Am J Transl Res 2023;15(6):4196-4202
www.ajtr.org /ISSN:1943-8141/AJTR0141442

Original Article

Diagnostic value of ultrasound for predicting the occurrence of airway difficulty in patients undergoing anesthesia

Chen Zhang, Lihai Chen, Ke Ding, Bei Sun, Xiaodan Zhang, Yong Zhang, Hongguang Bao

Department of Anesthesiology, Nanjing First Hospital, Nanjing Medical University, Nanjing 210006, Jiangsu, China

Received December 31, 2021; Accepted May 22, 2023; Epub June 15, 2023; Published June 30, 2023

Abstract: Objective: To investigate the diagnostic value of ultrasound for predicting occurrence of airway difficulty in patients undergoing anesthesia. Methods: A total of 273 patients airway difficultyundergoing general anesthesia admitted to the Department of Anesthesiology, Nanjing First Hospital, Affiliated to Nanjing Medical University from January 2017 to October 2021 were selected in this prospective study. Among them, 73 suffered airway difficulty and the airway difficultyremaining 200 did not. Factors relating to the occurrence of difficulty were observed, and the hyomental distance ratio [HMDR = hyomental distance at the extreme of head extension (HMDe)/hyomental distance in the neutral position (HMDn)] combined with the distance from skin to epiglottis midway (DSEM) were further studied for the prediction of airway difficulty occurrence. Results: Multivariate regression analysis revealed that HMDe, HMDR, and DSEM were factors associated with the occurrence of difficulty (all $P<0.05$). The specificity and the sensitivity of HMDR in diagnosing airway difficulty were 0.715 and 0.918 respectively at a cutoff value of 1.245 mm. The specificity and sensitivity of DSEM in diagnosing airway difficulty were 0.959 and 0.767 respectively at a cutoff value of 22.952 nm. When HMDR was combined with DSEM, the specificity of the diagnosis of airway difficulty was 0.973, and the sensitivity was 0.904. Conclusion: HMDe, HMDR and DSEM can be used to predict occurrence of airway difficultyand HMDR combined with DSEM has value in the diagnosis.

Keywords: Airway difficulty, HMDR, DSEM, diagnostic value

Introduction

Anesthesia safety is one of the clinical problems to be considered during surgery. Clinical studies have reported that airway difficultyis a key life-threatening factor for patients [1] and a potentially disastrous event that can even lead death [2]. Therefore, identification of airway difficulty in patients prior to surgery has important significance in ensuring a safe surgical procedure. At present, there are many approaches for identifying airway difficulty [3-5]. However, none of them has provided precise indexes for predicting the occurrence of airway difficulty during anesthesia induction [6]. With the development of medical technology, CT and MRI imaging, which can show the airway and the surrounding tissues precisely, are being applied in identifying airway difficulty. Nevertheless, neither of them is suitable for patients who need emergent surgery due to either radioactive or expensive with long operating process [7, 8]. So, ultrasound, which is easy and flexible to operate, seems to be a better approach for identifying airway difficulty, as compared with CT and MRI. With the use of ultrasound, we can not only visualize airway difficulty, but also measure indexes that could predict the occurrence of airway difficulty [9]. It was reported that application of ultrasound in measuring HMDR (HMDR = HMDe/HMDn) had certain value in predicting the occurrence of airway difficulty [10]. It was also reported that application of ultrasound in measuring DSEM had certain value for patients with difficult intubation [11]. Even though a single indicator has certain value for airway difficulty prediction, its precision and sensitivity remain to be improved. So far, no studies have reported the values of combined HMDR and DSEM in predicting the occurrence of airway difficulty. Based on these, our study collected the clinical data of patients who

underwent scheduled general anesthesia and analyzed the associated risk factors for patients who had airway difficulty. In addition, the value of HMDR combined with DSEM measured by ultrasound in predicting the occurrence of airway difficulty was also analyzed in this study.

Material and methods

General data

A total of 273 patients with airway difficultyundergoing general anesthesia who were admitted to the Department of Anesthesiology, Nanjing First Hospital affiliated to Nanjing Medical University from January 2017 to October 2021 were selected as the airway study group in thisprospective study. Among them, 73 developed airway difficulty and 200 did not. These patients were aged from 18 to 65 years, with an average age of 43.2±6.4 years. The study was approved by the Ethics Committee of the Nanjing First Hospital affiliated to Nanjing Medical University. Written informed consents were obtained from all patients.

Inclusion and exclusion criteria

Inclusion criteria: Patients aged over 18; Patients who signed the informed consent; Patients with ASA grade I-III who were scheduled to receive surgery [2] with general anesthesia; Patients who were scheduled to take airway intubation; Patients who agreed to receive ultrasound to assess airway-related factors.

Exclusion criteria: Patients with deformity in the neck, head or maxillary area; Patients complicated by head and neck malignant tumor; Patients who were scheduled to get surgery for cervical spine; Patients with incomplete clinical data.

Methods

Collection of general data and related information: First, the personal and clinical data of patients, including sex, age, weight, height, body mass index, ASA classification, intubation history, mouth opening degree, thyromental distance, modified Mallampati classification, HMDR and DSEM were collected. Factors associated with the occurrence of airway difficulty were observed. Approaches used to measure DSEM: Patients were placed pillow-free in a supine position. GE-HealthcareVenue4012L-SC (GE, USA) was placed in a sagittal position at the middle of left larynx (1 cm to the left along the middle line) to expose thyroid cartilage and hyoid bone. The linear hyperechogenicity of the interface between air and mucosa at the posterior epiglottis was observed below the thyroid cartilage. The distance from skin to epiglottis was measured. A high-frequency linear array probe of color Doppler ultrasound was placed between the mandibular eminence and thyroid cartilage. The probe was paralleled with the sagittal plane of the body but at a perpendicular angle to the skin. The location of the hyoid bone was marked on the body after it was shown by ultrasound. The distance from the hyoid bone to the mandible, that is the hyomental distance in a neutral position (HMDn), was measured with the use of a tape. Then, the patient's head was held in a "sniff" position with maximum retroversion (shoulders were still on the bed), and the hyomental distance at the extreme of head extension (HMDe) was also measured using the same approach. So, HMDR = HMDe/HMDn [12].

Definition of airway difficulty: According to *the Management Guidelines for Airway difficulty 2017*, airway difficulty is a clinical accident caused either by difficult respiration when wearing facial masks or difficult intubation under the supervision of an anesthesiologist with at least 5-year clinical experiences, or the occurrence of both [13]. The American Association of Anesthesiologists has defined airway difficulty as making multiple attempts for intubation of the airway, no matter the presence or absence of a pathogenic airway [14].

The diagnostic value of HMDR combined with DSEM for predicting airway difficulty was observed. See **Figure 1** for the workflow of the study.

Outcome measurement

Relevant clinical data were included for statistical analysis of factors associated with the occurrence of airway difficulty.

ROC curve was applied to assess the diagnostic value of HMDR combined with DSEM for predicting the occurrence of airway difficulty.

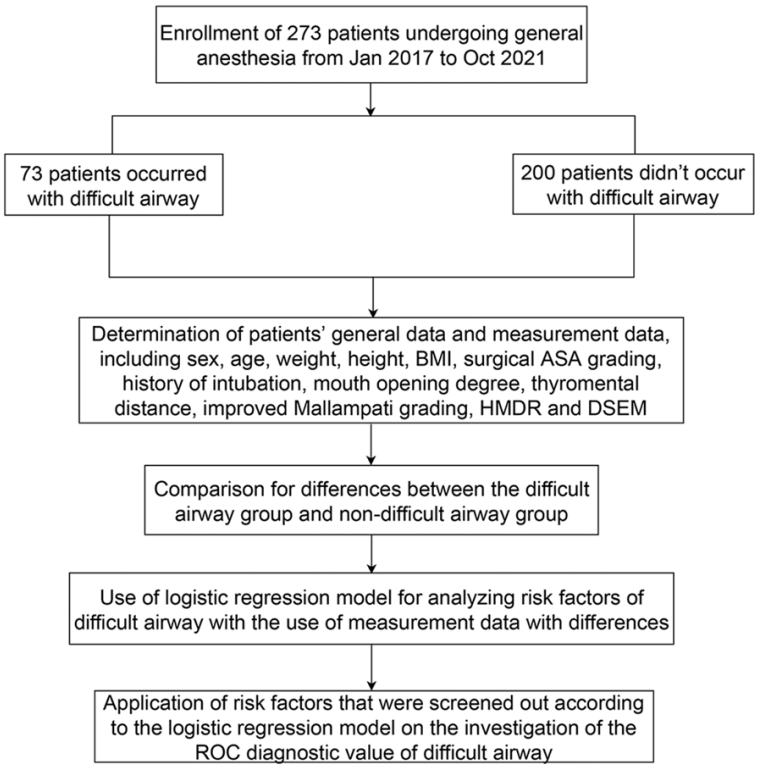

Figure 1. Workflow of the study.

Statistical analysis

Data were analyzed using SPSS 17.0 statistical software. Measured data conforming to a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm sd$), and those not conforming to a normal distribution were expressed as M (P25, P75). Independent sample t test was used for measured data conforming to normal distribution and homogeneity of variance, expressing as t. Rank Sum Test was used for measurement data not conforming to normal distribution and homogeneity of variance, expressing as F. Enumerated data were expressed as number (%) analyzed with Pearson chi-square test and expressed as chi-square. Logistic regression analysis was used to analyze factors associated with the occurrence of airway difficulty. Univariate analysis was used to analyze the variables with differences. Stepwise forward (Wald) method was used for variable screening, which was used when $P<0.1$ and excluded when $P\geq0.1$. The risk of airway difficulty was expressed as the odds ratio (OR) after calibration. ROC curve was drawn and the area under ROC curve (AUROC) was calculated. 95% confidence interval (95% CI) in addition to the application of logistic regression model were used to obtain the diagnostic probability of HMDR combined with DSEM, so as to evaluate the diagnostic value of HMDR combined with DSEM for predicting the occurrence of airway difficulty. DeLong test was applied for the comparison of diagnostic differences in ROC. $P<0.05$ was considered significant in two-sided tests.

Results

General data

The body mass index and DSEM in the airway difficulty group were all higher than those in the non-airway difficulty group (all $P<0.05$). The mouth opening degree, thyromental distance, HMDe and HMDR were all lower in the airway difficulty group than those in the non-airway difficulty group (all $P<0.05$). So, it was suggested that body mass index, mouth opening degree, thyromental distance, HMDe, HMDR and DSEM were the factors that could predict the occurrence of airway difficulty (all $P<0.05$). See **Table 1**.

Multivariate logistic regression analysis

Multivariate logistic regression analysis revealed that HMDe, HMDR and DSEM were independent factors for predicting the occurrence of airway difficulty (all $P<0.05$). See **Tables 2** and **3**.

Diagnostic value of HMDR combined with DSEM for patients with airway difficulty

The AUC of HMDR for predicting the occurrence of airway difficulty was 0.763; when HMDR was 1.245 mm, the Youden index was 0.633, the specificity was 0.715, and the sensitivity was 0.918. The AUC of DSEM for predicting the occurrence of airway difficulty was 0.829; when DSEM was 22.952 mm, the Youden index was 0.757, the specificity was 0.959, and the sensitivity was 0.767. The formula, $Log^{(6.121+0.986*HMDR+22.386*DSEM)}$, was used to predict the diagnostic value of HMDR combined with DSEM for airway difficulty. The AUC of

Table 1. Comparison of general data and possible variables that affect airway difficulty ($\bar{x} \pm sd$, n)

Item	Airway difficulty group (n=73)	Non-airway difficulty group (n=200)	χ^2/t	P
Sex			0.001	0.970
Male	48	132		
Female	25	68		
Age (year)	42.7±6.2	43.8±7.3	1.145	0.253
Height (cm)	166.54±8.23	164.82±8.15	1.539	0.125
Weight (kg)	66.22±15.82	63.82±9.34	1.536	0.126
Body mass index (kg/m^2)	24.89±4.22	23.82±3.02	2.315	0.021
Surgical ASA grading			0.375	0.540
Grade I-II (n)	63	178		
Grade I-II (n)	10	22		
History of intubation			2.276	0.131
Yes (n)	69	196		
No (n)	4	4		
Mouth opening degree (cm)	4.01±0.21	4.21±0.32	4.961	<0.001
Thyromental distance (cm)	6.83±0.73	7.11±0.68	2.952	0.003
Improved Mallampati grading			0.425	0.541
Grade I-II (n)	53	137		
Grade I-II (n)	20	63		
HMDn (cm)	4.44±0.77	4.42±0.62	0.220	0.826
HMDe (cm)	5.03±0.71	5.52±0.67	5.263	<0.001
HMDR	1.15±0.09	1.27±0.12	8.908	<0.001
DSEM (mm)	23.30±3.34	19.62±2.12	8.874	<0.001

Notes: χ^2 denotes for the result of chi-square test and t for t test. HMDn: hyomental distance in neutral position; HMDe: hyomental distance at the extreme of head extension; HDMR: hyomental distance rate; DSEM: distance from skin to epiglottis midway.

Table 2. Assignment of variables that may predict the occurrence of airway difficulty

Factor	Independent variable	Assignment
Body mass index (kg/m^2)	X1	>24.2=1, ≤24.2=0
Mouth opening degree (cm)	X2	≤4.11=1, >4.11=0
Thyromental distance (cm)	X3	≤6.91=1, >6.91=0
HMDe (cm)	X4	≤5.23=1, >5.23=0
HMDR	X5	≤1.24=1, >1.24=0
DSEM (mm)	X6	>22.60=1, ≤22.60=0

Notes: The average values were used as the assignment criteria. HMDe: hyomental distance at the extreme of head extension; HDMR: hyomental distance rate; DSEM: distance from skin to epiglottis midway.

assess the condition of patients' airway before surgery. It has been reported that there is a 25%-30% chance of having difficult intubation if the patient's airway is not evaluated before surgery [15, 16]. However, the occurrence of difficult intubation in patients after receiving anesthesia results in anoxia in the brain or cardiac arrest within a short period, thus threatening a patient's life [17]. So, identification of airway difficulty before surgery is crucial to ensure successful surgeries.

HMDR combined with DSEM was 0.911, the Youden index was 0.894, the specificity was 0.973, and the sensitivity was 0.904. See **Table 4** and **Figure 2**.

Discussion

Airway difficulty is the main cause of failed intubation. Therefore, it is of great importance to

Our study suggests that BMI, mouth opening degree, HMDe, HMDR, and DSEM were all factors contributing to the occurrence of airway difficulty. Patients with high BMI, namely obese patients, are susceptible to airway difficulty. It is also suggested that the correlation of BMI with the occurrence of airway difficulty is stronger in male patients than that in female patients [18]. Thyromental distance, the angle between

Table 3. Results of multivariate logistic regression analysis

Factor	β	SE	Wald value	OR value (95% CI)	P
Body mass index (kg/m^2)	1.182	0.733	2.762	3.412 (0.892-10.023)	0.135
Mouth opening degree (cm)	0.803	0.802	1.073	2.278 (0.493-10.677)	0.289
Thyromental distance (cm)	0.188	0.721	0.072	0.865 (0.192-3.674)	0.652
HMDe (cm)	1.248	0.685	2.631	2.431 (1.458-4.382)	0.032
HMDR	1.836	0.785	6.782	5.268 (1.569-23.654)	0.021
DSEM (mm)	0.682	0.208	10.823	1.972 (1.278-2.873)	0.001

Notes: HDMR: hyomental distance rate; DSEM: distance from skin to epiglottis midway; SE: standard error; CI: confidence interval.

Table 4. Value of each index for predicting the occurrence of airway difficulty

Index	HMDR	DSEM	HMDR combined with DSEM
Area under curve	76.30%	82.90%	91.10%
Sensitivity	91.80%	76.70%	90.40%
Specificity	71.50%	95.90%	97.30%
Missed diagnosis rate	8.20%	23.30%	9.60%
Missed diagnosis rate	28.50%	4.10%	2.70%
Erroneous diagnosis rate	0.633	0.757	0.894
Positive likelihood ratio	3.22	18.7	33.48
Negative likelihood ratio	0.11	0.24	0.1

Notes: HDMR: hyomental distance rate; DSEM: distance from skin to epiglottis midway.

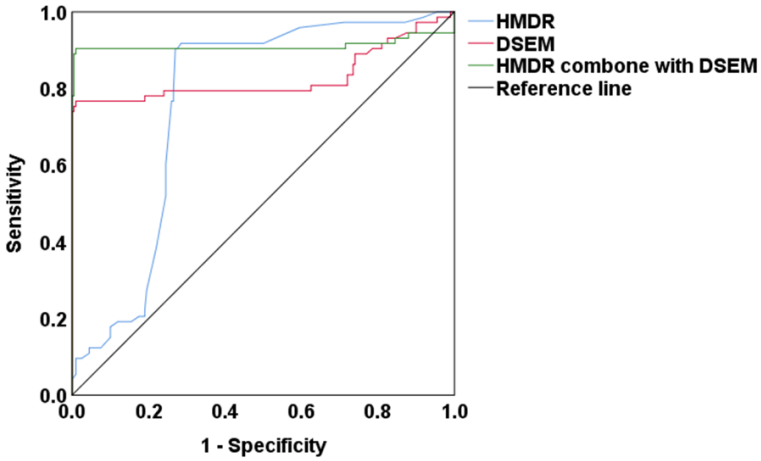

Figure 2. ROC curve of HMDR combined with DSEM for predicting the occurrence of airway difficulty. ROC: Receiver Operating Curve; HDMR: hyomental distance rate; DSEM: distance from skin to epiglottis midway.

pharyngeal axis and laryngeal axis, is another index with significance for assessing an airway. However, it was reported that the sensitivity and specificity of thyromental distance for predicting the occurrence of airway difficulty were poor [19]. HMDe and HMDR are indexes showing the flexibility of hyoid bone. It was suggested that the flexibility of hyoid bone had an influence on the exposure of the glottis during intubation, and also that there was a difference in HMDR between patients with airway difficulty and those without (1.21±0.12 vs. 1.36±0.14, P<0.001) [20-22]. With the development of ultrasound technology, a clinical study found that DSEM could effectively predict the occurrence of airway difficulty [23]. According to a study abroad, DSEM in healthy volunteers is about (11.4±2.4) mm [24]. A domestic Chinese study pointed out that significant differences in DSEM of patients with or without airway difficulty [25].

In our study, HMDR and DSEM were used to further predict the occurrence of airway difficulty. The result showed that the sensitivity of HMDR at a cutoff value of 1.245 mm in identifying airway difficulty was relatively high (0.918), while the specificity of DSEM at a cutoff value of 22.952 mm was relatively high (0.959). The combination of HMDR and DSEM produced both high sensitivity and high specificity for identifying airway difficulty (0.904 and 0.973). A domestic study showed that the sensitivity and specifici-

ty for predicting airway difficulty with HMDR were 0.818 and 0.705, respectively, when HMDR<1.19 [26]. Another study showed that the sensitivity and specificity were 0.897 and 0.579 when HMDR<1.22 [22]. According to a foreign study with only 12 samples, the sensitivity for predicting airway difficulty was 0.860 and the specificity was 0.720 when HMDR≤ 1.24 [27]. In 2018, a study including 120 Indian patients [28] showed that the sensitivity and specificity for predicting airway difficulty were 0.750 and 0.853 when HMDR≤1.085, which conforms to the results of this study. A domestic study showed that the sensitivity and specificity for predicting airway difficulty with DSEM>23.6 mm were 0.818 and 0.705, respectively [25]. A foreign study showed relatively accurate prediction of airway difficulty with DSEM at a cutoff value of 27.5 mm [11]. In our study, the sensitivity and specificity of DSEM at a cutoff value of 22.952 for predicting the occurrence of airway difficulty were 0.767 and 0.959, and the area under the ROC curve was 0.829 (95% CI: 0.754-0.905), which differs from the results mentioned above, probably owing to a different ethnic group and sample size. Previous studies suggested that predicting airway difficulty with one single index was not very accurate, but a combination of various indexes was more valuable [29]. Hence, we combined DSEM with HMDR and found that the sensitivity and specificity for prediction were both greater than using them individually.

However, this was a single-center study with small sample size; further multi-center studies with a bigger sample size should be conducted in the hope of shedding some light on clinical practice.

In summary, HMDe, HMDR, and DSEM are predictive factors for the occurrence of airway difficulty, and HMDR combined with DSEM perform better in identifying airway difficulty than their individual application.

Disclosure of conflict of interest

None.

Address correspondence to: Hongguang Bao, Department of Anesthesiology, Nanjing First Hospital, Nanjing Medical University, No. 68 Changle Road, Qinhuai District, Nanjing 210006, Jiangsu, China. Tel: +86-15050588165; E-mail: bao_hongguang@163.com

References

[1] Artime CA, Roy S and Hagberg CA. The airway difficulty. Otolaryngol Clin North Am 2019; 52: 1115-1125.

[2] Xu Z, Ma W, Hester DL and Jiang Y. Anticipated and unanticipated airway difficulty management. Curr Opin Anaesthesiol 2018; 31: 96-103.

[3] Faramarzi E, Soleimanpour H, Khan ZH, Mahmoodpoor A and Sanaie S. Upper lip bite test for prediction of airway difficulty: a systematic review. Pak J Med Sci 2018; 34: 1019-1023.

[4] Detsky ME, Jivraj N, Adhikari NK, Friedrich JO, Pinto R, Simel DL, Wijeysundera DN and Scales DC. Will this patient be difficult to intubate?: The rational clinical examination systematic review. JAMA 2019; 321: 493-503.

[5] Palczynski P, Bialka S, Misiolek H, Copik M, Smelik A, Szarpak L and Ruetzler K. Thyromental height test as a new method for prediction of difficult intubation with double lumen tube. PLoS One 2018; 13: e0201944.

[6] Vannucci A and Cavallone LF. Bedside predictors of difficult intubation: a systematic review. Minerva Anestesiol 2016; 82: 69-83.

[7] Buchanan A, Cohen R, Looney S, Kalathingal S and De Rossi S. Cone-beam CT analysis of patients with obstructive sleep apnea compared to normal controls. Imaging Sci Dent 2016; 46: 9-16.

[8] Avci S, Lakadamyali H, Lakadamyali H, Aydin E and Tekindal MA. Relationships among retropalatal airway, pharyngeal length, and craniofacial structures determined by magnetic resonance imaging in patients with obstructive sleep apnea. Sleep Breath 2019; 23: 103-115.

[9] Chen JW, Huang CC, Weng CK, Chang CH and Wang SJ. Simultaneous recording of ultrasound and polysomnography during natural sleep in patients with obstructive sleep apnea: a pilot study. J Sleep Res 2017; 26: 481-486.

[10] Huh J, Shin HY, Kim SH, Yoon TK and Kim DK. Diagnostic predictor of difficult laryngoscopy: the hyomental distance ratio. Anesth Analg 2009; 108: 544-548.

[11] Pinto J, Cordeiro L, Pereira C, Gama R, Fernandes HL and Assunção J. Predicting difficult laryngoscopy using ultrasound measurement of distance from skin to epiglottis. J Crit Care 2016; 33: 26-31.

[12] Gottlieb M, Holladay D, Burns KM, Nakitende D and Bailitz J. Ultrasound for airway management: an evidence-based review for the emer-

gency clinician. Am J Emerg Med 2020; 38: 1007-1013.
[13] Anesthesiology Branch of the Chinese Medical Association. Expert consensus on airway difficulty management. J Clin Anesthesiol 2017; 118: 251-270.
[14] Apfelbaum JL, Hagberg CA, Caplan RA, Blitt CD, Connis RT, Nickinovich DG, Hagberg CA, Caplan RA, Benumof JL, Berry FA, Blitt CD, Bode RH, Cheney FW, Connis RT, Guidry OF, Nickinovich DG and Ovassapian A; American Society of Anesthesiologists Task Force on Management of the Airway difficulty. Practice guidelines for management of the airway difficulty: an updated report by the American Society of Anesthesiologists Task Force on management of the airway difficulty. Anesthesiology 2013; 118: 251-270.
[15] Shirgoska B and Netkovski J. Predicting airway difficulty in apparently normal adult and pediatric patients. Pril (Makedon Akad Nauk Umet Odd Med Nauki) 2013; 34: 155-159.
[16] Scott JA, Heard SO, Zayaruzny M and Walz JM. Airway management in critical illness: an update. Chest 2020; 157: 877-887.
[17] Sanfilippo F, Sgalambro F, Chiaramonte G, Santonocito C, Burgio G and Arcadipane A. Use of a combined laryngo-bronchoscopy approach in airway difficultys management: a pilot simulation study. Turk J Anaesthesiol Reanim 2019; 47: 464-470.
[18] Heinrich S, Birkholz T, Irouschek A, Ackermann A and Schmidt J. Incidences and predictors of difficult laryngoscopy in adult patients undergoing general anesthesia: a single-center analysis of 102,305 cases. J Anesth 2013; 27: 815-821.
[19] Etezadi F, Ahangari A, Shokri H, Najafi A, Khajavi MR, Daghigh M and Moharari RS. Thyromental height: a new clinical test for prediction of difficult laryngoscopy. Anesth Analg 2013; 117: 1347-1351.
[20] Auvenshine RC and Pettit NJ. The hyoid bone: an overview. Cranio 2020; 38: 6-14.
[21] Langeron O, Cuvillon P, Ibanez-Esteve C, Lenfant F, Riou B and Le Manach Y. Prediction of difficult tracheal intubation: time for a paradigm change. Anesthesiology 2012; 117: 1223-1233.
[22] Yi SQ, Cai WB, Dong BH, Xiao L and Luo ZG. Value of ultrasonic measurement of hyomental distance ratio for predicting the airway difficulty. J Shanxi Med Univ 2021; 52: 231-234.
[23] Adhikari S, Zeger W, Schmier C, Crum T, Craven A, Frrokaj I, Pang H and Shostrom V. Pilot study to determine the utility of point-of-care ultrasound in the assessment of difficult laryngoscopy. Acad Emerg Med 2011; 18: 754-758.
[24] Hall EA, Showaihi I, Shofer FS, Panebianco NL and Dean AJ. Ultrasound evaluation of the airway in the ED: a feasibility study. Crit Ultrasound J 2018; 10: 3.
[25] Ni HW, He GB, Shi DP and Hang YN. Value of ultrasonic measurement of distance from skin to epiglottis for predicting the airway difficulty. J Shanghai Jiaotong Univ (Med Sci) 2017; 37: 373-376.
[26] Luo YF, Liu CH, Wang P, Wei ML and Chen X. Predictive value of ultrasonic measurement of hyomental distance ratio insupine position for airway difficulty in Zhuang people. Guangxi Med J 2020; 42: 1212-1214, 1256.
[27] Petrisor C, Szabo R, Constantinescu C, Prie A and Hagau N. Ultrasound-based assessment of hyomental distances in neutral, ramped, and maximum hyperextended positions, and derived ratios, for the prediction of airway difficulty in the obese population: a pilot diagnostic accuracy study. Anaesthesiol Intensive Ther 2018; 50: 110-116.
[28] Rana S, Verma V, Bhandari S, Sharma S, Koundal V and Chaudhary SK. Point-of-care ultrasound in the airway assessment: a correlation of ultrasonography-guided parameters to the cormack-lehane classification. Saudi J Anaesth 2018; 12: 292-296.
[29] De Jong A, Molinari N, Terzi N, Mongardon N, Arnal JM, Guitton C, Allaouchiche B, Paugam-Burtz C, Constantin JM, Lefrant JY, Leone M, Papazian L, Asehnoune K, Maziers N, Azoulay E, Pradel G, Jung B and Jaber S; AzuRéa Network for the Frida-Réa Study Group. Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. Am J Respir Crit Care Med 2013; 187: 832-839.