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Laryngeal inhalational injuries: A systematic review

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ABSTRACT

Laryngeal inhalation injury carries a significant increase in mortality rate and often indicates immediate airway evaluation. This may be difficult in the setting of clinical deterioration necessitating immediate intubation, which itself can synergistically cause mucosal damage. Prior studies do not encompass predictive factors or long-term outcomes for the laryngotracheal complex. This systemic review of PubMed, Embase, and Cochrane identified studies investigating inhalational injuries of the upper airway. Demographic data as well as presentation, physical findings, and delayed sequelae were documented. Laryngotracheal burn patients were divided into two cohorts based on timing of laryngeal injury diagnosis (before- versus after-airway intervention). 1051 papers met initial search criteria and 43 studies were ultimately included. Airway stenosis was more common in patients that were intubated immediately (50.0%, n = 18 versus 5.2%, n = 13; p = 0.57). Posterior glottic involvement was only identified in patients intubated prior to airway evaluation (71.4%, n = 15). All studies reported a closed space setting for those patients in whom airway intervention preceded laryngeal evaluation. Laryngeal inhalational injuries are a distinct subset that can have a variety of minor to severe laryngotracheal delayed sequelae, particularly for thermal injuries occurring within enclosed spaces. Given these findings, early otolaryngology referral may mitigate or treat these effects.

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1. Introduction

Inhalation injuries occur in about 10% of burn patients and are linked to an increased overall mortality in the range of 25% [1–5]. Diagnosis is generally made on clinical suspicion with flexible videolaryngoscopy [6–8] and imaging [9–11] employed for confirmation. Clinical deterioration may necessitate immediate intubation prior to upper airway evaluation. In addition, traditional criteria [12] for inhalational injury often lead to prophylactic intubation. Taken together, these factors limit quantification of laryngotracheal and pharyngeal injury patterns and tissue injury progression in many cases. Endotracheal intubation in the setting of an inhalation injury has been linked to long term laryngotracheal injuries ranging from dysphonia and dysphagia to tracheal and posterior glottic stenosis (PGS) [13–17]. Studies quantifying these laryngotracheal outcomes based on initial thermal injury pattern to the laryngotracheal complex and pharynx are lacking.

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Laryngotracheal mucosal injury with concomitant intubation may initiate posterior glottic stenosis [18]. During intubation and with an endotracheal tube (ETT) in place, the airway is at risk of insults to delicate epithelium and submucosal areolar and tracheal tissues leading to edema and subsequent airway narrowing [19]. Iatrogenic injury secondary to ETT intubation accounts for approximately 90% of acquired subglottic stenosis (SGS) and an even higher rate of PGS [20]. Dysregulated wound healing in response to ETT-induced ulceration helps to propagate rapidly progressive fibroplasia and pathologic scarring in subglottic injury [21]. A recent study identified acute laryngeal injury in more than half of patients intubated greater than 12 h, with findings persisting for more than two months [22]. Evidence also suggests early intervention may be ideal in treating these patients [23]. With the lack of therapies to prevent these complex complications, efforts traditionally have focused on improving treatments and minimizing the associated impacts. Although well studied in other intubated populations, the prevalence and impact of these adverse effects of ETT are less well understood in the cohort of patients with inhalation injury.

The majority of existing inhalational injury studies focus specifically on pulmonary injuries, as these play a direct impact in early survival outcomes. Despite numerous studies characterizing inhalational injuries, there is a paucity of data on thermal injury patterns or impact of inhalational injury on upper airway function. Specific to inhalational injury to the laryngotracheal complex, it is hypothesized that the subglottic region, comprised of respiratory epithelium, may be more sensitive to inhalational injury compared to the stratified squamous epithelium above the vocal folds [15]. In addition, airflow patterns below the vocal folds may increase the area of

PubMed Search

(("Pharynx"[Mesh:NoExp] OR "Oropharynx"[Mesh:NoExp] OR "Nasopharynx"[Mesh:NoExp] OR "Hypopharynx"[Mesh:NoExp] OR "Larynx"[Mesh:NoExp] OR "Glottis"[Mesh:NoExp] OR "Trachea"[Mesh:NoExp] OR pharyn*[tiab] OR oropharyn*[tiab] OR oro pharyn*[tiab] OR nasopharyn*[tiab] OR naso pharyn*[tiab] OR hypopharyn*[tiab] OR hypo pharyn*[tiab] OR laryn*[tiab] OR supraglotti*[tiab] OR glotti*[tiab] OR subglotti*[tiab] OR supra glotti*[tiab] OR sub glotti*[tiab] OR trachea*[tiab] OR laryngotrachea* [tiab] OR laryngo trachea*[tiab] OR upper aerodigestive tract*[tiab] OR upper aero digestive tract*[tiab] OR upper respiratory tract*[tiab] OR airway*[tiab] OR air way*[tiab])) AND (((("Burns"[Mesh:NoExp] OR burn*[tiab] OR thermal[tiab]) AND inhal*[tiab])) OR "Burns, Inhalation"[Mesh])

EmBase Search

('pharynx'/de OR 'oropharynx'/de OR 'nasopharynx'/de OR 'hypopharynx'/de OR 'larynx'/de OR 'supraglottis'/de OR 'glottis'/de OR 'subglottis'/de OR 'trachea'/de OR 'upper respiratory tract'/de OR pharyn*:ti,ab OR oropharyn*:ti,ab OR subglotti*:ti,ab OR trachea*:ti,ab OR laryngotrachea*:ti,ab OR 'upper aerodigestive tract':ti,ab OR 'upper airway':ti,ab OR 'upper respiratory tract':ti,ab OR 'oro pharyn*':ti,ab OR 'naso pharyn*':ti,ab OR 'hypo pharyn*':ti,ab OR 'supra glotti*':ti,ab OR 'sub glotti*':ti,ab OR 'laryngo trachea*':ti,ab OR 'upper aero digestive tract*':ti,ab OR 'upper air way*':ti,ab) AND ('burn'/de OR burn*:ti,ab OR 'thermal injury'/de OR thermal:ti,ab) AND (inhal*:ti,ab OR 'inhalation injury'/exp)

Cochrane Search

((MeSH descriptor: [Pharynx] this term only OR MeSH descriptor: [Oropharynx] this term only OR MeSH descriptor: [Nasopharynx] this term only OR MeSH descriptor: [Hypopharynx] this term only OR MeSH descriptor: [Larynx] this term only OR MeSH descriptor: [Glottis] this term only OR MeSH descriptor: [Trachea] this term only) OR ((pharyn*):ti OR (pharyn*):ab OR (oropharyn*):ti OR (oropharyn*):ab OR (oro-pharyn*):ti OR (oro-pharyn*):ab OR (nasopharyn*):ti OR (nasopharyn*):ab OR (naso-pharyn*):ti OR (naso-pharyn*):ab OR (hypopharyn*):ti OR (hypopharyn*):ab OR (hypo-pharyn*):ti OR (hypo-pharyn*):ab OR (laryn*):ti OR (laryn*):ab OR (supraglotti*):ti OR (supraglotti*):ab OR (supra-glotti*):ti OR (supra-glotti*):ab OR (glotti*):ti OR (glotti*):ab OR (subglotti*):ti OR (subglotti*):ab OR (subglotti*):ti OR (sub-glotti*):ab OR (trachea*):ti OR (trachea*):ab OR (laryngotrachea*):ti OR (laryngotrachea*):ab OR (laryngo-trachea*):ti OR (laryngotrachea*):ab OR ("upper aerodigestive tract"):ti OR ("upper aerodigestive tract"):ab OR ("upper aero-digestive tract"):ti OR ("upper aero-digestive tract"):ab OR ("upper respiratory tract"):ti OR ("upper respiratory tract"):ab OR ("upper airway"):ti OR ("upper airway"):ab OR ("upper air-way"):ti OR ("upper air-way"):ab)) AND ((burn*):ti OR (burn*):ab OR (thermal*):ti OR (thermal*):ab) AND (MeSH descriptor: [Burns, Inhalation] explode all trees AND ((inhal*):ti OR (inhal*):ab))

Fig. 1 – Search terms used in the PubMed, Embase, and Cochrane databases.

exposure to toxin and thermal injury [24]. Conversely, the glottic closure reflex, an airway protective mechanism activated by receptors within the larynx [25], may functionally create a heat sink protecting the lower airway from thermal injury. Additionally, heat capacities of inhaled fluids can vary by orders of magnitude, such as with steam verses hot dry air, widely altering resulting tissue damage from inhalational injuries [26].

Although there are systematic reviews of prognostic implications in inhalation injuries [27] and risk factors for developing dysphagia after thermal burn injuries [28], these do not encompass predictive factors or long term outcomes for the laryngotracheal complex in the setting of inhalation injury. As a result, in this systematic review, we sought to compile existing literature addressing thermal inhalation injuries to the laryngotracheal complex, defining the presentation, physical findings, and associated short- and long-term sequelae of inhalational injuries on the upper airway. Ultimately, this information may help to optimize early consultation and intervention, where applicable, to reduce long-term morbidity.

2. Methods

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29,30]. Guidance was provided by our institution's library information specialist (KB). A review protocol did not exist prior to this study and no study registration was required. Three search engines were used to conduct the systematic review: PubMed, Embase, and The Cochrane Library. An additional search through the Clinical Trials was performed. Search terms are defined in Fig. 1. The search was performed for all studies through November 2019. A specific start date was not set to ensure comprehensive review. Studies were included if they discussed inhalational or thermal burn injuries specific to the upper airway. Anatomical subsites included the pharynx, oropharynx, nasopharynx, hypopharynx, larynx, supraglottis, subglottis, glottis, laryngotrachea, upper respiratory tract, upper airway, or upper aerodigestive tract.

Studies were excluded if they were non-English full texts, animal studies, in-vitro studies (only histological/molecular analyses), review articles, or if full text was unavailable. In order to minimize risk of bias, we excluded any study from the same institution that included repeat cohorts (Fig. 2). Dedicated pediatric studies were excluded in order to limit any confounding factors attributed to differences in anatomy and physiology in children. Additionally, studies were excluded if they were limited to the lower respiratory tract, described inhalational injuries in general terms without objective upper

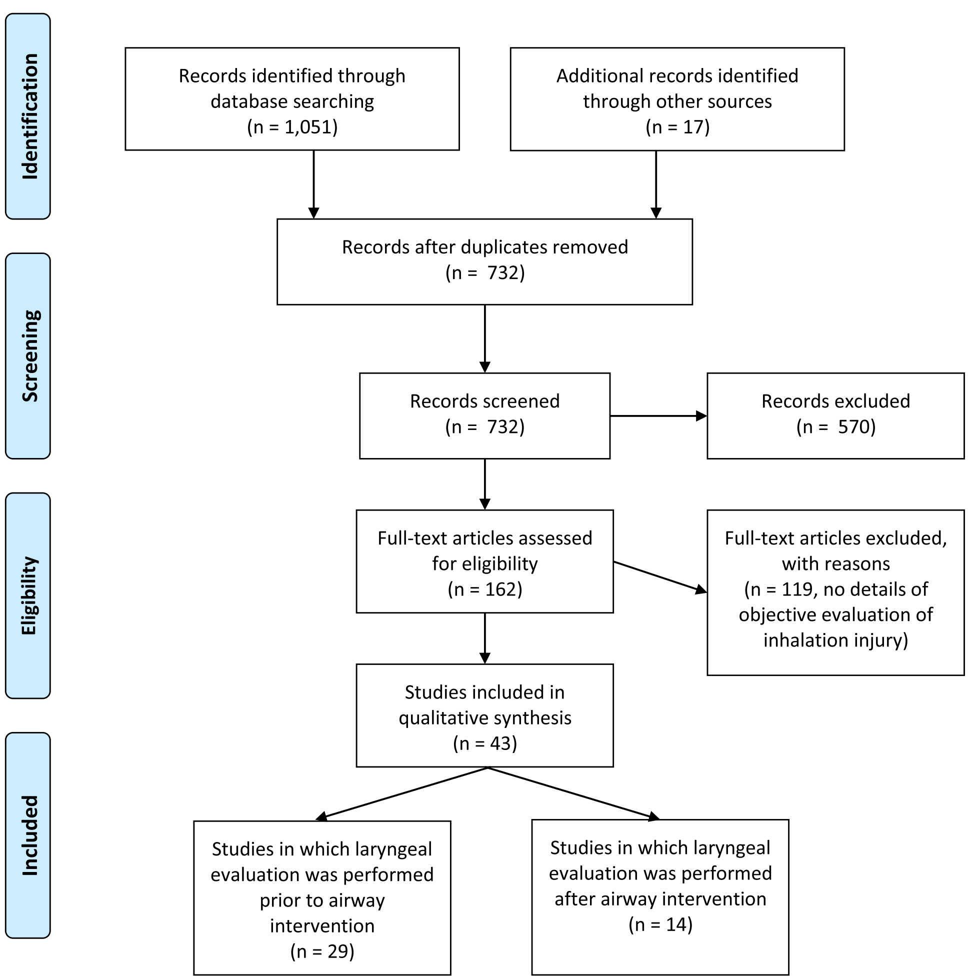

Fig. 2 – Flow chart of identification and screening as performed in accordance to PRISMA guidelines.

airway findings, reported non-inhalational mechanisms of injury (chemical, electric, iatrogenic airway fire), or involved blunt/penetrating laryngeal trauma. Many studies included laryngeal inhalational injuries as a subset of a larger group of burn patients; in these cases, only the patients and associated data specific to laryngeal inhalational injuries were collected for analysis.

All studies were reviewed independently by two authors (JAT, LN). Studies in which inclusion and exclusion criteria could not be determined based on abstracts alone warranted full text review. The bibliographies of all included studies were hand searched for additional studies potentially missing capture in the initial search criteria. When necessary, studies were discussed in detail to achieve consensus and consistency for inclusion.

All studies meeting inclusion criteria underwent data extraction (JAT, GA) for the following variables: article year, lead author, institution, study type, demographics (age, sex, and race if specified), etiology and circumstance of burn injury, percent total body surface area (% TBSA), clinical presentation, airway management, discharge disposition, mortality, delayed sequelae, and complications. Specifically, clinical presentation variables included dysphonia, dysphagia, dyspnea, stridor, wheezes/rales, and cough. Documented physical exam findings include singed nasal or facial hairs, cutaneous burns to the head and neck, and if endoscopic examination was performed, soot and/or edema, hyperemia, and hypersecretion. Delayed sequelae were defined as any result not present upon initial airway evaluation of the patient and included pneumonia, stricture or stenosis, posterior glottic web or stenosis, and tracheoesophageal fistula.

Laryngotracheal burn patients were divided into two cohorts based on the timing of laryngeal injury diagnosis (before- versus after-airway intervention). This grouping was selected to categorize patients where a formal airway evaluation was undertaken in a non-instrumented airway compared to those patients where airway evaluation was only possible after initial intubation, as the known impacts of endotracheal intubation may confound airway findings. Airway intervention was defined as any procedure performed to secure the airway to include: intubation, surgical tracheostomy, and cricothryoidotomy. Patients were included in the before-airway intervention group if objective laryngeal inhalation injury was documented before any airway interventions (intubation, etc.). Conversely, if the diagnosis of laryngeal inhalation injury was diagnosed at some point after initial airway intervention, patients were included in the after group. The mechanism of laryngeal burn was also investigated based on closed space (e.g. house fire, trailer) versus open space (e.g. outdoors).

The data was recorded using Microsoft Excel (Microsoft Corporations, Redmond, WA). Overall outcome variables were reported using descriptive statistics (IBM SPSS Statistics, Version 20, Chicago, IL). When applicable, patient percentages were among reported only as a percentage of the patient population in those studies reporting the variable of interest. Overall mortality, tracheostomy rates, and airway stenosis were reported between groups based on the timing of laryngeal injury diagnosis (pre- or post-airway intervention).

3. Results

A total of 1051 papers met initial search criteria of which 41 studies met inclusion criteria (Fig. 2). Hand searches of the grey literature to include bibliographies of the above 41 articles identified two additional papers for a total of 43 included studies. Initial conflicts with 23 studies were resolved through reviewer discussion.

Included studies were published between 1973 and 2019. In total, there were nine prospective observational studies, 16 retrospective reviews, and 18 case reports or series. Collectively, a total of 12,474 burn patients were identified, 1517 of which had objective documentation of laryngeal inhalation injuries (12.15%). Across 29 studies [6–12,14,31–51], 1400 patients had laryngeal inhalational injuries documented prior to airway intervention (Table 1). An additional 117 patients from 14 studies [13,16,52–63] were noted to have laryngeal inhalational injuries documented after airway intervention (Table 2). Laryngeal inhalational injuries were most commonly identified by flexible endoscopy. A small subset of patients were diagnosed via virtual bronchoscopy in which CT scans were used to specifically assess laryngotracheal structures [9].

Clinical diagnosis (Fig. 3), physical exam findings (Fig. 4), and delayed sequelae (Fig. 5) are summarized based on laryngeal findings of inhalation injury documented before and after airway intervention. Intubation was the most common means of airway intervention (n = 483) with surgical airway/tracheostomy and emergent cricothyroidotomy.

Patients with laryngeal inhalational injury noted prior to airway intervention had a mortality rate of 17.4%, n = 143 of 824, compared to findings after airway intervention of 4.2%, n = 3 of 79. Both cohorts underwent tracheotomy at similar rates (34.2%, n = 181 of 527, and 34.3%, n = 30 of 77). Airway stenosis was more common in patients that were intubated immediately (50.0%, n = 18 of 36, versus 5.2%, n = 13 of 246). Posterior glottic involvement was only identified in patients intubated prior to airway evaluation (71.4%, n = 15 of 21). Airway stenosis was identified as early as one to fourteen weeks after injury [61]. All studies reported a closed space setting for the subset of patients in whom airway intervention preceded laryngeal evaluation and environment was documented.

4. Discussion

This is the first systematic review assessing laryngotracheal complex sequelae from thermal upper airway injury, adding to a growing body of literature documenting the voice, swallow, and breathing effects of upper airway and inhalation burns. Results of this systematic review illustrate varying physical exam and clinical presentations and delayed outcomes of patients with laryngeal thermal inhalational injuries. Long term sequelae may be minor or may include tracheo-esophageal fistula or tracheal or posterior glottic stenosis. Appropriately, most research and patient studies to date on inhalation injuries focus on acute life-saving therapies; however, data are lacking on the laryngotracheal sequelae from these thermal injuries that can negatively impact quality

Table 1 – Study characteristics including demographics of study population for those in which laryngeal inhalational injuries were noted prior to airway intervention. N represents the laryngeal inhalational injury sample size. NA, *not available*; No., *number of*; trach, *tracheostomy*; Avg, *average*; yrs, *years*.

Lead author	Institution	Country	Published date	Study dates	Journal	Study type	Closed/ open space	Total sample size	N	No. deaths	No. intubated	No. trach	Sex (M/F)	Avg age (yrs)	TBSA
Haponik et al. [31]	Johns Hopkins University	USA	1987	1982–1984	Am Rev Respir Dis	Prospective	NA	38	36	0	6		27/9	34.8	Mean 15.7 ± 15%
Desai et al. [32]	Singapore General Hospital	Singapore	2019	2017	Singapore Med J	Case Report/ Series	NA	5	5	0	5		5/0		Range 0 –22.5
Ching et al. [33]	Morsani College of Medicine	USA	2016	2002–2010	J Burn Care Res	Retrospective chart review	NA	9775	22					43.7	Mean 21.74%
Bai et al. [6]	Changhai Affiliated Hospital of the Second Military Medical University	China	2013	2010	Diagn Pathol	Case Report/ Series	Closed	20	20	0	1	7	14/6	54.2	Range 1 –5%
Edelman et al. [34]	Wayne State University/Detroit Receiving Hospital	USA	2008	2001–2006	J Burn Care Res	Retrospective chart review	NA	11	7	0	7	7	5/2	44	Mean (range) 30.7% (10 –60%)
Megahed et al. [36]	Menoufiya University Hospitals	Egypt	2008	2004–2008	Ann Burns Fire Disasters	Retrospective chart review	NA	281	130	54			61/69		
Yamamura et al. [11]	Osaka City University	Japan	2013		Crit Care	Prospective	NA	37	37	4	25	0	31/6	63	Mean 11.5%
Badulak et al. [12]	University of Washington	USA	2018	2008–2013	Burns	Retrospective chart review	NA	218	10		10				
Freno et al. [7]	University of South Alabama School of Medicine	USA	2018	2012–2015	Burns	Retrospective chart review	Closed	210	73		10			41	Median 5% (IQR 2.5 –9%)
Goh et al. [37]	Changi General Hospital	Singapore	2006	27-Jun-05	Eur J Emerg Med	Case Report/ Series	Open	22	15		0	0		38.7	
Rhodes et al. [38]	Mount Sinai Hospital Miami	USA	1973	1973	Am Rev Respir Dis	Case Report/ Series	Closed	15	12			2	3/9		
Muehlberger et al. [8]	Johns Hopkins University	USA	1998	1996–1997	Arch Otolaryngol Head Neck	Retrospective chart review	Closed	11	11				8/3	43	
Tilney [39]	Albany Medical Center	USA	2010		Air Med J	Case Report/ Series	Open	1	1	1	1		1/0	80	Mean 100%
Madnani et al. [40]	Albert Einstein College of Medicine	USA	2006	1998–2003	Ear Nose Throat J	Retrospective chart review	NA	41	41		8		28/13	36	
Marek et al. [41]	Slaskie Burn Center	Poland	2007	2001–2004	Burns	Prospective	NA	292	111						
Lowery et al. [42]	Vanderbilt University School of Medicine	USA	2019	2012–2017	J Burn Care Res	Retrospective chart review	NA	129	129		129	19	76/53	47.1	Mean 10.5% non-LTS Mean 30.3% LTS

(continued on next page)

Table 1 *(continued)*

Lead author	Institution	Country	Published date	Study dates	Journal	Study type	Closed/ open space	Total sample size	N	No. deaths	No. intubated	No. trach	Sex (M/F)	Avg age (yrs)	TBSA
Onishi et al. [43]	Japan Community Health Care Organization Chukyo Hospital	Japan	2017	2012–2014	Acute Med Surg	Retrospective chart review	NA	80	71		9			59	Median 9.5%
Fang-Gang et al. [44]	Beijing Jishuitan Hospital	China	2015	2009–2013	Burns	Retrospective chart review	NA	443	443	31		164	353/90	37.2	Mean 46.63 ± 33.01% tracheostomy Mean 21.90 ± 20.49% non-tracheostomy
Arakawa et al. [45]	Hamamatsu Medical Center	Japan	2007	2002–2004	Burns	Prospective	Closed	5	5		4	2	2/3		>20%
Costa Santos et al. [46]	Hospital da Prelada	Portugal	2015	2009–2013	Ann Burns Fire Disasters	Retrospective	NA	136	12	6	104			49.8	
Moshrefi et al. [47]	Santa Clara Valley Medical Center	USA	2019	2013–2017	J Burn Care Res	Retrospective	NA	51	51		1		41/10	40.5	Mean (range) 6.5% (0.5–38.0%)
Ikonomidis et al. [48]	University Hospital	Switzerland	2012		Burns	Prospective	NA	100	79	8	79				
Yang et al. [49]	Chang Gung Memorial Hospital	Taiwan	1998	1987–1995	Burns	Retrospective	NA	7	1	0	1	1	1/0	45	Mean 80%
Ribeiro et al. [35]	Centro Hospitalar de Vila Nova de Gaia	Portugal	2013		J Bronchol Intervent Pulmonol	Case Study	Closed	1	1		1		0/1		
Lee and O'Connell [10]	Institute of Radiological Sciences	Ireland	1988		Clin Radiol	Prospective	Closed	45	13						
Colice et al. [14]	Tampa General Hospital	USA	1986		Am Rev Respir Dis	Case Study	Open	3	1		1		1/0		
Jones et al. [50]	New York Hospital – Cornell	USA	1988	1982–1986	Ann Surg	Retrospective	NA	99	54	39					
Gore et al. [9]	Lokmanya Tilak Municipal Medical	India	2004		Burns	Case Study	NA	10	8				0/8		Range 25–70%
Kim et al. [51]	Pusan National University Hospital	Korea	2019		Iran J Otorhinolaryngol	Case Study	Closed	1	1				0/1	47	

Table 2 – Study characteristics including demographics of study population for those in which laryngeal inhalational injuries were noted after airway intervention. N represents the laryngeal inhalational injury sample size. NA, *not available*; No., *number of*; trach, *tracheostomy*; Avg, *average*; yrs, *years*.

Lead author	Institution	Country	Published date	Study dates	Journal	Study type	Closed/ open space	Total sample size	N	No. deaths	No. intubated	No. trach	Sex (M/F)	Avg age (yrs)	TBSA
Gherardini et al. [52]	Karolinska Hospital	Sweden	1994	1987−1992	Eur J Plast Surg	Case Study	NA	5	4	1	4	4	2/2		Range 10−50%
Bassi et al. [53]	Universidade de São Paulo	Brazil	2014	2013	Rev Bras Ter Intensiva	Case Study	Closed	4	1	0	1	0	1/0		0%
Al Kassis et al. [54]	Yale New Haven Hospital	USA	2014	2006−2012	J Am Coll Surg	Retrospective	Closed	28	28	0	28	0	15/13	63.8	Mean (range) 4% (0−10%)
Cobley et al. [55]	Frenchay Hospital	UK	1999		Burns	Case Study	NA	1	1	0	1	1	0/1	41	35%
Irrazabal et al. [56]	Hospital de Clinicas Jose de San Martin	Argentina	2008	26-Jun-05	Burns	Case Study	Closed	15	13	2	13	4	8/5	22.5	
Hantson et al. [57]	Hopital Fernand Widal, Universite Paris VII	France	1997	1987−1992	Chest	Retrospective	Closed	64	34					47.3	0%
Valdez et al. [58]	Texas Children's Hospital	USA	2006	2003−2004	Laryngoscope	Prospective	Closed	9	9	0	9	4	2/7	35	Mean (range) 19% (9−45%)
Jayawardena et al. [59]	Vanderbilt University Medical Center	USA	2019		J Burn Care Res	Case Study	Closed	3	3	0	3	2	3/0	32	4%, 50%, 10%
Cha et al. [13]	Kyungpook National University Hospital	Korea	2007	2003	Burns	Prospective	Closed	96	6	0	6			35.2	0%
Casper et al. [16]	State University of New York and the Upstate Medical University	USA	2002		J Burn Care Rehabil	Prospective	NA	10	7	0	7	6			
Koshkareva et al. [60]	Temple University Hospital	USA	2018		World J Otol Head Neck Surg	Case Study	Closed	139	1	0	1	0	0/1	34	29%
Flexon et al. [61]	Massachusetts General Hospital	USA	1989	1968−1987	Ann Otol Rhinol Laryngol	Case Study	Closed	11	8		6	7	6/2		
Furák et al. [62]	University of Szeged	Hungary	2011		Interact Cardiovasc Thorac Surg	Case Study	Closed	1	1	0	1	1	1/0	22	
Ashraf et al. [63]	BronxCare Health System, affiliated with Icahn School of Medicine at Mount Sinai	USA	2018		Medicine	Case Study	Closed	1	1	0	1	1	1/0	58	

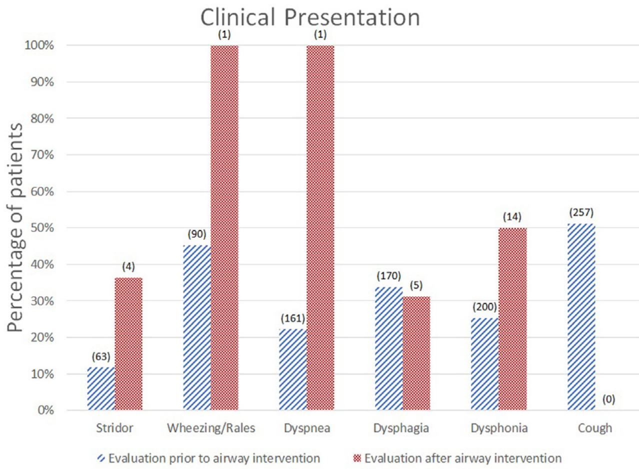

Fig. 3 – Clinical diagnosis of patients presenting with laryngeal inhalational injuries stratified by whether laryngeal evaluation was performed prior to or after airway intervention. Data is displayed as percentages of patients in which studies documented the presence or absence of signs and symptoms. Raw numbers of patients are displayed above each bar in parentheses.

Fig. 5 – Delayed sequelae of patients presenting with laryngeal inhalational injuries stratified by whether laryngeal evaluation was performed prior to or after airway intervention. Data is displayed as percentages of patients in which studies documented the presence or absence of delayed sequelae (defined as those not present immediately upon evaluation). Raw numbers of patients are displayed above each bar in parentheses.

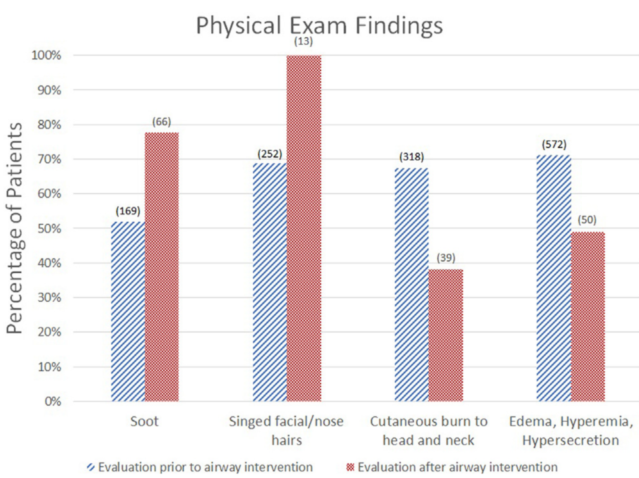

Fig. 4 – Physical findings of patients presenting with laryngeal inhalational injuries stratified by whether laryngeal evaluation was performed prior to or after airway intervention. Data is displayed as percentages of patients in which studies documented the presence or absence of physical exam findings including endoscopic findings. Raw numbers of patients are displayed above each bar in parentheses.

of life in survivors. Our study identified a number of early and late clinical signs and sequelae of these injuries.

Of all the patients with objective documentation of laryngeal inhalational injury in this review, cough followed by dysphonia were the most frequently noted clinical presentations. Dysphagia, dyspnea, wheezes/rales, and stridor were also commonly reported. In general, clinical signs and symptoms were specifically mentioned in patients that did not receive immediate attention to secure the airway, as often reporting of clinical signs is impossible for those patients who remained intubated for more than a few days.

On physical exam, cutaneous burns to the head and neck as well as singed facial and nasal hairs were more frequently present than absent in patients with laryngeal findings of inhalational injury. Endoscopic exam also demonstrated edema, hyperemia, and hypersecretion in a majority of patients, with or without the presence of soot. Collectively, in the reported literature in this systematic review, the presence of soot, singed facial or nose hair, cutaneous burns to the head and neck, and edema, hyperemia, and hypersecretion were each present in more than 50% of cases of laryngeal thermal injury, though reported to a lesser extent in patients intubated prior to formal laryngeal exam. All of these physical exam findings are suggestive of significant thermal injury and not isolated to predominately smoke inhalation injury, which can occur at much lower temperatures. These associated physical exam findings may be suggestive of laryngeal thermal injury more so than smoke inhalation lung injury.

Airway stenosis or stricture, most commonly in the subglottic region, was identified in half of patients intubated before laryngeal visualization and developed as early as one week to fourteen weeks after injury. In addition, all cases of posterior glottic stenosis or webs were only seen in the group of patients that were intubated prophylactically. The trend of patients intubated prior to laryngeal evaluation having comparatively more severe laryngotracheal complex injuries may indicate an uncovered link to TBSA or local tissue characteristics predisposing to injury. Additionally, local tissue trauma to the delicate laryngeal tissues from even careful intubation may precipitate long term injury to the laryngotracheal complex. Beginning at the time of injury, a myriad of patient and situational factors in the setting of an inhalation injury, from mental status to acute signs of airway obstruction or distress, play an important role in if and how quickly an airway intervention, generally orotracheal intubation, is undertaken. In this review, all scenarios where intubation or a surgical airway was performed to secure the airway prior to formal diagnostic visualization of the laryngotracheal complex were burns that occurred in an enclosed space, such as within a trailer or house fire. Many of these patients were intubated on the scene or during transport to the hospital. Smoke inhalation injury is more common in enclosed spaces due to the inability of smoke to dissipate quickly in enclosed spaces as it would outdoors, and inhalation of large concentrations of products of combustion such as hydrogen cyanide and carbon monoxide can quickly lead to a reduced level of consciousness and subsequent inability to protect the airway [64].

Aside from an altered mental status, upper airway obstruction has been noted in up to a third of patients with inhalational injury [65] and may necessitate immediate intubation. Inhalation injury can have variable effects above and below the glottis, and injury to the upper airway does not automatically imply injury to the lower airway or vice versa [43]. In fact, Head noted that in patients with oropharyngeal exams consistent with inhalational injury, bronchoscopy was negative 38% of the time [66]. Conversely, the respiratory epithelium immediately below the vocal folds may be more sensitive to inhalational injury than the squamous epithelium above the vocal fold [15], potentially attributable to subglottic airflow eddy currents that increases local exposure to toxic components of smoke [24]. Ultimately, either injury to the supraglottic or subglottic region can necessitate intubation.

Often, intubation may be performed urgently prior to visualization of the larynx and upper airway, especially in the setting where impending airway compromise is anticipated. However, some studies suggest intubation may be performed more often than necessary. In fact, Moshrefi et al. [47] reported that the majority of such intubations are unnecessary, with 50 of 51 intubated patients having a normal flexible exam. There was one patient who was intubated only after repeat laryngoscopy, which also speaks to the need for serial surveillance as the initial airway exam can evolve. It has been shown that those who undergo more than one endoscopic exam have shorter lengths of hospital stay [67].

There is likely a synergistic effect of damage from inhalational injury and intubation that could account for the increased finding of airway stenosis in patients intubated prior to laryngeal evaluation [13–15]. When patients are ultimately extubated, it can be challenging to define a clear distinction or compound impact between the contributions of inhalational injury and intubation to mucosal injury, stenosis, and other soft tissue injuries in the laryngotracheal complex.

Cha et al. [13] noted a high frequency of vocal fold and tracheal stenosis in patients with isolated smoke inhalational injuries despite only short term endotracheal intubation. Tracheal stenosis has even been observed as early as 64 h after intubation, suggesting that intubation alone could not have been the only factor contributing to such early development of airway stenosis [14]. Furthermore, more severe thermal injury and longer duration of intubation have been shown to be associated with the development of laryngotracheal stenosis [42]. Given the potential dire consequences that can result from the combined effects of intubation and inhalational injury, diagnostic laryngeal examination prior to intubation may provide diagnostic information on potential long term voice, airway, and swallowing function.

As with all systematic reviews, limitations exist in the variability of each paper in reporting variables important to the current study. Not every study was systematic in their documentation of symptoms, and not every study documented each one of our study variables of interest. We attempted to display the data in as representative a way as possible by only counting the population of studies that mentioned the presence or absence of each variable when portraying percentages and performing our statistical analyses, rather than counting the entire population of the studies combined. Unfortunately, not many studies included long term follow up, which may subsequently underestimate the prevalence of delayed sequelae reported in this study.

Although limited by the available data in existing literature, the findings of this review illustrate the frequency and broad range of secondary effects from laryngeal thermal injuries, particularly coupled with early intubation. One consideration would be more comprehensive or standardized evaluations of the larynx and upper airway both before intubation, when possible, involving immediate and repeat after extubation examination to minimize any negative effects on these delicate tissues. More globally, the frequent identification of dysphonia, dysphagia, dyspnea, and cough combined with the identified long term sequelae of tracheal or posterior glottic stenosis or tracheo-esophageal fistula suggest that early Otolaryngology Head and Neck Surgery referral or consultation may be warranted to supplement care and potentially mitigate or engage in treatment of delayed sequelae. Future prospective studies and meta-analyses may better elucidate these complex injuries and sequelae.

5. Conclusions

Laryngeal inhalational injuries are a distinct subset of inhalational injuries that can have a variety of minor to severe laryngotracheal delayed sequelae, particularly for thermal injuries occurring within enclosed spaces. Given these findings, early Otolaryngology Head and Neck Surgery referral may be useful to mitigate or treat these effects.

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Authorship declaration

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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Declarations of interest

None.

Submission declaration

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REFERENCES

[1] You K, Yang HT, Kym D, Yoon J, Yim Haejun, Cho YS, et al. Inhalation injury in burn patients: establishing the link between diagnosis and prognosis. Burns 2014;40:1470–5.
[2] Dries DJ, Endorf FW. Inhalation injury: epidemiology, pathology, treatment strategies. Scand J Trauma Resusc Emerg Med 2013;21:31.
[3] Enkhbaatar P, Murakami K, Shimoda K, Mizutani A, Traber L, Phillips GB, et al. The inducible nitric oxide synthase inhibitor BBS-2 prevents acute lung injury in sheep after burn and smoke inhalation injury. Am J Respir Crit Care Med 2003;167:1021–6.
[4] Shirani KZ, Pruitt Jr. BA, Mason Jr. AD. The influence of inhalation injury and pneumonia on burn mortality. Ann Surg 1987;205:82–7.
[5] Walker PF, Buehner MF, Wood LA, Boyer NL, Driscoll IR, Lundy JB, et al. Diagnosis and management of inhalation injury: an updated review. Crit Care (London, England) 2015;19:351.
[6] Bai C, Huang H, Yao X, Zhu S, Li B, Hang J, et al. Application of flexible bronchoscopy in inhalation lung injury. Diagn Pathol 2013;8:174.
[7] Freno D, Sahawneh J, Harrison S, Sahawneh T, Patterson S, Kahn SA. Determining the role of nasolaryngoscopy in the initial evaluation for upper airway injury in patients with facial burns. Burns 2018;44:539–43.
[8] Muehlberger T, Kunar D, Munster A, Couch M. Efficacy of fiberoptic laryngoscopy in the diagnosis of inhalation injuries. Arch Otolaryngol Head Neck Surg 1998;124:1003–7.
[9] Gore MA, Joshi AR, Nagarajan G, Iyer SP, Kulkarni T, Khandelwal A. Virtual bronchoscopy for diagnosis of inhalation injury in burnt patients. Burns 2004;30:165–8.
[10] Lee MJ, O'Connell DJ. The plain chest radiograph after acute smoke inhalation. Clin Radiol 1988;39:33–7.
[11] Yamamura H, Kaga S, Kaneda K, Mizobata Y. Chest computed tomography performed on admission helps predict the severity of smoke-inhalation injury. Criti Care (London, England) 2013;17:R95.
[12] Badulak Jh, Schurr M, Sauaia A, Ivashchenko A, Peltz E. Defining the criteria for intubation of the patient with thermal burns. Burns 2018;44:531–8.
[13] Cha SI, Kim CH, Lee JH, Park JY, Jung TH, Choi WI, et al. Isolated smoke inhalation injuries: acute respiratory dysfunction, clinical outcomes, and short-term evolution of pulmonary functions with the effects of steroids. Burns 2007;33:200–8.
[14] Colice GL, Munster AM, Haponik EF. Tracheal stenosis complicating cutaneous burns: an underestimated problem. Am Rev Respir Dis 1986;134:1315–8.
[15] Gaissert HA, Lofgren RH, Grillo HC. Upper airway compromise after inhalation injury. Complex strictures of the larynx and trachea and their management. Ann Surg 1993;218:672–8.
[16] Casper JK, Clark WR, Kelley RT, Colton RH. Laryngeal and phonatory status after burn/inhalation injury: a long term follow-up study. J Burn Care Rehabil 2002;23:235–43.
[17] Pfannenstiel TJ, Gal TJ, Hayes DK, Myers KV. Vocal fold immobility following burn intensive care. Otolaryngol Head Neck Surg 2007;137:152–6.
[18] Hillel AT, Karatayli-Ozgursoy S, Samad I, Best SR, Pandian V, Giraldez L, et al. Predictors of posterior glottic stenosis: a multi-institutional case-control study. Ann Otol Rhinol Laryngol 2016;125:257–63.
[19] Soose RJ, Carrau RL. Acquired laryngeal stenosis. In: Myers EN, editor. Operative otolaryngology: head and neck surgery. 2 ed. Philadelphia, PA: Saunders Elsevier; 2008. p. 357–78.
[20] Maeda K, Ono S, Baba K. Management of laryngotracheal stenosis in infants and children: the role of re-do surgery in cases of severe subglottic stenosis. Pediatr Surg Int 2013;29:1001–6.
[21] Hillel AT, Samad I, Ma G, Ding D, Sadtler K, Powell JD, et al. Dysregulated macrophages are present in bleomycin-induced murine laryngotracheal stenosis. Otolaryngol Head Neck Surg 2015;153:244–50.
[22] Shinn JR, Kimura KS, Campbell BR, Sun Lowery A, Wootten CT, Garrett CG, et al. Incidence and outcomes of acute laryngeal injury after prolonged mechanical ventilation. Crit Care Med 2019;47:1699–706.
[23] Nouraei SA, Singh A, Patel A, Ferguson C, Howard DJ, Sandhu GS. Early endoscopic treatment of acute inflammatory airway lesions improves the outcome of postintubation airway stenosis. Laryngoscope 2006;116:1417–21.
[24] Mallory TB, Brickley WJ. Pathology: with special reference to the pulmonary lesions. Ann Surg 1943;117:865–84.
[25] Ikari T, Sasaki CT. Glottic closure reflex: control mechanisms. Ann Otol Rhinol Laryngol 1980;89:220–4.
[26] Moritz AR, Henriques FC, McLean R. The effects of inhaled heat on the air passages and lungs: an experimental investigation. Am J Pathol 1945;21:311–31.
[27] Galeiras R, Seoane-Quiroga L, Pértega-Díaz S. Prevalence and prognostic impact of inhalation injury among burn patients: a systematic review and meta-analysis. J Trauma Acute Care Surg 2020;88:330–44.
[28] Vo E, Kurmis R, Campbell J, Greenwood J. Risk factors for and characteristics of dysphagia development in thermal burn injury and/or inhalation injury patients: a systematic review protocol. JBI Database System Rev Implement Rep 2016;14:31–43.

[29] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
[30] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009151: 264-9, W64.
[31] Haponik EF, Meyers DA, Munster AM, Smith PL, Britt EJ, Wise RA, et al. Acute upper airway injury in burn patients. Serial changes of flow-volume curves and nasopharyngoscopy. Am Rev Respir Dis 1987;135:360–6.
[32] Desai SR, Zeng D, Chong SJ. Airway management in inhalation injury: a case series. Singapore Med J 2019 [epub ahead of print].
[33] Ching Ja, Ching Yh, Shivers Sc, Karlnoski Ra, Payne Wg, Smith Jr Dj. An analysis of inhalation injury diagnostic methods and patient outcomes. J Burn Care Res 2016;37:e27–32.
[34] Edelman DA, Sheehy-Deardorff DA, White MT. Bedside assessment of swallowing is predictive of an abnormal barium swallow examination. J Burn Care Res 2008;29:89–96.
[35] Ribeiro C, Guimarães M, Antunes A, Oliveira A, Neves S, Almeida J, et al. "The black bronchoscopy" A case of airway soot deposition. J Bronchol Interventional Pulmonol 2013;20:271–3.
[36] Megahed MA, Ghareeb F, Kishk T, El-Barah A, Abou-Gereda H, El-Fol H, et al. Blood gases as an indicator of inhalation injury and prognosis in burn patients. Ann Burns Fire Disasters 2008;21:192–8.
[37] Goh SH, Tiah L, Lim HC, Ng EK. Disaster preparedness: experience from a smoke inhalation mass casualty incident. Eur J Emerg Med 2006;13:330–4.
[38] Rhodes ML. Early recognition of upper airway obstruction following smoke inhalation. Am Rev Respir Dis 1973;108:1421–6.
[39] Tilney P. Extensive burns in an elderly man found in a brush fire. Air Med J 2010;29:98–103.
[40] Madnani DD, Steele NP, de Vries E. Factors that predict the need for intubation in patients with smoke inhalation injury. Ear Nose Throat J 2006;85:278–80.
[41] Marek K, Piotr W, Stanislaw S, Stefan G, Justyna G, Mariusz N, et al. Fibreoptic bronchoscopy in routine clinical practice in confirming the diagnosis and treatment of inhalation burns. Burns 2007;33:554–60.
[42] Lowery AS, Dion G, Thompson C, Weavind L, Shinn J, McGrane S, et al. Incidence of laryngotracheal stenosis after thermal inhalation airway injury. J Burn Care Res 2019;40:961–5.
[43] Onishi S, Osuka A, Kuroki Y, Ueyama M. Indications of early intubation for patients with inhalation injury. Acute Med Surg 2017;4:278–85.
[44] Fang-Gang N, Yang C, Yu-Xuan Q, Yan-Hua R, Wei-Li D, Cheng W, et al. Laryngeal morphologic changes and epidemiology in patients with inhalation injury: a retrospective study. Burns 2015;41:1340–6.
[45] Arakawa A, Fukamizu H, Hashizume I, Kasamatsu N, Nagayoshi M, Shinozuka N, et al. Macroscopic and histological findings in the healing process of inhalation injury. Burns 2007;33:855–9.
[46] Costa Santos D, Barros F, Frazao M, Maia M. Pre-burn centre management of the airway in patients with face burns. Ann Burns Fire Disasters 2015;28:259–63.
[47] Moshrefi S, Sheckter CC, Shepard K, Pereira C, Davis DJ, Karanas Y, et al. Preventing unnecessary intubations: a 5-year regional burn center experience using flexible fiberoptic laryngoscopy for airway evaluation in patients with suspected inhalation or airway injury. J Burn Care Res 2019;40:341–6.
[48] Ikonomidis C, Lang F, Radu A, Berger MM. Standardizing the diagnosis of inhalation injury using a descriptive score based on mucosal injury criteria. Burns 2012;38:513–9.
[49] Yang JY, Yang WG, Chang LY, Chuang SS. Symptomatic tracheal stenosis in burns. Burns 1999;25:72–80.
[50] Jones WG, Madden M, Finkelstein J, Yurt RW, Goodwin CW. Tracheostomies in burn patients. Ann Surg 1989;209:471–4.
[51] Kim Gh, Wang Sg, Lee Yw, Kwon Sb. Voice recovery in a patient with inhaled laryngeal burns. Iran J Otorhinolaryngol 2019;31:55–9.
[52] Gherardini G, Jernbeck J, Kuylenstierna R, Jonsson CE. Anatomical and functional complications after tracheostomy in patients with burns and inhalation injuries. Eur J Plastic Surg 1994;17:127–30.
[53] Bassi E, Miranda LC, Tierno PF, Ferreira CB, Cadamuro FM, Figueiredo VR, et al. Assistance of inhalation injury victims caused by fire in confined spaces: what we learned from the tragedy at Santa Maria. Rev Bras Ter Intensiva 2014;26:421–9.
[54] Al Kassis S, Savetamal A, Assi R, Crombie RE, Ali R, Moores C, et al. Characteristics of patients with injury secondary to smoking on home oxygen therapy transferred intubated to a burn center. J Am Coll Surg 2014;218:1182–6.
[55] Cobley TD, Hart WJ, Baldwin DL, Burd DA. Complete fusion of the vocal cords; an unusual case. Burns 1999;25:361–3.
[56] Irrazabal CL, Capdevila AA, Revich L, Del Bosco CG, Luna CM, Vujacich P, et al. Early and late complications among 15 victims exposed to indoor fire and smoke inhalation. Burns 2008;34:533–8.
[57] Hantson P, Butera R, Clemessy JL, Michel A, Baud FJ. Early complications and value of initial clinical and paraclinical observations in victims of smoke inhalation without burns. Chest 1997;111:671–5.
[58] Valdez TA, Desai U, Ruhl CM, Nigri PT. Early laryngeal inhalation injury and its correlation with late sequelae. Laryngoscope 2006;116:283–7.
[59] Jayawardena A, Lowery AS, Wootten C, Dion GR, Summitt JB, McGrane S, et al. Early surgical management of thermal airway injury: a case series. J Burn Care Res 2019;40:189–95.
[60] Koshkareva YA, Hughes WB, Soliman AMS. Laryngotracheal stenosis in burn patients requiring mechanical ventilation. World J Otorhinolaryngol Head Neck Surg 2018;4:117–21.
[61] Flexon PB, Cheney ML, Montgomery WW, Turner PA. Management of patients with glottic and subglottic stenosis resulting from thermal burns. Ann Otol Rhinol Laryngol 1989;98:27–30.
[62] Furak J, Szakacs L, Nagy A, Rovo L. Multiple costal cartilage graft reconstruction for the treatment of a full-length laryngotracheal stenosis after an inhalation burn. Interact Cardiovasc Thorac Surg 2011;13:453–5.
[63] Ashraf U, Bajantri B, Roa-Gomez G, Venkatram S, Cantin A, DI-F G. Nebulized heparin and N-acetylcysteine for smoke inhalational injury: a case report. Medicine (United States) 201897:.
[64] Antonio AC, Castro PS, Freire LO. Smoke inhalation injury during enclosed-space fires: an update. J Bras Pneumol 2013;39:373–81.
[65] Mlcak RP, Suman OE, Herndon DN. Respiratory management of inhalation injury. Burns 2007;33:2–13.
[66] Head JM. Inhalation injury in burns. Am J Surg 1980;139:508–12.
[67] Carr JA, Phillips BD, Bowling WM. The utility of bronchoscopy after inhalation injury complicated by pneumonia in burn patients: results from the National Burn Repository. J Burn Care Res 2009;30:967–74.