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Clinical predictors of endotracheal intubation in patients presenting to the emergency department with angioedema

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ABSTRACT

Objectives: The objective of this study is to identify predictors of airway compromise among patients presenting to the emergency department with angioedema in order to develop and validate a risk score to augment clinician gestalt regarding need for intubation.
Methods: Retrospective chart review of emergency department patients with a diagnosis of angioedema. After data extraction they were randomly divided into a training and test set. The training set was used to identify factors associated with intubation and to develop a model and risk score to predict intubation. The model and risk score were then applied to the test set.
Results: A total of 594 patients were included. Past medical history of hypertension, presence of shortness of breath, drooling, and anterior tongue or pharyngeal swelling were independent predictors included in our final model and risk score. The Area Under the Curve for the Receiver Operator Characteristic curve was 87.55% (83.42%–91.69%) for the training set and 86.1% (77.62%–94.60%) for the test set.
Conclusions: A simple scoring algorithm may aid in predicting angioedema patients at high and low risk for intubation. External validation of this score is necessary before wide-spread adoption of this decision aid.

1. Introduction

Angioedema is nonpitting, non-pruritic swelling of the skin or mucosa [1], typically involving the face, oropharyngeal and laryngeal structures. In most cases it is sudden in onset and has a relatively short duration [2]. It is estimated that angioedema accounts for between 80,000 and 111,000 Emergency Department (ED) visits annually in the United States. [3]

Management of angioedema commonly includes discontinuation of inciting medications and initiation of steroids, antihistamines, and epinephrine. The most immediate threat to life among angioedema patients is airway occlusion and subsequent asphyxiation. For this reason, the cornerstone of management of angioedema is airway assessment, monitoring, and early endotracheal intubation when indicated.

Some authors have suggested management based on location of anatomic swelling. Isolated facial swelling can likely be monitored and discharged home while those with laryngeal involvement should be monitored in an ICU if intubation is not initially required [2,4,5]. Unfortunately, guidance from the medical literature regarding disposition and intervention with these patients is limited. Therefore, emergency physicians frequently must base the decision of which patients should be monitored and safely discharged versus which require intubation and/or admission for airway monitoring largely on previous clinical experience alone.

Balancing resource allocation with appropriate monitoring is difficult without evidence-based guidance. We hypothesize that there is a subset of angioedema patients who can be discharged from the ED, however distinguishing between those safe for discharge and those needing emergent airway intervention is not clear. In this retrospective study, we identify important clinical predictors of airway compromise to devise a clinical risk score that may help guide clinicians in their disposition and management of patients presenting with angioedema of the face, mouth, or larynx.

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2. Methods

2.1. Study design and setting

This is a retrospective chart review designed to identify predictors of need for intubation among patients presenting to the Emergency Department with a clinical diagnosis of angioedema and develop a risk score to augment clinical gestalt. The study was approved by the Institutional Review Board at the University of Florida.

2.2. Selection of participants and data abstraction

We retrospectively identified all charts with International Classification of Disease 9/10 codes for angioedema, 995.1 and T78.3, for patients who presented to the Emergency Department of a single tertiary hospital from November 1, 2012 to August 31, 2017. Charts were individually reviewed by trained research assistants to verify the diagnosis of angioedema. Research assistant training consisted of one-on-one training with the lead investigator (JA) on the specific data elements to be abstracted from the medical record. The lead and senior investigator were available to answer any questions regarding abstracted data elements. Questionable cases were reviewed collectively by the lead and senior investigator (JA, FWG). Cases were included if the documentation by the treating clinicians concluded that angioedema was the primary diagnosis. Cases were excluded if the patient was <18 years of age at presentation, was incarcerated at the time of presentation, was currently undergoing or had previously undergone treatment for head or neck malignancy, had a tracheostomy, had symptoms which developed while in the emergency department, or if the treating clinician documentation suggested that there was a more likely alternative cause than angioedema for the patient's presentation (e.g., infections such as Ludwig's angina, peritonsillar abscess, and facial or tongue abscesses). Ten percent of potential cases were independently reviewed by the lead investigator (JA). Percent agreement between the lead investigator and research assistants was 100% for inclusion or exclusion of cases. Abstracted data included demographic information, comorbidities, historical factors, previous outpatient medications, season, day of the week, symptoms, time from symptom onset to evaluation, progression of symptoms, clinical signs, location of airway swelling, medications administered, and details of intubation. Presenting signs and symptoms were determined from the emergency provider's notes. Presence and location of airway edema was identified based upon by the emergency provider's exam documentation and procedure notes from fiberoptic laryngoscopy and/or intubation.

2.3. Measurements

Categorical variables are presented as counts and percentages while continuous variables are presented as means and standard deviations. Our patient sample was randomly divided into a training set ($N = 446$; 75% of the sample) and a test set ($N = 148$; 25% of the sample). Using the training set, we screened variables using the following process. First, we compared the demographic and medical characteristics of patients based on their intubation status using Fisher's exact tests or Wilcoxon rank-sum tests, as appropriate. Variables with p-values >0.15 or categorical variables with very low (<5%) or very high (>95%) prevalence were excluded. Second, we used the Spearman correlation coefficient to define a dissimilarity matrix from which we performed hierarchical clustering to identify variables that were highly correlated. When such a cluster was identified, we chose a single variable that was most readily available to treating clinicians to represent the cluster in the analysis. We subsequently fit a multivariable logistic regression model using the least absolute shrinkage and selection operator (LASSO) method to further reduce the number of variables. We used the reduced set of variables to fit a final logistic regression model from which we used the β-coefficients to create the weights for each variable for the new risk score, which was calculated as the weighted sum of the variables. The test set was then used to assess the operating characteristics of the final model and the risk score. Operating characteristics included sensitivity, specificity, positive predictive value, and negative predictive value. Additionally, receiver operator characteristic curves were generated for the training and test sets with areas under the curve calculated. Statistical analysis was performed using R (R Core Team, 2013).

3. Results

We identified 715 potential cases during the study period, of which 594 met inclusion criteria. Table 1 shows the baseline characteristics of

Table 1
Patient characteristics.

Characteristic	All	Training	Test
Total No. of patients	594	446	148
Male, % (No.)	46.5 (276)	47.8 (213)	42.6 (63)
Age > 50y, % (No.)	64.5 (383)	65.7 (293)	60.8 (90)
Race, % (No.)			
White	18.7 (111)	17.3 (77)	23.0 (34)
Black	77.9 (463)	80.3 (358)	70.9 (105)
Other	3.4 (20)	2.5 (11)	6.1 (9)
Insurance,* % (No.)			
Commercial	19.1 (113)	19.3 (86)	18.2 (27)
Medicaid	16.9 (100)	17.3 (77)	15.5 (23)
Medicare	31.7 (188)	30.8 (137)	34.5 (51)
Tricare	6.1 (36)	6.1 (27)	6.1 (9)
Self-Pay	26.3 (156)	26.5 (118)	25.7 (38)
Residence, % (No.)			
Home	97.1 (577)	96.9 (432)	98.0 (145)
Nursing Home	2.0 (12)	2.2 (10)	1.4 (2)
Long-Term Acute Care	0.3 (2)	0.4 (2)	0.0 (0)
Homeless	0.3 (2)	0.2 (1)	0.7 (1)
Other	0.2 (1)	0.2 (1)	0.0 (0)
Season, % (No.)			
Spring	28.3 (168)	28.5 (127)	27.7 (41)
Summer	30.1 (179)	29.1 (130)	33.1 (49)
Fall	22.2 (132)	22.6 (101)	20.9 (31)
Winter	19.4 (115)	19.7 (88)	18.2 (27)
Allergies, % (No.)			
Any	45.8 (272)	45.1 (201)	48.0 (71)
Peanut	0.7 (4)	0.7 (3)	0.7 (1)
Shell	5.9 (35)	5.6 (25)	6.8 (10)
Iodine	2.2 (13)	1.8 (8)	3.4 (5)
Contrast	0.3 (2)	0.2 (1)	0.7 (1)
Penicillin	11.1 (66)	12.1 (54)	8.1 (12)
ACE inhibitors	8.6 (51)	9.4 (42)	6.1 (9)
Other	33.2 (197)	31.6 (141)	37.8 (56)
Comorbidities, % (No.)			
GCS = 15†	98.3 (580)	98.0 (434)	99.3 (146)
Diabetes	26.4 (157)	27.8 (124)	22.3 (33)
COPD	6.9 (41)	6.5 (29)	8.1 (12)
End-Stage Renal Disease	1.7 (10)	1.8 (8)	1.4 (2)
Cardiac Disease	13.1 (78)	14.3 (64)	9.5 (14)
Cancer	5.9 (35)	5.4 (24)	7.4 (11)
Hypertension	75.1 (446)	76.9 (343)	69.6 (103)
Asthma	14.3 (85)	14.3 (64)	14.2 (21)
Thyroid Disease	10.8 (64)	9.9 (44)	13.5 (20)
Tobacco Use	36.2 (215)	37.0 (165)	33.8 (50)
Hyperlipidemia	23.9 (142)	23.8 (106)	24.3 (36)
Gastric/Esophageal Reflux	11.3 (67)	12.1 (54)	8.8 (13)
Head/Neck Surgery or Radiation	3.4 (20)	3.1 (14)	4.1 (6)
Angioedema	24.9 (148)	25.6 (114)	23.0 (34)
Medications, % (No.)			
ACE Inhibitor	57.1 (339)	58.5 (261)	52.7 (78)
Lisinopril	54.7 (325)	56.7 (253)	48.6 (72)
NSAIDS	18.9 (112)	19.3 (86)	17.6 (26)
ARB	4.5 (27)	5.4 (24)	2.0 (3)
Intubated, % (No.)	17.3 (103)	18.2 (81)	14.9 (22)

GCS, Glasgow Comma Score.
* One patient in the training group did not have insurance information on file, $N = 445$.
† Four patients, three in the training group, one in the testing group did not have a documented GCS score, $N = 590$.

the training and test sets. Most patients were older (64.5% were > 50 years of age), African American (77.9%), and female (53.5%). Medical comorbidities were common, including hypertension (75.1%), diabetes (26.4%), hyperlipidemia (23.9%), tobacco use (36.2%), allergies (45.8%), and prior history of angioedema (24.9%). Angiotensin Converting Enzyme (ACE) inhibitor use was common among patients (57.1%). A total of 103 (17.3%) of the 594 were intubated.

The training set consisted of 446 cases including 81 intubations. Table 2 lists swelling locations, signs and symptoms among the training set. In univariate comparisons, symptoms associated with increased rates of intubation in the training set included drooling, stridor, difficulty swallowing, hoarseness, voice change, or shortness of breath ($p \leq 0.05$). Intubation was more common among those with pharynx, anterior or posterior tongue swelling ($p \leq 0.0001$). Among the training set, intubation occurred more often among those insured by Medicare ($p = 0.0001$), >50 years of age ($p = 0.014$), or with pre-existing cardiac disease (p = 0.014), end-stage renal disease ($p = 0.04$), or hypertension ($p = 0.0040$). Intubation occurred more frequently with the use of any ACE inhibitor ($p = 0.00027$), and specifically lisinopril ($p = 0.00122$), however lisinopril comprised the overwhelming majority of ACE inhibitors in his population.

Parameter estimates of the reduced model included Medicare insurance, hypertension, ACE inhibitor use, location of swelling of the anterior tongue or pharynx, or symptoms including drooling, shortness of breath, or voice changes. Voice change and ACE inhibitor use were not found to be significant predictors after adjustment for other factors and were excluded from the final reduced model. Tables listing parameter estimates of the final modes are shown in Supplementary Table 1. Parameter estimates included in the final logistic regression model included hypertension, edema of the anterior tongue or pharynx, and symptoms of shortness of breath or drooling. We used the β-coefficients from this model to develop the Angioedema Risk Score, which we scaled and weighted to create a score ranging from 0 (low risk) to 15 (high risk). The area under the curve (AUC) of the receiver operator characteristic (ROC) curve for the total score was 87.55% (83.42%–91.69%) for the training set. Fig. 1 shows the ROC curve for the risk score among the training set. Table 3 lists the variables included in the Angioedema Risk Score along with their prevalence, odds ratio, and score weights.

The risk score was then applied to the test set of 148 cases including 22 intubations. The AUC of the ROC for the total score was 86.1% (77.62%–94.60%) for the test set. Fig. 2 shows the ROC curve for the risk score among the test set. We then proposed cut points for low risk (0–4), moderate risk (5–7), and high risk (>7) for a need for intubation. Table 4 shows the risk score distribution among each category for the training and test sets. Intubations in the training and test sets occurred in 3.4% and 5.1% among the low risk group, 22.6% and 16.7% in the moderate risk group, and 72.1% and 78.6% in the high-risk group, respectively.

To objectify the need for intubation we evaluated the duration of intubation by score. Supplemental Tables 2 and 3 show the intubation duration by risk score for both the training and the test set. In general, patients with allergic or ACE inhibitor-induced angioedema have swelling lasting >24 h [6]. Among the training set a larger proportion of patients were intubated for <24 h in the low-risk group than the high-risk group, at 56% and 23% respectively. This trend persisted in the test set, where 40% in the low-risk and 28% in the high-risk group were intubated for <24 h.

4. Discussion

In this study of 594 patients with angioedema, we derived and internally validated a score to predict intubation. We found that prior history of hypertension, presence of shortness of breath, drooling, or swelling to the anterior tongue or pharynx were predictive of intubation. Patients with low, intermediate, and high scores had 5.1%, 16.7%, and 78.6% rates of intubation. The score was also highly predictive with an AUC of 86.1%.

To our knowledge this is the first study to derive and validate a score to predict intubation of emergency department patients with angioedema. Epidemiologic data shows that >80% of U.S. patients with angioedema are discharged from Emergency Departments while <1% require intubation [3]. However, retrospective studies have shown rates of intubation ranging from 3.8 to 34.8% [2,4,5,7,8]. Demographically, angioedema has a tendency towards female sex with rates of approximately 60% [2,7,9]. Our data further supports this, as males constituted only 46.5% of cases. Most studies demonstrate an African American preponderance [2,7,8], however one large study with 586 cases showed relatively equal numbers of white and African American cases [9]. Our data suggests that African Americans bear the majority of the burden of disease in angioedema, with African Americans representing 77.9% of our cases.

Flexible fiberoptic laryngoscopy is used to evaluate for laryngeal edema and is recommended in all patients with lingual or upper airway complaints [10]. Some studies have demonstrated higher rates of intubation among patients based on anatomic site of edema. However, grouping of anatomic sites of edema among studies is highly variable, making direct comparison difficult. In general, edema of deeper

Table 2
Summary of reported locations of edema and angioedema symptoms of patients in the training set.

Variable	All N = 446	Not Intubated N = 385	Intubated N = 61	P-value
Location of Edema, % (No.)				
Anterior Tongue	29.1 (130)	22.7 (83)	58.0 (47)	<0.0001
Face	50.9 (227)	52.1 (190)	45.7 (37)	0.3268
Isolated Lip	21.5 (96)	25.8 (94)	2.5 (2)	<0.0001
Pharynx	12.8 (57)	5.5 (20)	45.7 (37)	<0.0001
Posterior Tongue	1.6 (7)	0.0 (0)	8.6 (7)	<0.0001
Soft Palate	7.4 (33)	6.6 (24)	11.1 (9)	0.1623
Signs & Symptoms, % (No.)				
Abdominal Pain	2.7 (12)	2.7 (10)	2.5 (2)	1.0000
Drooling	8.7 (39)	3.3 (12)	33.3 (27)	<0.0001
Hoarseness	5.4 (24)	4.1 (15)	11.1 (9)	0.0244
Nausea	6.1 (27)	5.5 (20)	8.6 (7)	0.3019
Shortness of Breath	22.9 (102)	17.5 (64)	46.9 (38)	<0.0001
Stridor	3.1 (14)	0.5 (2)	14.8 (12)	<0.0001
Difficulty Swallowing	22.9 (102)	17.3 (63)	48.1 (39)	<0.0001
Odynophagia	0.4 (2)	0.3 (1)	1.2 (1)	0.3306
Edema	4.7 (21)	4.9 (18)	3.7 (3)	0.7788
Globus Sensation	15.0 (67)	14.0 (51)	19.8 (16)	0.2276
Voice Change	26.0 (116)	19.5 (71)	55.6 (45)	<0.0001
Vomiting	3.8 (17)	3.0 (11)	7.4 (6)	0.0991

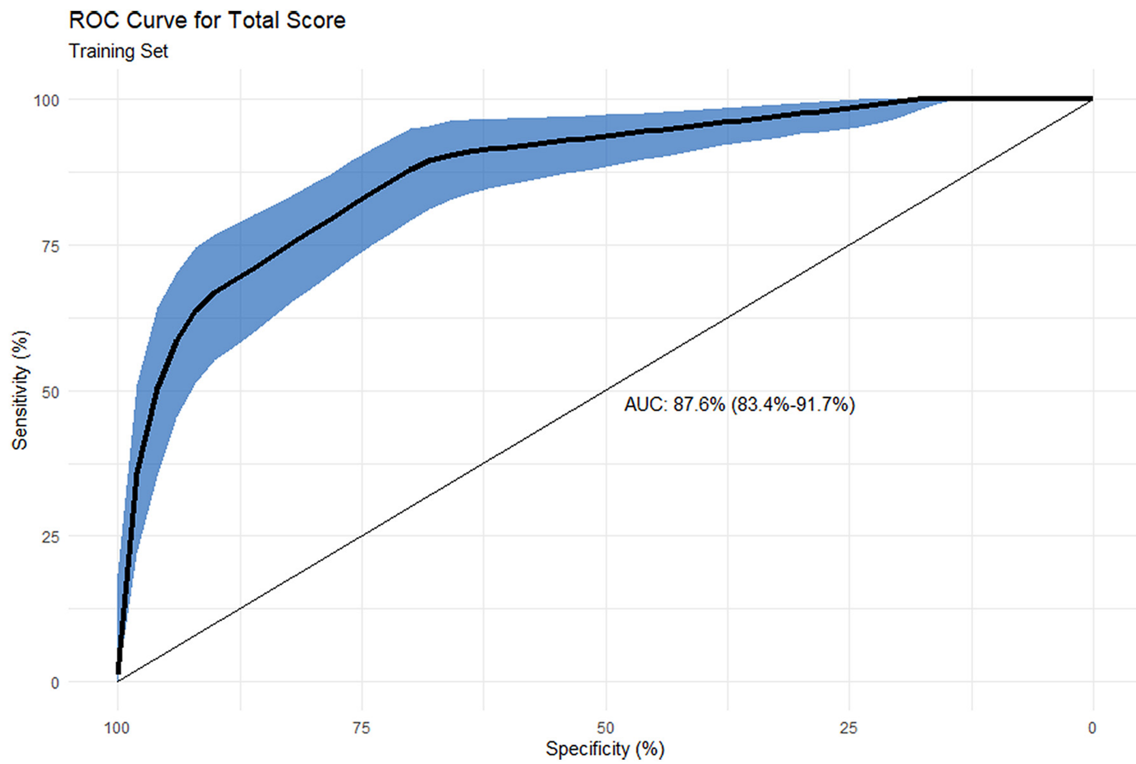

Fig. 1. ROC curve.

laryngeal or pharyngeal structures are more often managed with intubation than facial or oropharyngeal edema [2,4,5]. Our data support this concept as anterior tongue, posterior tongue, and pharyngeal edema occurred more often among those intubated in our data. Our model somewhat simplified this into two anatomic predictors of intubation: anterior tongue and pharynx, with pharynx being more predictive of intubation and thereby further supporting the concept that involvement of deeper structures is a stronger predictor of intubation. Importantly, isolated lip edema conveyed a protective effect against intubation in our model.

Previous authors have found that in patients with angioedema attributed to ACE Inhibitors, the tongue and soft palate were among those anatomic areas at increased risk of being managed with intubation, with an odds ratio of >5 [2]. We did not perform subset analysis of those receiving ACE inhibitors to evaluate if this held true in our population. Often information about specific medications is unavailable during the immediate ED evaluation, and therefore fitting a model to a more general population is more useful for clinicians in the emergency department.

Previous studies have shown that patients with symptoms of voice change, hoarseness, stridor, dyspnea, drooling, dysphonia, dysphagia, globus sensation, and respiratory distress were more likely to be intubated [2,4]. Our study confirms many of these findings, with greater proportions of drooling, dyspnea, hoarseness, shortness of breath, stridor, difficulty swallowing, and voice change seen among those intubated than those not intubated. Our final model identified shortness of breath and drooling as predicting intubation. Our study helps to operationalize these findings by creating a score for assessing risk of intubation in patients with angioedema.

Table 3
Score weights associated with each predictor.

	Prevalence	Odds Ratio (95% CI)	β-coefficient	Score
Hypertension	76.9	5.53 (2.03, 15.09)	1.71	3
Anterior Tongue Edema	29.1	3.48 (1.86, 6.53)	1.25	2
Pharyngeal Edema	12.8	8.98 (4.32, 18.66)	2.19	4
Drooling	8.7	8.76 (3.47, 22.14)	2.17	4
Shortness of Breath	22.9	3.12 (1.62, 6.03)	1.14	2

Finally, two studies have suggested that a longer duration of symptoms from onset to presentation was met with a lower likelihood of intubation among angioedema attributed to ACE inhibitor [2,11]. However in two additional studies which included all causes of angioedema this was not found [5,8]. While duration of symptoms is an appealing concept, we did not investigate this possibility for use in this risk score as we felt that there may be ambiguity due to a patient's inability to recall the onset and thereby limit the utility of this score.

There are multiple limitations to this study. This study is a single center retrospective study. As with all retrospective studies of this design, signs and symptoms may not be perfectly documented and it is possible that patients were discharged and subsequently sought care at another facility. Data abstractors were not blinded to the purpose of the study and while the possibility of data abstraction errors is possible, all research assistants were trained on the specific data points for this study and had close oversight by the lead investigators (JA and FWG). In absence of external validation, the conclusions reached may reflect a single center's practice patterns for airway management. Our center has an urban, inner city demographic, and may differ from other institutions in a variety of ways. There was disproportionate representation of African-American patients, a greater proportion of self-insured patients (than the average U.S. emergency department) [12], and a greater proportion of patients on ACE inhibitors (and lisinopril, specifically) than the U.S. average [13]. Finally, one of our study assumptions was that there is a tight correlation between perceived need to intubate and actual need for endotracheal intubation due to impending airway obstruction. Several patients with low-risk scores were intubated in this study, underscoring that this score may be useful to support, but not replace, expert clinical judgment. We reasoned based on prior published studies that patients rapidly extubated (within 24 h) had been intubated due to a perceived rather than actual need for

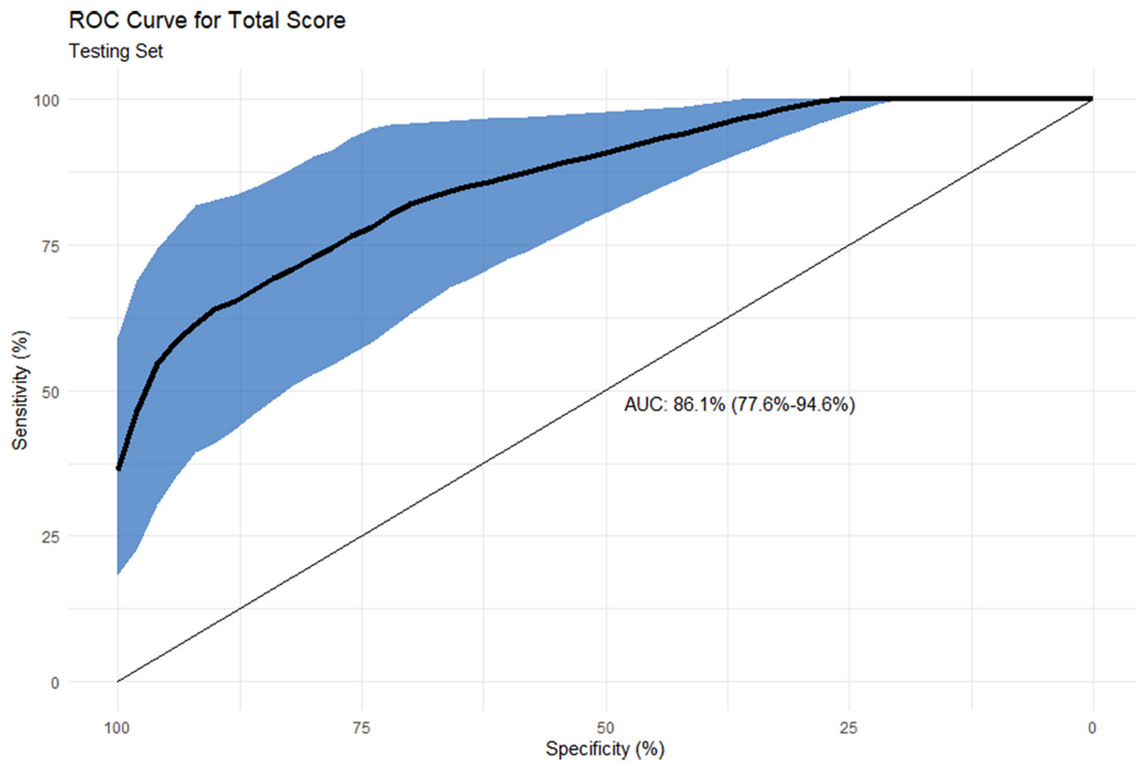

Fig. 2. ROC curve.

Table 4
Risk score distribution.

Sample	Category	N (% Sample)	% Intubated (n)
Training (N = 446)	0–4	261 (58.5)	3.4 (9)
	5–7	124 (27.8)	22.6 (28)
	>7	61 (13.7)	72.1 (44)
Test (N = 148)	0–4	98 (66.2)	5.1 (5)
	5–7	36 (24.3)	16.7 (6)
	>7	14 (9.5)	78.6 (11)

intubation [6]. We selected 24 h as a pragmatic cut point because extubation in this institution primarily occurs after morning rounds by critical care faculty and following a leak test. However, it is difficult to exclude the possibility of longer or shorter duration of intubation as a consequence of the day of the week and time of day the patient was intubated.

5. Conclusion

This study suggests that a simple scoring algorithm may aid in predicting angioedema patients at high and low risk for intubation. The presence of a diagnosis of hypertension, shortness of breath, drooling, pharyngeal or anterior tongue edema are predictors of intubation. Operationalization of these factors into a scoring algorithm may provide a promising diagnostic aid for emergency clinicians. External validation of this scoring algorithm is necessary prior to clinical implementation.

Meetings

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Author contributions

JA, DC, ST, SC, SG, and FG conceptualized the study. JA and MH designed and supervised data collection and data curation. JA verified the data. HS designed the statistical plan and performed the formal statistical analysis. JA, FG, HS, BD, and DC were responsible for study investigation and methodology. JA drafted the manuscript and all authors contributed substantially to its revision and approved the final version. JA and FWG take responsibility for the paper as a whole.

CRediT authorship contribution statement

Jason Arthur: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **David Caro:** Writing – review & editing, Validation, Methodology, Investigation, Data curation, Conceptualization. **Stephen Topp:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Steven Chadwick:** Writing – review & editing, Investigation, Conceptualization. **Brian Driver:** Writing – review & editing, Validation, Formal analysis. **Morgan Henson:** Writing – review & editing, Supervision, Project administration. **Ashley Norse:** Writing – review & editing. **Horace Spencer:** Writing – review & editing, Validation, Funding acquisition, Formal analysis. **Steven A. Godwin:** Writing – review & editing, Conceptualization. **Faheem Guirgis:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors have no known conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2022.10.017.

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