Serum anion gap on admission predicts intensive care unit mortality in patients with aortic aneurysm

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Received March 16, 2018; Accepted June 22, 2018

DOI: 10.3892/etm.2018.6391

Abstract. It has been widely reported that the serum anion gap is significantly associated with mortality in intensive care unit (ICU); however, it remains unknown whether the association is present in aortic aneurysm (AA) patients. The present study aimed to investigate the association between the admission serum anion gap and ICU mortality in AA patients. Data extracted from a publicly accessible clinical database using a modifiable data mining technique were analyzed retrospectively, mainly by employing multivariable logistic regression analysis. The primary study outcome was ICU mortality. A total of 273 patient records were analyzed. The ICU mortality was 8.79% (24/273). The median serum anion gap was significantly higher in non-survivors [17.50 mEq/l, interquartile range (IQR) 15.75-22.50 mEq/l] compared with survivors [13.00 mEq/l, IQR 11.00-15.00 mEq/l, P<0.001]. Multivariate analysis resulted in identification of a clear association between admission serum anion gap and ICU mortality in AA patients [odds ratio (OR) 1.38 per 1 mEq/l increase, 95% confidence interval (CI) 1.08-1.76]. The area under the receiver operating characteristic curve showed an outstanding discrimination ability in predicting ICU mortality (area under curve 0.8513, 95% CI 0.7698-0.9328). In conclusion, admission serum anion gap may serve as a strong predictor of ICU mortality for AA patients.

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Abbreviations: ICU, intensive care unit; AA, aortic aneurysm; IQR, interquartile range; OR, odds ratio; CI, confidence interval; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; MIMIC-III, Medical Information Mart for Intensive Care III; ROC, receiver operating characteristic; AUC, area under the ROC curve; SOFA, Sepsis-related Organ Failure Assessment; APACHE III, Acute Physiology and Chronic Health Evaluation III; ICD-9, International Classification of Diseases, 9th Revision

Key words: acid-base equilibrium, intensive care units, aortic aneurysm, mortality, prognosis

Introduction

Aortic aneurysm (AA), defined as an enlargement of the aorta to greater than 1.5 times normal size (1) is usually asymptotic, but when rupture occurs, this may lead to internal bleeding, shock and mortality, unless treated immediately (2). Although AA is rather rare with an incidence of approximately 10 per 100,000 for thoracic aortic aneurysm (TAA) (3) and 55-298 per 100,000 for abdominal aortic aneurysm (AAA) (4), the burden of the disease is heavy and may be underestimated (5-7). Given the high total mortality estimated at 80-100% for ruptured AA (8,9), the best way to reduce the overall mortality of the disease may be to detect and treat it prior to rupture. In fact, many predictors or predictive models of mortality risk in AA patients have been reported (10-14), but further validation is required. Herein, we focused on AA patients in intensive care unit (ICU) and investigated the predictive value of serum anion gap on ICU mortality, a routine clinical indicator which has been reported to be associated with mortality of several diseases (15-18). Although a few studies have reported the association between anion gap with ICU mortality (19,20), to the best of our knowledge, no research to date has specially investigated the association in AA patients admitted to ICU. Considering the extremely low incidence of AA, we performed a retrospective analysis on a large publicly accessible clinical database, hoping to clarify the association between anion gap and ICU mortality.

Patients and methods

Database introduction. The retrospective analysis was conducted using data from the Medical Information Mart for Intensive Care III (MIMIC-III) database (version 1.4) (21), a large and freely-available database comprising deidentified

health-related data of patients admitted to ICU of the Beth Israel Deaconess Medical Center between 2001 and 2012. The database contains information including demographics, laboratory test results, and clinical outcomes. The access of the database was approved by the institutional review boards of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates.

Study design. Adult patients (age ≥18 years old) with first hospital admission and first ICU admission were considered for inclusion. AA patients were selected according to their primary diagnoses based on ICD-9 codes (4412-4415, and 4419), and patients with a length of ICU stay less than 24 h or a missing value of admission serum anion gap were excluded.

We used the codes from the MIMIC Code Repository (https://github.com/MIT-LCP/mimic-code) (22) to extract data from the database. Variables were extracted or calculated including admission serum anion gap (item ID=50868 in the database, detected within 24 h after ICU admission), severity scores including SOFA (23) and APACHE III (24), sepsis defined by ICD-9 codes (99592 and 78552), sepsis defined by Angus criteria (25) and comorbidities (26) based on ICD-9 codes. For patients >89 years old, date of birth had been shifted to exactly 300 years before by the database to obscure age, therefore this was corrected (age-300+89) prior to analysis. No informed consent was required as the data were anonymized.

Outcomes. ICU mortality was chosen as the primary study outcome before analysis. Hospital mortality, length of ICU stay, and length of hospital stay were also calculated. Although only patients of first hospital admission were included, it is possible for a patient to be transferred from one type of ICU to another. In this case, the primary outcome ICU mortality and length of ICU stay were determined only by the first ICU stay. Apart from statistical description, only the primary outcome was analyzed further.

Statistical analysis. Data are presented as median and interquartile range (IQR) for continuous variables and numbers and percentages for categorical variables. Kruskal Wallis and Chi-square (or Fisher's exact) tests were used to analyze continuous and categorical variables, respectively. Relationship between admission serum anion gap and ICU mortality was explored using the smoothing plot with an adjustment for potential confounders (age, sex, and SOFA were selected before analysis). A two-piecewise linear regression model was applied to examine the threshold effect of admission serum anion gap on ICU mortality according to the smoothing plot. Factors associated with ICU mortality were evaluated by univariate logistic analysis and variables that showed statistically significant association with ICU mortality in the univariate analysis ($P<0.05$) were included in the multivariable logistic regression model, but variables with missing values >10% were excluded. Considering that there was a certain overlap in the two severity scores and sepsis based on different criteria, we only selected SOFA and sepsis based on ICD-9 codes to be enrolled in the multivariable analysis if the variables were statistically significant

Table I. Numbers of subjects with missing values.

Variables	Numbers of subjects with specific missing value
Hemoglobin	1
Lactate	61
Platelet	1
PTT	11
INR	12
PT	12
WBC	2
Urine output in first day	4
Heartrate	2
Systolic pressure	3
Diastolic pressure	3
Respiratory rate	2
Temperature	23
SpO_2	2

PTT, partial thromboplastin time; INR, international normalised ratio; PT, prothrombin time; WBC, white blood cell.

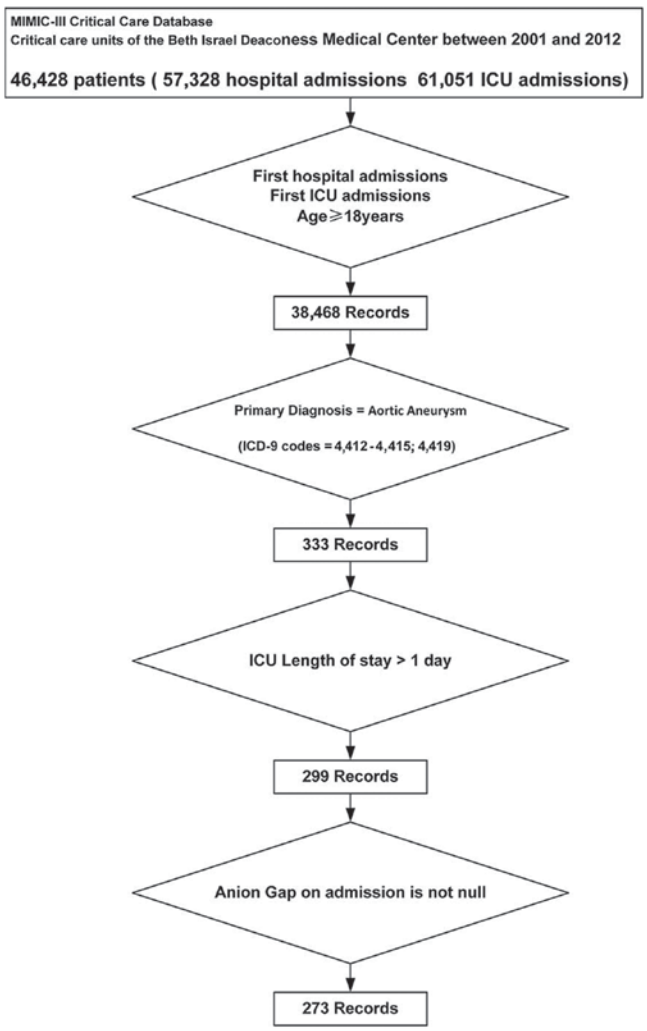

Figure 1. Flow chart of the study population. ICU, intensive care unit; ICD-9, International Classification of Diseases, 9th Revision.

Table II. Clinical characteristics of study subjects.

Parameter	All (n=273)	Survivors (n=249)	Non-survivors (n=24)	P-value
Age (years)	73.16 (65.14-80.06)	72.58 (64.59-79.76)	77.74 (72.11-82.80)	**0.009**
Sex (male), n (%)	154 (56.41%)	143 (57.43%)	11 (45.83%)	0.274
Type of aortic aneurysm				**0.002**
Thoracic aneurysm without mention of rupture	109 (39.93%)	104 (41.77%)	5 (20.83%)	
Abdominal aneurysm (ruptured)	48 (17.58%)	37 (14.86%)	11 (45.83%)	
Abdominal aneurysm without mention of rupture	116 (42.49%)	108 (43.37%)	8 (33.33%)	
Anion gap (mEq/l)	13.00 (11.00-15.00)	13.00 (11.00-15.00)	17.50 (15.75-22.50)	**<0.001**
ICU mortality	24 (8.79%)			
Hospital mortality	27 (9.89%)	3 (1.20%)	24 (100.00%)	**<0.001**
ICU length of stay (days)	3.23 (1.90-9.22)	3.16 (1.81-8.99)	10.88 (2.58-15.06)	**0.008**
Hospital length of stay (days)	9.32 (6.25-16.92)	9.30 (6.39-17.04)	10.84 (4.62-16.38)	0.317
Severity score				
SOFA	5.00 (4.00-8.00)	5.00 (3.00-7.00)	9.00 (8.00-11.25)	**<0.001**
APACHE III	39.00 (29.00-54.00)	38.00 (28.00-50.00)	70.00 (52.00-85.75)	**<0.001**
Vital signs				
Heartrate (bpm)	80.60 (73.07-88.98)	79.86 (72.69-87.77)	88.60 (83.54-95.75)	**0.002**
Systolic pressure (mmHg)	113.98 (106.58-124.29)	114.80 (106.79-124.01)	109.67 (104.60-124.98)	0.273
Diastolic pressure (mmHg)	57.68 (52.97-62.38)	57.32 (52.60-61.97)	59.78 (57.10-65.19)	**0.036**
Respiratory rate (bpm)	17.26 (14.96-19.27)	17.02 (14.94-19.21)	18.69 (16.13-21.00)	**0.040**
Temperature (˚C)	37.64 (37.10-38.10)	37.67 (37.18-38.10)	37.25 (36.72-37.82)	**0.041**
SpO_2 (%)	93.00 (91.00-95.00)	93.00 (91.00-95.00)	92.00 (86.75-94.00)	**0.023**
Urine output in first day (ml)	1,670.00 (981.00-2,580.00)	1,730.00 (1,071.50-2,602.50)	450.00 (246.25-1,342.00)	**<0.001**
RTT in first day	5 (1.83%)	2 (0.80%)	3 (12.50%)	**0.005**
Ventilation in first day	227 (83.15%)	205 (82.33%)	22 (91.67%)	0.390
Sepsis (based on ICD-9 codes)	8 (2.93%)	4 (1.61%)	4 (16.67%)	**0.003**
Sepsis (based on Angus criteria)	78 (28.57%)	63 (25.30%)	15 (62.50%)	**<0.001**
Lab examination				
WBC (K/ul)	12.50 (9.70-15.80)	12.10 (9.60-15.65)	14.75 (12.90-16.92)	**0.025**
Platelet (K/ul)	147.50 (111.88-190.12)	151.00 (112.38-192.75)	132.00 (106.00-149.88)	**0.027**
Hemoglobin (g/dl)	9.00 (7.80-10.30)	9.25 (7.90-10.33)	8.20 (6.97-8.80)	**0.002**
Creatinine (mg/dl)	1.10 (0.80-1.60)	1.00 (0.80-1.50)	1.95 (1.45-2.20)	**<0.001**
BUN (mg/dl)	19.00 (15.00-26.00)	18.00 (15.00-25.00)	27.50 (21.75-35.75)	**<0.001**
Glucose (mg/dl)	172.00 (140.00-204.00)	171.00 (138.00-200.00)	215.00 (155.75-316.25)	**0.005**
Lactate (mmol/l)	3.15 (1.98-5.30)	2.80 (1.90-4.60)	7.00 (5.20-10.80)	**<0.001**
PTT (sec)	35.57 (30.54-42.75)	34.80 (30.16-42.21)	42.72 (36.30-65.26)	**0.002**
INR	1.30 (1.20-1.50)	1.30 (1.16-1.45)	1.45 (1.20-1.77)	0.064
PT (sec)	14.45 (13.40-15.85)	14.40 (13.35-15.64)	15.85 (13.45-17.35)	0.082
Comorbidities				
Congestive heart failure	11 (4.03%)	10 (4.02%)	1 (4.17%)	1.000
Cardiac arrhythmias	12 (4.40%)	11 (4.42%)	1 (4.17%)	1.000
Valvular disease	3 (1.10%)	2 (0.80%)	1 (4.17%)	0.242
Pulmonary circulation disorder	2 (0.73%)	2 (0.80%)	0 (0.00%)	1.000
Peripheral vascular disorder	71 (26.01%)	64 (25.70%)	7 (29.17%)	0.808
Hypertension	23 (8.42%)	19 (7.63%)	4 (16.67%)	0.130
Paralysis	7 (2.56%)	6 (2.41%)	1 (4.17%)	0.479
Other neurological disease	4 (1.47%)	2 (0.80%)	2 (8.33%)	**0.040**
Chronic pulmonary disease	79 (28.94%)	72 (28.92%)	7 (29.17%)	1.000
Uncomplicated diabetes	41 (15.02%)	39 (15.66%)	2 (8.33%)	0.549
Complicated diabetes	4 (1.47%)	4 (1.61%)	0 (0.00%)	1.000

Table II. Continued.

Parameter	All (n=273)	Survivors (n=249)	Non-survivors (n=24)	P-value
Hypothyroidism	26 (9.52%)	23 (9.24%)	3 (12.50%)	0.487
Renal failure	31 (11.36%)	26 (10.44%)	5 (20.83%)	0.167
Liver disease	8 (2.93%)	6 (2.41%)	2 (8.33%)	0.150
Lymphoma	3 (1.10%)	3 (1.20%)	0 (0.00%)	1.000
Metastatic cancer	2 (0.73%)	2 (0.80%)	0 (0.00%)	1.000
Solid tumor	4 (1.47%)	4 (1.61%)	0 (0.00%)	1.000
Rheumatoid arthritis	8 (2.93%)	7 (2.81%)	1 (4.17%)	0.526
Coagulopathy	47 (17.22%)	39 (15.66%)	8 (33.33%)	**0.043**
Obesity	21 (7.69%)	21 (8.43%)	0 (0.00%)	0.233
Weight loss	7 (2.56%)	7 (2.81%)	0 (0.00%)	1.000
Fluid and electrolyte disorders	76 (27.84%)	67 (26.91%)	9 (37.50%)	0.339
Blood loss anemia	5 (1.83%)	4 (1.61%)	1 (4.17%)	0.371
Deficiency anemias	35 (12.82%)	34 (13.65%)	1 (4.17%)	0.333
Alcohol abuse	8 (2.93%)	8 (3.21%)	0 (0.00%)	1.000
Psychoses	4 (1.47%)	3 (1.20%)	1 (4.17%)	0.309
Depression	12 (4.40%)	12 (4.82%)	0 (0.00%)	0.608

Data are expressed as median (interquartile range) or n (%). Kruskal Wallis and Chi-square (or Fisher's exact) tests were used to compare continuous and categorical variables of the two groups, respectively. Statistical significance (P<0.05) is shown in bold. ICU, intensive care unit; SOFA, Sepsis-related Organ Failure Assessment; APACHE III, Acute Physiology and Chronic Health Evaluation III; RTT, renal replacement therapy; ICD-9, International Classification of Diseases, 9th Revision; WBC, white blood cell; BUN, blood urea nitrogen; PTT, partial thromboplastin time; INR, international normalised ratio; PT, prothrombin time.

in the univariate analysis. If a nonlinear relationship and a threshold effect were found in the previous analysis, then the subjects were stratified according to the threshold level and the logistic analysis was repeated. Receiver operating characteristic (ROC) curves were constructed and the area under the ROC curve (AUC) was calculated to evaluate the predictions. Consistency of the results in several subgroups was also explored using logistic regression models. To maximize statistical power and minimize potential bias that may have occurred if variables with missing values >10% were excluded from analyses, missing values of continuous and categorical covariates in outcome analysis were handled using multiple imputation with 5 imputed data sets, and results were pooled according to Rubin's rules (27). A multivariable analysis was also performed after excluding patients with ruptured AA. A P-value of <0.05 was considered statistically significant. Empower(R) (www.empowerstats.com; X&Y solutions, Inc., Boston, MA, USA) and R software, version 3.4.3 (http://www.r-project.org) were used for all statistical analyses.

Results

Population and baseline characteristics. A total of 273 patients were included and analyzed (Fig. 1). The number of missing values for all variables are presented in Table I. As shown in Table II, The median age of the study subjects was 73.16 years (IQR 65.14-80.06 years) and 154 of the 273 cases (56.41%) were male. The median admission serum anion gap was 13.00 mEq/l (IQR 11.00-15.00 mEq/l) with a median SOFA score of 5 (IQR 4-8). Among them, 8 (2.93%) patients were diagnosed as sepsis based on ICD-9 codes and 227 (83.15%) patients required ventilation. The five most common comorbidities were chronic pulmonary disease (28.94%), fluid and electrolyte disorders (27.84%), peripheral vascular disorder (26.01%), coagulopathy (17.22%), and uncomplicated diabetes (15.02%).

Survival status of the population. The ICU mortality was 8.79% with 24 non-survivors and 249 survivors and the hospital mortality was 9.89% (27/273). The median length of ICU stay and hospital stay was 3.23 (IQR 1.90-9.22) and 9.32 (IQR 6.25-16.92) days, respectively. As shown in Table II, non-survivors had significantly higher SOFA and APACHE (P<0.001). Furthermore, they were more likely to suffer from sepsis and require renal replacement therapy in first day. A significantly lower admission serum anion gap was observed in survivors (P<0.001).

Association between serum anion gap on admission and ICU mortality. Further analysis indicated that admission serum anion gap increased with increased ICU mortality when patients were stratified according to serum anion gap levels on admission (Table III), but no significant nonlinear relationship or threshold effect between them were observed (Fig. 2 and Table IV). After adjustment for potential confounders according to the univariate analysis (presented in Table V), admission serum anion gap was found to be significantly associated with ICU mortality [odds ratio (OR) 1.38 per 1 mEq/l increase, 95% confidence interval (CI), 1.08-1.76; P=0.0088] (Table VI). As shown in Fig. 3, AUC of serum anion gap for discrimination of survivors

Table III. Clinical characteristics of study subjects stratified by anion gap levels on ICU admission.

Parameter	Tertile 1 (n=81)	Tertile 2 (n=61)	Tertile 3 (n=131)	P-value
Age (years)	69.77 (60.37-79.58)	69.67 (63.65-78.14)	76.14 (70.24-82.05)	**<0.001**
Sex (male), n(%)	39 (48.15%)	35 (57.38%)	80 (61.07%)	0.180
Type of aortic aneurysm				**<0.001**
Thoracic aneurysm without mention of rupture	45 (55.56%)	31 (50.82%)	33 (25.19%)	
Abdominal aneurysm (ruptured)	5 (6.17%)	7 (11.48%)	36 (27.48%)	
Abdominal aneurysm without mention of rupture	31 (38.27%)	23 (37.70%)	62 (47.33%)	
Anion Gap (mEq/l)	10.00 (9.00-11.00)	13.00 (12.00-13.00)	16.00 (14.00-17.50)	**<0.001**
ICU mortality	1 (1.23%)	2 (3.28%)	21 (16.03%)	**<0.001**
Hospital mortality	2 (2.47%)	3 (4.92%)	22 (16.79%)	**<0.001**
ICU length of stay (days)	2.27 (1.33-4.10)	3.11 (1.44-8.55)	5.75 (2.20-12.60)	**<0.001**
Hospital length of stay (days)	7.84 (5.46-12.28)	9.27 (6.26-14.63)	12.22 (6.54-20.45)	**0.002**
Severity score				
SOFA	5.00 (3.00-6.00)	4.00 (3.00-7.00)	6.00 (4.50-9.00)	**<0.001**
APACHE III	33.00 (24.00-44.00)	36.00 (27.00-46.00)	49.00 (36.00-64.00)	**<0.001**
Vital signs				
Heartrate (bpm)	79.79 (72.67-86.79)	79.86 (73.07-87.19)	81.90 (73.75-91.75)	0.438
Systolic pressure (mmHg)	109.73 (105.03-118.55)	117.89 (108.29-124.83)	117.79 (107.62-128.83)	**0.002**
Diastolic pressure (mmHg)	56.74 (52.82-61.74)	57.59 (53.28-62.43)	58.61 (53.25-63.48)	0.508
Respiratory rate (bpm)	16.36 (14.63-18.54)	17.31 (15.22-18.58)	18.08 (15.21-19.91)	0.029
Temperature (˚C)	37.82 (37.40-38.18)	37.60 (37.03-38.00)	37.60 (37.03-38.06)	0.115
SpO_2 (%)	93.00 (91.00-95.00)	93.00 (91.00-95.00)	93.00 (91.00-95.00)	0.357
Urine output in first day (ml)	2,200.00 (1,605.00-2,730.00)	1,670.00 (1,087.00-2,515.00)	1,172.00 (650.00-2,229.50)	**<0.001**
RTT in first day	0 (0.00%)	0 (0.00%)	5 (3.82%)	0.085
Ventilation in first day	71 (87.65%)	53 (86.89%)	103 (78.63%)	0.158
Sepsis (based on ICD-9 codes)	2 (2.47%)	0 (0.00%)	6 (4.58%)	0.257
Sepsis (based on Angus criteria)	11 (13.58%)	15 (24.59%)	52 (39.69%)	<0.001
Lab examination				
WBC (K/ul)	13.00 (9.70-15.60)	11.90 (10.10-13.83)	12.10 (9.22-16.67)	0.647
Platelet (K/ul)	153.50 (121.00-190.00)	151.00 (108.00-184.00)	137.50 (108.88-194.00)	0.747
Hemoglobin (g/dl)	8.90 (7.90-10.00)	9.30 (7.70-10.30)	9.25 (7.82-10.28)	0.612
Creatinine (mg/dl)	0.80 (0.70-1.10)	1.00 (0.80-1.30)	1.40 (1.00-1.95)	**<0.001**
BUN (mg/dl)	16.00 (13.00-19.00)	17.00 (15.00-21.00)	24.00 (18.00-30.00)	**<0.001**
Glucose (mg/dl)	160.00 (138.00-180.00)	162.00 (139.00-191.00)	185.00 (153.00-236.00)	**<0.001**
Lactate (mmol/l)	2.50 (2.00-3.90)	3.15 (2.03-4.85)	3.60 (1.95-6.65)	0.034
PTT (sec)	35.42 (31.22-41.99)	34.55 (30.40-41.95)	36.80 (30.57-44.38)	0.702
INR	1.30 (1.20-1.45)	1.30 (1.15-1.40)	1.30 (1.20-1.60)	0.371
PT (sec)	14.50 (13.62-15.53)	14.35 (13.20-15.22)	14.55 (13.26-16.04)	0.596

Data are expressed as median (interquartile range) or n (%). Kruskal Wallis and Chi-square (or Fisher's exact) tests were used to analyze continuous and categorical variables, respectively. Statistical significance (P<0.05) is shown in bold. ICU, intensive care unit; SOFA, Sepsis-related Organ Failure Assessment; APACHE III, Acute Physiology and Chronic Health Evaluation III; RTT, renal replacement therapy; ICD-9, International Classification of Diseases, 9th Revision; WBC, white blood cell; BUN, blood urea nitrogen; PTT, partial thromboplastin time; INR, international normalised ratio; PT, prothrombin time.

and non-survivors was 0.8513 (95% CI, 0.7698-0.9328), which suggested its potentially efficient predictive role in ICU mortality for AA patients.

Subgroup analysis. The results of the stratified and interaction analyses of the association between admission serum anion gap and ICU mortality are presented in Fig. 4 and Table VII.

Table IV. Threshold effect analysis of anion gap on ICU mortality using piecewise linear regression.

Inflection point of anion gap on ICU mortality (mEq/l)	β (95% CI)	Δβ (95% CI)	P-value	P for Δβ
<17	1.51 (1.12, 2.04)		0.0074	
>17	1.14 (0.97, 1.34)		0.1148	
		0.76 (0.51-1.12)		0.1580

Adjusted for age, SOFA, and sex. ICU, intensive care unit; CI, confidence interval; SOFA, Sepsis-related Organ Failure Assessment.

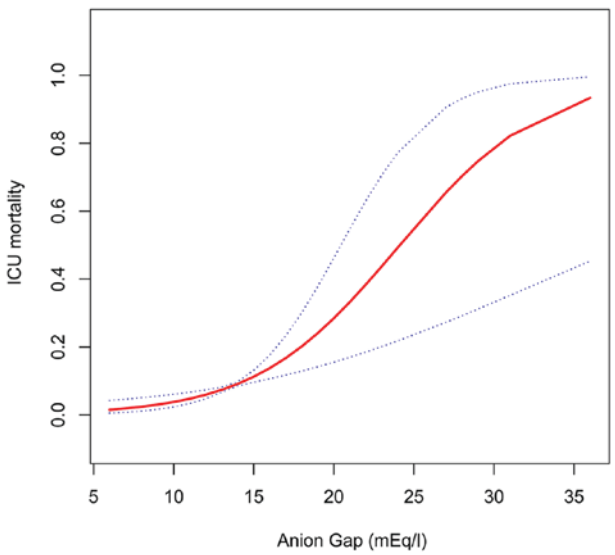

Figure 2. Non-linear curve fitting of the relationship between anion gap and ICU mortality. Adjusted for age, SOFA and sex. ICU, intensive care unit.

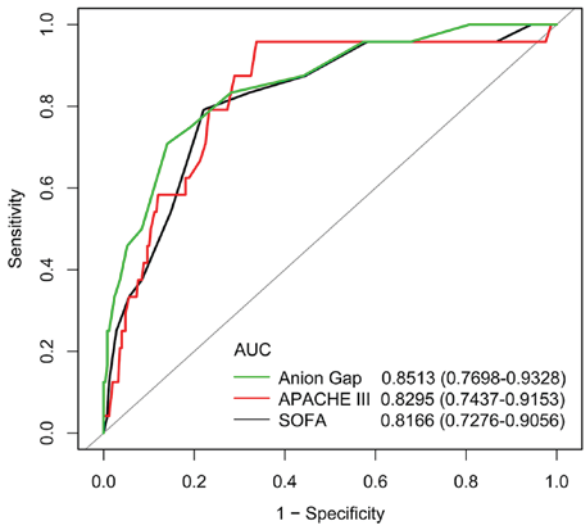

Figure 3. ROC curves of anion gap in the prediction of ICU mortality. The gray line represents the reference line. ROC curves, Receiver operating characteristic curves; ICU, intensive care unit; AUC, area under the ROC curves; APACHE III, Acute Physiology and Chronic Health Evaluation III; SOFA, Sepsis-related Organ Failure Assessment.

The association appeared to be similar when compared with the results of the multivariable analysis shown in Table VI. A

Table V. Univariate analysis of intensive care unit mortality.

Variable	OR (95% CI)	P-value
Age	1.07 (1.01, 1.12)	**0.0116**
Sex		
Male	1.0	
Female	1.59 (0.69, 3.70)	0.2772
Type of aortic aneurysm		
Thoracic aneurysm without mention of rupture	1.0	
Abdominal aneurysm (ruptured)	6.18 (2.01, 18.98)	**0.0015**
Abdominal aneurysm without mention of rupture	1.54 (0.49, 4.86)	0.4610
Anion Gap (mEq/l)	1.36 (1.22, 1.52)	**<0.0001**
Severity score		
SOFA	1.46 (1.26, 1.69)	**<0.0001**
APSIII	1.05 (1.03, 1.07)	**<0.0001**
Vital signs		
Heartrate (bpm)	1.07 (1.03, 1.10)	**0.0004**
Systolic pressure (mmHg)	0.98 (0.95, 1.02)	0.3266
Diastolic pressure (mmHg)	1.04 (0.99, 1.10)	0.1182
Respiratory rate (bpm)	1.15 (1.02, 1.29)	**0.0183**
Temperature (°C)	0.59 (0.32, 1.09)	0.0909
SpO_2 (%)	0.97 (0.93, 1.01)	0.0993
Urine output in first day (ml)	1.00 (1.00, 1.00)	**0.0014**
RTT in first day		
No	1.0	
Yes	17.64 (2.79, 111.52)	**0.0023**
Ventilation in first day		
No	1.0	
Yes	2.36 (0.54, 10.41)	0.2564
Sepsis (based on ICD-9 codes)		
No	1.0	
Yes	12.25 (2.85, 52.69)	**0.0008**
Sepsis (based on Angus criteria)		
No	1.0	
Yes	4.92 (2.05, 11.8)	**0.0004**
Lab examination		
White blood cell (K/ul)	1.05 (0.98, 1.13)	0.1357

Table V. Univariate analysis of ICU mortality.

Variable	OR (95% CI)	P-value
Platelet (K/ul)	0.99 (0.98, 1.00)	**0.0248**
Hemoglobin (g/dl)	0.71 (0.56, 0.89)	**0.0035**
Creatinine (mg/dl)	2.00 (1.39, 2.90)	**0.0002**
Blood urea nitrogen (mg/dl)	1.06 (1.03, 1.10)	**0.0003**
Glucose (mg/dl)	1.01 (1.00, 1.01)	**0.0005**
Lactate (mmol/l)	1.41 (1.22, 1.61)	**<0.0001**
PTT (sec)	1.03 (1.01, 1.05)	**0.0017**
INR	3.24 (1.30, 8.1)	**0.0116**
Prothrombin time (sec)	1.08 (1.01, 1.16)	**0.0270**
Comorbidities		
Congestive heart failure		0.9714
No	1.0	
Yes	1.04 (0.13, 8.48)	
Cardiac arrhythmias		0.9543
No	1.0	
Yes	0.94 (0.12, 7.62)	
Valvular disease		0.1767
No	1.0	
Yes	5.37 (0.47, 61.50)	
Pulmonary circulation disorder		0.9897
No	1.0	
Yes	0.00 (0.00, Inf)	
Peripheral vascular disorder		0.7121
No	1.0	
Yes	1.19 (0.47, 3.00)	
Hypertension		0.1389
No	1.0	
Yes	2.42 (0.75, 7.81)	
Paralysis		0.6076
No	1.0	
Yes	1.76 (0.20, 15.27)	
Other neurological disease		0.0182
No	1.0	
Yes	11.23 (1.51, 83.62)	
Chronic pulmonary disease		0.9793
No	1.0	
Yes	1.01 (0.40, 2.54)	
Uncomplicated diabetes		0.3465
No	1.0	
Yes	0.49 (0.11, 2.17)	
Complicated diabetes		0.9905
No	1.0	
Yes	0.00 (0.00, Inf)	
Hypothyroidism		0.6046
No	1.0	
Yes	1.40 (0.39, 5.07)	
Renal failure		0.1343
No	1.0	
Yes	2.26 (0.78, 6.55)	
Liver disease		0.1235
No	1.0	
Yes	3.68 (0.70, 19.34)	
Lymphoma		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9918
Metastatic cancer		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9897
Solid tumor		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9905
Rheumatoid arthritis		
No	1.0	
Yes	1.50 (0.18, 12.76)	0.7088
Coagulopathy		
No	1.0	
Yes	2.69 (1.08, 6.72)	0.0339
Obesity		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9909
Weight loss		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9875
Fluid and electrolyte disorders		
No	1.0	
Yes	1.63 (0.68, 3.90)	0.2725
Blood loss anemia		
No	1.0	
Yes	2.66 (0.29, 24.83)	0.3899
Deficiency anemias		
No	1.0	
Yes	0.27 (0.04, 2.10)	0.2135
Alcohol abuse		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9913
Psychoses		
No	1.0	
Yes	3.57 (0.36, 35.67)	0.2793
Depression		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9893

Statistical significance (P<0.05) is shown in bold. OR, odds ratio; CI, confidence interval; SOFA, Sepsis-related Organ Failure Assessment; APACHE III, Acute Physiology and Chronic Health Evaluation III; RTT, renal replacement therapy; ICD-9, International Classification of Diseases, 9th Revision; PTT, partial thromboplastin time; INR, international normalised ratio.

significant interaction (P<0.05) was found among subgroups of tertile of hemoglobin.

Table VI. Multivariate logistic regression for effects of anion gap on intensive care unit mortality.

Variable	Odds ratio	95% confidence interval	P-value
Non-adjusted	1.36	1.22-1.52	**<0.0001**
Model I	1.26	1.11-1.42	**0.0003**
Model II	1.38	1.08-1.76	**0.0088**

Model I, adjusted for age, sex, and SOFA. Model II, adjusted for type of aortic aneurysm, age, SOFA, blood urea nitrogen, heartrate, international normalised ratio, platelet, prothrombin time, PTT, respiratory rate, RTT in first day, urine output in first day, coagulopathy, hemoglobin, other neurological disease, glucose, sepsis (based on ICD-9 codes), and creatinine. Statistical significance (P<0.05) is shown in bold. SOFA, Sepsis-related Organ Failure Assessment; PTT, partial thromboplastin time; RTT, renal replacement therapy; ICD-9, International Classification of Diseases, 9th Revision.

Table VII. Subgroup analysis of associations between anion gap and intensive care unit mortality.

Variable	n	OR	95% CI Low	95% CI High	P-value	P-value (interaction)
Type of aortic aneurysm						0.1361
Thoracic aneurysm without mention of rupture	109	1.22	0.98	1.53	0.0781	
Abdominal aneurysm (ruptured)	48	1.25	1.00	1.57	**0.0464**	
Abdominal aneurysm without mention of rupture	116	2.02	1.19	3.42	0.0087	
Sepsis (based on Angus criteria)						0.8300
No	195	1.29	1.07	1.55	**0.0069**	
Yes	78	1.25	1.03	1.52	**0.0216**	
Coagulopathy						0.2672
No	226	1.39	1.15	1.67	**0.0006**	
Yes	47	1.19	0.98	1.44	0.0814	
Hemoglobin						0.0134
Low	91	1.13	0.99	1.28	0.0727	
Middle	86	1.94	1.20	3.13	**0.0065**	
High	95	1.53	1.00	2.35	0.0522	
Fluid and electrolyte disorders						0.9546
No	197	1.27	1.09	1.49	**0.0022**	
Yes	76	1.26	1.04	1.54	**0.0197**	

Adjusted for: Age, sex and SOFA. Statistical significance (P<0.05) is shown in bold. OR, odds ratio; CI, confidence interval.

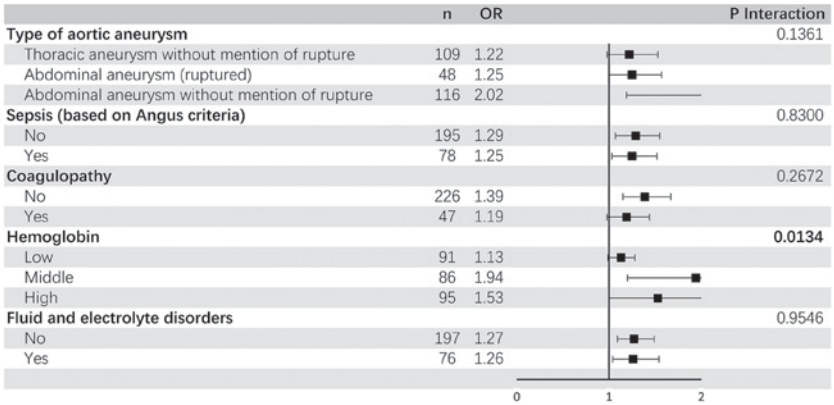

Figure 4. Subgroup analysis of association between admission serum anion gap and ICU mortality. Horizontal lines represent 95% confidence intervals. P-values for interactions were calculated with the use of likelihood-ratio tests comparing logistic regression models (after adjusting for age, sex and SOFA) with and without cross-product terms for each level of baseline stratifying variables, with admission serum anion gap as an explanatory variable. Detailed data are shown in Table VII. ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

Table VIII. Multivariate logistic regression for effects of anion gap on ICU mortality using imputed datasets.

Variable	OR	95% CI	P-value
Dataset 1			
Non-adjusted	1.36	1.22-1.52	**<0.0001**
Model I	1.26	1.11-1.42	**0.0003**
Model II	1.26	1.01-1.59	**0.0440**
Dataset 2			
Non-adjusted	1.36	1.22-1.52	**<0.0001**
Model I	1.26	1.11-1.42	**0.0003**
Model II	1.35	1.06-1.71	**0.0141**
Dataset 3			
Non-adjusted	1.36	1.22-1.52	**<0.0001**
Model I	1.26	1.11-1.42	**0.0003**
Model II	1.36	1.07-1.74	**0.0125**
Dataset 4			
Non-adjusted	1.36	1.22-1.52	**<0.0001**
Model I	1.26	1.11-1.42	**0.0003**
Model II	1.39	1.10-1.76	**0.0052**
Dataset 5			
Non-adjusted	1.36	1.22-1.52	**<0.0001**
Model I	1.26	1.11-1.42	**0.0003**
Model II	1.44	1.12-1.84	**0.0043**
Pooled			
Non-adjusted	1.36	1.22-1.52	<0.0001
Model I	1.26	1.11-1.43	0.0002
Model II	1.36	1.05-1.76	0.0195

Model I, adjusted for age and SOFA. Model II, adjusted for type of aortic aneurysm, age, SOFA, BUN, heartrate, INR, platelet, PT, PTT, respiratory rate, RTT in first day, urine output in first day, hemoglobin, other neurological disease, glucose, sepsis (based on ICD-9 codes), creatinine, and lactate. Dataset 3-5 were adjusted for model II and coagulopathy. Statistical significance (P<0.05) is shown in bold. OR, odds ratio; CI, confidence interval; ICU, intensive care unit; SOFA, Sepsis-related Organ Failure Assessment; BUN, blood urea nitrogen; INR, international normalised ratio; PT, prothrombin time; PTT, partial thromboplastin time; RTT, renal replacement therapy; ICD-9, International Classification of Diseases, 9th Revision.

Sensitive analysis. The imputation of missing variables did not affect the results (Table VIII), which were virtually unchanged (<10%) after excluding ruptured AA patients (Table IX and X).

Discussion

The present study examined for the first time the predictive value of serum anion gap on ICU mortality in AA patients, and the results suggested that the risk of ICU mortality may increase by 38% per 1 mEq/l increase in admission serum anion gap.

Table IX. Univariate analysis of ICU mortality after excluding patients with ruptured aortic aneurysm.

Variable	OR (95% CI)	P-value
Age	1.07 (1.00, 1.14)	0.0523
Sex		
Male	1.0	
Female	3.36 (1.00, 11.27)	**0.0494**
Type of aortic aneurysm		
Thoracic aneurysm without mention of rupture	1.0	
Abdominal aneurysm without mention of rupture	1.54 (0.49, 4.86)	0.4610
Anion gap (mEq/l)	1.44 (1.19, 1.75)	**0.0002**
Severity score		
SOFA	1.38 (1.16, 1.65)	**0.0002**
APSIII	1.05 (1.02, 1.08)	**0.0003**
Vital signs		
Heartrate (bpm)	1.06 (1.01, 1.10)	**0.0161**
Systolic pressure (mmHg)	0.98 (0.94, 1.03)	0.4983
Diastolic pressure (mmHg)	1.02 (0.95, 1.09)	0.5753
Respiratory rate (bpm)	1.12 (0.96, 1.31)	0.1427
Temperature (˚C)	0.52 (0.23, 1.18)	0.1193
SpO_2 (%)	0.97 (0.93, 1.01)	0.1316
Urine output in first day (ml)	1.00 (1.00, 1.00)	0.1029
RTT in first day		
No	1.0	
Yes	8.75 (0.74, 103.44)	0.0852
Ventilation in first day		
No	1.0	
Yes	2.79 (0.35, 22.09)	0.3309
Sepsis (based on ICD-9 codes)		
No	1.0	
Yes	23.11 (4.96, 107.61)	**0.0001**
Sepsis (based on angus criteria)		
No	1.0	
Yes	5.62 (1.75, 17.98)	**0.0036**
Lab examination		
WBC (K/ul)	1.04 (0.94, 1.14)	0.4594
Platelet (K/ul)	0.99 (0.98, 1.00)	0.0758
Hemoglobin (g/dl)	0.70 (0.50, 0.98)	**0.0398**
Creatinine (mg/dl)	1.66 (1.05, 2.64)	**0.0310**
BUN (mg/dl)	1.06 (1.01, 1.10)	**0.0106**
Glucose (mg/dl)	1.01 (1.00, 1.01)	0.0585
Lactate (mmol/l)	1.53 (1.21, 1.93)	**0.0004**
PTT (sec)	1.02 (0.99, 1.05)	0.1386
INR	1.43 (0.26, 7.73)	0.6795
PT (sec)	0.95 (0.72, 1.27)	0.7441

Table IX. Continued.

Variable	OR (95% CI)	P-value
Comorbidities		
Congestive heart failure		
No	1.0	
Yes	2.44 (0.28, 21.47)	0.4213
Cardiac arrhythmias		
No	1.0	
Yes	2.12 (0.25, 18.41)	0.4938
Valvular disease		
No	1.0	
Yes	8.75 (0.74, 103.44)	0.0852
Pulmonary circulation disorder		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9935
Peripheral vascular disorder		
No	1.0	
Yes	1.92 (0.60, 6.14)	0.2693
Hypertension		
No	1.0	
Yes	3.67 (0.92, 14.71)	0.0659
Paralysis		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9908
Other neurological disease		
No	1.0	
Yes	17.58 (1.04, 298.62)	**0.0473**
Chronic pulmonary disease		
No	1.0	
Yes	1.51 (0.48, 4.80)	0.4832
Uncomplicated diabetes		
No	1.0	
Yes	0.45 (0.06, 3.59)	0.4529
Complicated diabetes		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9908
Hypothyroidism		
No	1.0	
Yes	1.85 (0.38, 8.95)	0.4462
Renal failure		
No	1.0	
Yes	2.59 (0.66, 10.13)	0.1712
Liver disease		
No	1.0	
Yes	3.45 (0.37, 31.91)	0.2752
Lymphoma		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9921
Metastatic cancer		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9930
Solid tumor		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9908
Rheumatoid arthritis		
No	1.0	
Yes	2.44 (0.28, 21.47)	0.4213
Coagulopathy		
No	1.0	
Yes	2.80 (0.81, 9.7)	0.1034
Obesity		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9913
Weight loss		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9921
Fluid and electrolyte disorders		
No	1.0	
Yes	0.97 (0.26, 3.67)	0.9666
Blood loss anemia		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9921
Deficiency anemias		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9895
Alcohol abuse		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9916
Psychoses		
No	1.0	
Yes	8.75 (0.74, 103.44)	0.0852
Depression		
No	1.0	
Yes	0.00 (0.00, Inf)	0.9901

Statistical significance (P<0.05) is shown in bold. ICU, intensive care unit; OR, odds ratio; CI, confidence interval; SOFA, Sepsis-related Organ Failure Assessment; APACHE III, Acute Physiology and Chronic Health Evaluation III; RTT, renal replacement therapy; ICD-9, International Classification of Diseases, 9th Revision; WBC, white blood cell; BUN, blood urea nitrogen; PTT, partial thromboplastin time; INR, international normalised ratio; PT, prothrombin time.

Many studies have explored the relationship between anion gap and clinical outcomes of critically ill patients. In fact, as early as 1987, Shackleton *et al* (14) noted that an elevation of the unmeasured anion gap was significantly and independently associated with mortality for ruptured AAA patients. Grist and Thomas (28) reported that anion gap is a risk factor in long-term extracorporeal support. Kim *et al* (19) found a similar association in a

Table X. Multivariate logistic regression for effects of anion gap on ICU mortality after excluding patients with ruptured aortic aneurysm.

Variable	OR	95% CI	P-value
Non-adjusted	1.44	1.19-1.75	**0.0002**
Model I	1.33	1.08-1.62	**0.0064**
Model II	1.46	1.09-1.97	**0.0112**

Model I, adjusted for age, sex, and SOFA. Model II, adjusted for sex, SOFA, BUN, heartrate, hemoglobin, sepsis (based on ICD-9 codes), other neurological disease, and creatinine. Statistical significance ($P<0.05$) is shown in bold. ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

pediatric ICU. However, Rocktaeschel *et al* (29) concluded that unmeasured anions, irrespective of the calculated methods, were not practical predictors of hospital mortality in critically ill patients. In addition, the use of anion gap for risk stratification in critically ill patients is not supported for the significant statistical heterogeneity according to a recent systematic review and meta-analysis conducted by Glasmacher and Stones (20). Considering the urgent need for a practical and useful predictive model of AA (30), which is notorious for high mortality, it is essential to keep exploring predictors of clinical outcomes for AA patients. As anion gap is routinely determined in all patients admitted to ICU and there is no extra cost for this potential beneficial test, a study that specifically focused on AA patients was necessary, given the extremely low incidence of AA. The results of our study validated the association between serum anion gap and ICU mortality, which was in accordance with most previous studies (20), suggesting that serum anion gap may serve as a mortality predictor for AA patients in ICU. The AUC of anion gap was similar to the SOFA and APACHE III values in our study. As anion gap is a traditional tool used to assess acid-base status, most previous studies usually attribute the association to acid-base disorders, which contribute significantly to morbidity and mortality in critically ill patients (31). Taylor *et al* (32) reported that anion gap is independently associated with higher blood pressure, which is associated with negative outcomes for AA patients (33), thus the underlying mechanism requires further research.

Several limitations of our study should be noted. First, although hypoalbuminemia could affect its interpretation, anion gap was not corrected for serum albumin level in our study as most subjects analyzed lacked albumin records. Second, although attempts were taken to control bias and confounders, many other known or unknown factors may still exist and have contributed to bias. For example, although we took into consideration fluid and electrolyte disorders (identified by ICD-9 codes) as a potential confounder, the quantities and types of intravenous infusion fluids before ICU admission may have affected the value of serum anion gap on ICU admission. Other potential confounders including smoking status, diameters of the aorta, and surgical procedures were not considered in the study. In addition, given the observational nature of our study, it is not possible to conclude that the relationship between admission serum anion gap and ICU mortality reflects cause and effect.

In summary, the present retrospective observational study provided confirmation of the association between serum anion gap on admission and ICU mortality of AA patients. However, further prospective clinical studies are still required, particularly to explore the potential value of anion gap in improving various predictive models for ICU outcomes.

Acknowledgements

Not applicable.

Funding

This work was supported by the Natural Science Foundation of Guangdong Province China (grant number 2015A030310346); the Special Funds for the Cultivation of Guangdong College Students' Scientific and Technological Innovation ('Climbing Program' Special Funds).

Availability of data and materials

The datasets generated and analyzed during the current study are available in the PhysioBank repository, https://mimic.physionet.org/.

Authors' contributions

KH, QCC, and QGC designed the study. QCC, QGC, LL, XL, and SIC performed data extraction and the data were analyzed by QCC, QGC, YL, ZT, and WL. The manuscript draft was prepared by LL and revised by KH, QCC and QGC. All authors approved the final manuscript.

Ethics approval and consent to participate

The access of the database was approved by the institutional review boards of both Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates. No informed consent was required because the data are anonymized.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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