<0.01
Cl (mg/dL) > 100	0.92 (0.81, 1.05)				
CK (U/L) > 4000	3.51 (2.11, 5.93)				
BUN (mg/dL) > 20	1.2 (0.97, 1.43)	16.5	90.6	0.55	<0.01
CK (U/L) > 4000	3.50 (2.11, 5.96)				
Cr (mg/dL) > 1	1.40 (1.18, 1.70)				
BUN (mg/dL) > 30	1.63 (1.24, 2.15)	21.5	86.0	0.56	<0.01
CK (U/L) > 4000	2.95 (1.74, 5.10)				
Cr (mg/dL) > 1	1.26 (1.06, 1.49)				
Lactate (mmol/L) > 2	1.75 (1.30, 2.36)				
Ca (mg/dL) < 8	1.21 (1.02, 1.42)				
CK (U/L) > 4000	3.52 (2.12, 5.96)	2.9	99.2	0.52	<0.01
Cl (mg/dL) > 104	1.14 (0.95, 1.36)				
BUN (mg/dL) < 10	0.92 (0.80, 1.06)	2.9	99.2	0.52	<0.01
Cl (mg/dL) > 104	1.15 (0.96, 1.37)				
CK (U/L) > 4000	3.52 (2.11, 5.95)				

BUN, blood urea nitrogen; Ca, calcium; CK, creatinine kinase; Cl, chloride; Cr, creatinine.

Further work is needed to determine if the time-of-injury variable could aid in the predictive model.

We did not exclude concomitant injuries from our patient population to develop a pragmatic model that could be used to screen for acute compartment syndrome in all ED patients over 18 years old. If we had included only isolated injuries, perhaps our model would be different.

5 | DISCUSSION

This study is the first to evaluate the utility of serum lab markers in the diagnosis of acute compartment syndrome in ED patients. By applying the previously published[10] thresholds to an ED population, we aimed to create a generalizable model for detection of acute compartment syndrome. The model demonstrated an acceptable specificity of 99.2% but had a sensitivity of only 2.9%.

Once we determined the Valdez model[10] did not have the sensitivity required for use in the acute care setting, we specifically evaluated multiple other models through multivariate analysis. Unfortunately, none of the models (Table 3) reached an acceptable sensitivity for ruling out the diagnosis of acute compartment syndrome in the ED but did reach adequate specificity.

Using the univariate models, the mean values for 5 serum markers were found to be statically significantly associated with acute compartment syndrome, but only 1 marker, CK, was found to be in the abnormal physiologic range when associated with acute compartment syndrome. Sodium bicarbonate, BUN, Cr, and K, although found to be statistically different compared with the control group, all remained within normal physiologic ranges, indicating they have no utility for detecting acute compartment syndrome in isolation.

Optimal thresholds for improving sensitivity and specificity were determined (Table 2). Markedly elevated BUN and Cr (BUN >50 mg/dL and Cr >1.5 mg/dL) had >91% specificity but poor sensitivity at 3.8% and 15.4% respectively. This may be because azotemia and acute kidney injury are more likely to be seen in the critically ill trauma patient than the control population. Significantly elevated LA (>6.1 mmol/L) and CK (>3000 U/L) had a >98% specificity. These thresholds coupled with low sensitivity characteristics are of little value in the ED where the primary objective is to rule out a disease process.

6 | CONCLUSION

Our model demonstrates that use of serum biomarkers in the ED does aid in the diagnosis of acute compartment syndrome, but we could not identify a sensitive model to rule out acute compartment syndrome. Clinical experience, and when required, direct compartment pressure measurement remain the diagnostic gold standard. Acute compartment syndrome is a progressive process and therefore is not amenable to diagnoses using initial static serum assays.

Prospective research is required to further evaluate the utility of using serum biomarkers to diagnose acute compartment syndrome.

AUTHOR CONTRIBUTIONS

LG did the statistical analysis. PJ and KY helped with study design, writing the manuscript and data analysis. GSW- lead author, had the original idea, assembled the research team, obtained IRB approval and oversaw the project from start to finish.

REFERENCES

1. Whitesides TE, Heckman MM. Acute compartment syndrome: update on diagnosis and treatment. *J Am Acad Orthop Surg*. 1996;4(4):209-218.
2. Taylor RM, Sullivan MP, Mehta S. Acute compartment syndrome: obtaining diagnosis, providing treatment, and minimizing medicolegal risk. *Curr Rev Musculoskelet Med*. 2012;5(3):206-213.
3. Mubarak SJ, Owen CA, Hargens AR, Garetto LP, Akeson WH. Acute compartment syndromes: diagnosis and treatment with the aid of the wick catheter. *J Bone Joint Surg Am*. 1978;60:1091-1095.
4. Rorabeck CH, Bourne RB, Fowler PJ, Finlay JB, Nott L. The role of tissue pressure measurement in diagnosing chronic anterior compartment syndrome. *Am J Sports Med*. 1988;16:143-146.
5. Allen MJ, Stirling AJ, Crawshaw CV, Barnes MR. Intracompartmental monitoring of leg injuries. An aid to management. *J Bone Joint Surg Br*. 1985;67:53-57.
6. Uliasz A, Ishida JT, Fleming JK, Yamamoto LG. Comparing the methods of measuring compartment pressures in acute compartment syndrome. *Am J Emerg Med*. 2003;21:143-145.
7. Morris MR, Harper BL, Hetzel S, et al. The effect of focused instruction on orthopaedic surgery residents' ability to objectively measure intracompartmental pressures in a compartment syndrome model. *J Bone Joint Surg Am*. 2014;96(19):e171.
8. Boody AR, Wongworawat MD. Accuracy in the measurement of compartment pressures: a comparison of three commonly used devices. *J Bone Joint Surg Am*. 2005;87(11):2415-2422.
9. Halanski MA, Morris MR, Lee Harper B, Doro C. Intracompartmental pressure monitoring using a handheld pressure monitoring system. *JBJS Essent Surg Tech*. 2015;5(1):e6.
10. Valdez C, Schroeder E, Amdur R, Pascual J, Sarani B. Serum creatine kinase levels are associated with extremity compartment syndrome. *J Trauma Acute Care Surg*. 2013;74:441-445.

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APPENDIX 1

***International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9 CM) and *Tenth Revision* (ICD-10-CM) inclusion codes for acute compartment syndrome and tibia/fibula fractures**

ICD-9-CM	958.9 729.71 729.72 729.79 998.89 958.91 958.92 958.99
ICD-10-CM	M79.A
	T79.A0
	T79.A
	T79.A0XA
	M79.A11
	M79.A12
	M79.A21
	M79.A22
	M79.A19
	M79.A29
	T79.A11
	T79.A12
	T79.A19
	T79.A21
	T79.A22
	T79.A29
	T79.A9X2
	M79.A1
	M79.A2
	T79.A1
	T79.A2
	M79.A9