

ORIGINAL ARTICLE

Iatrogenic subglottic tracheal stenosis after tracheostomy and endotracheal intubation: A cohort observational study of more severity in keloid phenotype

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Background: Tracheostomy and endotracheal intubation can result in subglottic tracheal stenosis, and predisposition to keloid scar formation can increase stenosis risk after tracheal injury. This study aims to compare the incidence and severity of subglottic tracheal stenosis in keloid and non-keloid patients following iatrogenic tracheal injury, in particular tracheostomy.

Methods: From 2012 to 2017, 218573 patients were intubated for surgery; 2276 patients received tracheostomy in People's Hospital of Zhengzhou University, China. Among these patients, 133 patients, who developed tracheal stenosis after intubation and/or tracheostomy, were divided into keloid or non-keloid groups; their Myer and Cotton grading of tracheal stenosis, time-to-onset of airway stenosis, and treatment outcome were assessed and compared.

Results: The percentages of high grade (Myer and Cotton grading III/IV) tracheal stenosis were higher among keloid patients than non-keloid patients (intubation: 83.3% vs 25.7%; tracheostomy: 77.7% vs 33.3%). Time-to-onset of airway stenosis following intubation (tracheostomy) was 27 ± 5 (38 ± 13) and 41 ± 7 (82 ± 14) days for keloid and non-keloid patients, respectively ($P < 0.01$). The incidence of tracheal stenosis is higher in keloid than non-keloid subjects (19.4% vs 1.82%, $P < 0.001$). Keloid patients also required more frequent treatment ($P < 0.01$) of longer duration, yet cure rate was significantly lower ($P < 0.01$).

Conclusions: Our study suggests that tracheostomized patients with keloid phenotype are more susceptible to develop iatrogenic tracheal stenosis of greater severity and with poorer treatment outcome. Greater cautions may be required when performing tracheostomy in keloid subjects. More substantive analysis is warranted to establish keloid phenotype as a risk factor for tracheal stenosis.

1 | INTRODUCTION

Despite the introduction of supraglottic airway devices in general anesthetic practice, endotracheal intubation is still widely performed in anesthesia. In the intensive care setting, patients requiring prolonged mechanical lung ventilation have tracheostomy surgery and insertion of tracheostomy tubes because it improves comfort, facilitates many aspects of nursing care, and is associated with fewer airway complications compared to endotracheal tubes. Unfortunately, both procedures can result in injury to the airway with the development of subglottic tracheal stenosis being a rare but major complication. Tracheal intubation and tracheostomy can cause the majority of cases of iatrogenic subglottic tracheal stenosis (ITS), such that tracheal intubation accounts for 19% and tracheostomy accounts for 65% of the cases.¹ Post-intubation tracheal stenosis requiring surgical intervention is thankfully rare. In a survey, conducted over a 3-year period, of adult cases of post-intubation laryngotracheal stenosis referred from primary care trusts in the Greater London area to 2 hospitals with subspecialist airway reconstruction services, the authors estimated that the population incidence of post-intubation tracheal stenosis was 4.9 cases per million per year.² Other studies have estimated the incidence to be higher, and as this study only captures patients who are referred for specialist input, it raises the possibility that a large number of patients with significant post-intubation stenosis are going undiagnosed.³⁻⁵

The incidence of tracheal stenosis following tracheostomy is higher; it is estimated to occur in 1.1% and up to 1.9% following percutaneous tracheostomy and open tracheostomy, respectively.^{6,7} In another study, the authors reported severe tracheomalacia/stenosis in 2.6% of patients who had undergone percutaneous tracheostomy.⁸ Furthermore, using computer axial tomography (CT) imaging of the neck, they identified a higher rate of mild tracheal stenosis (defined as narrowing between 11% and 25%) of 21%, and moderate stenosis (narrowing between 26% and 50%) of 8.3% in that studied population.⁸ Airway stenosis is caused mainly by the cicatrization of the airway mucosa and is the result of an over-repaired wound during the healing process which leads to fibrosis with tissue deformation following the injury. Excessive keloid formation of connective tissues, with similar histological features, can also be observed in healed injured skin of susceptible patients and is described as keloid.⁹

Keloid can occur in a population with a diathesis for hypertrophic scar formation during the healing process of injured tissue. It is characterized by a lump consisting of an abnormal proliferation of connective tissue into the scar which develops during the repair process. Keloid occurs because the cicatrix continues to increase in size well in excess of the normal repair process. It is red in color, hard in texture, and in the early phase of its formation there is an inflammatory infiltration zone around the scar. Keloid formation can occur on any part of the body but has a predilection for the sternum, neck, shoulders, ear, and throat. The pathological feature of keloid is a collagenous fiber-based transitional expression of extracellular

Editorial comments

Iatrogenic tracheal stenosis following anesthesiologic airway management is a very unwelcome situation, and consequently every possible precaution should be identified to possibly avoid it. Individuals prone to keloid formation may be identified as a group at risk. Here, an observational study in a Chinese patient population points out this possible risk.

matrix with an abnormal distribution in the scar. Patients with keloid have a familial genetic predisposition to the condition with autosomal dominant phenotype expression.

Patients who have keloid are potentially more likely to develop tracheal stenosis after tracheal injury because they have an abnormal proliferation of connective tissue in response to traumatic injury. Furthermore, there have been reports of ITS in patients with keloid.¹⁰

We therefore conducted this retrospective study to compare the incidence and severity of tracheal stenosis in patients with keloid phenotype in comparison with non-keloid patients following iatrogenic tracheal injury, in particular tracheostomy.

2 | MATERIAL AND METHODS

2.1 | Patients' data collection

The study was approved by the hospital's Ethical Review Board. All patients had been informed of the potential use of their medical records and histological samples. Written consent was obtained from each patient and was approved by the hospital's Ethical Review Board.

Using hospital's electronic databank, we identified a total of 218573 patients who received endotracheal intubated from previous surgical procedure (intubation group), and 2276 of those were further tracheotomized in intensive care (tracheostomy group) from year 2012 to 2017. The procedures had been performed at local hospitals or Henan Provincial People's Hospital but these patients had been admitted to our hospital for airway treatment. There were 133 patients identified with iatrogenic tracheal stenosis from both the intubation and tracheostomy pools. The severity of tracheal stenosis between keloid and non-keloid patients were assessed and compared. Each of these patients was examined for superficial keloid scar formation resulting from previous injury and an example of keloid scar is given (the supplementary Figure S1), and these patients were divided into keloid or non-keloid subtypes based on the presence or absence of keloid scar.

The location and the degree of the tracheal stenosis were determined by endoscopy and pre-operative CT. The severity of the subglottic tracheal stenosis was assessed using the Myer and Cotton

grading system. The mean intervals between the time of tracheal intubation or tracheostomy and clinical presentation with tracheal stenosis were recorded. The incidence of post-operative tracheal stenosis, time of occurrence, degree of stenosis, and time of restenosis were recorded. All patients were treated with electrocoagulation, argon knife, freezing, or stent under interventional bronchoscopy. The patients in these studied groups were followed regularly for up to 12 months following their last airway treatment.

2.2 | Statistical analysis

Number of patients were indicated for keloid and non-keloid groups, and were compared using chi-square test. Numerical parameters (duration of intubation, time to stenosis, treatment frequencies, and treatment period) were tabulated for each patient, and compared between keloid and non-keloid groups using 2-tailed, unpaired Student's t-test with 95% confidence interval (Prism 6.06, GraphPad, La Jolla, California, U.S.A.).

3 | RESULTS

The mean age of onset of the presentation of tracheal stenosis in the patients with keloid was younger than that of the patients without keloid, ($P < 0.01$; Table 1). The demographics and disease distribution in these 2 groups were similar, no statistical difference.

There were 24 patients post-tracheal intubation and 27 patients post-tracheostomy with keloid. One of those patients, a 47-year-old female patient, who had a very small skin surgery in her chest and developed a large keloid formation at 3 months after surgery, received an abdominal surgery under general anesthesia under tracheal intubation. She finally developed airway stenosis (Supplementary Figure

S1). There were 43 patients post-tracheal intubation and 39 patients post-tracheostomy without keloid

There were more patients with severe tracheal stenosis (Myer and Cotton Grades III and IV) in the groups with keloid following intubation (20 patients; 83.3%) and tracheostomy (21 patients; 77.8%) compared to the groups without keloid following intubation (11 patients; 25.7%) and tracheostomy (13 patients; 33.3%), ($P < 0.01$; Table 2). In contrast, there were fewer patients with minor severity of tracheal stenosis (Grades I and II) in the with keloid group after intubation (4 patients; 16.7%) and tracheostomy (6 patients; 22.2%) compared to the without keloid group after intubation (32 patients; 74.3%) and tracheostomy (26 patients; 66.7%), ($P < 0.01$; Table 2).

The average duration of intubation in the keloid group was 3 ± 2 days and tracheal stenosis presented clinically on average 27 ± 5 days after extubation (Table 3). In contrast, the duration of intubation in the group without keloid was longer (7 ± 2 days), and tracheal stenosis presented significantly later at 41 ± 7 days after extubation, ($P < 0.01$; Table 3). Intubation conditions were similar in both groups. It took more frequencies to treat (Electrocoagulation, Argon knife, Freezing or Stent) the cicatrix in the group with keloid than non-keloid patients (20 ± 3 vs 8 ± 2 respectively, $P < 0.01$; Table 3).

In the Tracheostomy patients, the duration of mechanical ventilation in the 2 groups was similar, (114 ± 18 vs 116 ± 26 days, respectively; Table 3). However, the time to re-stenosis was shorter in the group with keloid than group without (38 ± 13 vs 82 ± 14 days, respectively, $P < 0.01$; Table 3). Furthermore, the group with keloid required more frequent treatments than the group without (18 ± 6 and 6 ± 3 times, respectively, $P < 0.01$; Table 3).

Interventional bronchoscopy treatment was more successful in the group without keloid, with cure rates of 88.4% after tracheal intubation and 71.8% after tracheostomy, compared to the keloid group (58.3% cure rate after tracheal intubation and 44.4% after tracheostomy, $P < 0.01$; Table 4). It took longer for the scar to heal in

TABLE 1 Demographic data of 133 patients with iatrogenic subglottic stenosis with or without keloid

	Number	Gender (M/F)	Age	Cardiac surgery (%)	Abdominal surgery (%)	Neurosurgery (%)	Other surgery (%)
Keloid	51	29/22	36 ± 9	9 (17.6)	12 (23.5)	27 (52.9)	3 (6.0)
Non-keloid	82	45/37	47 ± 13	11 (13.4)	19 (23.2)	47 (57.3)	5 (6.1)

Patient mean age shown as mean \pm SD, number, and percentage of patient for each surgery type is shown.

TABLE 2 Classification of subglottic tracheal stenosis by Myer-Cotton grading scale

	Intubation					Tracheostomy				
	Number	I (%)	II (%)	III (%)	IV (%)	Number	I (%)	II (%)	III (%)	IV (%)
Keloid	24	0 (0)	4 (16.7)	13 (54.2)	7 (29.1)	27	0 (0)	6 (22.2)	12 (44.4)	9 (33.3)
Non-keloid	43	7 (16.2)	25 (58.1)	8 (18.6)	3 (7.1)	39	7 (17.9)	19 (48.7)	8 (20.5)	5 (12.8)
		$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$		$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$

Patients receiving intubation or tracheostomy were divided into keloid or non-keloid phenotypes, and using Myer-Cotton Subglottic Stenosis Grading Scale, patients were stratified by severity levels I-IV (percentages indicated in the brackets). For each column, the number of keloid and non-keloid patients were compared using Chi-square test, with P -value < 0.01 indicating a significant difference between keloid and non-keloid subgroups.

TABLE 3 Intubation duration, tracheal restenosis time, and airway treatment frequencies in keloid and non-keloid patients following intubation or tracheostomy

	Intubation				Tracheostomy			
	Number	Duration of intubation (d)	Time to stenosis (d)	Treatment frequencies	Number	Duration of intubation (d)	Time to stenosis (d)	Treatment frequencies
Keloid	24	3 ± 2	27 ± 5	20 ± 3	27	114 ± 25	38 ± 13	18 ± 6
Non-keloid	43	7 ± 2	41 ± 7	8 ± 2	39	116 ± 34	82 ± 14	6 ± 3
		<i>P</i> < 0.01	<i>P</i> < 0.01	<i>P</i> < 0.01		<i>P</i> > 0.05	<i>P</i> < 0.01	<i>P</i> < 0.01

For both intubation and tracheostomy treatments, patients were divided into keloid and non-keloid phenotypes. Duration of intubation (days), restenosis time (period after the initial treatment before second treatment is required), and treatment frequencies were compared between keloid and non-keloid groups using unpaired Student's *t*-test. Data are shown as Mean ± SD. *P*-value <0.01 indicating a significant difference between keloid and non-keloid subgroups.

TABLE 4 Keloid and non-keloid in patients are prognosis of tracheal stenosis and their cure rate and treatment lasts time

	Intubation			Tracheostomy		
	Number	Cure rate (%)	Treatment period (month)	Number	Cure rate (%)	Treatment period (month)
Keloid	24	14 (58.3)	9 ± 2	27	12 (44.4)	11 ± 3
Non-keloid	43	38 (88.4)	4 ± 1	39	28 (71.8)	6 ± 2
		<i>P</i> < 0.01	<i>P</i> < 0.01		<i>P</i> < 0.01	<i>P</i> < 0.01

For both intubation and tracheostomy treatments, patients were divided into keloid and non-keloid phenotypes. Number of patients cured (cure rate) between keloid and non-keloid groups were compared with Chi-square test, and treatment period (months) was compared using unpaired Student's *t*-test and shown as mean ± SD. *P*-value <0.01 indicating significant difference between keloid and non-keloid subgroups.

the with keloid group with average durations of 9 ± 2 months following tracheal intubation and 11 ± 3 months following tracheostomy compared to 4 ± 1 months following tracheal intubation and 6 ± 2 months following tracheostomy in the non-keloid group (*P* < 0.01) (Table 4).

For 2276 cases of tracheostomy patients, 139 patients were identified to be keloid, while 2137 counterparts to be non-keloid. The incidence of tracheal stenosis among keloid was significantly higher than for the non-keloid patients (19.4% vs 1.82%, respectively, *P* < 0.001; Table 5). On the other hand, due to the large sample size of patients receiving endotracheal intubation (218 573 cases) and incomplete medial record, we have yet to determine the keloid or non-keloid phenotype of each subject, and therefore the incidence of tracheal stenosis based on keloid formation were not available for such population of patients from year 2012 to 2017.

Of note, a 46-year-old male patient with non-keloid formation following long-term intubation developed Grade III "smooth"

subglottic tracheal stenosis (Supplementary Figure S2). In contrast, a 23-year-old female patient with keloid, who had undergone laparoscopic appendectomy for treatment of acute appendicitis under general anesthesia with tracheal intubation for 4 hours. The intra-operative and immediate post-operative periods were uneventful. Three weeks after the surgical procedure, this patient admitted to the hospital with increasing stridor. On clinical examination and assessment of the airway, she was developed Myer and Cotton Grade III iatrogenic subglottic airway stenosis. The patient received various treatments including electrocoagulation, argon knife, freezing, or stent for 21 times. Her re-stenosis was developed so fast and, therefore, treatment intervals were sometime even less than a week (Supplementary Figure S3). Tragically, the patient was so depressed and committed suicide.

The histological tissue samples of the lateral part of the subglottic tracheal stenosis, taken from a patient with keloid and a patient not with keloid, respectively. They demonstrate cicatrization and non-cicatrization of tissues (Figure 1).

	Intubation		Tracheostomy		
	Keloid	Non-keloid	Keloid	Non-keloid	
Tracheal Stenosis	24	43	27	39	
Subgroup	-	-	139	2137	
Total	218 573		2276		
TS incidence	-	-	19.4%	1.82%	<i>P</i> < 0.001

TABLE 5 Keloid and non-keloid patients who developed tracheal stenosis (TS) between intubated and tracheostomized patients

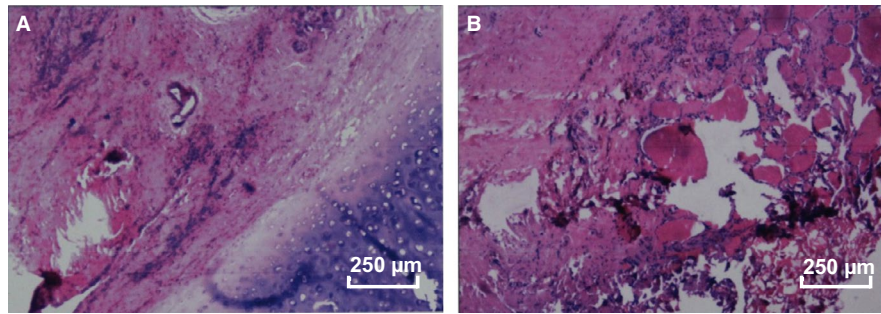


FIGURE 1 Representative histological micrographs in comparing lateral part of subglottic tracheal stenosis between (A) patient with keloid formation and (B) patient non-keloid formation (hematoxylin-eosin staining; $\times 40$ magnification). A, Squamous metaplasia, slight thickening, and scarring of mucosa, considerable interstitial fibrosis. B, Mucous epithelial cells proliferate, submucous vessels dilate, hyperemia, and granulation tissue proliferate [Colour figure can be viewed at wileyonlinelibrary.com]

The proportion of patients with keloid who showed evidence of cicatrix formation on thoracoscopic assessment were 79.2% for tracheal intubation and 81.5% for tracheostomy in contrast to 41.9% for tracheal intubation and 51.7% for tracheostomy in the group without keloid (Table 6).

4 | DISCUSSION

Our data showed that tracheal stenosis occurred more severe in the population with keloid (Table 2). This correlated with the unusual healing process which occurs after trauma to tissues in the population with keloid. To our knowledge, we are the first to report the time of onset of tracheal stenosis in a population at risk of keloid and we are therefore unable to compare with published data. We showed that tracheal stenosis occurred 27 ± 5 days after 3 ± 2 days of tracheal intubation in the population with keloid and this is significantly earlier than that in the population without keloid (Table 3). Interestingly, our data of the onset time of tracheal stenosis of 41 ± 7 days, in the group without keloid, is similar to the one reported by Galluccio and colleagues.¹¹

We observed that the histopathological and tracheoscopy findings in the keloid group were dominated by cicatricial tissue formation (about 80% of the tissues), while cicatricial and non-cicatricial tissues were found in equal proportions in the group without keloid. In addition, it took a shorter time and more success for the tracheal stenosis to heal after treatment in the group without keloid

compared to the keloid group. These observations are compatible with previously reported the time course and cicatrix formation in patients with keloid.¹²

Surprisingly, keloid as a potential risk factor in the formation of tracheal stenosis was not identified in previous studies. For example, in a retrospective case control study of 74 consecutive patients admitted to a hospital with laryngotracheal stenosis, the authors identified previous tracheostomy, previous intubation of trachea for non-airway surgery, and irradiation of orotracheal and laryngeal cancers as significant risk factors for the development of tracheal stenosis.¹³ In another retrospective study of 150 consecutive adult patients admitted to a hospital with laryngotracheal stenosis, the authors identified the cause to be iatrogenic in 54.7%, idiopathic in 18.5%, autoimmune in 18.5%, and traumatic in 8% of the studied population.¹⁴

Tracheal intubation and tracheostomy are the two most common causes of benign airway stenosis.¹⁵ Post-intubation or post-tracheostomy tracheal stenosis is mostly due to the ischemia-induced necrosis of tracheal mucosa. The blood supply to the trachea is segmental with blood vessels perforating the tracheal wall between the tracheal rings.¹⁶ In a study in anesthetized patients, where blood pressure was maintained at normal levels, the authors demonstrated that inflation of the cuff of the endotracheal tube to a pressure of 30 cmH₂O resulted in the mucosa over the tracheal rings in contact with cuff becoming less pink than those over the intercartilaginous areas but the vessels were of normal caliber.¹⁷ The risk of ischemic injury to the tracheal mucosa leading to tracheal stenosis also increases

TABLE 6 Histological analysis of tracheal stenosis in patients with keloid or non-keloid

	Intubation			Tracheostomy		
	Number	Scar tissue (%)	Non-scar tissue (%)	Number	Scar tissue (%)	Non-scar tissue (%)
Keloid	24	19 (79.2)	5 (20.8)	27	22 (81.5)	5 (18.5)
Non-keloid	43	18 (41.9)	25 (58.1)	39	15 (51.7)	14 (48.3)
		$P < 0.01$	$P < 0.01$		$P < 0.01$	$P < 0.01$

For both intubation and tracheostomy treatments, patients were divided into keloid and non-keloid phenotypes. Histological analysis was performed to compare number of patients with scar or non-scar tissue formation between keloid and non-keloid subgroups, using Chi-square test. P -value < 0.01 indicating significant difference between keloid and non-keloid groups.

with the duration of intubation but it has also been reported to occur after short period of intubation.¹⁸

Iatrogenic subglottic airway stenosis is a very devastated complication of tracheal intubation but when it occurs it can cause severe upper airway obstruction leaving patients in severe distress with significantly reduced quality of life. Furthermore, patients with laryngotracheal stenosis are at increasing risk of developing obstructive sleep apnea with an incidence 7.2 times that of those without stenosis.¹³ Sadly, 2 patients in our study who suffered severe airway obstruction following tracheal intubation, committed suicide because they could not bear to continue living with such troubling airway condition.

Although the introduction of high-volume, low-pressure disposable endotracheal tubes has significantly reduced the risk of tracheal injury, we should establish whether the patient has keloid and consider alternative anesthetic techniques which do not require tracheal intubation. The cuff pressure must be monitored at least intermittently to avoid not only tracheal stenosis but also bilateral recurrent nerve paralysis. It has been suggested that measurement of endotracheal cuff pressures should be performed during general anesthesia, maintaining it between 20 and 25 cm H₂O; nurses in ICU routinely monitor the pressure. Unfortunately, this is not routinely done in the operation room.¹⁹ The cuff is often inflated according to individual operator's experience and often it is overinflated.²⁰

In the ICU, physicians should weigh the benefits and risks of tracheostomy in patients with keloid and if it has to be performed, great care must be taken to minimize trauma to the trachea. In a retrospective study of 155 patients who had tracheostomies, the authors reported that surgical closure of tracheostomy site after decannulation resulted in less tracheal stenosis than allowing the tracheostomy wound to heal spontaneous (the incidence of 2% vs 22% in surgical closure compared to spontaneous wound healing).²¹

Identification of patients who are prone to keloid scarring can sometimes be difficult. We propose that examination of the scarring from the Bacillus Calmette-Guerin (BCG) vaccination, often a fairly ubiquitous scar in populations where keloid is prevalent, may offer some clue to identify individuals who may be at risk of keloid.

Treatment management of tracheal stenosis can include either endoscopic or open approaches.^{15,17} Often, endoscopic approaches such as dilatation or endoscopic scar excision are attempted for stenosis of Myer-Cotton Grades I and II, and open approaches are commonly used for more severe stenosis of Grades III and IV. Patients with keloid who develop tracheal stenosis tend to receive bronchoscopy and corresponding bronchoscopic treatment because of their relatively higher recurrence rate of tracheal stenosis. The bronchoscopic treatment that is often used involves cryotherapy, electrocautery, balloon dilatation, and self-expanding metal stent which is embedded into the trachea.²² Although these treatments are effective at relieving the airway stenosis for a short time, they can also cause further tissue injury and leading to more cicatrization, particularly in patients with keloid.²³ Endoscopic dilatation, in severe tracheal stenosis, is usually a temporary measure pending definitive correction of the stenosis.¹⁵

There are several limitations to this study. The first and main weakness of this study is that due to its retrospective nature of our study, the general picture of keloid and non-keloid phenotype in the whole population, in particular in our all intubated patients, is not available. It has been reported that the incidence of keloid phenotype among American Caucasians is approximately 0.1% but it varies widely among people of African descent from 4% to 16%. However, the keloid incidence rate among Asian population is unclear.²⁴ The second limitation of our study is that determination of keloid phenotype for tracheostomy group is restricted to the patients who had information on superficial keloid scar noted in their medical record/journal, along with further information from those 2276 tracheostomized patients individually by telephone or text message to confirm the presence or absence of superficial keloid scar. One can argue is that keloid phenotype may also present without superficial keloid scar, indicating that keloid phenotype can be underestimated in our study. The third limitation is that the causal relationship between keloid, other risk factors (eg, genic, ethnicities, duration of intubation, cuff pressure, and BMI) and tracheal stenosis remains unknown. Keloids have a high incidence among certain ethnicities; the development of the disease appears to be closely related to certain genetic properties.^{25,26} Linkage analyses have revealed that a keloid susceptibility locus is present on chromosomes 7p11, 2q23, and 18q21.1 in African American, Japanese,²⁷ and Chinese ethnic lineages, respectively.²⁸ Previous studies on Caucasians have indicated that a positive association exists between the HLA-DRB1*15 allele and keloid susceptibility,²⁹ and that the HLA-DRB5 copy number is associated with keloid development at sites of minor puncture wounds.³⁰ In addition, the HLA-DQA and DQB alleles have been reported to be associated with keloid susceptibility in ethnic Chinese populations.³¹ However, again due to its retrospective nature of our study, the incidence of tracheal stenosis in patients with keloid and the relationship between genetic susceptibility, familial, and other related factors in our patient population cannot be established.

In conclusion, our study suggests that the incidence of tracheal stenosis is higher in subjects predisposed to keloid follow tracheostomy, and these patients demonstrate an earlier onset of tracheal stenosis requires more frequent and lengthy treatment albeit poorer treatment success, when compared to non-keloid subjects. Our data may suggest keloid formation as a risk factor for the development of iatrogenic tracheal stenosis in tracheostomized subjects; however, substantive analysis on all of the intubation cases would be necessary for us to convincingly and conclusively establish keloid phenotype as a predictor of iatrogenic tracheal stenosis. Findings from the present study would urge a more cautioned approach to intubation and/or tracheostomy for the perioperative patient management with known keloid. Whether regional nerve block or intraspinal anesthesia should be considered, and/or whether laryngeal mask should be used instead of intubation to minimize airway injury and avoid stenosis complications, are subjected for further study. However, there are circumstances in which tracheal intubation or tracheostomy cannot be avoided; in those cases, regular monitoring of cuff pressure should be strongly

carried out in every patient, in particular, in those at a high risk of developing keloid.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

EQ.C., JQ.Z., D.M.: Study design/planning. EQ.C.: Study conduct. S.Z.: Pathological assessment. EQ.C., LZ.W., J.L.: Data analysis. EQ.C., LZ.W., J.M., WL.Z., TX.L., JQ.Z., FM.M., C.S, D.M.: Writing paper. Revising paper: All authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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