The Voice and Laryngeal Investigation Standards Post-Extubation

by

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LIST OF ABBREVIATIONS

APACHE II	Acute physiology and chronic health evaluation II
BMI	Body mass index
CAPE-V	Consensus auditory perceptual evaluation of voice
ETT	Endotracheal tube
FLIS	Flinders laryngeal injury score
ICC	Intraclass correlation
ICCU	Intensive and critical care unit
NGT	Nasogastric tube
PELLS	Post-extubation laryngeal lesions scale
PPI	Proton pump inhibitor
VAS	Visual analogue scale
VALI	Voice-vibratory assessment with laryngeal imaging
VHI	Voice handicap index
V-RQOL	Voice-related quality of life

THESIS SUMMARY

Background

Laryngeal injury post prolonged intubation in the ICCU population is commonly thought to resolve spontaneously within a short period of time. However, there are some injuries that may persist to affect laryngeal function. These patients are not routinely assessed after prolonged intubation. This study aims to assess whether bedside voice assessments are able to identify laryngeal injuries for early referral to speech pathology or otolaryngology. The secondary aim is to assess the natural history of intubation-related laryngeal injuries prior to discharge from hospital. In order to answer these questions, the Flinders laryngeal injury score (FLIS) was developed to evaluate laryngeal injuries and severity.

Methods

Patients intubated for at least 24 hours and able to follow instructions after extubation were recruited. Those with head and neck injury, unable to phonate and conversion to tracheostomy were excluded. Patients were assessed at 24-48 hours and at 5-7 days after extubation using digital video nasoendoscopy (constant white light and stroboscopy) and voice assessments (s/z ratio, GRBAS and CAPE-V). Endoscopic findings were correlated with voice outcomes. Patient demographics and risk factors were also assessed for correlation with laryngeal and voice outcomes.

FLIS was developed in conjunction with two senior otolaryngologists after reviewing the literature of the common injuries secondary to intubation. It is a point-based scoring system which identifies and grades laryngeal pathology (oedema, erythema, ulceration, granuloma, stenosis and vocal fold mobility). The FLIS inter- and intra-rater reliability was assessed by 3

otolaryngology consultants, 3 otolaryngology trainees, 1 ICCU consultant and 1 speech pathologist after reviewing 20 videos of videolaryngoscopy in the ICCU population who have been intubated for at least 24 hours.

Results

60 patients participated in the study, and 37 patients completed both assessments. The median (IQR) duration of intubation was 60.1 (38.2-136.5) hours. The incidence of laryngeal injury was high (97% and 84% at 24 hours and 5 days post extubation). The most common injury identified was vocal process ulceration or granuloma. There were no statistical correlations between laryngeal examination findings and voice assessments.

The total FLIS score demonstrated moderate inter-rater reliability (ICC=0.59) with an intra-rater percentage agreement of 85% with all raters. When analysed separately, the consultant group had the best inter-rater reliability (ICC=0.91) and intra-rater percentage agreement of 91%. The trainee group also demonstrated good inter-rater reliability (ICC=0.81), with the remaining group scoring an ICC of 0.56.

Conclusion

Laryngeal injury and dysphonia are very common after prolonged intubation and the incidence remained high after 5 days. Bedside voice assessments were not able to determine the laryngeal injuries in this population. It is important to refer early to speech therapy and otolaryngology if these patients have persistent symptoms of dysphagia, dysphonia or dyspnoea after prolonged intubation. The FLIS demonstrated good inter-rater reliability amongst the otolaryngology consultant and trainee group. The FLIS is a simple

system that may be used to quantify the severity of translaryngeal injury and to assess the recovery or response to therapy.

DECLARATION

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; and to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text.

Lucy Huang

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1 INTRODUCTION

1.1 Larynx

Prolonged intubation is a common practice in the intensive care setting in order to protect a patient's airway or assist with oxygenation and ventilation. However, the endotracheal tube (ETT) used for intubation have been described to cause short and long term effects on a patient's larynx and its associated function(Brodsky et al., 2018). This thesis will assess the laryngeal pathology and voice outcome following prolonged intubation in the intensive care setting. In order to understand this, this section will present an overview of the relevant anatomy of the larynx and its function.

1.1.1 Anatomy

The larynx is the organ situated between the pharynx and the trachea. It is developed from the fourth and sixth branchial arches and is positioned between the third and sixth cervical spine(Burdett & Mitchell, 2008). There is a difference in the dimensions of the adult larynx depending on the gender(Jotz et al., 2014). The larynx has several important functions such as protection of the airway, swallowing, respiration and phonation(Fink, Frederickson, Gans, & Huggins, 1976; Thurnher, Moukarbel, Novak, & Gullane, 2007).

1.1.1.1 Cartilages

The larynx is made up of nine cartilages. There are three paired cartilages (arytenoids, corniculates and cuneiforms) and three single cartilages (epiglottis, thyroid and cricoid)(Burdett & Mitchell, 2008).

The structures are discussed from cranial to caudal. The hyoid bone is connected inferiorly to the thyroid cartilage via the thyrohyoid membrane. The epiglottis is a leaf shaped

cartilage situated at the tongue base above the glottis. It attaches to the midline of the thyroid cartilage. The inferior horns of the thyroid cartilage articulate with the cricoid cartilage(Burdett & Mitchell, 2008). The cricoid cartilage is the only complete ring in the larynx. The movement of the cricothyroid joint allows the adjustment of the length of the vocal folds(Hammer, Windisch, Prodinger, Anderhuber, & Friedrich, 2010). The arytenoid cartilages sit above the lamina of the cricoid. The corniculate and cuneiform cartilages lie on top of the arytenoid within the aryepiglottic fold(Tarrazona & Deslauriers, 2007).

1.1.1.2 Ligaments and membranes

The thyrohyoid membrane connects the body and the greater horn of the hyoid to the upper border and superior horns of the thyroid cartilage(Burdett & Mitchell, 2008). The epiglottis is connected to the arytenoid cartilages by the aryepiglottic folds, to the thyroid cartilage by the thyroepiglottic ligaments, to the tongue base by the glossoepiglottic folds and to the hyoid via the hypoepiglottic fold(Tarrazona & Deslauriers, 2007). The aryepiglottic fold is the superior border of the quadrangular membrane, which extends between the edge of the epiglottis and the arytenoid cartilage(Burdett & Mitchell, 2008). The inferior border forms the vestibular fold, also called the false fold. The superior free edge of the cricovocal membrane joins the thyroid cartilage anteriorly and the vocal process posteriorly, forming the vocal fold(Burdett & Mitchell, 2008). Mucus membrane overlies this free edge forming the true vocal fold. The space between the two vocal folds is the rima of the glottis(Sinnatamby, 2013). The cricoid cartilage attaches to the first tracheal ring via the cricotracheal membrane(Sinnatamby, 2013).

1.1.1.3 Muscles

The muscles of the larynx are divided into the extrinsic and intrinsic muscles. The extrinsic laryngeal muscles, also known as the strap muscles, elevate and depress the larynx. This movement of the position of the larynx is especially important during swallowing(Park et al., 2017). The intrinsic muscles of the larynx control the movement of the vocal folds. It is important to note that the posterior cricoarytenoid muscle is the only muscle that abducts the vocal folds to open the glottis(Thurnher et al., 2007). The muscles and their actions are listed in Table 1 and Table 2.

Table 1 Intrinsic muscles of the larynx and their actions

Muscle	Actions
Aryepiglottic muscle	Lower the epiglottis to the laryngeal inlet
Oblique arytenoid	Oppose the arytenoid cartilage
Transverse arytenoid	Medial movement of the arytenoid without rotation, adduction of the vocal folds
Posterior cricoarytenoid	Lateral movement of the arytenoid, abduction of the vocal folds
Lateral cricoarytenoid	Rotate arytenoids medially, adduction of the vocal folds
Cricothyroid	Upward tilt of the cricoid arch, lengthening of the vocal folds
Thyroarytenoid	Shortens the vocal folds
Vocalis	Pulls up the cricovocal membrane, Increase contact area of the vocal folds

Note. From Johnson J. Bailey's Head and Neck Surgery: Otolaryngology. Philadelphia, United states: Wolters Kluwer Health; 2013.

Table 2 Extrinsic muscles of the larynx

Muscle	Actions
Digastric	Elevate the hyoid bone.
Stylohyoid	Elevate the hyoid bone.
Omohyoid	Depress the hyoid bone.
Sternohyoid	Depress the hyoid bone.
Sternothyroid	Depresses the larynx.
Thyrohyoid	Depress the hyoid bone or elevate the larynx.

Note. From Tarrazona V, Deslauriers J. Glottis and Subglottis: A Thoracic Surgeon's Perspective. Thoracic Surgery Clinics. 2007;17(4):561-70.

1.1.1.5 Epithelium

The epiglottis, aryepiglottic folds and vocal folds are lined with stratified squamous epithelium. The rest of the larynx is lined with pseudostratified columnar ciliated epithelium(Thurnher et al., 2007). The layers of the vocal fold are the epithelium, lamina propria (superficial, intermediate and deep), and the vocalis muscle(Gray, 2000). The lamina propria separates the epithelium from the muscle and allows vibration without restriction by the underlying muscle(Thurnher et al., 2007).

1.1.1.6 Innervation

The larynx is supplied by the two branches of the vagus nerve - superior laryngeal nerve and recurrent laryngeal nerve(Thurnher et al., 2007). The external branch of the superior laryngeal nerve supplies the cricothyroid muscle, while the internal branch provides sensory fibres to the larynx above the vocal folds. The anterior branch of the recurrent laryngeal nerve provides motor supply to the remainder of the intrinsic laryngeal muscles and the posterior branch supplies the sensation of the vocal fold and the larynx below it(Sinnatamby, 2013).

1.1.1.7 Vascular supply

The larynx is supplied by the superior, inferior thyroid arteries and the subclavian artery(Burdett & Mitchell, 2008).

1.1.2 Function

The larynx was thought to originate as a sphincter valve to protect the lungs from water. It has evolved to produce many functions as outlined below(Fink et al., 1976).

1.1.2.1 Respiration

The larynx developed from a valve-like structure from lung-fish to support respiration(Negus, 1937). The posterior cricoarytenoid is the only muscle that abducts the vocal folds and is constantly active to allow the passage of air through the larynx(Ludlow, 2015). During inspiration, the upper airway dilates and the posterior cricoarytenoid contracts to rotate the arytenoids backwards, upwards and laterally. During expiration, the other muscles contract to close the vocal fold(Ludlow, 2015). There is little movement of the vocal folds during quiet respiration.

1.1.2.2 Coughing

The sensory receptors in the larynx are stimulated by food particles or mechanical and chemical irritants. The afferent pathway is then conveyed to the brainstem via the superior and recurrent laryngeal nerves, triggering the cough response(Polverino et al., 2012). A deep inhalation is followed by forced exhalation against the adducted vocal folds. Air is compressed through increasing intrathoracic pressure and when the vocal folds are suddenly abducted to allow an expulsion of air at 6-10L per second, a characteristic sound known as coughing occurs, expelling the stimulant(Sandhu & Kuchai, 2013).

1.1.2.3 Deglutition

The lower airway is protected by the upward movement of the larynx, closing it off against the epiglottis during swallowing. The extrinsic laryngeal muscles are active during the pharyngeal phase of swallowing and assist in the hyo-laryngeal elevation. The superior laryngeal nerve provides the afferent pathway which results in the pharyngeal phase of swallowing including hyo-laryngeal elevation and abduction of the ventricular folds and the vocal folds(S. Berke & L. Long, 2009).

1.1.2.4 Increasing intrathoracic and intra-abdominal pressure

Closing the ventricular and vocal folds allow an increase in intrathoracic and intraabdominal pressure by preventing air escape and upward movement of the diaphragm(Ludlow, 2015). This stiffens the trunk which increases the efficiency of the muscles attached to the thorax, especially during lifting(Fink et al., 1976). The intrathoracic pressure rises to 185mmHg during valsalva manoeuvres(Bartlett, 1989). The increase in abdominal pressure assists in micturition or defaecation.

1.1.2.5 Phonation

Phonation plays an important role in socialisation and communication, however, it is the last evolutionary role of the larynx(S. Berke & L. Long, 2009). Vocal folds are held in the midline position at specific tension and as expired air escapes between the opposed vocal folds it produces oscillations which allows phonation. The sound is then modified through fine control of the laryngeal muscles, and as it passes through the pharynx, oral cavity and nasal cavity, producing the spoken language(S. Berke & L. Long, 2009).

1.2 Laryngeal Injury

The causes of laryngeal injuries include trauma, surgery, inhalation and intubation(AAO-HNS, 2012). Injuries to the larynx may result in a loss function, namely respiration, deglutition, airway protection and phonation(Kahue & Gelbard, 2017). This section will include a brief mention of each of the mechanism of laryngeal injury followed by an in-depth discussion of the pathophysiology, types of injury and risk factors for injuries secondary to intubation.

1.2.1 Trauma

Trauma to the larynx have been further divided into blunt or penetrating trauma. Blunt forces are often sustained from motor vehicle accidents, strangulation or clothesline injury. It may cause endolaryngeal mucosal tears, oedema, haematoma, fractures of the cartilages or cricotracheal separation(Johnson, 2013; Schaefer, 2014). Penetrating trauma are usually caused by knives or gunshot and may injure deep neck structures or directly damage the larynx(Johnson, 2013).

1.2.2 Surgery

Surgery to the larynx may result in structural complications such as strictures, stenosis, fistula or functional complications such as dysphonia and dysphagia(Kreuzer et al., 2000; Sato Hermann et al., 2012). However, the most common cause of laryngeal pathology following surgery is secondary to recurrent laryngeal nerve injury. The recurrent laryngeal nerve travels a long and convoluted path through the thorax on the left side and the neck on the right side(Koutelidakis, Doundis, Chatzimavroudis, & Makris, 2015). It serves an important function in supplying the majority of the muscles that control the larynx. Dividing or injuring it may temporarily or permanently affect its function. The contralateral vocal fold

can sometimes compensate when the injury is unilateral. It is a recognised surgical complication following thyroidectomy, parathyroidectomy, oesophagectomy, carotid endarterectomy and thoracic surgery(Hulscher, van Sandick, Devriese, van Lanschot, & Obertop, 1999; Prasad, Fakhoury, Helou, Lawson, & Remacle, 2017; Steurer et al., 2002).

1.2.3 Inhalation

Inhalation injury to the larynx can be due to steam, hot gases, soot or chemicals. The larynx is prone to inhalation injury in patients with burns as it is the inlet to the airway. The resultant swelling affects the supraglottis significantly which has the potential to cause airway obstruction. The glottis and subglottis have a lower tendency for swelling as the lamina propria is attached more firmly to the underlying tissue, but when injured these structures are more likely to heal with scarring and stenosis(Reid & Ha, 2018).

1.2.4 Intubation

An ETT exerts pressure on the posterior larynx due to the supine position of the patient, the natural cervical lordosis, and the V-shape of the glottis(Azoulay et al., 2017; Gordin et al., 2010; Van der Meer, Ferreira, & Loock, 2010). Canine models have found that the tube exerts pressure up to 400mmHg in the posterolateral area of the larynx which exceeds capillary pressure and causes local ischemia of the mucosa resulting in congestion and oedema(B. Benjamin, 1993; Weymuller, Bishop, Fink, Hibbard, & Spelman, 1983). Persistent tissue ischemia leads to ulceration of the tissue starting at the epithelium but can progress on through the basement membrane and eventually to the cartilage. Superficial injury starts to occur as early as 3 hours of intubation(Donnelly, 1969). Once the insult is removed, re-epithelisation occurs with the formation of granulation tissue as chronic inflammatory cells infiltrate the site(Harrison & Tonkin, 1968). Injury involving the perichondrium or cartilage

can result in fibrosis which may lead to laryngeal stenosis(Gordin et al., 2010). In patients intubated for three or more days, the reported incidence of laryngeal injury is as high as 97%(Santos, Afrassiabi, & Weymuller, 1994).

Significant oedema post extubation can cause airway obstruction resulting in post extubation stridor and respiratory distress requiring steroids, nebulisers and potential re-intubation. This usually presents within minutes to hours after extubation(Wittekamp, van Mook, Tjan, Zwaveling, & Bergmans, 2009). Visualisation of the larynx prior to extubation is difficult as the ETT obstructs the view. The cuff leak test has recently gained attention to identify patients who have significant oedema and may fail extubation(Antonaglia et al., 2010). A leak from the closed ventilatory system when the balloon cuff of the ETT is deflated indicates a positive cuff-leak test, suggesting the laryngeal oedema is not significant enough to cause airway obstruction once the patient has been extubated(Antonaglia et al., 2010).

Granulomas most commonly occur over the vocal processes. Trauma as a result of the ETT pressure causes a reactive inflammatory process with polymorphonuclear cells and lymphocyte infiltration of the mucosa and resultant granuloma formation(Rimoli, Martins, Cataneo, Imamura, & Cataneo, 2018). Granulomas caused by intubation largely resolve spontaneously with a low recurrence rate(Lee, Yoon, Lee, & Lim, 2018; Rimoli et al., 2018). However, persistent granuloma may warrant treatment. These patients generally present with ongoing hoarseness and a sensation of globus(Lee et al., 2018). Treatment options include voice therapy, proton pump inhibitor, botulinum toxin injection, zinc sulphate, mitomycin C and steroids(Rimoli et al., 2018). If the healing process results in permanent tissue loss over the medial arytenoids, it may result in a persistent breathy voice with

reduced efficiency when speaking, termed postintubation phonatory insufficiency(Bastian & Richardson, 2001).

Adhesions may form during the healing process if two ulcers or granulomas come in contact(Carrat et al., 2000). The deposition of fibrous tissue may result in strictures or stenosis, forming some of the most severe complications of intubation – interarytenoid bridge, posterior glottic stenosis, subglottic stenosis or tracheal stenosis(Harrison & Tonkin, 1968). Interarytenoid adhesions are often misdiagnosed as vocal fold immobility(Howard, Shiba, Pesce, & Chhetri, 2015). The two case reports by Howard et al demonstrate that these lesions develop weeks after extubation and present as persistent or worsening dyspnoea due to partial airway obstruction(Howard et al., 2015). The delayed response is due to scar contracture, pulling the arytenoids even closer together(Carrat et al., 2000). Interarytenoid adhesions may then go on to develop early glottic stenosis(Howard et al., 2015) and 14% of patients intubated for over 10 days are at risk of developing posterior glottic stenosis(Whited, 1983). Stenosis of the trachea arises from the pressure of the ETT cuff on the tracheal mucosa. However the incidence has decreased after the introduction of low-pressure high-volume cuffs(Gordin et al., 2010) as cuff pressure under 30mmHg is unlikely to cause long term tracheal injury(Bishop, 1989).

Vocal fold paresis from intubation is thought likely secondary to neuropraxia from compression of the anterior branch of the recurrent laryngeal nerve by the cuff at the subglottis level where it enters between the cricoid and thyroid cartilage(Weymuller, 1992). Van der Meer et al demonstrated reduced or absent vocal fold mobility in 12.5% patients who have been intubated for a median duration of 40 hours(Van der Meer et al., 2010). Other studies described between 20 - 41% of their patients have a degree of vocal fold

immobility after a mean intubation duration of 9.1 days(Brodsky et al., 2018; Colton House, Noordzij, Murgia, & Langmore, 2011; Santos et al., 1994). Santos et al found that vocal fold immobility correlated significantly with the size of the ETT whereas Colton House found that there is a trend of worsening vocal fold immobility with larger ETT but no significant difference(Colton House et al., 2011; Santos et al., 1994). Impaired vocal fold mobility along with laryngeal sensory denervation and reduced gag reflex, these patients may experience recurrent aspiration resulting in pneumonitis or pneumonia(Colice, Stukel, & Dain, 1989).

Post-intubation laryngeal injury is common, but most injuries resolve spontaneously with time. At 24 hours post-extubation, 79% of patients had subjective voice improvement compared to 4 hours post-extubation and the majority of injuries resolved within 1 month(Colice et al., 1989; Van der Meer et al., 2010). However, the long-term sequelae of persistent laryngeal injury can have a significant impact on the patient's quality of life(Whited, 1984). This may be evident soon after extubation as dysphonia or dysphagia or it may manifest weeks to months later as persistent dyspnoea or dysphonia. These complications are often not appreciated by those who performed the endotracheal intubation(Bastian & Richardson, 2001; Beckford, Mayo, Wilkinson, & Tierney, 1990). Intervention for laryngeal injury is dependent on the severity of patient symptoms and can require permanent tracheostomy, stenting, and multiple endoscopic or open surgeries. These treatments themselves can compromise other functions of the larynx such as swallowing and voice and may require long term follow up(Lahav, Shoffel-Havakuk, & Halperin, 2014).

1.2.4.1 Risk factors of laryngeal injury

Patients with certain risk factors are more likely to develop oedema and injury to the larynx. The female gender is more likely to sustain injury due to thinner mucoperichondrium(Bain, 1972; Harrison & Tonkin, 1968). Females also have a smaller glottic opening, with an average length of 17mm compared to 23mm in males, resulting in a larger tube to trachea ratio(Bishop, Weymuller, & Fink, 1984). Height is another factor that correlates with laryngeal and sub-cricoid tracheal diameter(Coordes et al., 2011). After considering the need for bronchoscopic procedures and ensuring adequate ventilation, the smallest possible ETT size should be used to minimise laryngeal trauma(Wittekamp et al., 2009).

The pathophysiology of laryngeal injury post-intubation is secondary to ischaemia resulting from the pressure exerted by the tube. The duration of intubation correlates with the severity of laryngeal injury in the acute setting and the likelihood of developing long term laryngeal complications secondary to intubation(Brodsky et al., 2018; Rangachari, I, V, & Kkrishna, 2006; Santos et al., 1994; Whited, 1984).

The skill level of the operator, number of attempts and the environment under which endotracheal intubation is performed are also associated with a significant difference in the presence of laryngeal damage(Stauffer, Olson, & Petty, 1981). The laryngoscope blade and the ETT itself may traumatise any site from the lips to the carina(Weymuller, 1992). There have been reports where traumatic intubations have avulsed the vocal fold or dislocated the arytenoids(Stauffer et al., 1981; Vyshnavi & Kotekar, 2013). The use of muscle relaxant has increased the ease of intubation and reduced laryngeal injury(Harrison & Tonkin, 1968; Mencke et al., 2003). While the initial injury from a traumatic intubation may be small, the

persistent pressure of the cuff during prolonged intubation can prevent healing leading to significant long term sequalae.

Patient anatomy and existing co-morbidities are other risk factors for laryngeal trauma associated with intubation related laryngeal injury(Böttcher et al., 2014; Weymuller, 1992). Obesity, limited neck movement and distorted anatomy are all predictors of a difficult airway. Bottcher et al demonstrated the mandibular protrusion test class B or C and the upper lip bite test (class II or III) were associated with higher causes of laryngeal injury in the acute setting. Patient comorbidities, including diabetes and malnutrition, may also contribute to the worsening of an existing injury due to vascular insufficiency, poor healing and susceptibility to infection(Gaynor & Greenberg, 1985). Gaynor et al found that those with insulin dependent diabetes may be at risk of significant airway injuries when intubated for four days or more(Gaynor & Greenberg, 1985).

The presence of a nasogastric tube (NGT) has been demonstrated to increase the amount of laryngeal injury after prolonged intubation(Santos et al., 1994). The ischaemia of the post-cricoid region is worsened by the compression exerted from the ETT and the NGT(Brousseau & Kost, 2006). The presence of NGT also impairs the function of the lower oesophageal sphincter which along with impaired neurological function and the supine position, place these patients at increased risk of gastroesophageal reflux. The gastric acid then exacerbates the underlying injury caused by the ETT(Gaynor, 1988; Wain, 2009). Proton pump inhibitors (PPI) are important in those with an NGT when intubated and those with a history of gastroesophageal reflux disease.

Movement of the ETT and inflated cuff secondary to respiration, neck position, suctioning and intrinsic laryngeal motor activity result in ongoing shearing against the laryngeal and

tracheal mucosa(Feder, 1983). This adds further insult and abrasion to the oedematous and traumatised tissue(Bishop et al., 1984; Colice et al., 1989; Conrardy, Goodman, Lainge, & Singer, 1976). A study of chest radiographs in intubated patients demonstrated an average movement of ETT of 3.8cm between flexion and extension of the neck(Conrardy et al., 1976).

Laryngeal pathology as a result of intubation may have significant impact on a patient's wellbeing and their quality of life(Brodsky et al., 2018; Mendels et al., 2012). Treatment requiring repeated operative procedures and outpatient follow up will also increase the burden on the health system. While prolonged intubation is often a life-saving and necessary treatment, it is important to be aware of the above risk factors in order to optimise them.

1.3 Assessment Methods

1.3.1 Overview

In a systematic review of injuries in short term anaesthesia of less than 5 hours, assessment methods of the larynx post intubation included flexible laryngoscopy, videostroboscopy, subjective interviews, acoustic analysis and perceptual analysis for voice assessments(Mendels et al., 2012). In another systematic review assessing post-extubation laryngeal injuries in the ICCU setting, methods of examination included laryngeal mirror, rigid endoscopy, flexible laryngoscopy and flexible bronchoscopy(Brodsky et al., 2018).

Phonation is one of the many functions of the larynx that allows for easy bedside assessment and is also one that may significantly impact on a patient's quality of life. Documented assessment tools of the voice post-extubation included acoustic analysis, hoarseness severity grading and the s/z ratio(Beckford et al., 1990; Böttcher et al., 2014; Chen et al., 2018; Hamdan, Sibai, Rameh, & Kanazeh, 2007; Paulauskiene, Lesinskas, & Petrulionis, 2013; Van der Meer et al., 2010). However, recently auditory perceptual evaluations of a patient's voice have been determined as the gold standard for assessments of the voice but have not yet been used to assess the voice in the post-extubation population. Managing a patient's laryngeal injury should be individualised as every patient has different expectations and needs. Therefore, it is also important to obtain a patient's perspective of the impact of the injury. Patient reported outcome measures are useful tools to gather such information. Validated tools such as voice handicap index (VHI) and voice-related quality of life (V-RQOL) are comprehensive and will allow ease of comparison between studies(Mendels et al., 2012). Various studies also report various tools that lack consistency and validity, often in the form of an interview to identify the presence and

severity of hoarseness and dysphagia(Hamdan et al., 2007; Zimmert, Zwirner, Kruse, & Braun, 1999).

1.3.2 Laryngoscopy

Methods to visualise the larynx are divided into direct and indirect laryngoscopy. Direct laryngoscopy is most commonly used to visualise the larynx during intubation or to expose the glottis during upper airway surgery(Bruce Benjamin & Lindholm, 2003). It requires the patient to be under deep sedation to avoid the gag reflex and laryngospasm(Pani & Kumar Rath, 2009). Historically, indirect laryngoscopy involves the use of mirrors and rigid endoscopes(Brodsky et al., 2018). With the improvement in optical quality and image resolution, flexible laryngoscopy has largely replaced the use of mirror and rigid instruments to examine the larynx(Rosen et al., 2009). Other forms of indirect laryngoscopy include videolaryngoscopy, with a distal tip camera fitted onto a direct laryngoscope blade, to assist in difficult intubations.

Flexible transnasal laryngoscopy is the investigation of choice in otolaryngology for visualising and diagnosing laryngeal and pharyngeal pathology. Flexible laryngoscopy may utilise fibreoptic bundles for both viewing and illumination, or integrate video chips at the distal tip to allow viewing on a screen. Distal chip laryngoscopy has been demonstrated to have identical diagnostic accuracy but superior image quality to that of fibreoptic laryngoscopy(Plaat, van der Laan, Wedman, Halmos, & Dikkers, 2014). It can be performed at the bedside with or without topical anaesthetic spray and allows for dynamic assessment of the larynx during respiration and phonation. It can be used in combination with stroboscopy, high speed videoendoscopy, narrow band imaging or to assist in intubation(Laeeq et al., 2010).

There are scoring systems in the literature to assess laryngeal pathology but none of them have been validated or widely used for injuries secondary to endotracheal intubation. Below are the scoring or grading systems in the literature along with their strengths and weaknesses.

Table 3 Schaefer classification system

Groups	Severity of injury in ascending order
Group 1	Minor endolaryngeal haematomas or lacerations without detectable fractures.
Group 2	More severe oedema, haematoma, minor mucosal disruption without exposed cartilage, or nondisplaced fractures.
Group 3	Massive oedema, large mucosal lacerations, exposed cartilage, displaced fractures or vocal cord immobility.
Group 4	Same as group 3, but more severe, with disruption of anterior larynx, unstable fractures, two or more fracture lines, or severe mucosal injuries.
Group 5	Complete laryngotracheal separation.

Note. From Schaefer SD. The acute management of external laryngeal trauma. A 27-year experience. Arch Otolaryngol Head Neck Surg. 1992;118(6):598-604.

Schaefer described this classification system (Table 3) for external laryngeal injury caused by blunt or penetrating mechanisms. As the mechanism of injury is very different to that of translaryngeal causes, it is difficult to apply the same classification system to assess the larynx post-extubation.

Table 4 Grading system for transnasal flexible laryngoscopy

Classification		Glottis	Arytenoids	Epiglottis
Grade 1		100% visible	100% visible	100% visible
Grade 2	2a	50% <		
	2b	50% >		
Grade 3		Not visible		
Grade 4			Not visible	

Note. From Tasli H, Karakoc O, Birkent H. A Grading System for Transnasal Flexible Laryngoscopy. J Voice. 2018.

This classification system (Table 4) describes the indirect view of the larynx, much like the Cormack-Lehane classification system, but in an awake patient in the sniffing position using a flexible transnasal laryngoscopy. It is used to describe the view obtained and not the pathology of the larynx. The purpose of the system is for communication of the view during transnasal flexible laryngoscopy and allow precaution to be taken before general anaesthesia in case of a difficult airway.

Table 5 Laryngeal injury graded by visual examination

Severity	Examination findings
None	No damage.
Mild	Presence of erythema and mucosal ulcerations but no reduction in laryngeal orifice size during inspiration.
Moderate	Presence of erythema and mucosal ulcerations and mucosal swelling reducing laryngeal orifice area during inspiration by less than half.
Severe	Presence of erythema, mucosal ulcerations and mucosal swelling reducing laryngeal orifice area during inspiration by more than 50 percent or laryngospasm

Note. From Colice GL, Stukel TA, Dain B. Laryngeal complications of prolonged intubation. Chest. 1989;96(4):877-84.

Colice et al. uses this severity scoring system (Table 5) to describe laryngeal damage post prolonged intubation. It is an easy system to apply as the increase in severity is dependent on one factor, being the patency of the laryngeal orifice. However, it does not describe other injuries, such as granuloma, vocal fold paresis or the severity of erythema and ulcerations.

Table 6 Description of the larynx in the post-mortem

Grade	Examination findings
Grade I	Hyperaemia, oedema, discolouration but no definite ulceration or necrosis
Grade II	Ulceration or necrosis of mucous membrane with involvement of subepithelial layers but not reaching to the cartilage
Grade III	Deep ulceration or necrosis penetrating the mucous membrane down to the cartilage

Note. From Eckerbom B, Lindholm CE, Alexopoulos C. Airway lesions caused by prolonged intubation with standard and with anatomically shaped tracheal tubes. A post-mortem study. Acta Anaesthesiol Scand. 1986;30(5):366-73.

This three-grade scale (Table 6) used by Eckerbom et al was used to describe larynx in post-mortem examinations after being intubated using two different types of ETT. The scale increases with the presence and depth of ulceration or necrosis of the mucous membrane. This scale does not take into consideration other pathologies that can be caused by endotracheal intubation.

Table 7 Lesions due to endotracheal intubation or laryngeal mask insertion

Type		Description
I		Vocal cord lesions impairing vibratory movement
	A	Epithelial 1. Inflammation 2. Pigmentation
	B	Lamina Propria 1. Reinke space oedema 2. Hematoma 3. Acquired scar/ laceration
	C	Arytenoid granuloma
II		Movement disorders of vocal cords
	A	Neurologic: paralysis/ paresis of laryngeal nerve(s)
	B	Cricoarytenoid joint disorders (arytenoid luxation)

Note. From Mendels EJ, Brunings JW, Hamaekers AE, Stokroos RJ, Kremer B, Baijens LW. Adverse laryngeal effects following short-term general anesthesia: a systematic review. Arch Otolaryngol Head Neck Surg. 2012;138(3):257-64.

A systematic review done by Mendels et al determining the type of laryngeal injury after short term (<5 hours) general anaesthesia resulted in a proposal of a classification system for injuries from endotracheal intubation or laryngeal mask insertion (Table 7) in order to have a uniform outcome measure for comparison in future research. This classification is split into I and II with I being vocal fold lesions and II being movement disorders. There is little explanation on how to use this classification system if multiple pathologies are present. Movement disorder is also divided into neurological and mechanical causes which may be difficult to discern at times with flexible transnasal laryngoscopy. This also confuses the classification system which is based upon visualisation of the type of injury sustained rather than the underlying mechanism of injury. This system also does not include injuries that may present after longer periods of intubation such as ulcerations and adhesions.

Table 8 Post-extubation laryngeal lesions scale

Degree	Lesions
0	No injury or hyperaemia
1 mild oedema	Supraglottic oedema
2 moderate oedema	Both supraglottic and glottic oedema and/or in the presence of vocal process granuloma, vocal cord ulcers and/or arytenoid luxation
3 severe oedema	More intense supraglottic and glottic oedema with or without haematomas
4 total oedema	Involvement of subglottic lesions

Note. From Antonaglia V, Vergolini A, Pascotto S, Bonini P, Renco M, Peratoner A, et al. Cuff-leak test predicts the severity of postextubation acute laryngeal lesions: a preliminary study. Eur J Anaesthesiology. 2010;27(6):534-41.

This scale was described by Antonaglia et al in patients who have been intubated for over 72 hours (Table 8). With increasing value in the degree of scoring, one would usually assume increase in severity of the appearance or natural history of pathology. However, large vocal process granuloma obstructing the airway (degree 2) may be of more severe consequences than a mild subglottic lesion (degree 4). Total oedema would suggest complete airway obstruction which would make visualisation of the subglottic space difficult to identify lesions.

Table 9 Fibreoptic laryngoscopy evaluation sheet

Points	0	1	2	3
Arytenoid oedema	none	Mild	Moderate	severe
Arytenoid oedema	None	Mild	Moderate	severe
Interarytenoid oedema	None	Mild	Moderate	severe
Vocal fold oedema	None	Mild	Moderate	severe
Vocal fold erythema	None	Mild	Moderate	severe
Right vocal process ulceration	None	Mild	Moderate	severe
Left vocal process ulceration	None	Mild	Moderate	severe
Right vocal process granulation tissue	None	Small	Medium	Large
Left vocal process granulation tissue	None	Small	Medium	Large
Right vocal fold immobility	None	Mild	Moderate	Severe/fixed
Left vocal fold immobility	None	Mild	Moderate	Severe/fixed
Subglottic oedema/narrowing	None	Mild	Moderate	severe

Note. From Colton House J, Noordzij JP, Murgia B, Langmore S. Laryngeal injury from prolonged intubation: a prospective analysis of contributing factors. The Laryngoscope. 2011;121(3):596.

Colton House assessed patients within 24 hours post-extubation and assigned an overall score for each patient in their study. This evaluation system (Table 9) covers most of the injuries but is largely limited to the glottis with only one parameter assessing the subglottis. It does not include the supraglottis which may be potentially significant. There is no division into right and left for the arytenoid or vocal fold oedema and erythema. The same number of points would be given for a unilateral ulceration, granulation tissue and immobility as it would be for bilateral oedema or erythema.

Each of the scoring system described above have deficiencies with a potential for improvement. There is no comprehensive system to describe laryngeal pathology following translaryngeal injury. There is a need to develop one to assess the pathology following ETT extubation for the purpose of research and communication between clinicians in clinical practice.

1.3.3 Videostroboscopy

The human vocal folds vibrate up to 1000Hz which is much faster than what human eyes can visualise. Stroboscopy uses synchronised light to capture successive vocal fold movement at different phases to create a slow-motion estimate of vocal fold movement(Powell et al., 2016). It is regarded as the gold standard for evaluation of vocal fold vibratory function(Gora, Yavin, Elad, Wolf, & Primov-Fever, 2016). It requires an acoustic signal or electroglottographic signal through a contact microphone to allow quasi-synchronisation. However, the literature reports 17- 63% of patients fail to synchronise to the fundamental frequency due to perturbation in those with moderate to severe dysphonia(Powell et al., 2016).

The validated stroboscopy Voice-Vibratory Assessment with Laryngeal Imaging (VALI) rating form is used for the assessment of both high speed videoendoscopy and stroboscopy (Appendix 3). The following parameters were assessed: glottal closure, amplitude, mucosal wave, non-vibrating portion, supraglottic activity, vertical level of vocal fold, regularity, free edge contour, phase closure and phase symmetry(Poburka, Patel, & Bless, 2017). This is an updated version which has improved from the originally described Stroboscopy Evaluation Rating Form(Poburka, 1999).

1.3.4 High speed videoendoscopy

Most recently, high speed videoendoscopy has been developed with xenon light technology, utilising high frame rates to capture vocal fold vibration(Rosen et al., 2009). It is able to capture images at a frame rate faster than the eye can process. It is then played back at a slower-rate in order for us to identify subtle vocal fold abnormalities(Deliyski, Hillman, & Mehta, 2015). High speech videoendoscopy is valuable in assessing vocal folds that are aperiodic or when stroboscopy fail to synchronise(Zacharias, Deliyski, & Gerlach, 2018). However, this technology is expensive and not yet widely used.

1.3.5 Acoustic analysis

Acoustic analysis has often been performed to correlate with vocal pathology. The parameters assessed are usually fundamental frequency, perturbation and harmonics to noise ratio(Beckford et al., 1990). Beckford et al performed acoustic analysis on patients who received short term intubation for gynaecological procedures and demonstrated some reduction in fundamental frequency (F_0) and an increase in frequency perturbation post-extubation. It was not statistically different to the control group, but this could be due to the small sample size of 10 patients. A larger study consisting of 35 patients by Hadman et al also did not show a significant change in fundamental frequency or other acoustic parameters but did demonstrate a significant change in habitual pitch and a decrease in maximum phonation time(Hamdan et al., 2007). This is consistent with the largest study performed to date by Paulauskiene et al with a sample size of 108 patients(Paulauskiene et al., 2013). Both these studies were done in patients who have were intubated for short durations for general anaesthesia. The results cannot be extrapolated to those who were

intubated for more than 24 hours as the pathophysiology of injury is different for patients with short-term and long-term intubations.

1.3.6 Auditory-perceptual rating

Auditory-perceptual assessment of the voice is considered the gold standard for assessing voice disorders(Nemr et al., 2012). The two commonly used evaluation tools in research and clinical assessments are the GRBAS scale and the Consensus Auditory Perceptual Evaluation – Voice (CAPE-V). The GRBAS scale, developed by the Japan Society of Logopedics and Phoniatrics, assesses the overall grade, roughness, breathiness, asthenia and strain on any type of speech sample(Omori, 2011). The rater scores each of the parameters with 0 (normal), 1 (mild), 2 (moderate), 3 (severe). CAPE-V was only recently described by the American Speech-Language-Hearing Association in 2002 and requires a pre-determined set of vowels, sentences and conversational speech to be recorded (Appendix 2). A different laryngeal behaviour is elicited for each sentence asked of the patient (Table 10)(Association, 2002). It assesses the parameters from the GRBAS scale, with additional parameters such as pitch, loudness, resonance and the option to comment on other features such as diplophonia, fry, falsetto, asthenia, aphonia, pitch instability, tremor, wet/ gurgly, pitch breaks, phonation breaks, voice arrest(Association, 2002). Each parameter in CAPE-V is rated on a visual analogue scale (VAS) of 100mm and whether the rated parameter is consistent or intermittent. When comparing the two evaluation tools, CAPE-V is more sensitive and has higher inter-rater reliability than GRBAS, however, GRABS is easier to learn and apply as it only has 5 parameters(Karnell et al., 2007). The grading outcomes are also consistent when using the two different scoring systems on the same voice samples(Karnell et al., 2007).

Table 10 CAPE-V sentences and elicited behaviour

CAPE-V sentences	Elicited behaviour
The blue spot is on the key again.	Requires production of every vowel in English language.
How hard did he hit him?	Emphasises easy onset with the /h/.
We were away a year ago.	All the sounds in this sentence are voiced.
We eat eggs every Easter.	This sentence elicits hard glottal attack.
My mama makes lemon muffins.	Nasal sounds are incorporated.
Peter will keep at the peak.	Weighted with plosive sounds.

1.3.7 S/Z ratio

S/Z ratio is an easy, non-invasive test assessing vocal function. Glottal vibration is required to pronounce the /z/ sound, whereas /s/ does not(Eckel & Boone, 1981). Boone hypothesised a patient with normal vocal folds should have an s/z ratio of 1(Eckel & Boone, 1981). Eckel and Boone theorised that those with vocal fold pathology would have a decrease in glottal resistance when attempting to phonate /z/, shortening phonation time, resulting in an s/z ratio of more than 1.4(Eckel & Boone, 1981).

However the s/z ratio for healthy and pathological vocal folds overlap significantly in the literature(Gelfer & Pazera, 2006). In 40 healthy participants with controlled the intensity, the s/z ratio ranged between 0.48 – 1.50.

Van der Meer et al assessed 32 patients who were intubated for a mean duration of 65 hours at 4 hours and 24 hours post extubation with flexible laryngoscopy and the s/z ratio. 91% patients had oedema, 87% had vocal process injury, 12% have vocal fold palsy or paresis. 40% of their patients had a s/z ratio greater than 1.4. They found the s/z ratio has a 100% sensitivity and 74% specificity at diagnosing vocal fold movement disorder when used within 6 hours of extubation. A second endoscopic laryngoscopy was not repeated, however, 19% of patients had persistent s/z ratio above 1.4 at 24 hours. Amongst these patients were 4 who were initially diagnosed with reduced vocal fold mobility. As most pathologies have resolved by 24 hours with s/z ratio improvement, their recommendation is for otolaryngology referral for visualisation of the vocal fold if s/z ratio continues to be abnormal at 24 hours(Van der Meer et al., 2010).

1.3.8 Patient reported outcome measures

The two most commonly used patient surveys are the VHI and the V-RQOL questionnaires. These outcome measures are able to evaluate the patient's perspective of the functional impact and allow clinicians to tailor the treatment to maximise benefits(Reghunathan & Bryson, 2019). However, there are studies that demonstrate there is no correlation between VHI and acoustic or auditory-perceptual measures(Gillespie, Gooding, Rosen, & Gartner-Schmidt, 2014; Lopes et al., 2017). Patient reported outcome measures are however not suitable to be used in the critically ill population as they often do not use their voice enough at the time of the assessment for the full impact of dysphonia to be recognised.

1.4 Clinical literature reviewing laryngeal and voice outcomes following extubation

There are limited studies in the literature assessing both the voice and laryngeal outcomes following extubation. Half of the studies assessed patients after short term intubation for a surgical operation and the other half assessed patients who have been intubated beyond the duration of an operation. There is one study by Bp et al which correlated voice outcomes with vocal fold palsies specifically in post-thyroidectomy patients(Bp, S, Rr, St, & V, 2014). While patients in Bp's study were intubated for the operation, the focus of the study is on the injury to the recurrent laryngeal nerve as a complication of thyroidectomy. However, as this study correlated the voice outcome with flexible laryngoscopy findings, we've included it in this review. Summaries of the studies are presented in Table 11 and 12.

Table 11 Type of assessment for larynx and voice after short-term intubation for an operation

Authors	Year	Number of patients	Mean time of intubation	Type of laryngeal assessment	Type of voice assessment
Beckford et al.	1990	10	66 minutes	Flexible laryngoscopy, videostroboscopy	Fundamental frequency, frequency perturbation, electroglottography, subjective speech analysis
Bottcher et al	2014	53	97.8 (+/- 37.0) minutes	Videostroboscopy	Hoarseness severity grading
Sah et al	2014	42	Not documented	Flexible laryngoscopy	Maximum phonation time, phonatory frequency range

Beckford et al were the first to assess the vocal function, electroglottography (EGG), laryngoscopy and stroboscopy post-intubation. They reported the outcome in a small sample size (n=10) after short term intubation (mean [SD] time of 66[19.7] minutes). They had a further 10 patients in the control group who were not anaesthetised, nor did they have surgery. Voice, EGG, laryngoscopy and stroboscopy were performed before and after the operation or at an 8-hour interval for the control group. For voice analysis, they found a significant increase in frequency perturbation in the intubated group. EGG revealed a difference in width of the peak and altered wave form symmetry compared to pre-op EGG, however, no statistically significant changes were noted. Laryngoscopy revealed one vocal fold haematoma, and no further abnormalities. Videostroboscopy also revealed largely normal vocal fold mucosal function with some decrease in mucosal wave propagation and amplitude. Correlation was not performed between the voice and the endoscopic or stroboscopy findings(Beckford et al., 1990).

Bottcher et al performed a study to determine anatomical parameters that may predict a higher risk of laryngeal injury after an elective short duration endotracheal intubation(Böttcher et al., 2014). The anatomical parameters assessed were the Cormack-Lehane classification, modified Friedman's tonsil size, inter-incisor gap, modified Mallampati index, mandibular protrusion test, neck circumference, posterior pillar webbing, upper-lip-bite test and thyromental distance. Pre and post-operative videostroboscopy and Friedman et al hoarseness severity grading was performed. The endoscopic and stroboscopic findings were scored using the grading system Eckerbom et al developed for a post-mortem study(Eckerbom, Lindholm, & Alexopoulos, 1986). Positive findings from the study were the mandibular protrusion test correlated with the post-operative Eckerbom grade and the

upper-lip-bite test correlated to a decrease in post-operative vocal fold oscillation. Again, the hoarseness severity grading was not correlated with the endoscopic or stroboscopic findings(Böttcher et al., 2014).

Bp et al conducted a study in Nepal to determine whether simple voice assessments such as a reduction in maximum phonation time or a change in phonation frequency can diagnose patients with vocal fold pathology, specifically reduced mobility, after thyroidectomy. Patients were assessed pre-operatively and at 5^{th} and 30^{th} day post-operatively(Bp et al., 2014). The study demonstrated objective voice changes could diagnose vocal fold palsy with a sensitivity and specificity of 80% and 81% at post-operative day 5 and 85% and 85% at post-operative day 30. They reported there were confounding effects such as intubation, psychogenic dysphonia and strap muscle injuries that may also cause voice changes. Therefore, they have concluded that simple voice assessments cannot predict post-operative vocal fold palsy. Injury to the recurrent laryngeal nerve is a well-documented complication of thyroidectomy and if simple voice assessments are able to raise awareness regarding reduced or absent vocal fold mobility, it would an extremely useful and non-invasive assessment during the follow up period. However, the negative results from this study may be due to the simplicity of the two objective voice assessments that were performed.

Table 12 Type of assessment after prolonged intubation in an ICCU setting

Authors	Year	Number of patients	Duration of intubation	Type of laryngeal assessment	Type of voice assessment
Bastian et al	2001	138	Not specified	Flexible endoscopy	Vocal capability battery – projected voice, maximum phonation time, upper vocal range
Van der Meer et al.	2010	32	Median 40 hours	Flexible endoscopy	Clinician-administered speech therapy questionnaire, S/Z ratio

Bastian et al described post-intubation phonatory insufficiency upon a previous history of intubation(Bastian & Richardson, 2001). In their study they described most persistent injuries are a result of prolonged intubation. However, they did not specify the duration of intubation or the duration since extubation in their patient population. The presentation of the results were entirely descriptive and statistical tests were not employed. In this study, they described a patient cohort who had a history of intubation and were diagnosed with posterior commissure defect or reduced arytenoid mobility. Their voice complaints are generally of breathiness, increased effort, loss of projection, reduced efficiency and loss of high pitch.

Van der Meer et al is the only study to date that has correlated voice outcome using the s/z ratio with the endoscopic view of the larynx(Van der Meer et al., 2010). 32 patients were included in the study and were all intubated for at least 12 hours. Patients were examined with flexible laryngoscopy within 6 hours post-extubation and voice assessed using the s/z ratio within 6 hours and again at 24 hours. While the majority of patients had laryngeal pathology – 91% had oedema, 87% had vocal process pathology and 12% had reduced vocal fold mobility – only 40% of the patients had abnormal s/z ratio greater. Of those with abnormal s/z ratio, 19% had persistently elevated s/z ratio at 24 hours post-extubation which included all four patients with reduced vocal fold mobility. Therefore the recommendation is to refer for otolaryngology assessment in patients with s/z ratio greater than 1.4 at 24 hours after extubation(Van der Meer et al., 2010).

1.5 Justification for further studies

Since the description of fibroscope by Hopkins(Hopkins & Kapany, 1954), rapid advances in optic and imaging technology have improved the quality of the images and accessibility of the flexible laryngoscope in daily practice(Paul, Rafii, Achlatis, Amin, & Branski, 2012). It is considered minimally invasive and generally well tolerated in an awake patient. However, the reported risks in the literature for flexible laryngoscopy included epistaxis, aspiration, vomiting, laceration, ecchymosis, perforation and cross-contamination(Paul et al., 2012). While generally well tolerated, a study of 250 patient's perspective on fibreoptic laryngoscopy reported a gagging sensation in 25%, dyspnoea and discomfort in 10%. Patients who have been intubated for a prolonged period while critically ill may be more apprehensive with a lower tolerance for flexible laryngoscopy. It is also not routine practice nor practical to perform flexible laryngoscopy in all patients post-extubation. In a systematic review by Brodsky et al on laryngeal injuries in the critical care population, it identified the lack of screening tools and guidelines to assist in identifying patients who may be at high risk of laryngeal injury and dysphagia post-extubation(Brodsky et al., 2018). Observation remains the most commonly employed treatment for the majority of upper airway symptoms after extubation(Brodsky et al., 2018). If easy bedside assessments of the voice can raise awareness of potential laryngeal injury without using flexible laryngoscopy, early investigation and intervention involving otolaryngologist and speech therapists may improve long term outcome for these patients.

There is no clear definition of prolonged intubation in the literature. The safe duration of translaryngeal intubation has increased from eight hours in 1966 to two weeks in 1981(Bishop et al., 1984). The minimum intubation time in studies that assess the laryngeal

outcome post prolonged intubation range from 12 hours(Nordang, Lindholm, Larsson, & Linder, 2016) to 4 days(Colice et al., 1989), with a minimum of 24 hours being the most frequently used inclusion criteria(Eckerbom et al., 1986; Gaynor & Greenberg, 1985; Kastanos, Estopa Miro, Marin Perez, Xaubet Mir, & Agusti-Vidal, 1983; Van der Meer et al., 2010). The definition of prolonged intubation in this study is therefore a minimum of at least 24 hours.

There are studies discussing the use of voice to assist in diagnosing vocal fold palsy post thyroidectomy and short term intubation, however, there have only been two studies that have attempted to examine voice outcomes and laryngeal injury in patients who received prolonged intubation(Bastian & Richardson, 2001; Van der Meer et al., 2010). No studies have used validated auditory perceptual assessments to assess prolonged intubation, nor correlated it to the laryngeal pathology sustained. It is well documented that most laryngeal pathology secondary to intubation resolve spontaneously(Colice et al., 1989; Whited, 1984). Therefore, we are not aiming to capture the lesions that may resolve within the first 24-48 hours, but injuries which persist beyond that time point. Short-term progression of laryngeal pathologies and voice outcomes secondary to intubation have also not been investigated. Therefore, we also aim to assess the progress of laryngeal pathologies and voice outcomes after 5-7 days.

So far, there is no grading system to assess for laryngeal injury secondary to iatrogenic or translaryngeal injuries in the literature that is validated or widely used. Therefore, a system needed to be developed in order to systematically identify pathologies and grade its severity. It is important to have a reliable and validated scoring system for communication and diagnostic purposes in both clinical and research settings. In order to correlate voice

outcomes with endoscopic findings, a validated endoscopic system is needed. However, the existing grading systems have been designed to classify laryngeal injuries in histological or post-mortem studies and do not cover all pathologies(Antonaglia et al., 2010; Colice et al., 1989; Eckerbom et al., 1986; Harrison & Tonkin, 1968; Mendels et al., 2012; Sinha et al., 2018). Therefore, a point-based grading system covering all anatomical subsites was designed to identify laryngeal injuries and evaluate the severity. This study will introduce its use and correlate the scores to the voice assessments.

1.6 Research questions and aims

1. **What is the incidence of laryngeal injury after intubation for at least 24 hours?**

   Hypothesis: The incidence of laryngeal injury is common for patients who have been intubated for at least 24 hours(Kastanos et al., 1983).

   Aim: To determine the incidence of laryngeal injury in patients who have been intubated for at least 24 hours.

2. **What laryngeal pathologies are caused by intubation duration for at least 24 hours?**

   Hypothesis: Laryngeal pathologies post intubation for at least 24 hours will include oedema, ulcers, granulomas, vocal fold immobility and stenosis.

   Aim: To determine the types of laryngeal pathologies in patients who have been intubated for at least 24 hours.

3. **How many of the laryngeal pathologies sustained from prolonged intubation persist at 5-7 days?**

   Hypothesis: The majority of laryngeal pathologies sustained from intubation resolve by 5-7 days.

   Aim: To assess the progression or resolution of laryngeal pathologies in patients who have been intubated for more than 24 hours.

4. **What are the risk factors for laryngeal injury after intubation for at least 24 hours?**

Hypothesis: The female gender, duration of intubation, ETT size, increased weight, high body mass index (BMI), smoker, diabetes, multiple intubation attempts, emergency intubation, presence of NGT, absence of steroid and proton pump inhibitors, increased cuff pressure are factors that will have increased risk of laryngeal pathology after intubation for at least 24 hours.

Aim: To determine the risk factors that may contribute to increased laryngeal pathology in patients after intubation for 24 hours or more. These include their medical history, intubation setting, difficulty of intubation, intubation duration, ETT size, presence of NGT, the use of proton pump inhibitors and the use of steroids in our institution

5. **Are voice assessments able to diagnose laryngeal injury?**

Hypothesis: The severity of voice dysfunction when assessed using the voice evaluation tools (s/z ratio, GRBAS, CAPE-V) will correlate with laryngeal injury sustained in patients who have been intubated for at least 24 hours.

Aim 1: To examine the correlation of voice outcomes (S/Z ratio, GRBAS, CAPE-V) with laryngeal injuries in patients who have been intubated for at least 24 hours.

Aim 2: To determine if voice assessments are able to predict short term laryngeal outcomes at 5-7 days' time.

Aim 3: To determine if laryngeal findings are able to predict short term voice outcomes at 5-7 days' time

6. **Is Flinders laryngeal injury scoring system valid and reliable?**

Hypothesis: The Flinders laryngeal injury scoring system is valid with good inter-rater and intra-rater reliability.

Aim: To introduce and validate the Flinders laryngeal injury scoring system.

2 MATERIALS AND METHODS

2.1 Ethics

Ethical approval has been obtained from the Southern Adelaide Human Research Ethics Committee. The Human Research Ethics Committee office research number is 208.17 (Appendix 1).

2.2 Study 1 The voice and laryngeal investigation standards post extubation (VOCALISE)

2.2.1 Study design

This is a prospective cohort study conducted at Flinders Medical Centre Intensive and Critical Care unit (ICCU) between October 2018 – October 2019. This is a 34-bed level III ICCU with medical, surgical, trauma and obstetric patients. Participants were recruited through the Department of Otorhinolaryngology Head and Neck Surgery and the Department of Intensive and Critical Care.

2.2.2 Study population

We have defined prolonged intubation in our study as patients who have been intubated for equal to or more than 24 hours. All patients who have been intubated for 24 hours or more were admitted to the ICCU therefore only ICCU patients have been screened and recruited.

The ETT care provided is standardised according to the institution's protocol. All patients received a chest x-ray to ensure correct positioning of the ETT once intubated. The ventilator settings were adjusted according to the patient's needs by the intensivist. The cuff of the ETT was checked every 8 hours to ensure the pressure is between 25-30cmH_2O. Regular suction was performed by the bedside nurse with a flexible Y-suction catheter.

2.2.3 Inclusion and exclusion criteria

The inclusion criteria for this study were:

i. 18 years of age or above.
ii. Translaryngeal intubation for 24 hours or more.
iii. Patients who have the capacity to consent and follow instructions.

The exclusion criteria for this study were:

i. Patients who underwent a tracheostomy.
ii. Head and neck injury.
iii. Inhalation injury.
iv. Thyroid, neck, cervical spine surgery.
v. Cognitive impairment.
vi. Inability to follow instructions.
vii. Dysphasic, dysarthric or unable to phonate.
viii. ICCU team deem not medically appropriate.

2.2.4 Study Protocol

The patients who have been extubated were identified by the nursing staff or medical team then liaised with the research team. The patients were approached between 24 to 48 hours after extubation and invited to participate in the study. Informed consent was obtained prior to the enrolment in the study. A flow chart of the study protocol has been attached (Figure 1).

All data collection was performed by the primary author.

Information collected from the case notes include:

i. Patient demographic: age, gender.
ii. Physical characteristics: height, weight
iii. Significant medical history: smoking history, diabetes, use of proton pump inhibitor, use of steroids, history of voice abuse, acute physiology and chronic health evaluation II (APACHE II) score.
iv. Indication for ICCU admission and endotracheal intubation
v. Intubation information: date and time of intubation, site of intubation, number of attempts, Cormack-Lehane score, endotracheal tube size, neuromuscular blockers, mean cuff pressure, self-extubation
vi. Nasogastric tube information: presence of NGT, dysphagia post extubation
vii. Length of ICCU stay and length of hospital stay

Topical anaesthesia Co-Phenylcaine Forte™ (5% lidnocaine, 0.5% phenylephrine) was sprayed into the patient's right nostril, unless there was an NGT in situ or a severely deviated septum to the right. Digital video transnasal endoscopy with continuous white light and videostroboscopy using Karl Storz Tele Pack x LED TP100 and Strobo-Video-Rhino-Laryngoscope 11101 VPS were used to examine the larynx. A recording of it was saved onto a USB. The laryngoscope has an angle of view of 85° with deflection up and down at 140°. The Tele Pack includes a microphone set and foot pedal to activate stroboscopy. The resolution is 1024 x 768 pixels. Patients were asked to whistle, inhale gently, repeat /i/, gliding /i/, prolonged /a/, and count to ten in order to assess the larynx under continuous white light. Patient were asked to say a prolonged /i/ and gliding /i/ under stroboscopy.

Laryngeal assessments videos were evaluated by two senior otolaryngologists who were blinded to the patients' identities. Disagreements were resolved by consensus. The following assessment tools were used:

i. Flinders laryngeal injury score (FLIS)
ii. Post-extubation laryngeal lesions scale (PELLS) (Table 8)(Antonaglia et al., 2010)
iii. Voice-vibratory assessment with laryngeal injury (VALI) (Appendix 3) (Poburka et al., 2017)

The VALI stroboscopy form had the following definitions for each parameter:(Poburka et al., 2017)

i. Glottal closure: appearance of the glottis during the most closed portion of the glottal cycle.
ii. Amplitude: magnitude of lateral movement of the vocal folds. Rated as percentage of movement laterally from the midline for right and left.
iii. Mucosal wave: magnitude of movement of mucous membrane. Rated as percentage of movement from the midline for right and left.
iv. Non-vibrating portion: adynamic segments of tissue that appears stiff. Rated as percentage for right and left.
v. Supraglottic activity: constriction of supraglottic structures. Rated from 0-5 with increasing severity of constriction in anteroposterior and mediolateral planes.
vi. Vertical level: the plane the vocal folds meet. Options are on-plane, left lower, right lower.
vii. Free edge contour: smoothness or straightness of free edge. Options are normal, convex, concave, irregular and rough.

viii. Phase closure: the relative durations of appearance of consecutive glottal cycles. Options are open phase predominates, nearly equal and closed phase predominates.

ix. Phase symmetry: the degree to which the vocal folds move as mirror opposite images of each other. Rated on a scale from 0-100% of exam time that vibration is symmetrical.

x. Regularity: consistency of cycles. Rate from 0-100% of time that vibration is regular.

Voice assessment was performed using a Shure SM48 microphone on a stand which is attached to Zoom H5 Handy Recorder. The microphone is placed at approximately 15 cm away from the patient's mouth. The patient is asked to speak directly into the microphone. Recordings were made by the patient's bedside in the intensive care unit or on the ward. The recordings were anonymised, so the examiners were blinded to the identity and the dates. The voice recordings were evaluated independently by two senior speech pathologists with special interests in voice disorders. The evaluation tools used were:

i. S/Z ratio (Eckel & Boone, 1981)

ii. GRBAS scale (Hirano, 1981)

iii. Consensus auditory perceptual evaluation of voice (CAPE-V) (Appendix 2)(Zraick et al., 2011)

S/Z ratio is assessed by asking the patient to sustain /s/ and /z/ for as long as possible and to repeat each of them three times. The longest /s/ and /z/ were chosen and a ratio calculated. Using the maximal phonation time to calculate the quotient eliminates the effect of respiratory effort(Gamboa, Nieto, del Palacio, Rivera, & Cobeta, 1995). The intensity has not been controlled for, but the patients have been asked to phonate at a volume that is comfortable for them.

To comply with the instructions of CAPE-V, patients were asked repeat /a/ and /i/ three times and sustain for 3-5 seconds. They were then asked to read the following sentences:

i. The blue spot is on the key again.
ii. How hard did he hit him?
iii. We were away a year ago.
iv. We eat eggs every Easter
v. My mama makes lemon muffins.
vi. Peter will keep at the peak.

Lastly, questions were asked of the patient to elicit 20-30 seconds of conversational speech.

The evaluation form for CAPE-V consists of VAS for the assessment of each attribute. The VAS is labelled underneath the 100mm line with the legends MI, MO, SE meaning mildly deviant, moderately deviant, severely deviant as a guide for the assessors. At the end of the line the assessors were asked to rate whether each attribute was consistent (C) or intermittent(I). The specific nature of the abnormality for pitch and loudness also needed to be defined. A copy of the instruction and the evaluation form has been attached (Appendix 2).

GRBAS scale assesses the following components: overall grade, roughness, breathiness, asthenia and strain. It consists of a 4-point ordinal scale - normal (0) mild (1) , moderate (2) or severe (3) (Nemr et al., 2012). GRBAS was assessed using the same audio recordings. The definitions of each of the voice components are as follows(Yamauchi, Imaizumi, Maruyama, & Haji, 2010):

i. Grade: degree of hoarseness or abnormality of the voice.

ii. Roughness: impression of irregularity of the vibration of the vocal folds.

iii. Breathiness: degree to which air escaping from between the vocal folds can be heard by the examiner.

iv. Asthenia: degree of weakness heard in the voice.

v. Strain: extent to which strain or hyperfunctional use of phonation is heard.

As CAPE-V produces scale data from a VAS, a difference greater than 10 points was resolved by consensus. For the parameters with differences smaller than 10 points, an average was taken for each value.

2.2.5 Statistical analysis

Statistical analysis was performed with the R Project for Statistical Computing version 3.6.1. Normality was assessed using Shapiro-Wilk test. The data was not normally distributed; therefore, non-parametric tests have been selected. Wilcoxon signed-rank test was used when assessing paired data. Mann-Whitney U test used for unpaired continuous data. Chi-squared test used for unpaired categorical data. Univariate regression was used for assessing the association of risk factors with laryngeal injury. Spearman rho correlation coefficient was used for assessing the association between laryngeal and voice outcomes.

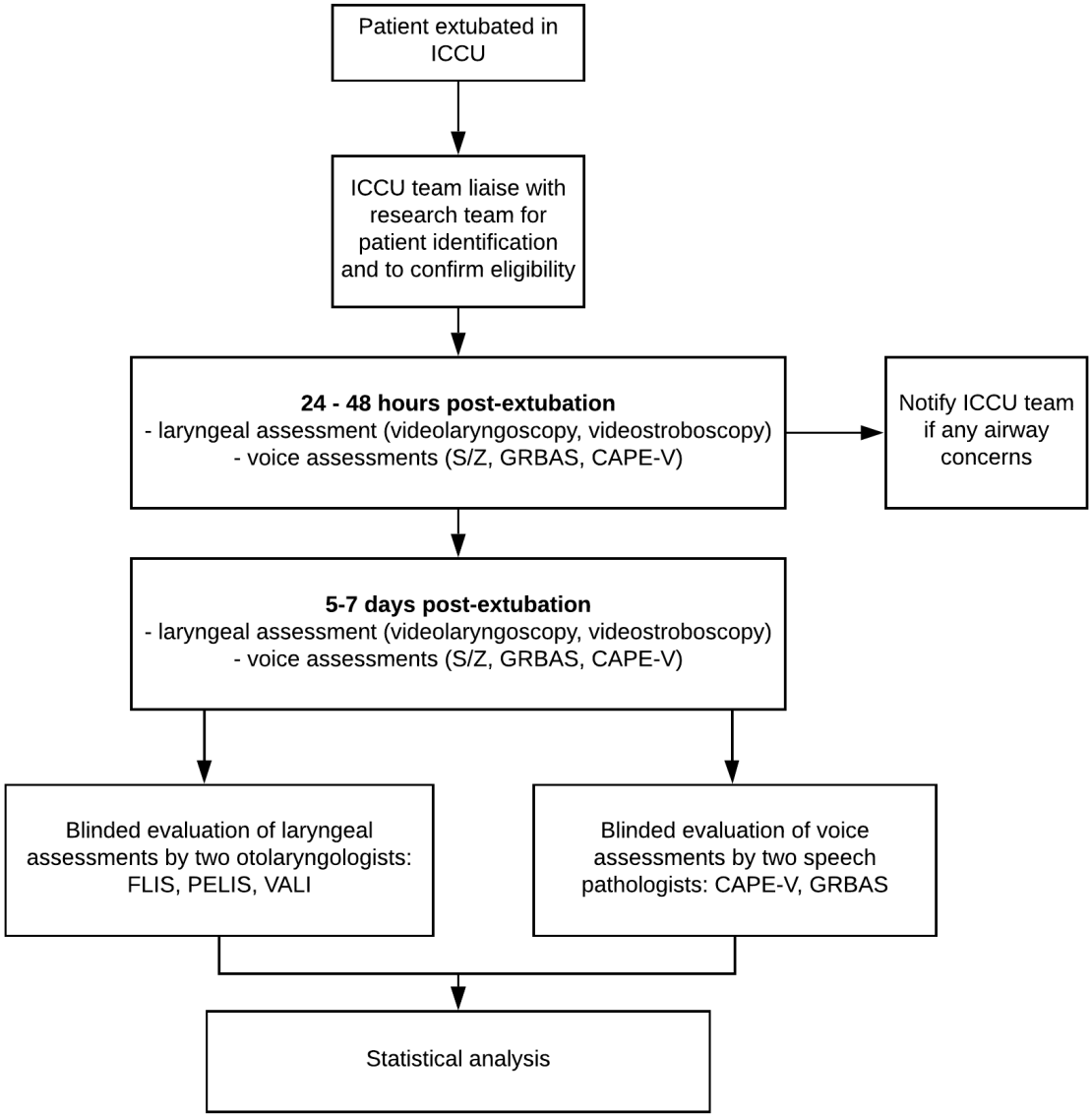

Figure 1. Methodology of VOCALISE.
Abbreviations: ICCU, intensive and critical care unit; CAPE-V, consensus auditory perceptual evaluation of voice; FLIS, Flinders laryngeal injury score; PELLS, post-extubation laryngeal lesions scale; VALI, voice-vibratory assessment with laryngeal injury form.

2.3 Study 2 Validity and reliability of the Flinders laryngeal injury score

2.3.1 Study design

This thesis aims to assess the laryngeal and voice outcome in the ICCU population who have been intubated for more than 24 hours. However, there are no widely used scoring systems for examining the larynx in this setting. In order to systematically examine the larynx and provide a score to communicate the severity of the injuries a new scoring system, the FLIS, is proposed (Table 13). It was developed in conjunction with two senior otolaryngologists after reviewing the literature of the common injuries secondary to intubation. It is a point-based scoring system, similar to that presented by Colton House et al (Table 9)(Colton House et al., 2011). It addresses pathology that may be unilateral or bilateral and is divided into the three anatomical subsites of the larynx – supraglottis, glottis and subglottis. The right side of the examination is listed in the left column and vice versa as this corresponds to the view that would be obtained when performing a flexible transnasal endoscopy or videolaryngoscopy when facing the patient. The severity rating for the common injuries are listed in the far-right column. The higher the value of points, the more severe the laryngeal pathology. The minimum score is 0, indicating a normal laryngeal examination. The maximum score is 58. It is intended for use in any translaryngeal mechanism of injury including pathology sustained from prolonged intubation. This study aims to assess the validity and reliability of this scoring system.

Table 13 Flinders laryngeal injury score

		Right	Left
Supraglottis	Oedema		
	Ulceration/granuloma		
	Erythema		
Glottis	Oedema		
	Ulceration/granuloma		
	Erythema		
	Mobility		
	Stenosis		
Subglottis	Oedema		
	Ulceration/granuloma		
	Erythema		
	Stenosis		
Total			

Oedema
0: none
1: <25%
2: 25-50%
3: >50%

Ulceration/granuloma
0: none
1: mild
2: moderate
3: severe

Erythema
0: none
1: hyperaemia
2: haematoma

Stenosis
0: none
1: <25%
2: 25-50%
3: >50%

Mobility
0: normal
1: reduced mobility
2: immobility

2.3.3 Raters

The raters consisted of three otolaryngology consultants, three otolaryngology trainees, one senior speech pathologist and one senior ICCU consultant.

2.3.4 Study protocol

All participants attended the introduction session. Training was provided by introducing the scoring system, defining the pathology and using photos to demonstrate the common laryngeal pathology seen after prolonged intubation. All videos were anonymised. Fourteen video recordings were randomly selected from Study 1 to assess the reliability of this scoring system. Two video recordings on normal controls were also included, allowing for sixteen videos for the assessment of inter-rater reliability. Four videos with laryngeal pathology were repeated and randomised to assess intra-rater reliability. All raters were blinded to the history of the patients. The videos did not included audio. Each video was played twice. All raters were provided with hard copies of the scoring system for rating.

The simplified definition of validity is the ability of the instrument to measure what it was designed to measure(Boateng, Neilands, Frongillo, Melgar-Quiñonez, & Young, 2018). While there are many different types of validities, it is broadly categorised into internal and external validities(Cizek, 2012). Content validity and concurrent validity are subcategories of validities that have been assessed in this study. Both target population and expert judges participated in assessing the content validity. The target population includes all clinicians with the potential to assess the larynx, being otolaryngologists, speech pathologists and intensivists. They have been included to assess face validity, as part of content validity(Boateng et al., 2018). Expert judges solely consisted of otolaryngology consultants.

To assess face validity, all raters were asked to rate on a VAS two questions:

1. Do you think the FLIS is useful in diagnosing laryngeal injury secondary to intubation?
2. Do you think FLIS covers most types of laryngeal injury secondary to intubation?

The first question assesses the target population's perception of the utility of FLIS. The second question assesses if the score derived from FLIS is able to capture the majority of laryngeal injuries with potential clinical implications.

Content validity mandates expert judges to evaluate the necessity of individual items within an instrument. To assess content validity, content validity ratio (CVR) using the Lawshe test was performed (Equation 1). 5 otolaryngology consultants who are considered experts in this field were asked if all the items in this scoring system are essential(Ayre & Scally, 2014; Boateng et al., 2018). Two separate groups of items were assessed for necessity. One group was the injuries for each of the subsite and the other being the severity rating of these injuries. CVR will yield a result between -1 to +1, with positive values indicating more than half of the experts deeming the items are essential(Grimm & Widaman, 2012).

$$\boldsymbol{CVR} = \frac{\boldsymbol{n_e} - \left(\boldsymbol{N}/\boldsymbol{2}\right)}{\boldsymbol{N}/\boldsymbol{2}}$$

Equation 1. Content validity ratio proposed by Lawshe.
CVR, content validity ratio; n_e, number of panel members indicating an item is essential; N the number of panel numbers.

Concurrent validity is usually assessed against an instrument which has previously been validated(Cizek, 2012). However, there were no previous evaluation tools that have been validated. Therefore, concurrent validity of FLIS was assessed by correlating the FLIS total score with the other scoring system available in the literature PELLS(Antonaglia et al., 2010).

2.3.5 Statistical analysis

Statistical analysis was performed using IBM SPSS statistics version 25. Ratings for inter-rater reliability was assessed using the intraclass correlation coefficient (ICC) single measures, absolute agreement, two-way random model (Trevethan, 2016). While there are no standard interpretation for ICC, the generally accepted interpretation is: poor reliability if ICC <0.5, moderate reliability when ICC is 0.5-0.75, good reliability when 0.75-0.9 and excellent reliability when ICC is above 0.90(Koo & Li, 2016). Intra-rater reliability was assessed using the average of percentage agreement between raters. Spearman rho correlation was used to assess FLIS total score and PELLS.

3 RESULTS

3.1 Study 1 The voice and laryngeal investigation standards post extubation (VOCALISE)

145 ICCU patients who fulfilled the inclusion criteria were screened for eligibility. Amongst them 60 patients consented to participate in this study. All 60 patients completed the first assessment within 24-48 hours after extubation and 37 patients completed both the first and second assessments at 5-7 days after extubation (Figure 2).

3.1.1 Patient characteristics

This patient population had a median age of 65 years old and were predominantly male with an APACHE II score of 19. Patient demographic and characteristics are presented in Table 14. For comparison, the patient characteristics for the Australian ICCU adult patients are presented in Table 15 (ANZICS, 2019). The age and gender are similar but with higher APACHE II and longer length of ICCU stay when compared to the general Australian ICCU population. Patients were intubated for a median duration of 60.1 (38.2-136.5) hours. The first laryngeal and voice assessments were conducted at a median of 1.1 (0.9-1.2) days after extubation. In a subset of patients (n=37) a second assessment was conducted prior to discharge or at 5-7 days after extubation (6.1 (5.1-7.1) days). Endotracheal intubation details are presented in Table 16. All the patients were intubated via the orotracheal route. None of the ETTs had above cuff suction. None of the included patients had post-extubation stridor that resolved prior to participation.

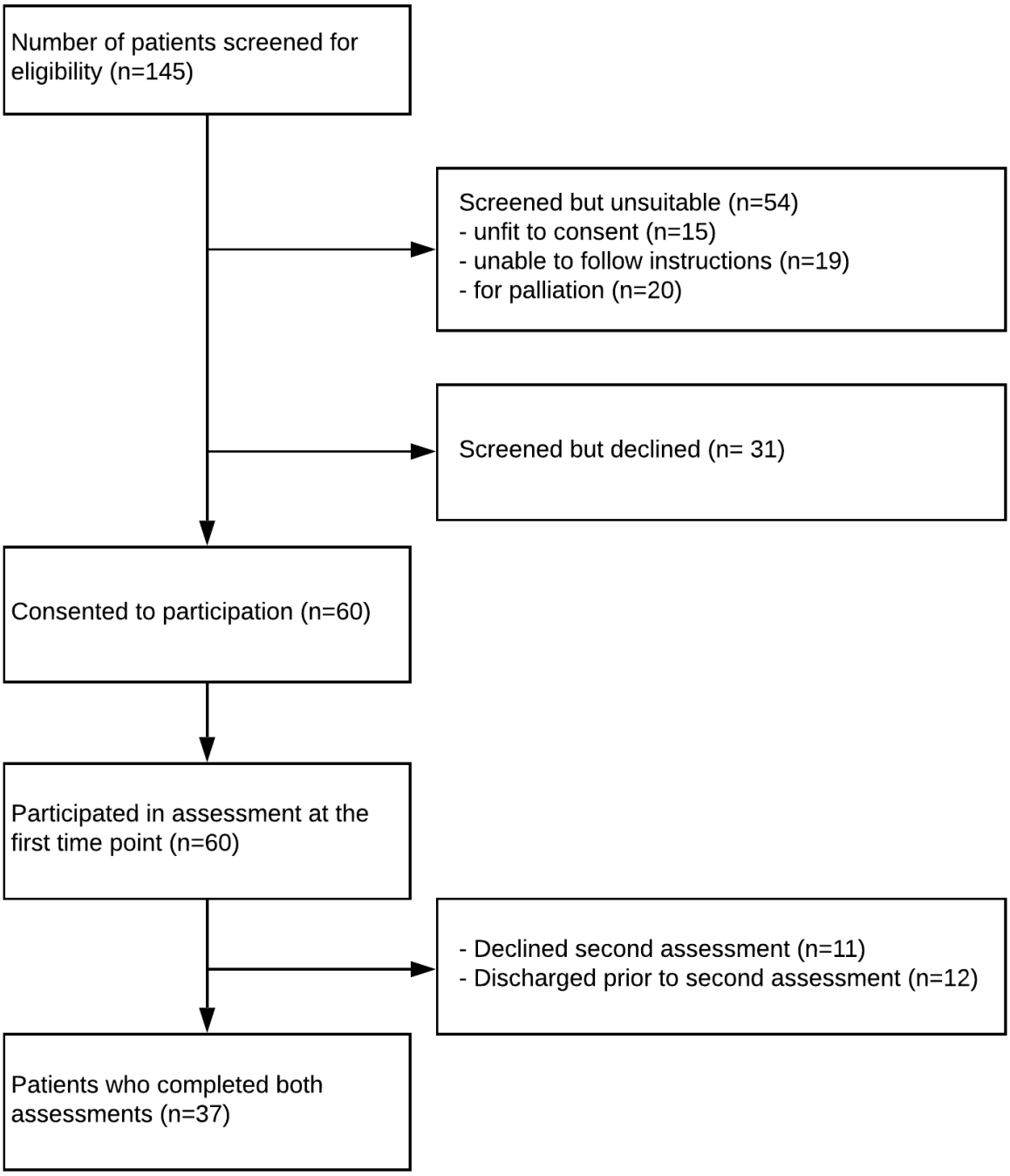

Figure 2. Flow-chart of patient selection and participation for VOCALISE

Table 14 Patient demographic and characteristics

Characteristics	Patients who completed first assessment (n=60)	Patients who completed first and second assessments (n=37)
Age (years)	65 (57-75)	65 (57-78)
Gender (male; female)	Male 65%; Female 35%	Male 59%; female 41%
APACHE II score	19 (17-23)	19 (17-23)
Length of ICCU stay (days)	3.9 (2.8-8.8)	4.3 (2.6-9.0)
Length of hospital admission (days)	16.1 (8.4-29.9)	25.6 (11.5–45.4)
Body mass index (kg/m^2)	26 (24-33)	26 (23-30)
Height/tube ratio (cm)	22.7 (21.9-23.3)	22.8 (21.8-23.6)
Smoking history (n, %)		
Ex-smoker	30 (50%)	17 (35%)
Non-smoker	19 (32%)	13 (46%)
Active smoker	11 (18%)	7 (19%)
Admission specialty (n, %)		
Medicine	33 (55%)	20 (54%)
Respiratory	11 (18%)	4 (11%)
General medicine	7 (12%)	4 (11%)
Gastroenterology	7 (12%)	6 (16%)
Cardiology	7 (12%)	5 (14%)
Renal	1 (1%)	1 (3%)
Surgery	27 (45%)	17 (28%)
Cardiothoracic	12 (20%)	7 (19%)
General surgery	8 (13%)	6 (16%)
Urology	3 (5%)	2 (5%)
Orthopaedic	2 (3%)	0 (0%)
Vascular	1 (2%)	1 (3%)
Neurosurgery	1 (2%)	1 (3%)
Nasogastric tube inserted (n, %)	48 (80%)	32 (86%)
Proton pump inhibitor use (n, %)	42 (70%)	29 (78%)
Steroid (oral or parenteral) use (n, %)	20 (33%)	14 (38%)
Diabetes (n, %)	19 (32%)	13 (35%)

Data presented as median (IQR) or number of patients (%). First assessment is within 24-48 hours post extubation. Second assessment is at 5-7 days post extubation. Abbreviations: ICCU, intensive and critical care unit; APACHE II, Acute physiology, age, chronic health evaluation II.

Table 15. Patient characteristics for adult ICCU admission in Australia

Characteristics	Median (IQR) or percentage
Age	65 (51-75)
Male	56.1%
APACHE II score	14 (10-19)
Length of ICCU stay	1.7 (0.9-3.2)
Source of admission	
Ward	15.0%
Operating theatre	53.4%
Emergency department	25.4%
Other hospital	6.0%

Data obtained from Australian and New Zealand Intensive care society Adult patient database activity report 2017/2018(ANZICS, 2019).

Table 16 Endotracheal intubation details

Intubation information	Median (IQR) or number (%)
Intubation location (n, %)	
OT	30 (50%)
ICCU	15(25%)
Retrieval team at peripheral hospital	5 (8%)
Ward	2 (3%)
ED	8 (14%)
Cormack Lehane (n, %)	
1	36 (60%)
2	7 (11%)
3	3 (5%)
4	1 (2%)
Videolaryngoscopy with good view	7 (10%)
Not documented	6 (12%)
Number of intubation attempts (%)	
1	53 (88%)
2	4 (7%)
Not documented	3 (5%)
Use of muscle relaxant (%)	
Rocuronium	41 (68%)
Suxamethonium	8 (13%)
Vecuronium	6 (10%)
Pancuronium	4 (7%)
Not documented	1 (2%)
Size of endotracheal tube	
7	20 (33%)
7.5	2 (3%)
8	38 (63%)
Mean cuff pressure (cmH_2O)	27 (26-28)
Dysphagia post extubation (%)	13 (22%)

Abbreviations: OT, operating theatre; ED, emergency department. N=60.

3.1.2 Incidence of laryngeal injury

The incidence of laryngeal injury after intubation for a minimum of 24 hours was 96.6% when assessed at 24-48 hours after extubation. Laryngeal injuries were identified using the FLIS with some patients presenting with more than one laryngeal injury. Additional injuries that are not captured by the FLIS (vocal fold avulsion, cricoarytenoid dislocation, supraglottis stenosis) were not identified in this patient sample. The distribution of the types of injury is presented in Figure 3. The most common laryngeal injury was ulceration or granuloma of the glottis (82% of all patients). All of the ulceration or granuloma were situated posteriorly over the vocal process. In contrast, oedema was the most common injury identified in the supraglottis (40%) and subglottis (18%). However, it is worth noting that the injury to the subglottis may be underreported due to oedema superiorly or inadequate view. Examples of the injuries are presented in Figures 17-26.

Left sided injury is more commonly described in the literature as the majority of operators use their right hand to insert the ETT. The FLIS of the right and left side were 2.0 (1.8-4.3) and 3.0 (2.0-4.0) at the first assessment and 2.0 (1.0-3.0) and 2.0 (1.0-3.0) at the second assessment, however, there were no statistical differences when comparing the two sides at either time points. The FLIS total score ranged from 0-20. The frequency distribution of the total FLIS score and PELLS are presented in Figure 4 and 5. Most patients have a low total FLIS score between 2-6 and PELLS mostly in degree 2. The laryngeal and voice assessments are summarised in Table 17.

100% of patients assessed within 48 hours after extubation had some degree of voice deviation from normal. Both CAPE-V and GRBAS demonstrated a moderately abnormal voice compared to normal (Table 18). The most frequent score when assessing the CAPE-V

overall severity was between 31-40, and grade 2 when assessing overall grade using GRBAS (Figure 6 and 7). The worst voice component assessed was strain using CAPE-V. All GRBAS parameters, including strain, were reported to be mildly abnormal. The difference in GRABS and CAPE-V may reflect the limitation of GRBAS being an ordinal scale. 25% of patients had an s/z ratio greater than 1.4.

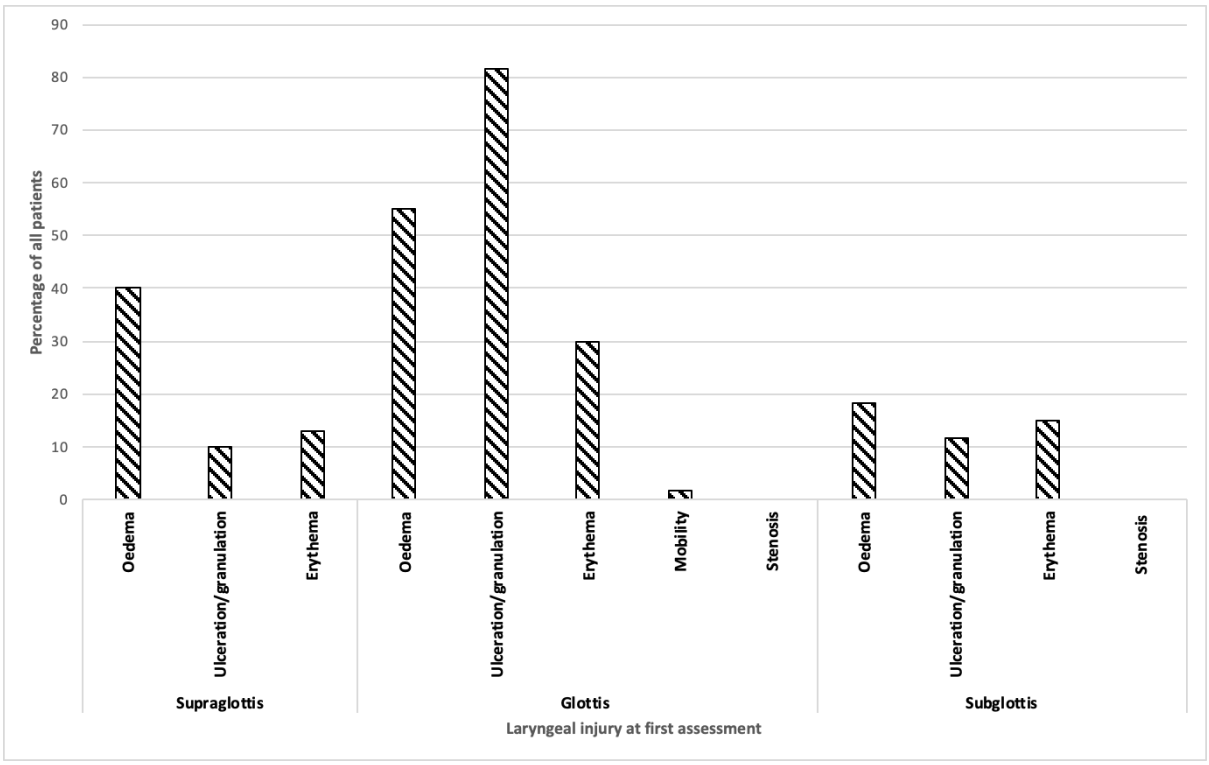

Figure 3 The percentage of laryngeal injuries within 48 hours post-extubation categorised by each subsite. n=60.

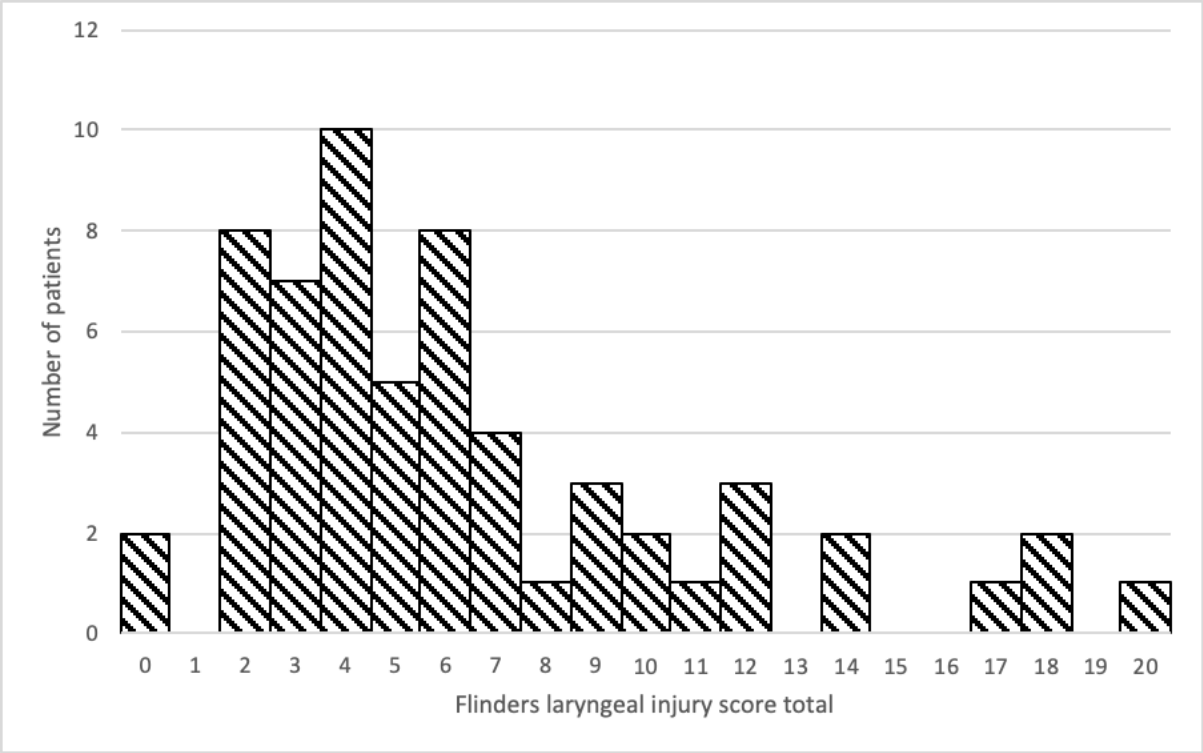

Figure 4 Frequency distribution of total FLIS within 24-48 hours post extubation.
n=60. FLIS of 0 indicates a normal laryngeal examination. Maximum FLIS is 58.

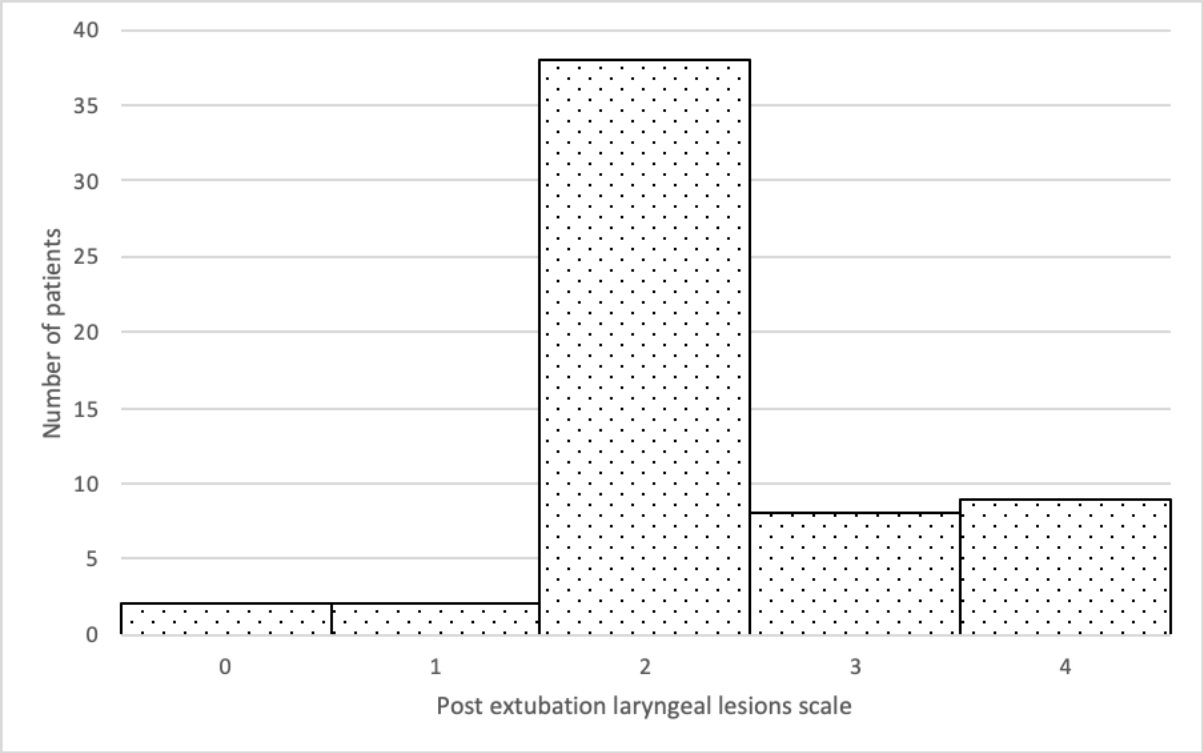

Figure 5 Frequency of distribution of PELLS within 24-48 hours post extubation.
n=60. PELLS 0 indicates normal laryngeal examination; 4 indicates the most severe laryngeal examination

Table 17 Endoscopic and laryngeal outcome at the first assessment

Types of assessment	First assessment (n=60)
FLIS total	5.0 (3.0-8.3)
PELLS	2.0 (2.0-3.0)
CAPE-V overall severity	33.8 (24.5-41.8)
GRBAS grade	2.0 (1.0-2.0)
Longest /s/ (second)	5.2 (3.7-6.8)
Longest /z/ (second)	4.3 (2.6-7.6)
S/Z	1.2 (0.8-1.4)

Data presented as median (IQR). Abbreviations: FLIS, Flinders laryngeal injury score; PELLS, post-extubation laryngeal lesions scale; CAPE-V, consensus auditory perceptual evaluation of voice. A score of 0 indicates a normal examination for FLIS, PELLS, CAPE-V, GRBAS. S/Z ratio greater than 1.4 indicates abnormality.

Table 18 Different voice parameters within 48 hours post extubation with CAPE-V and GRBAS

Voice parameters	CAPE-V	GRABS
Grade	33.8 (24.5-41.8)	2 (1-2)
Roughness	25.3 (19.5-39.6)	1 (1-2)
Breathiness	24.8 (20.0-31.8)	1 (1-2)
Asthenia	N/A	1 (1-2)
Strain	30.5 (21.4-40.0)	1 (1-2)
Pitch	17.3 (0.0-26.5)	N/A
Loudness	20.3 (3.4-30.0)	N/A

Data presented as median (IQR) in 60 patients. Abbreviations: CAPE-V, consensus auditory perceptual evaluation of voice; N/A, not applicable. CAPE-V is on a range from 0-100 continuous scale, with 100 being severely deviant from normal. GRBAS range from 0-3 ordinal scale with increasing severity.

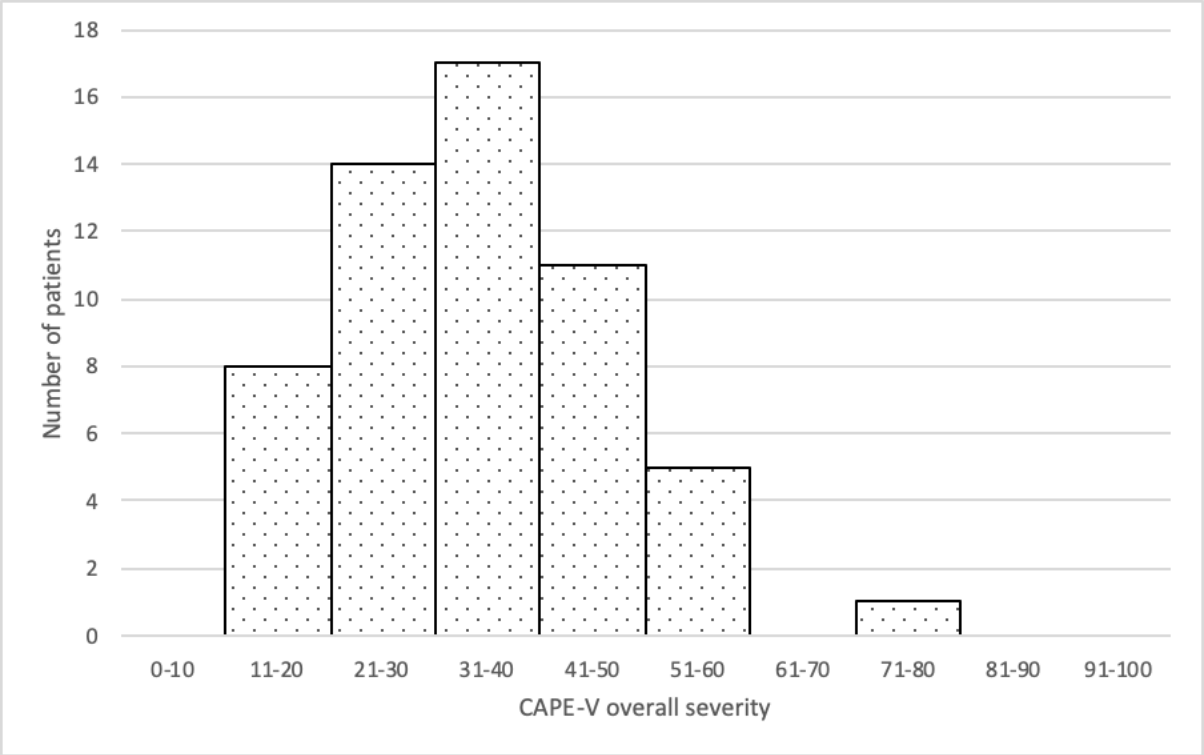

Figure 6 Frequency distribution of CAPE-V overall severity within 24-48 hours post extubation.
CAPE-V is assessed on a 100mm visual analogue scale with the left extreme labelled as mildly deviant and the right extreme as severely deviant from normal voice.

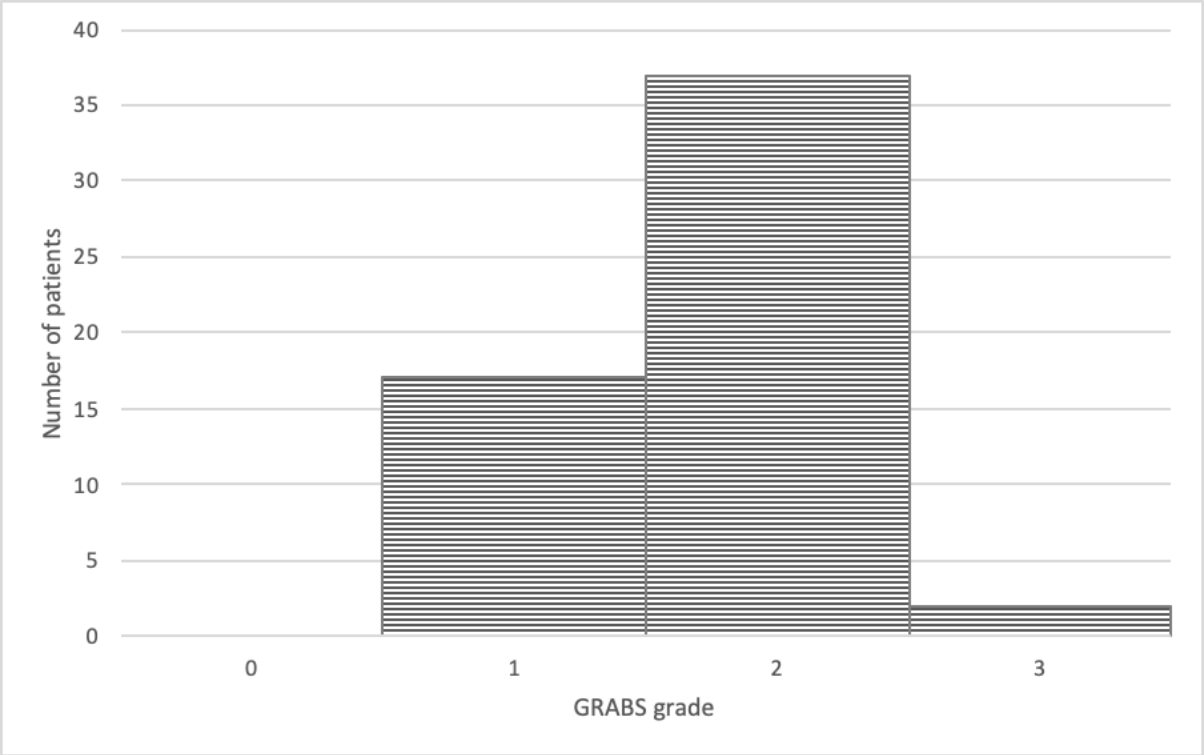

Figure 7 Frequency distribution of GRBAS grade within 24-48 hours post extubation.
Ordinal rating scale: 0, normal; 1, slight; 2, moderate; 3, severe.

Stroboscopy is the gold standard for detecting vocal fold pathology. When assessing the larynx using stroboscopy, 7 patients had incomplete stroboscopy assessment at the first time point using the VALI form due to asynchronous image sequences or supraglottic constriction impairing full examination of the vocal fold. The results of stroboscopy is presented as descriptive statistics in Table 19. 60% of patients had abnormal glottal closure. The median amplitude and mucosal wave were both below 100%. Only one patient had a 30% non-vibrating portion of the right vocal fold. 50% of patients had abnormal free edge contour of variable descriptions.

Table 19 Voice vibratory assessment with laryngeal imaging using stroboscopy at 24-48 hours post extubation

Stroboscopy parameters	Number (%) or Median (IQR)
Glottal closure	
Complete	n=23 (40%)
Anterior gap	n=3 (5%)
Posterior gap	n=14 (24%)
Hourglass	n=0 (0%)
Spindle gap	n=13 (22%)
Irregular	n=1 (2%)
Incomplete	n=4 (7%)
Amplitude (%)	
Right	60 (40-78)
Left	60 (40-78)
Mucosal wave (%)	
Right	60 (40-60)
Left	60 (40-60)
Vertical level	
On plane	n=56 (93%)
Off-plane; left lower	n=1 (2%)
Off-plane; right lower	n=1 (2%)
Supraglottic activity	
Anteroposterior	3 (2-3)
Mediolateral	3 (2-4)
Free edge contour (right/left)	
Normal	n=29 (50%)/ n=20 (50%)
Convex	n=19 (33%)/ n=17 (29%)
Concave	n=8 (14%)/ n=9 (16%)
Irregular	n=2 (3%)/ n=2 (3%)
Rough	n=0 (0%)/ n=1 (2%)
Phase closure	
Open phase predominates	n=14 (25%)
Nearly equal	n=39 (68%)
Closed phase predominates	n=4 (7%)
Phase symmetry (%)	80 (70-90)
Regularity (%)	80 (50-90)

n=60. Note: Please refer to the voice vibratory assessment with laryngeal injury (VALI) form for stroboscopy assessment in Appendix 3. Ranges: amplitude: 20-100%; mucosal wave: 20-100%; supraglottic activity: 0 minimal constriction, 5 maximal constriction; phase symmetry: 0-100%; regularity: 0-100%.

3.1.3 Progress of laryngeal injury and voice assessments

The progress of the injuries were compared between the two assessments with a median time of 5.0 (4.0-6.1) days between assessments. The scores for each assessment at the two time points are presented in Table 20. Amongst the subset of 37 patients who completed both assessments, the incidence of laryngeal injury was 97.3% at the first assessment and 83.8% at the second assessment. The comparison of injury at each subsite at the two time points are presented in Figure 8. The injuries with a significant reduction in incidence between the two assessments are supraglottis oedema, glottis oedema and erythema. Graphical presentations of the differences are presented for each assessment in Figures 9-14. A paired test using Wilcoxon signed rank test demonstrated there was significant improvement in the severity of laryngeal injury over time when assessing the total FLIS score ($p<0.001$), but not when assessed using the PELLS scoring system. A normal laryngeal examination (PELLS and FLIS of 0) was present in 2 and 6 patients at the first and second examinations respectively.

The distribution of the FLIS total score at the first and second assessments are shown on Figure 15 and 16. The frequency distribution is further skewed to the left at the second assessment where there were more patients with a FLIS of 0-2, illustrating an improvement in severity. The FLIS total score improved in 25 patients (median improvement of 3 points), remained stable in 7 patients and worsened in 5 patients (median worsening of 2 points). The injuries in the 5 patients with worsening FLIS were not uniform, being supraglottis oedema, glottis ulceration/granuloma and subglottis oedema. Despite worsening FLIS, the CAPE-V overall severity improved in all 5 of these patients by a median of 8 points and GRBAS remained stable in 4 and improved in 1 patient. Patient characteristics and risk factors of the 5 patients with worsening scores were compared to the remainder of the

group to determine if certain factors could contribute to worsening of their laryngeal injury severity. However, no factors were identified to be significant in this group of patients.

When assessing the patient's voice, there was a significant improvement when using the CAPE-V overall severity and the grade in GRBAS (Table 20). Only roughness and pitch demonstrated statistical improvement when assessing individual CAPE-V parameters whereas all parameters (roughness, breathiness, asthenia, strain) demonstrated improvement when using GRBAS. There was a trend of improvement which did not reach statistical difference between the s/z ratio assessed over time.

No patients required acute treatment for their laryngeal injury. Three patients were referred to laryngology clinic for further follow up - two had significant subglottic granuloma and one had severe glottic granulomas.

Table 20 Laryngeal and voice assessment for the subgroup of patients who completed both assessments (n=37)

	First assessment	Second assessment	P-value
FLIS total	5.5 (4.0-7.3)	4.0 (2.0-6.0)	<0.001*
PELLS	2.0 (2.0-2.5)	2.0 (2.0-2.0)	0.63
CAPE-V overall severity	33.8 (25.0-44.8)	24.5 (19.4-35.0)	0.002*
GRBAS grade	2 (1-2)	1 (1-2)	0.02*
Longest /s/ (second)	4.6 (3.1-6.5)	6.4 (4.6-7.6)	0.014*
Longest /z/ (second)	3.8 (2.5-6.5)	6.4 (3.9-7.4)	0.024*
S/Z	1.2 (1.0-1.4)	1.0 (0.9-1.2)	0.15

Abbreviation: FLIS, Flinders laryngeal injury score; PELLS, post-extubation laryngeal lesions scale; CAPE-V, consensus auditory perceptual evaluation of voice. Analysed using Wilcoxon signed rank test. * statistical significance with an alpha level of 0.05.

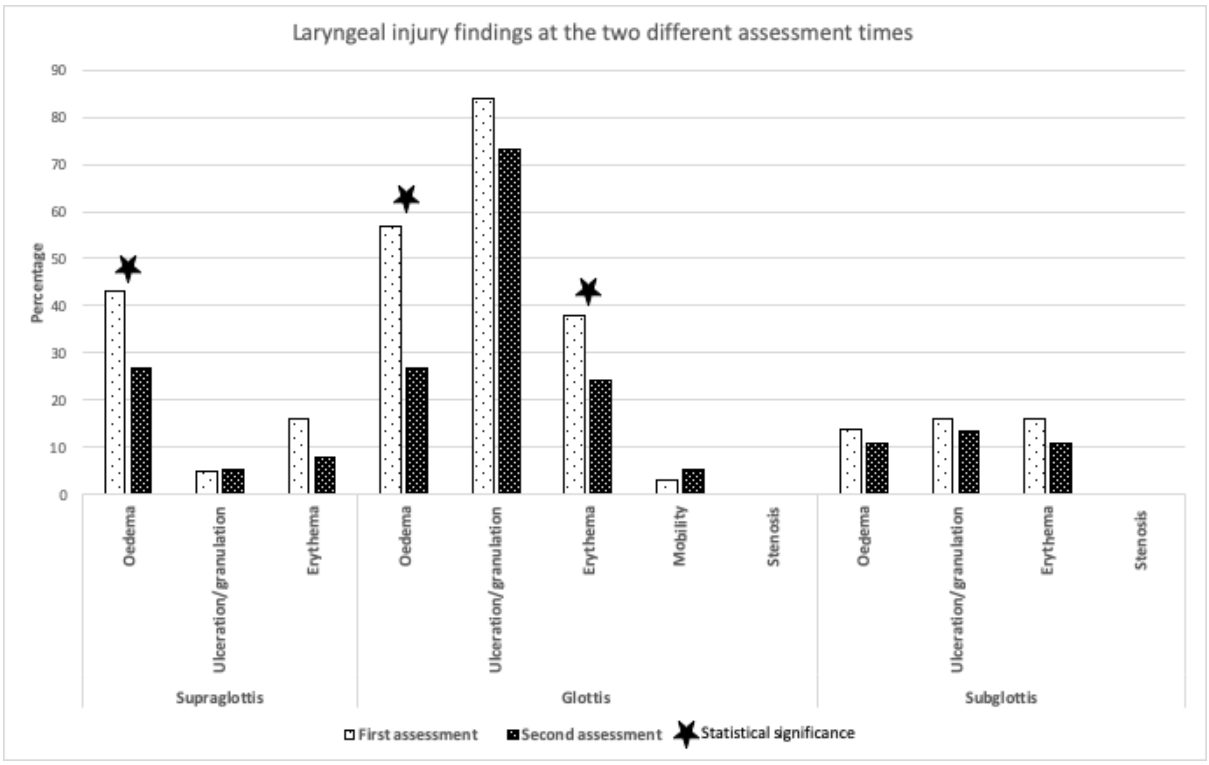

Figure 8 Laryngeal injury findings at the two different assessment times.
n=37. Laryngeal findings extracted from Flinders laryngeal injury score. Chi-squared test used for statistical analysis.

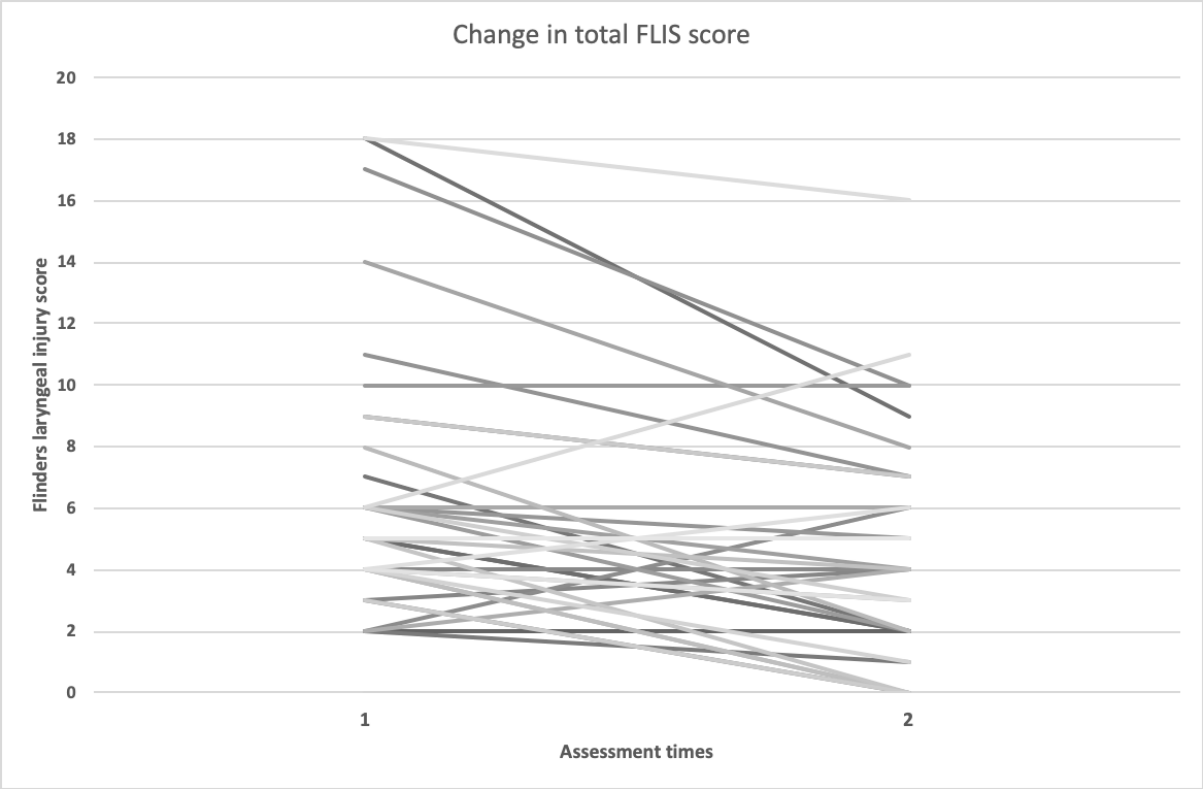

Figure 9 The change in Flinders laryngeal injury total score at the two assessment times.
n=37. First assessment time within 24-48 hours post extubation, second assessment time within 5-7 days post extubation. Wilcoxon signed-rank test used for statistical analysis, $p<0.001$

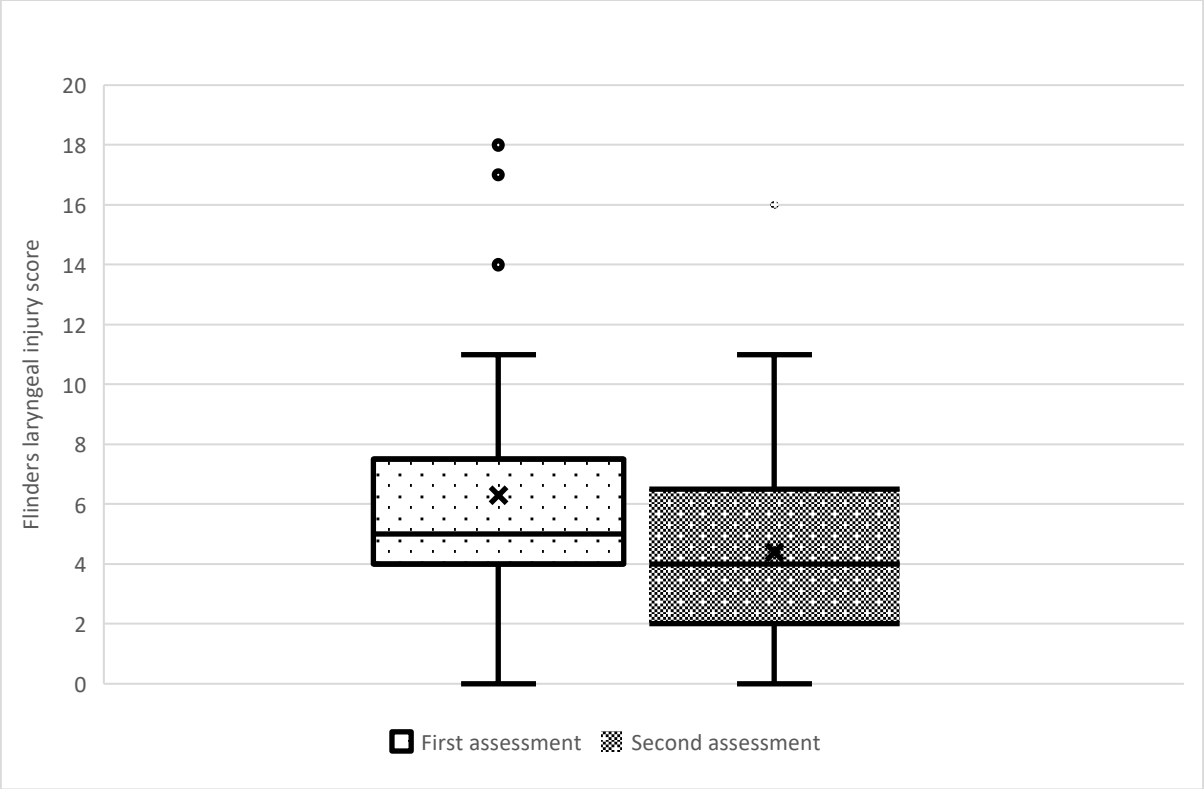

Figure 10 Box plot of the Flinders laryngeal injury score at the two assessment times.
The box indicates the first, median and third quartile from bottom to top. Mean is shown as X. Whiskers extend to 1.5 times the interquartile ranges from the edge of the box. Outliers are all the values beyond the whiskers.

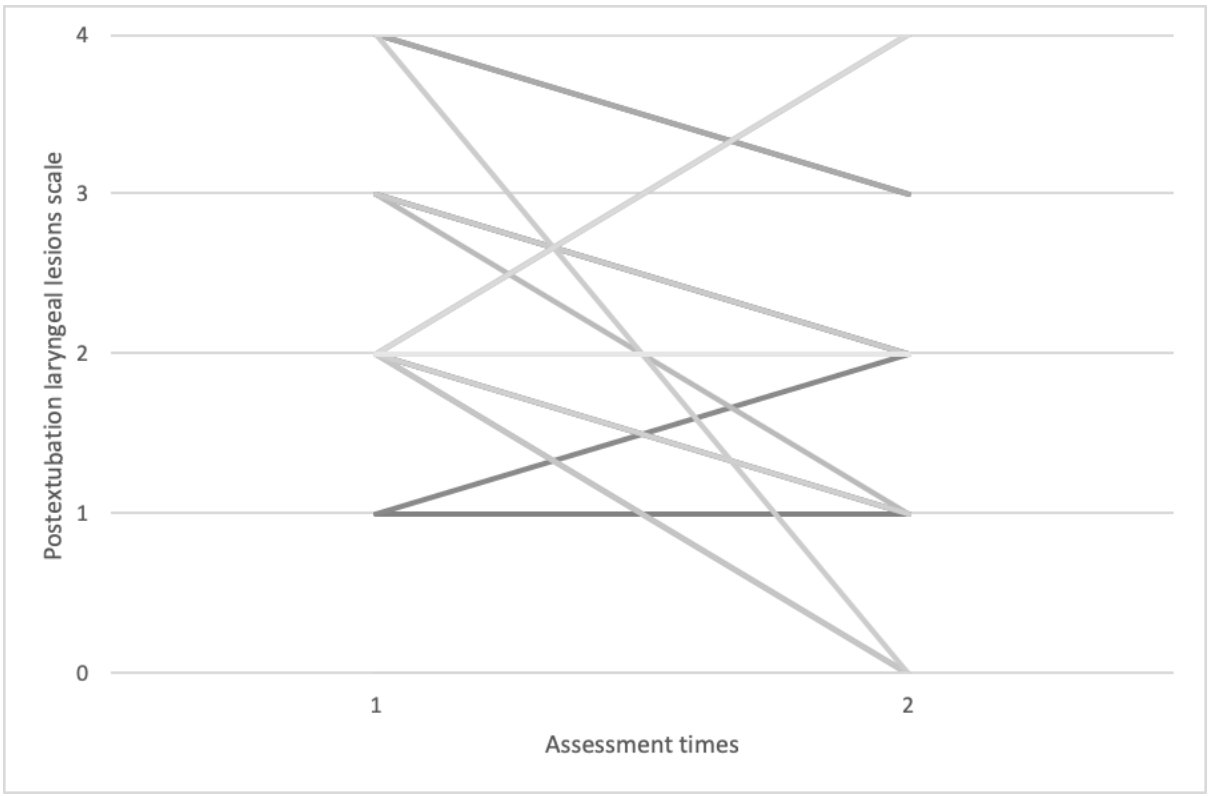

Figure 11 The change in post-extubation laryngeal lesions scale at the two assessment times.
n=37. Wilcoxon signed-rank test used for analysis, p=0.63.

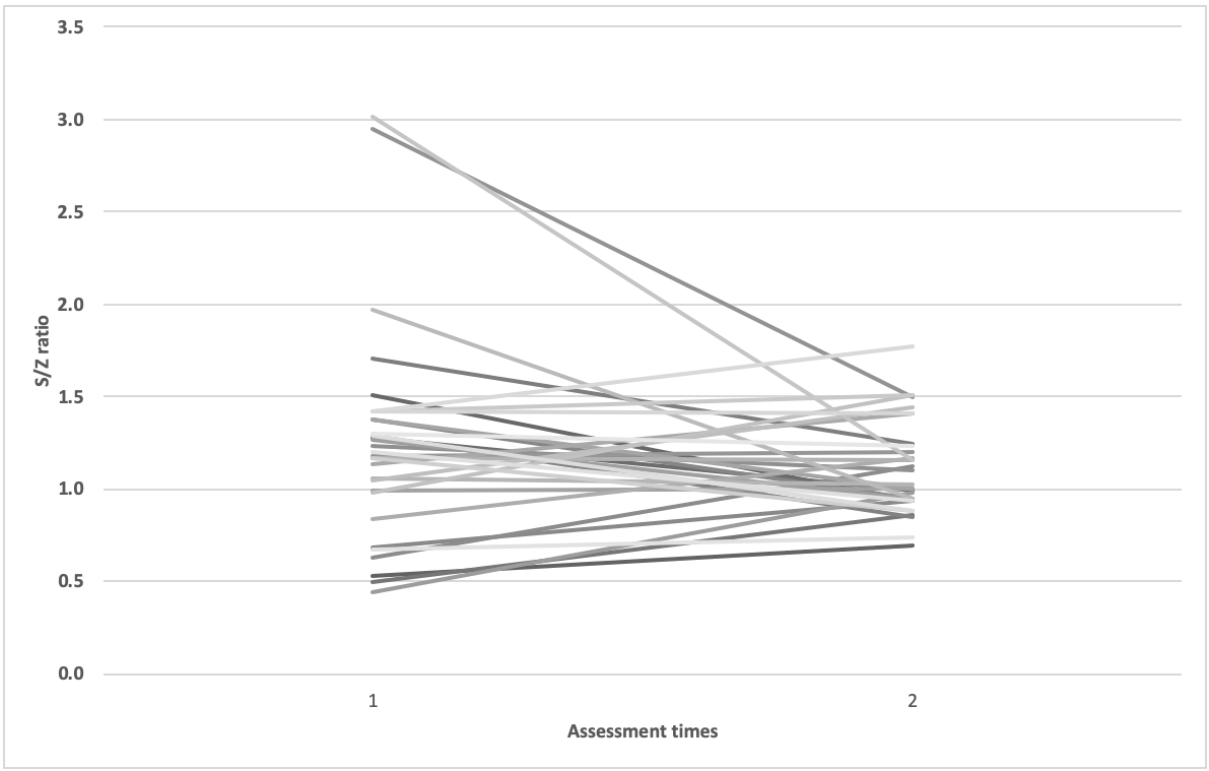

Figure 12 The change in s/z ratio at the two assessment times.
n=37. Wilcoxon signed-rank test used for analysis, p=0.15.

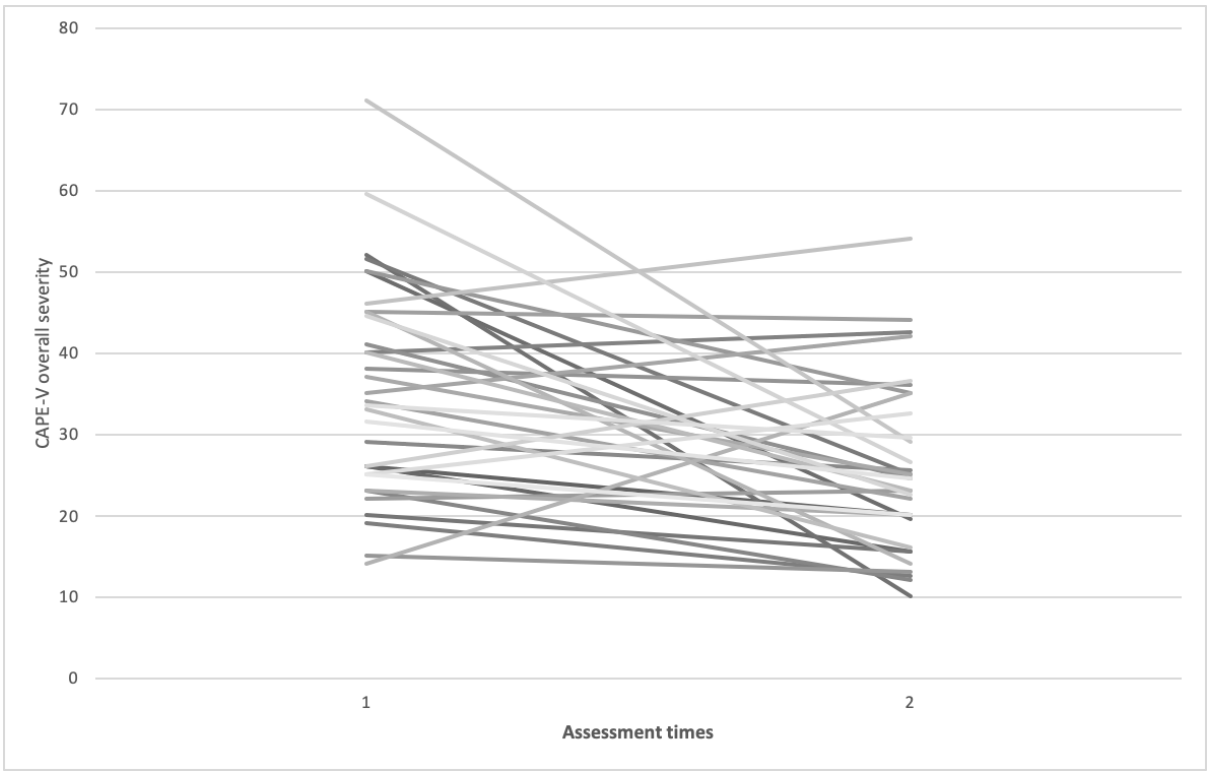

Figure 13 The change in CAPE-V overall severity at the two assessment times.
n=37. Wilcoxon signed rank test used for analysis, p=0.002.

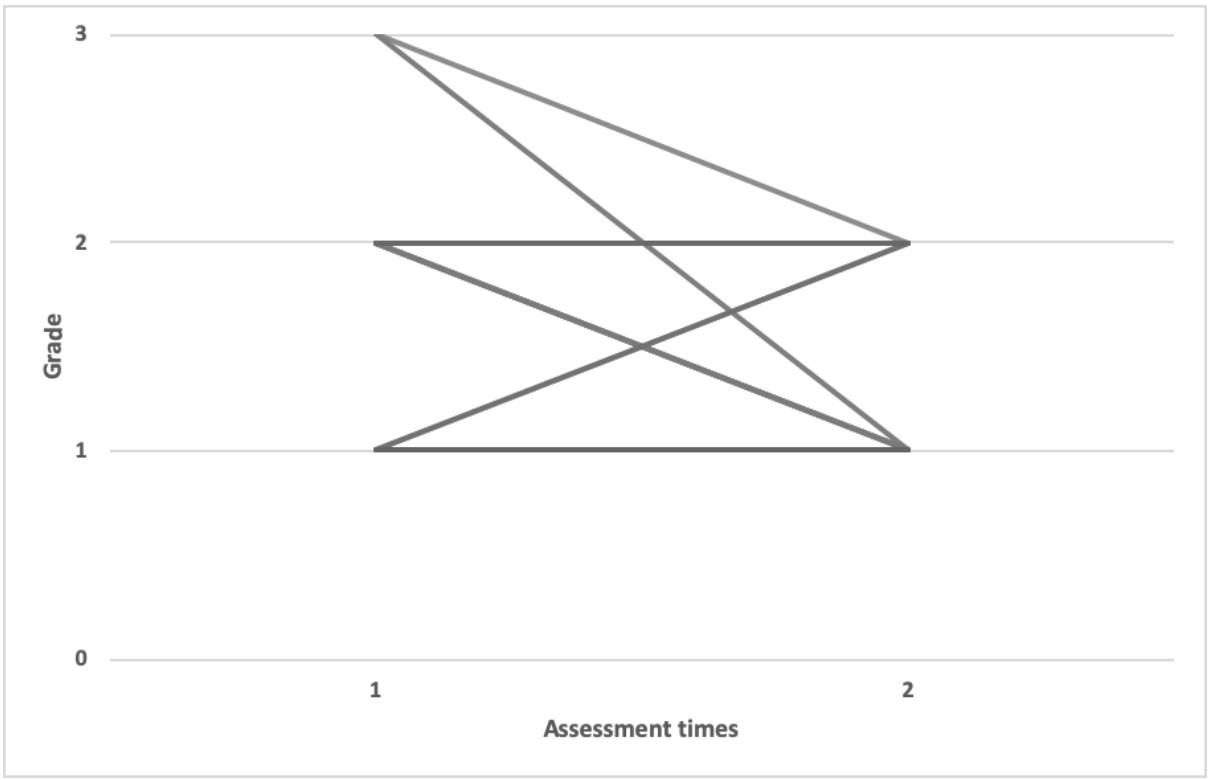

Figure 14 The change in GRBAS overall grade at the two assessment times.
n=37. Wilcoxon signed-rank test used for analysis, p=0.15.

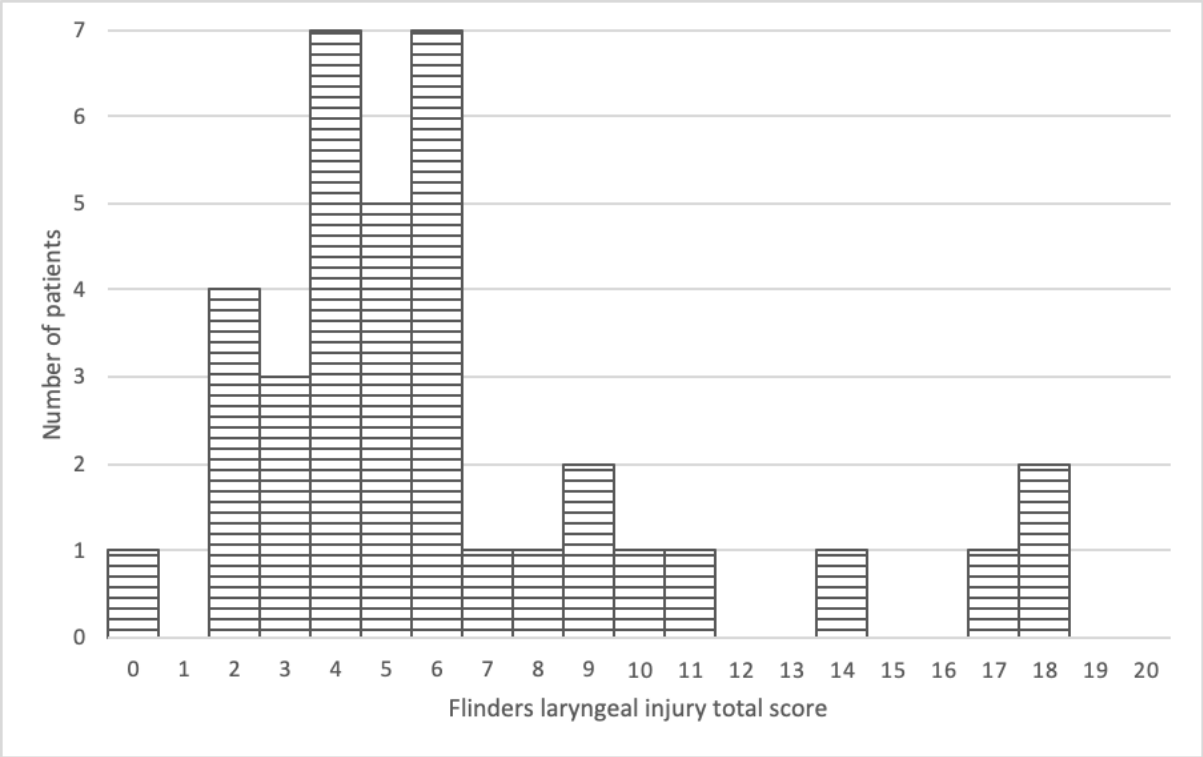

Figure 15 The frequency distribution of the Flinders laryngeal injury total score within 48 hours after extubation in the subset of patients who completed assessments at both time points.
n=37.

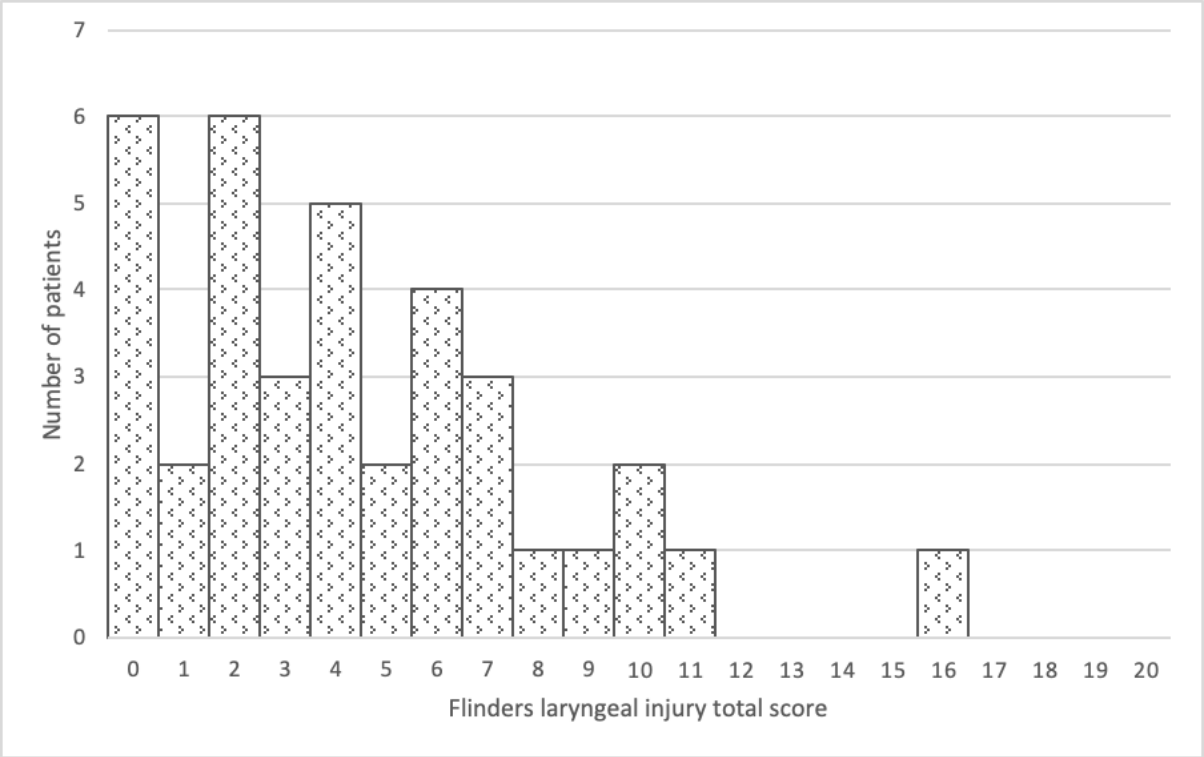

Figure 16 The frequency distribution of the Flinders laryngeal injury total score at 5-7 days after extubation in the subset of patients who completed assessments at both time points.
n=37.

Amongst the patients who received complete assessments at both time points, stroboscopy was incomplete for 3 patients at the second time points. The comparison of the stroboscopic examination is detailed in Table 21 for the 37 patients. Glottal closure was analysed as two groups – complete closure and others (anterior, posterior, hourglass, spindle, irregular and incomplete). Free edge contour was analysed as two groups – normal or abnormal (convex, concave, irregular, rough). Phase closure also analysed as two groups – nearly equal and others (open phase or close phase predominates). Chi-squared test was used to analyse the differences in these groups between the first and second assessment. Glottal closure and phase closure demonstrated significant improvement with more patients having complete closure ($p=0.04$) and equal phase closure ($p=0.04$) at the second assessment. There was a trend of improvement of free edge contour but was not statistically significant ($p=0.15$ and $p=0.25$ for right and left vocal folds respectively).

Table 21 Voice-vibratory assessment with laryngeal imaging using stroboscopy at the two assessment times

Stroboscopy parameters	First assessment	Second assessment
Glottal closure		
Complete	n=10 (31%)	n=15 (45%)
Anterior gap	n=2 (6%)	n=2 (6%)
Posterior gap	n=9 (28%)	n=5 (15%)
Hourglass	n=0 (0%)	n=1 (3%)
Spindle gap	n=9 (28%)	n=9 (27%)
Irregular	n=1 (3%)	n=0 (0%)
Incomplete	n=1 (3%)	n=1 (3%)
Amplitude (%)		
Right	60 (45-60)	60 (40-63)
Left	60 (45-60)	60 (40-63)
Mucosal wave (%)		
Right	55 (40-60)	60 (40-63)
Left	55 (40-60)	60 (40-63)
Supraglottic activity		
Anteroposterior	3 (2-3)	2 (1-3)
Mediolateral	3 (2-3)	3 (1-3)
Free edge contour (right/left)		
Normal	n=14 (41%)/ n=14 (41%)	n=18 (51%)/ n=17 (49%)
Convex	n=10 (29%)/ n=8 (24%)	n=8 (23%)/ n=10 (29%)
Concave	n=8 (24%)/ n=9 (26%)	n=7 (20%)/ n=6 (17%)
Irregular	n=2 (6%)/ n=2 (6%)	n=2 (6%)/ n=2 (6%)
Rough	n=0 (0%)/ n=1 (3%)	n=0 (0%)/ n=0 (0%)
Phase closure		
Open phase predominates	n=13 (38%)	n=11 (31%)
Nearly equal	n=18 (53%)	n=24 (67%)
Closed phase predominates	n=3 (9%)	n=1 (3%)
Phase symmetry (%)	80 (65-90)	90 (80-90)
Regularity (%)	80 (70-90)	90 (80-90)

Data presented as median (IQR) or number of patients (%). Please refer to the voice vibratory assessment with laryngeal injury (VALI) form for stroboscopy assessment in Appendix 3. n=37.

3.1.4 Risk factors for laryngeal injury

No risk factors were associated with the presence or severity of laryngeal injury (using PELLS and FLIS) secondary to intubation using univariate regression.

The presence of a NGT was described as a risk factor for developing laryngeal injury due to contact trauma on the post-cricoid region, however, the use of PPI is a protective factor(Friedman et al., 1981). 77% of patients in this study who received an NGT also received PPI. The patients with NGT who received PPI had a median (IQR) total FLIS score of 4.5 (3.0-6.0) while those who did not receive PPI had a score of 6.0 (2.0-8.5). Mann-Whitney U test was performed to assess the difference between the two groups with a p-value of 0.849.

Analysis was also conducted comparing the patients who were intubated in the operating theatre (FLIS total of 5.5 (4-9)) and those who were intubated outside of the operating theatre (FLIS total of 5 (2.25-6)) with no statistical difference (p=0.214).

Further analysis assessing patient characteristics and outcomes were conducted by dividing the groups according to age (above and below 65 years old) (Table 22), APACHE II score (above and below APACHE II of 19) (Table 23) and duration of intubation (less or more than 5 days) (Table 24). There were no statistical differences in risk factors, injury severity or voice outcomes when grouping the patients by age or APACHE II scores. However, intubation above 5 days is associated with a longer ICCU, hospital stay and worsening in voice outcomes of both CAPE-V overall severity and GRBAS grade (Table 24).

Table 22 Characteristics of patients above and below 65 years of age

	65 years old and below (n=30)	Above 65 years old (n=30)	p-value
Age (years)	56 (51-60)	76 (70-82)	<0.001*
Gender (male)	Male n=23 (77%)	Male n=16 (53%)	<0.001*
APACHE II	18 (16-22)	20(17-24)	0.158
Length of ICCU stay (days)	4.3 (2.7-8.8)	3.9 (2.9-6.7)	0.742
Length of hospital admission(days)	17.4 (8.3-38.6)	13.5 (8.8-26.7)	0.660
Body mass index (kg/m^2)	26 (24-30)	27 (24-34)	0.695
Height/tube ratio (cm)	22.7 (22.2-23.1)	22.8 (21.8-23.6)	0.836
Duration of intubation (days)	2.7 (1.7-6.6)	2.2 (1.6-3.9)	0.446
FLIS total score	5.0(3.0-6.7)	5.6(4.0-9.0)	0.444
PELLS	2(2-3)	2(2-3)	0.263
S/Z ratio	1.2 (0.7-1.4)	1.2 (1.0-1.3)	0.749
CAPE-V overall severity	35 (22-41)	34 (26-42)	0.985
GRBAS Grade	2(1-2)	1(1-2)	0.571

Continuous data presented as median (IQR) and analysed using Mann-Whitney U test, categorical data presented as number (%) and analysed using the Chi squared test. * statistical significance. Abbreviations: APACHE II, acute physiology and chronic health evaluation II; ICCU, intensive and critical care unit; FLIS, Flinders laryngeal injury score; PELLS, post-extubation laryngeal lesions scale; CAPE-V, consensus auditory perceptual evaluation of voice.

Table 23 Characteristics and outcome of patients with an APACHE II score above or below 19

	APACHE II of 19 or below (n=30)	APACHE II abo19ve (n=30)	p-value
Age (years)	61 (55-69)	70 (58-77)	0.122
Gender(male)	Male n=20 (66%)	Male n=19 (63%)	0.196
APACHE II	17 (14-18)	23 (21-26)	<0.001*
Length of ICCU stay (days)	3.5 (2.8-8.5)	5.2(3.1-9.0)	0.430
Length of hospital admission(days)	16.0 (8.3-29.9)	16.1 (8.7-29.1)	0.960
Body mass index (kg/m^2)	26 (23-35)	27 (24-31)	0.871
Height/tube ratio (cm)	22.5 (21.9-23.3)	22.8 (21.9-25.3)	0.496
Duration of intubation (days)	1.9 (1.3-4.7)	2.7 (1.7-6.1)	0.220
FLIS total score	5.5 (3-9)	5(3.3-7)	0.988
PELLS	2(2-3)	2(2-3)	0.575
S/Z ratio	1.24 (0.68-1.42)	1.18 (0.91-1.41)	0.755
CAPE-V overall severity	33 (22-42)	34(25-40)	0.909
GRBAS Grade	2(1-2)	2(1-2)	0.789

Continuous data presented as median (IQR) and analysed using Mann-Whitney U test, categorical data presented as number (%) and analysed using the Chi squared test. * statistical significance. Abbreviations: APACHE II, acute physiology and chronic health evaluation II; ICCU, intensive and critical care unit; FLIS, Flinders laryngeal injury score; PELLS, post-extubation laryngeal lesions scale; CAPE-V, consensus auditory perceptual evaluation of voice.

Table 24 Characteristics and outcome of patients who have been intubated for less and more than 5 days

	Intubation duration <5 days (n=42)	Intubation duration >5 days (n=18)	p-value
Age (years)	69 (57-77)	63(55-71)	0.366
Gender(male)	Male n=27 (64%)	Male n=12 (67%)	0.199
APACHE II	19 (16-22)	22(18-25)	0.055
Length of ICCU stay (days)	3.3 (2.5-4.9)	9.9 (7.6-11.6)	<0.001*
Length of hospital admission(days)	11.5 (7.2-26.5)	24.2 (16.3-46.0)	0.015*
Body mass index (kg/m^2)	27 (24-35)	26 (21-29)	0.134
Height/tube ratio (cm)	22.8 (21.9-23.3)	22.7 (22.3-23.2)	0.747
Duration of intubation (days)	1.8 (1.4-2.5)	7.4 (6.4-8.1)	<0.001*
FLIS total score	6(3-9)	5(3-6)	0.318
PELLS	2(2-3)	2(2-2)	0.562
S/Z ratio	1.2 (0.8-1.4)	1.2(1.0-1.4)	0.386
CAPE-V overall severity	32(22-40)	40(37-44)	0.043*
GRBAS Grade	2(1-2)	2(2-2)	0.026*

Continuous data presented as median (IQR) and analysed using Mann-Whitney U test, categorical data presented as number (%) and analysed using the Chi squared test. * statistical significance. Abbreviations: APACHE II, acute physiology and chronic health evaluation II; ICCU, intensive and critical care unit; FLIS, Flinders laryngeal injury score; PELLS, post-extubation laryngeal lesions scale; CAPE-V, consensus auditory perceptual evaluation of voice.

3.1.5 Association of laryngeal examination findings and voice assessments

To determine if voice assessment is able to identify laryngeal injury, a correlation analysis was firstly conducted between the presence of laryngeal injury (FLIS 0=no injury, 1=presence of injury) and voice assessments (s/z, CAPE-V and GRBAS) to determine if voice assessment is able to identify laryngeal injury. There was no correlation likely secondary to the high incidence of laryngeal injury at 97% in this group of patients. Correlation analysis was then conducted between laryngeal injury severity (rated using PELLS and FLIS total scores) and voice assessments (s/z, CAPE-V and GRBAS) using Spearman's rank correlation coefficient. No correlation was identified between endoscopic findings and voice assessments at either time points (Table 25). Specific laryngeal injuries identified from FLIS also did not correlate with individual parameters from CAPE-V and GRBAS. Stroboscopy findings (presence/absence of glottal gap, mucosal wave and amplitude) were also correlated with voice outcomes with no statistical significance.

Table 25 Correlation of endoscopic findings to voice assessment at the two assessment times

Endoscopic assessment	Voice assessment	First assessment (n=60)		Second assessment (n=37)	
		Correlation coefficient	p-value	Correlation coefficient	p-value
PELLS	S/Z	-0.66	0.641	0.053	0.759
	CAPE-V overall severity	0.145	0.291	0.241	0.151
	GRBAS grade	-0.058	0.673	0.273	0.107
FLIS total	S/Z	0.07	0.619	-0.193	0.253
	CAPE-V overall severity	0.116	0.393	0.162	0.332
	GRBAS grade	0.005	0.975	0.259	0.122

Abbreviation: PELLS, post-extubation laryngeal lesions scale; FLIS, Flinders laryngeal injury score; CAPE-V, consensus auditory perceptual evaluation of voice.

Linear regression was performed to determine if early laryngeal assessment is able to predict short term voice outcomes (Table 26). To determine if the early voice assessment can predict short term laryngeal outcome, the same analysis was performed and presented in Table 27. Neither laryngeal examination nor voice assessments at the early assessment were able to predict the short-term laryngeal and voice outcomes.

Table 26 Correlation of endoscopic assessment at first time point to voice assessment at the second time point

Endoscopic assessment at first assessment	Voice assessment at second assessment	R square	Regression significance
PELLS	S/Z	0.007	0.640
	CAPE-V overall severity	0.002	0.790
	GRBAS grade	0.001	0.831
FLIS total	S/Z	0.001	0.886
	CAPE-V overall severity	0.028	0.319
	GRBAS grade	0.040	0.234

Abbreviation: PELLS, post-extubation laryngeal lesions scale; FLIS, Flinders laryngeal injury score; CAPE-V, consensus auditory perceptual evaluation of voice.

Table 27 Correlation of voice assessment at the first time point to endoscopic outcome at the second time point

Voice assessment at first assessment	Endoscopic outcome at second assessment	R square	Regression significance
S/Z ratio	PELLS	0.099	0.085
	FLIS	0.001	0.871
CAPE-V overall severity	PELLS	0.018	0.448
	FLIS	0.002	0.722
GRBAS grade	PELLS	0.052	0.194
	FLIS	0.006	0.566

Abbreviation: PELLS, post-extubation laryngeal lesions scale; FLIS, Flinders laryngeal injury score; CAPE-V, consensus auditory perceptual evaluation of voice.

3.2 Study 2 Validity and reliability of the Flinders Laryngeal Injury Score

The results of inter- and intra-rater reliability along with the validity of the FLIS are presented here.

3.2.1 Inter-rater reliability of Flinders laryngeal injury score

The reliability of the FLIS has been assessed in this study. Eight raters with variable experiences in examining the larynx were selected. For analysis purposes, they were grouped into the consultant group, trainee group and others. 16 videos were taken from Study 2 with 22 variables assessed for inter-rater reliability. The inter-rater reliability for FLIS total score were assessed for all raters and for each group of raters (Table 28). The consultant group demonstrated the best inter-rater reliability with an ICC of 0.908. The trainees group also demonstrated excellent inter-rater reliability (ICC=0.807), however, when assessing the combined consultant and trainee groups the inter-rater reliability was much lower (ICC=0.623). The median FLIS total score given by the consultant group was 4 (3-8) whereas the median score given by the trainee was 9 (6-13). The inter-rater reliability for each injury was analysed and is presented in Table 29. The table includes two columns – one for the ICC for all the raters and the other for the ICC for the consultant group. When used by raters of variable experiences, the inter-rater reliability ranges from 0.661 for left sided supraglottis oedema to a low of 0.141 for supraglottis granuloma/ulceration. The inter-rater reliability within the consultant group range from 0.926 for right sided supraglottis erythema to a low of 0.098 for supraglottis granuloma. Certain injuries (supraglottic ulceration/ granuloma, glottic mobility, glottic stenosis and subglottic stenosis) were uncommon, resulting in many raters rating 0 for all cases. The statistical package removed all raters with zero variances during analysis resulting in an inability to perform the test or reduced number of raters, and therefore a lower correlation coefficient and a wider

confidence interval. These parameters have been highlighted in Table 29 and should be interpreted with caution.

Table 28 The inter-rater reliability of the different groups of raters when assessing the total Flinders laryngeal injury score

Raters	Intraclass correlation (2,1)	95% confidence interval	Interpretation
All	0.596	0.378 – 0.799	Moderate
Consultant	0.908	0.803 – 0.964	Excellent
Trainees	0.807	0.623 – 0.920	Good
Others	0.556	0.194 – 0.845	Moderate
Consultant and trainees	0.623	0.388 – 0.829	Moderate
Consultant s and others	0.554	0.278 – 0.787	Moderate
Trainees and others	0.643	0.410 – 0.834	Moderate

Intraclass correlation using single measures, absolute agreement and two-way random model. Interpretation of intraclass correlation: poor ICC<0.50, moderate ICC 0.50-0.75, good ICC 0.76-0.90, excellent ICC>0.90(Koo & Li, 2016).

Table 29 Inter-rater reliability of Flinders laryngeal injury score for all the raters

Subsite	Injury	Side	All raters (n=8)		Consultant group (n=3)	
			ICC coefficient (2,1)	95% confidence interval	ICC coefficient (2,1)	95% confidence interval
Supraglottis	Oedema	Right	0.653	0.451 – 0.817	0.699	0.444-0.871
		Left	0.661	0.480 – 0.833	0.721	0.450-0.884
	Granuloma/ulceration	Right	0.141*	0.00 0 – 0.396	0.098*	-1.666-0.455
		Left	0.297*	0.065 – 0.593	0.297*	0.065-0.593
	Erythema	Right	0.582	0.391 – 0.784	0.926	0.841-0.971
		Left	0.588	0.399 – 0.788	0.858	0.707-0.943
Glottis	Oedema	Right	0.334	0.159 – 0.588	0.590	0.311-0.811
		Left	0.303	0.136 – 0.898	0.675	0.400-0.860
	Granuloma/ulceration	Right	0.561	0.372 – 0.769	0.825	0.650-0.929
		Left	0.572	0.383 – 0.776	0.642	0.373-0.841
	Erythema	Right	0.346	0.176 – 0.595	0.543	0.245-0.789
		Left	0.451	0.265 – 0.687	0.776	0.568-0.907
	Mobility	Right	0.269*	0.053 – 0.563		§
		Left	0.535	0.347 – 0.751	0.486	0.192-0.750
	Stenosis		0.216*	-0.074 – 0.560		§
Subglottis	Oedema	Right	0.432	0.249 – 0.672	0.407	0.106-0.700
		Left	0.427	0.245 – 0.668	0.622	0.351-0.829
	Granuloma/ulceration	Right	0.640	0.460 – 0.820	0.858	0.713-0.943
		Left	0.481	0.294 – 0.711	0.622	0.351-0.829
	Erythema	Right	0.583	0.389 – 0.786	0.567	0.273-0.801
		Left	0.520	0.331 – 0.741	0.622	0.397-0.851

Stenosis	0.552*	0.348 – 0.768		§
Total	0.596	0.378 – 0.799	0.908	0.803-0.964

ICC, intraclass correlation; *Interpret with caution as some raters' variables were removed as they had zero variances; § Unable to perform statistics due to no variances in all raters.

3.2.3 Intra-rater reliability of the Flinders laryngeal injury score

The intra-rater reliability of FLIS was assessed by repeating 4 videos. The percentage agreement for each rater was averaged. The overall percentage agreement for all raters was 85%. The highest intra-rater agreement was demonstrated in the consultant group with a mean percentage agreement of 91% and the lowest in the trainee group with a mean percentage agreement of 79%.

3.2.4 Validity of the Flinders laryngeal injury score

The face validity, content validity and concurrent validity of the Flinders laryngeal injury score is assessed here.

The mean VAS score of assessing the usefulness of FLIS when diagnosing laryngeal injury secondary to intubation was 7.6. The mean VAS for assessing whether FLIS covers most types of laryngeal injury secondary to intubation was 9.2.

Content validity ratio was calculated assessing 5 experts' opinion on whether the items in the scale were essential. The CVR for the laryngeal injury for each subsite was 1.0, however, the CVR for the grading for each injury was -0.2.

The FLIS was assessed against the other endoscopic assessment tool in the literature, PELLS, to demonstrate concurrent validity(Antonaglia et al., 2010). While PELLS varies significantly to FLIS, the ordinal scale still indicates increasing severity. When assessing the correlation of PELLS with the total score of FLIS, the spearman rho correlation is 0.745 with a p-value of <0.001, indicating good correlation with statistical significance.

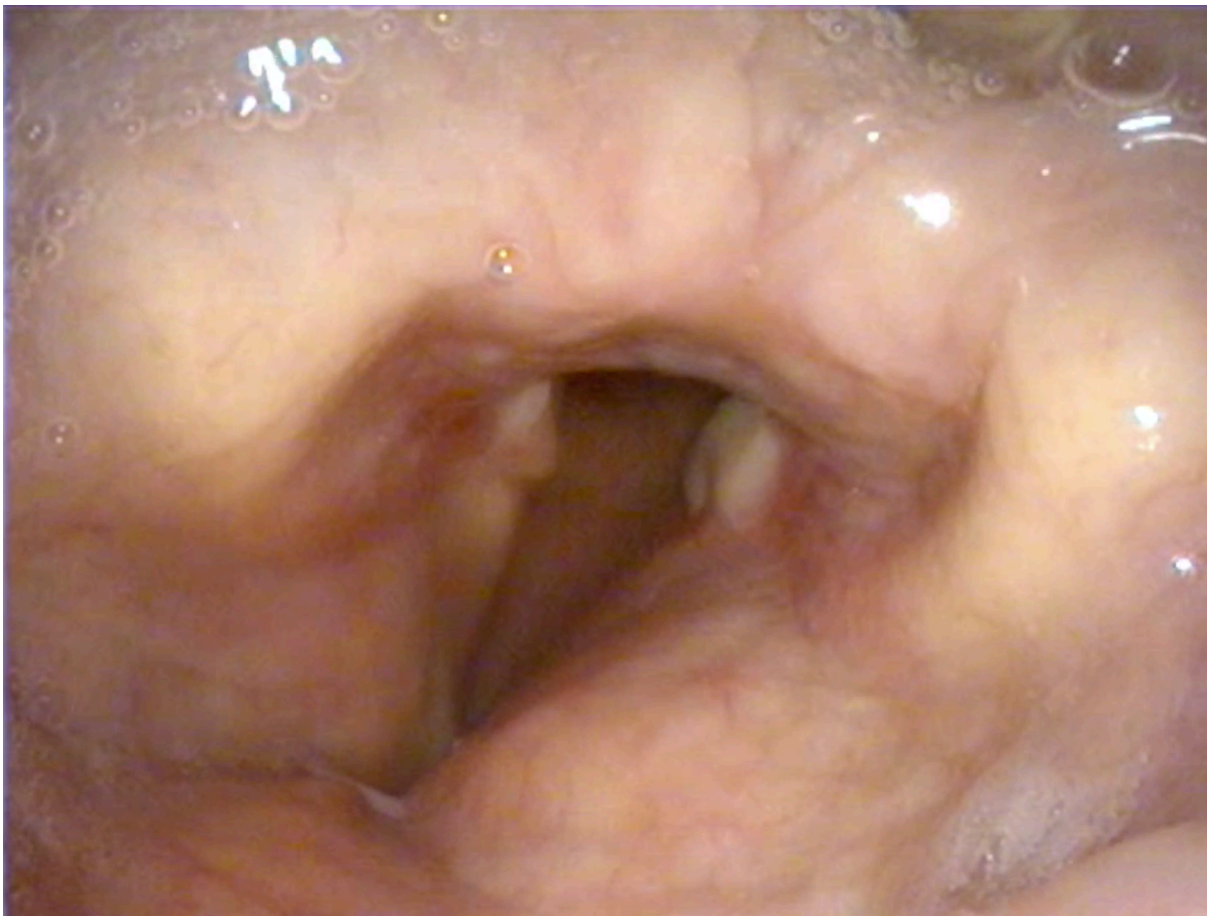

Figure 17 Supraglottis oedema with glottis granuloma

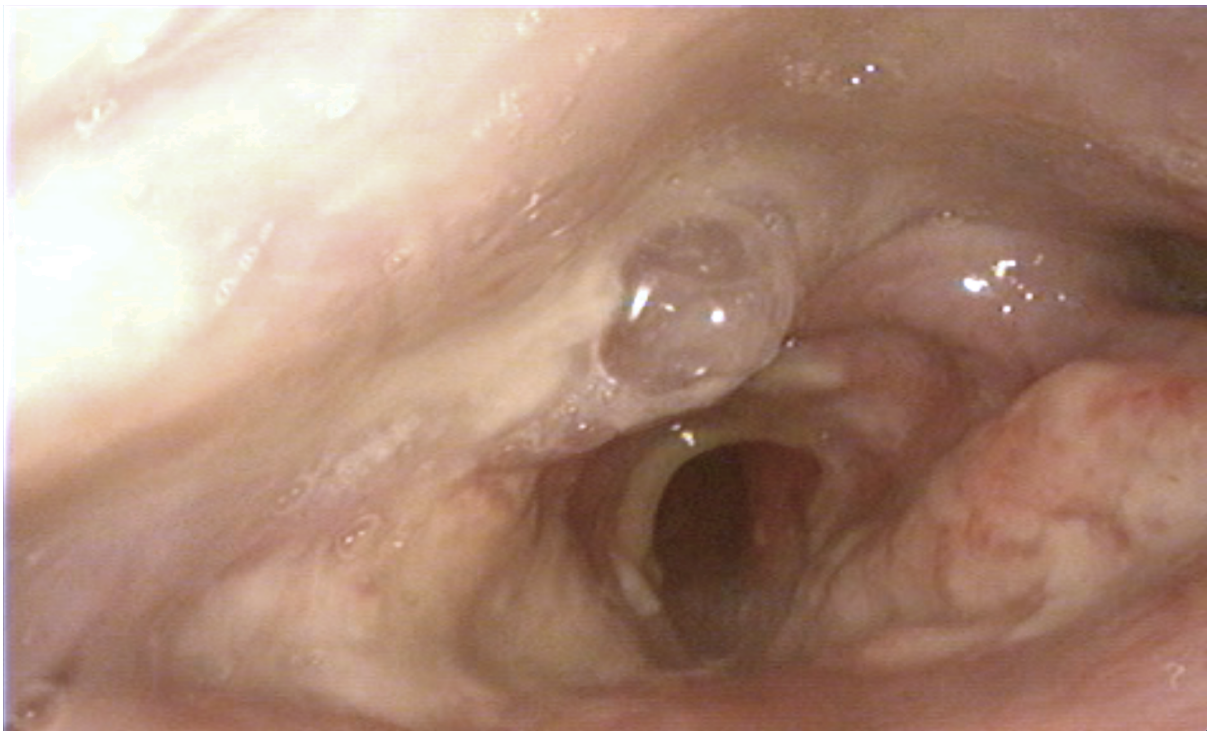

Figure 18 Supraglottis oedema and ulceration

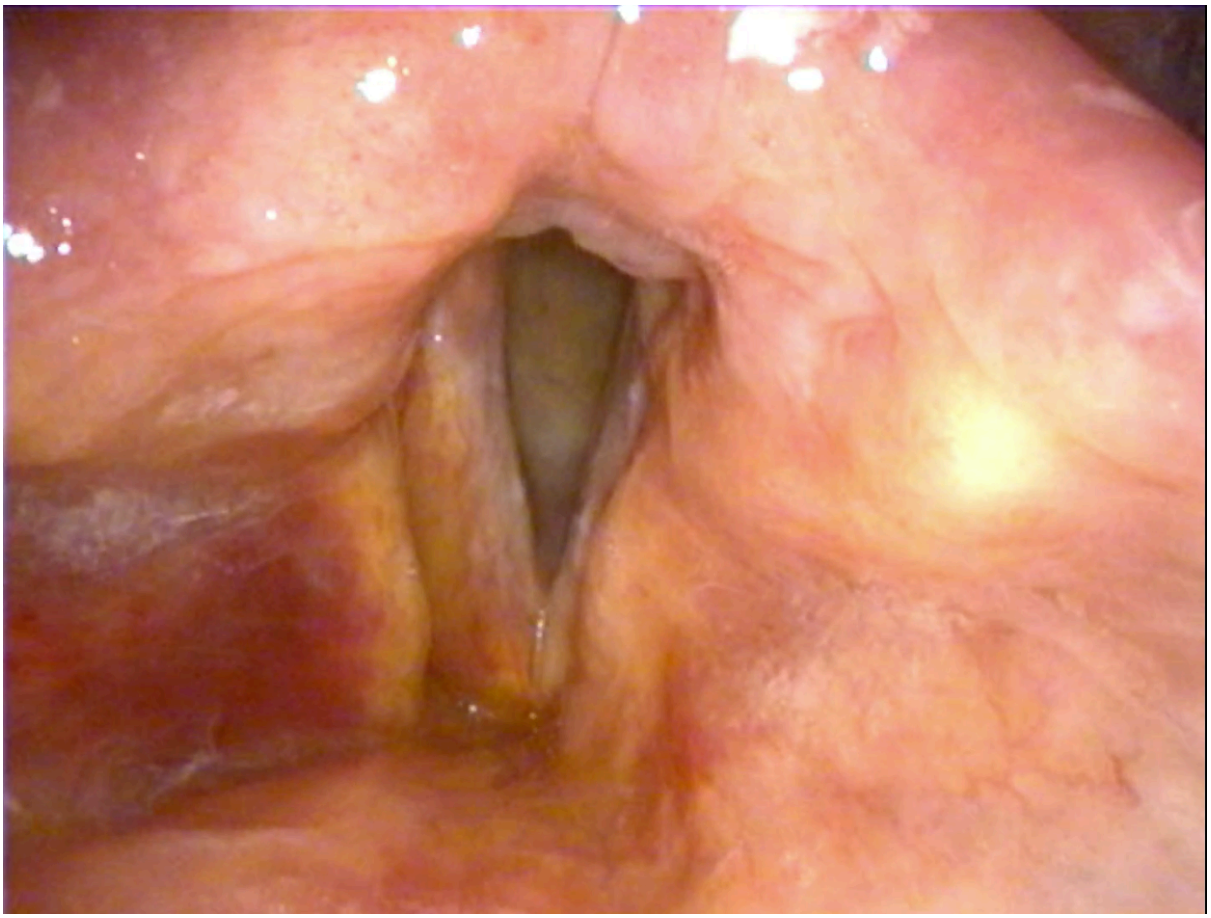

Figure 19 Supraglottis oedema and haematoma

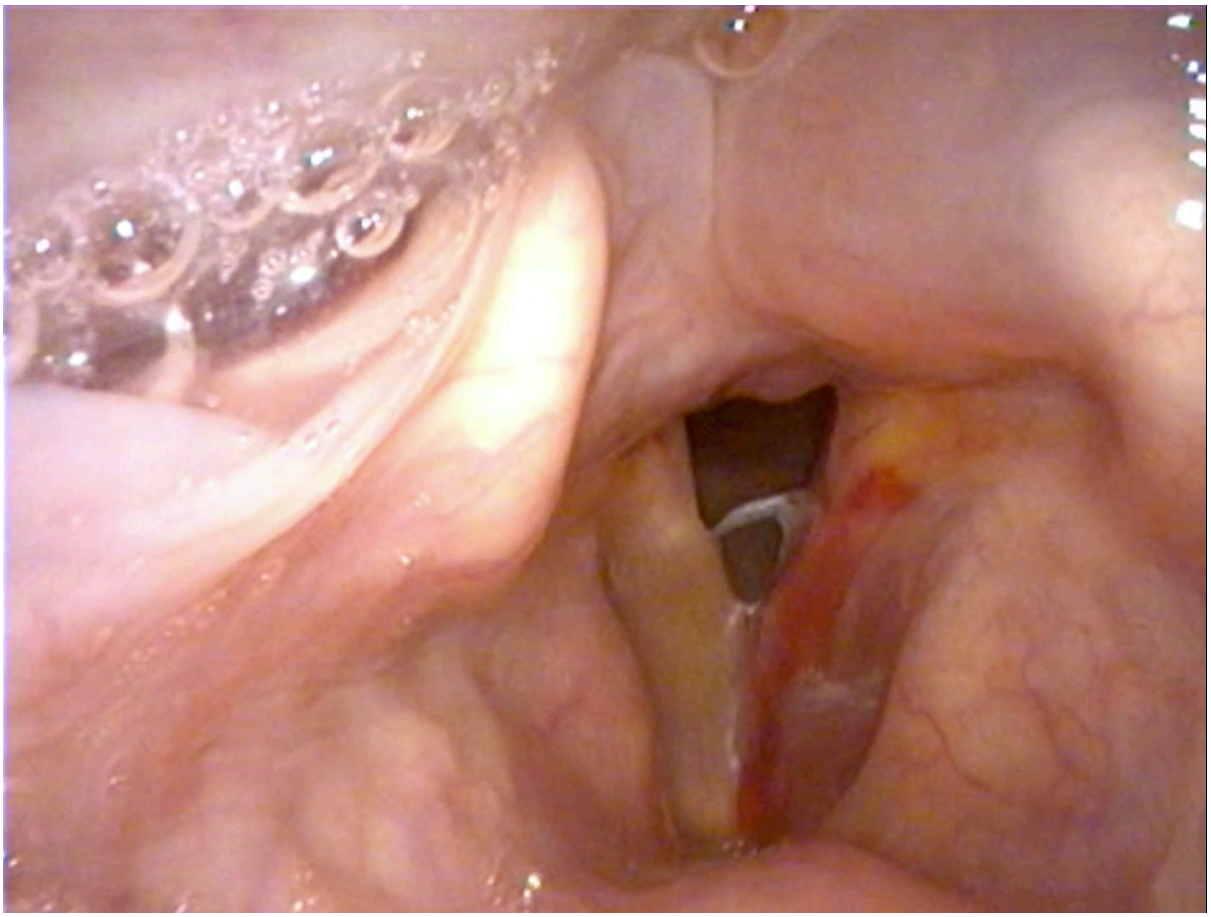

Figure 20 Glottis oedema and haematoma

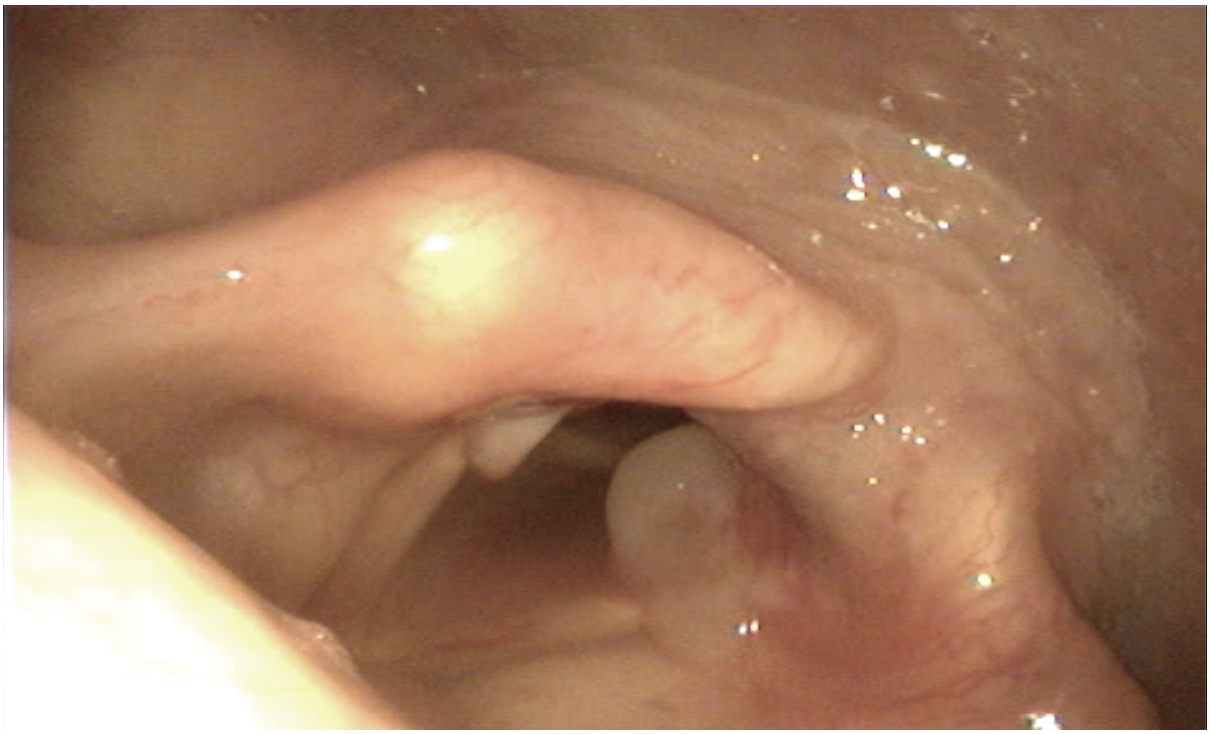

Figure 21 Glottis granuloma

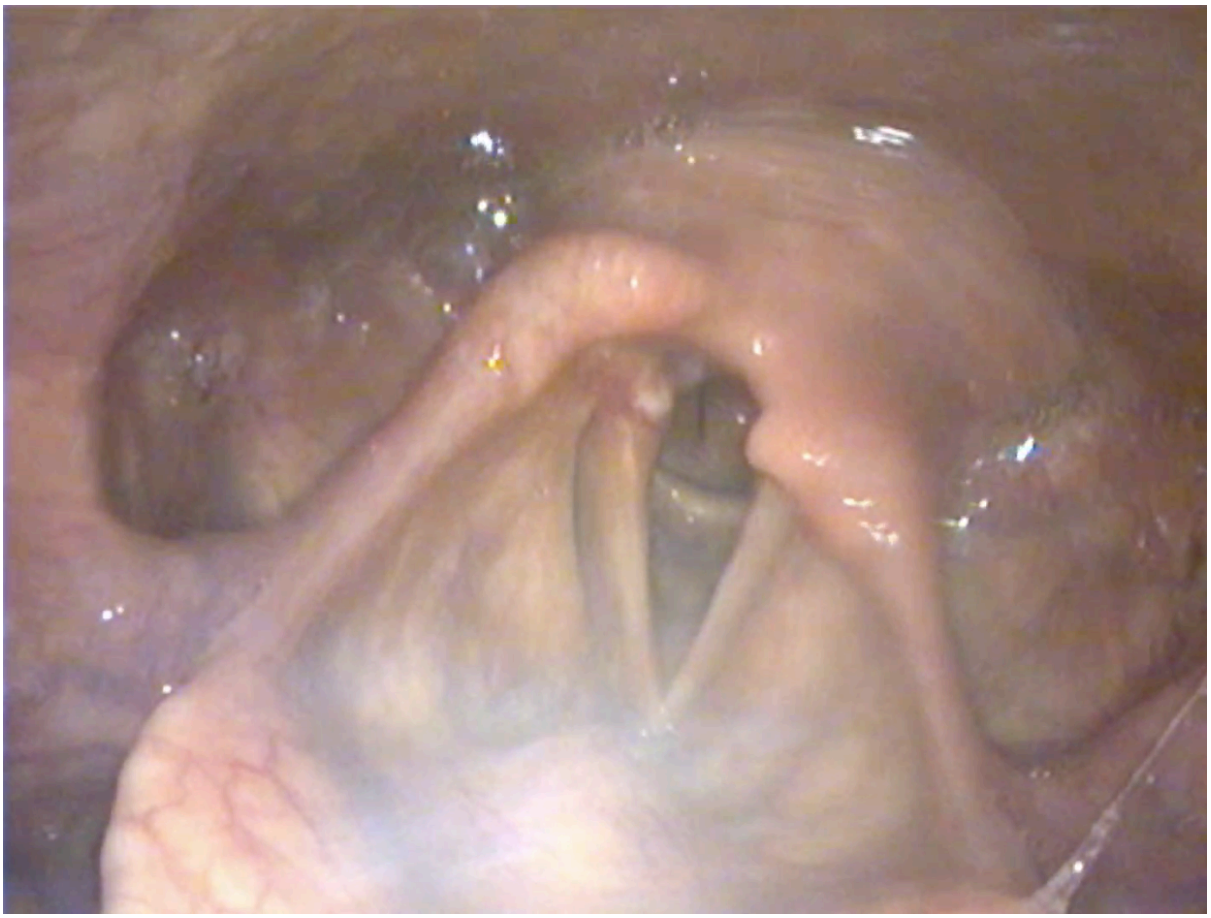

Figure 22 Left vocal fold paresis with glottic granuloma and subglottic oedema

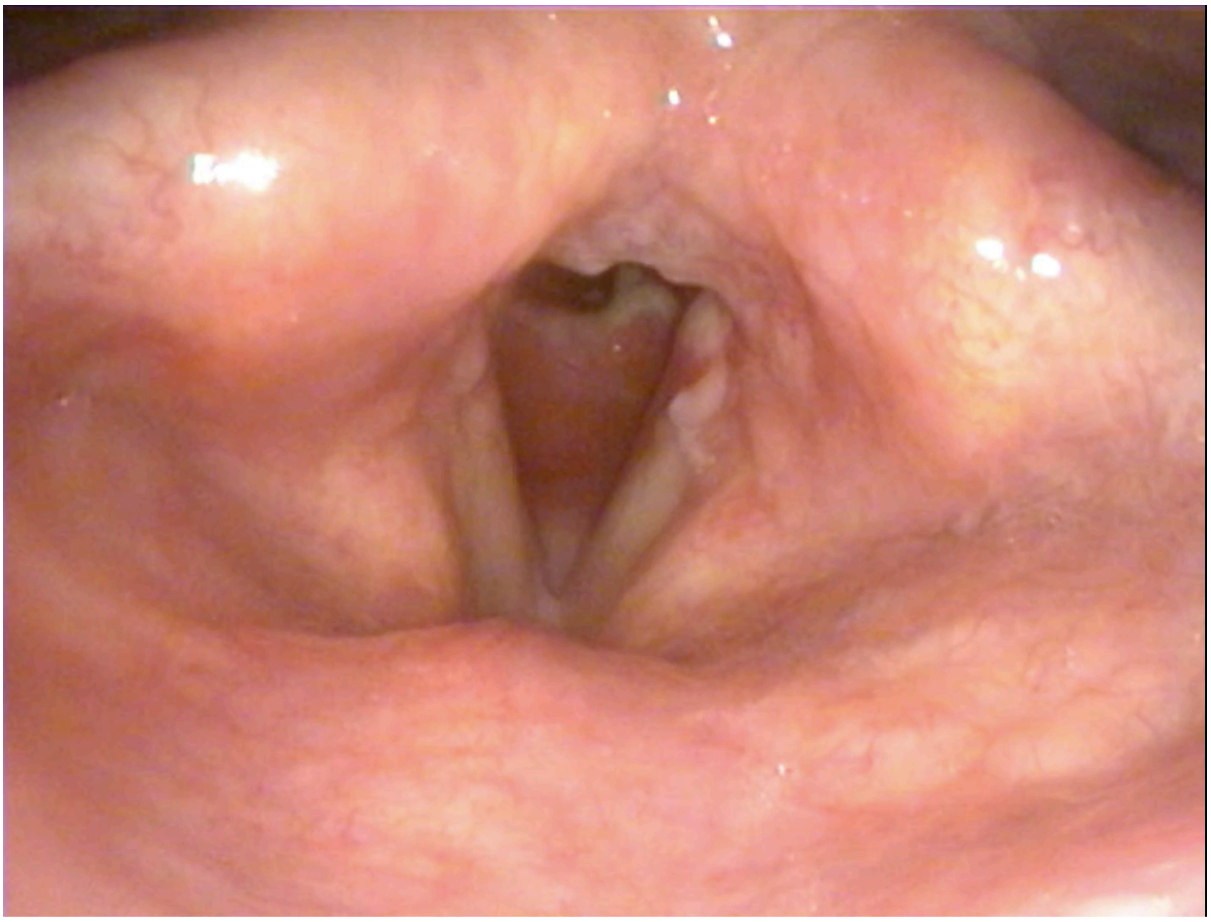

Figure 23 Supraglottic oedema and subglottic ulceration

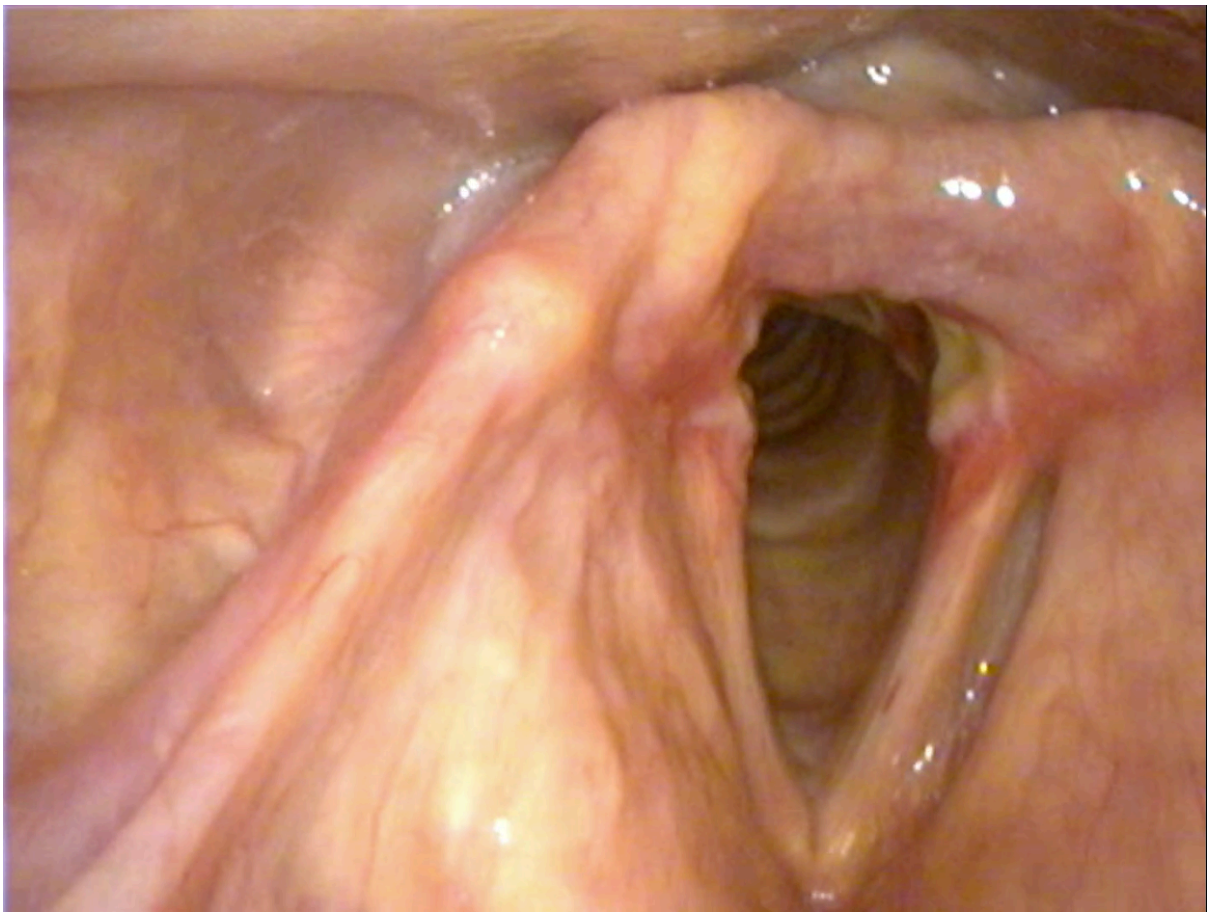

Figure 24 Glottic ulceration and subglottic ulceration

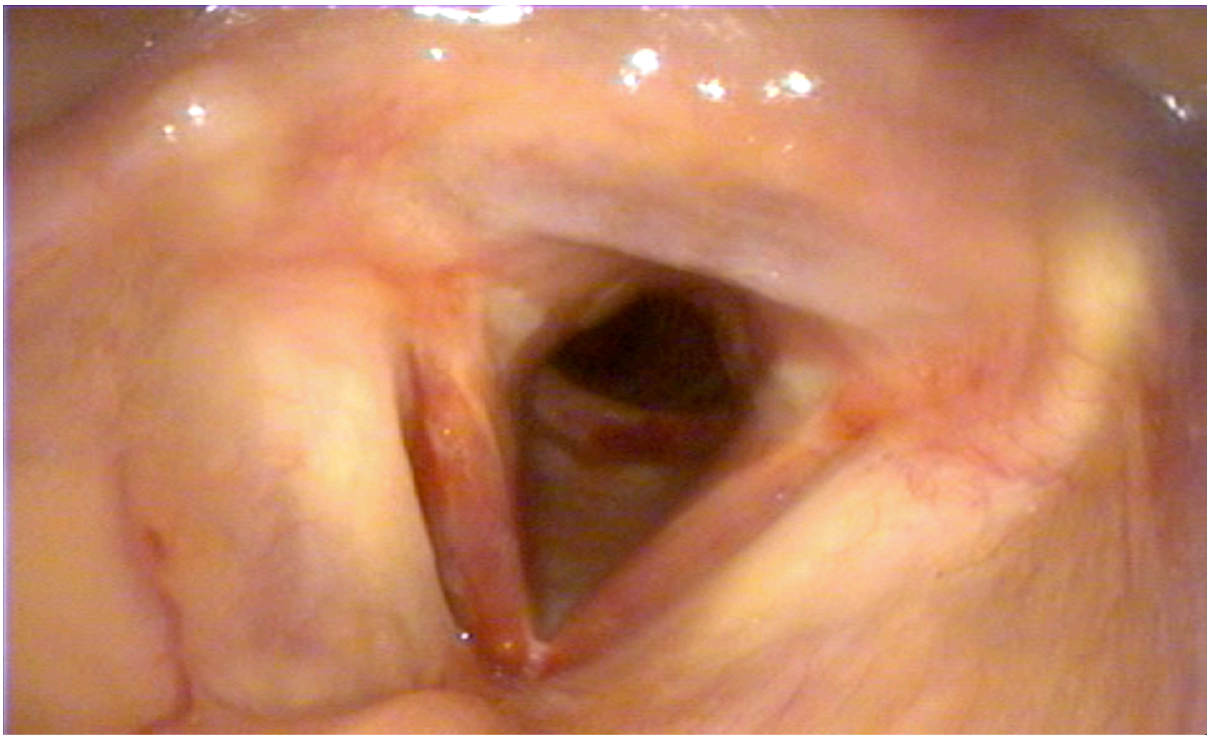

Figure 25 Subglottic erythema

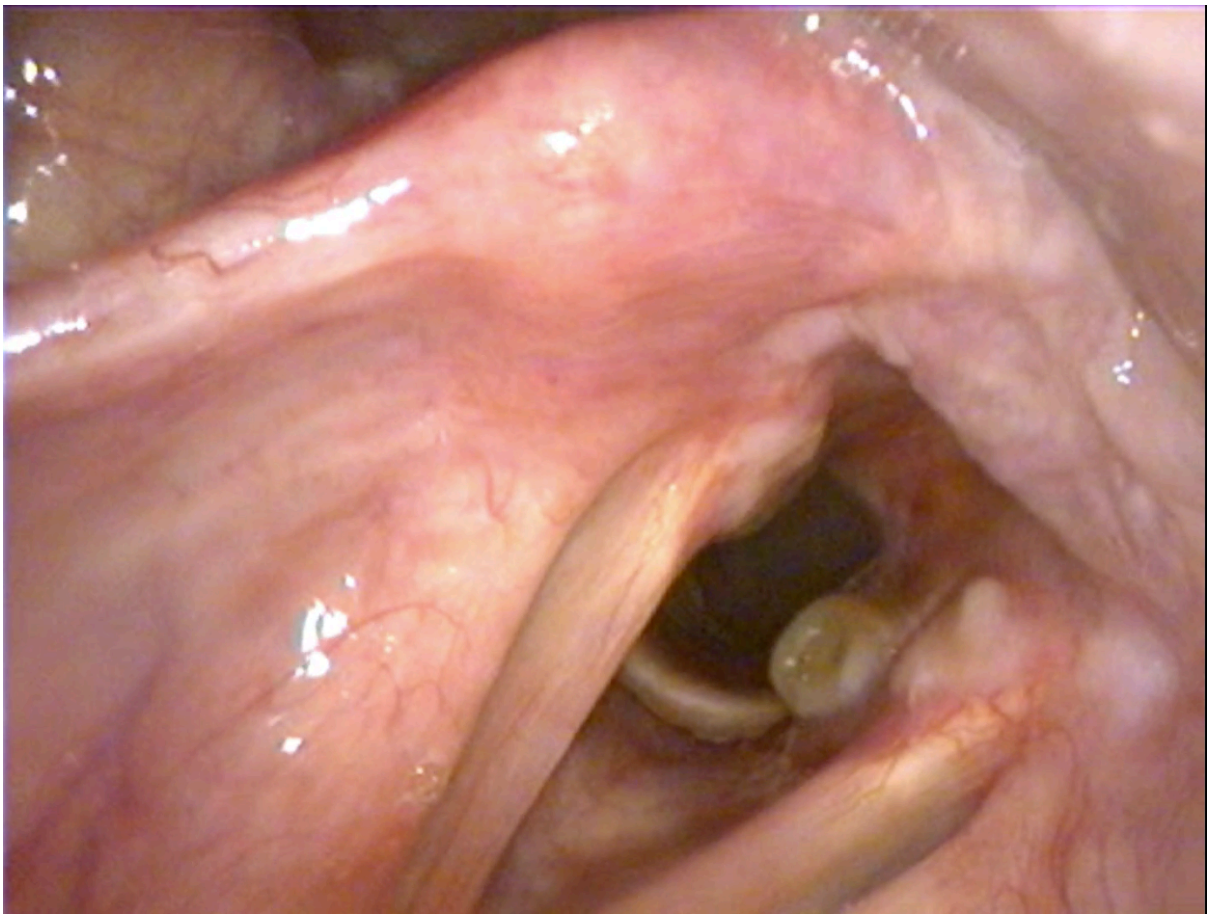

Figure 26 Subglottic granuloma

4 DISCUSSION

4.1 The voice and laryngeal investigation standards post extubation

Intubation practice has evolved considerably since first described in 1788 and was further refined in the First World War(McCartney & Wilkinson, 1995). This practice was abandoned temporarily in the early 1800s when the mortality was deemed to be too high(McCartney & Wilkinson, 1995). Today, following improvement in the ETT material, cuff pressure monitoring, introduction of propofol and neuromuscular blockades, endotracheal intubation is now a well-established life-saving measure widely adopted by anaesthetists, intensive care physicians and emergency physicians(Hunter, 2018). However, prolonged endotracheal intubation in the critically ill population can result in frequent and often unrecognised injury to the upper airway, specifically the larynx. This study set out to characterise the frequency, severity and location of laryngeal injuries after patients have been intubated for over 24 hours in the critical care setting. We hypothesised that bedside voice assessment tools were able to identify laryngeal injuries. However, the voice assessments from this study did not significantly correlate with the type and severity of the laryngeal injury as assessed by digital video transnasal endoscopy. This is an interesting observation and demonstrate that voice is a much more complex function of the larynx than originally thought.

The demographic of the patients and source of admission are similar to the Australian national audit for ICCU patients(ANZICS, 2019). However, the APACHE-II and length of stay were higher than that of the general Australian ICCU population. APACHE-II is the most frequently applied scoring system used in ICCU which measures 12 of the most common physiological parameters at the time of admission to provide information about the general

disease severity and predict outcome(Bouch & Thompson, 2008; Knaus, Draper, Wagner, & Zimmerman, 1985). While the general ICCU population in the national audit has an APACHE II score of 14 (10-19) with a lower estimated mortality, the patient population in this sample has an APACHE II score of 19 (17-23), with close to double the chance of mortality(Knaus et al., 1985). This is reflected by the longer length of ICCU admission of 3.9 days compared to 1.7 days reported by the national audit(ANZICS, 2019). This is likely due to selection bias as patients enrolled in this study have all been intubated for longer than 24 hours, illustrating a patient sample with more significant disease and higher morbidity and mortality compared to the general ICCU population in the national audit.

4.1.1 Incidence and progress of laryngeal injury

The presence of laryngeal injury in patients who were intubated for more than 24 hours in the critical care setting is high – 96.6% when assessed with digital video transnasal endoscopy at 24-48 hours of extubation. This is consistent with that reported in the literature (Brodsky et al., 2018; Colton House et al., 2011; Santos et al., 1994). However, following extubation these patients were not routinely examined by speech pathology or otolaryngology as assessments usually require specialised equipment and skilled personnel. Furthermore, it is not practical to do so with the number of patients extubated every day in a busy, acute-care hospital. Reassuringly, short term follow-up at 5-7 days demonstrated statistical and clinical improvement. However, 83.8% of patients still had some laryngeal injury and mild dysphonia at the second follow up. Despite the presence of laryngeal injury, the majority of patients were discharged with no routine speech pathology or otolaryngology follow up. A small subset of these patients will require intervention as a result of the injury sustained from intubation. The potentially life-threatening presentation of some of these injuries warrant early identification and monitoring.

The impact on vital laryngeal function following prolonged intubation may result in long term adverse outcomes such as dysphagia, dyspnoea and dysphonia. These symptoms can occur together or in isolation(Ta, Liu, & Krishna, 2016). The larynx plays an important role in protecting the airway during swallowing. Up to 24% of patients have diminished gag reflex as a result of sensory deficit immediately after extubation which can easily result in aspiration and increase associated morbidity(Bordon et al., 2011; Colice et al., 1989). Additionally, up to 60% of patients in this study had a glottal gap one day following extubation, further increasing the risk of aspiration. The likely cause of ongoing or progressive dyspnoea is stenosis of the larynx. The presentation of stenosis post intubation is often delayed as scar tissue matures and contracts(Whited, 1984). Posterior glottic stenosis is of particular concern as the posterior glottis is the area which sustains the highest pressure from the ETT and development of stenosis, even in the early stage, can reduce the glottic airway significantly(Lahav et al., 2014). If the airway is compromised enough a tracheostomy may be required to bypass the obstruction. Chronic dysphonia is the most common symptom of laryngeal injury and the most common cause of litigation in those with iatrogenic laryngeal injury(Ta et al., 2016). Dysphonia may result in negative implications for employment, socialisation and self-perception(Cohen, Kim, Roy, Asche, & Courey, 2012; Ta et al., 2016). Early management with speech therapy and voice hygiene may reduce the need for prolonged treatment(Feder, 1983). The impact on a patient's quality of life is not limited to the follow up and treatment for persisting laryngeal injury. The average cost for patients presenting with dysphonia is US $577.18 to US $953.21 per person per year in the United States(Cohen et al., 2012). The cost associated with intubation related moderate to severe laryngeal injury can be up to US $6000 to repair and tracheal injury can cost up to US $11025 per admission(Brodsky et al., 2018). Only three patients in

this study were referred to laryngology clinic due to the severity of their injury at 5-7 days post extubation. An additional patient had new vocal fold paresis. However, they were not dysphonic and had no symptoms of dysphagia. The patient was given the information for referral if required in the future. All other patients with demonstrated improvement in laryngeal injury scores on their second digital video transnasal endoscopy were managed conservatively with voice hygiene and proton pump inhibitors.

The most common injury in this study was glottal ulceration or granuloma with 82% of the patients sustaining this injury (Figure 3). This result is consistent with that reported in the literature(Colice et al., 1989; Colton House et al., 2011). Other commonly reported injuries were arytenoid oedema and erythema. Supraglottic oedema is present in 40% of all patients in this study. Only one patient (2%) had unilateral vocal fold paresis, however, varying degrees of vocal fold immobility is reported up to 41% in the literature(Colton House et al., 2011). The proposed mechanism of reduced vocal fold mobility after intubation is due to compression of the recurrent laryngeal nerve between the inflated ETT cuff and the thyroid cartilage, potentially with a component of myopathy of the intrinsic laryngeal muscles(Colton House et al., 2011).We were unable to demonstrate the association between the size of the tube and the incidence of vocal fold immobility as this study only had one patient with vocal fold palsy. The mean duration of intubation in Colton House's study was 9.1 days, which was three times longer than this study and may have contributed to the higher percentage of immobility observed. Variability in the management of ETT cuff pressure in other studies may also result in different reports of vocal fold mobility. In our institution, there is a strict protocol to ensure the cuff pressure is between 25-30 cmH_2O every 8 hours using a cuff pressure monitor. Other studies have not detailed the care that

was provided to the ETT cuff. The different methods of checking the cuff pressure - palpation of the pilot balloon, listen to air leaks or the use of a pressure monitor - has varying degrees of accuracy(Portia, Dalena Van, & Danie, 2012). The frequency of checking and the target cuff pressure were often not documented. Therefore, the attention given to the care of intubated patients in this institution may have reduced the incidence of vocal fold immobility and therefore also reduced the rate of dysphagia. Rare pathologies described in the literature such as arytenoid dislocation, vocal fold avulsion, or supraglottic stenosis were not observed in this study.

Interestingly, all laryngeal injury including vocal fold immobility were reported in the literature to be more common on the left side(Colton House et al., 2011; Sue & Susanto, 2003). Intubation is generally performed from the right side of the mouth which may cause direct injury to the left side of the larynx. (B. Benjamin, 1993; Colton House et al., 2011). All patients in this study had flexible transnasal endoscopy inserted through the right nasal cavity, unless an NGT was in situ or a deviated septum impeded insertion. This resulted in a better view of the left larynx with some restriction of view especially of the right glottis and right subglottis. At the first assessment, there was a slightly higher FLIS score of the left side indicating greater injury severity, but the difference was not statistically significant. The universal use of neuromuscular blockades in our institution, and success after one attempt in 88% of the intubations may have contributed to an uneventful intubation process and less direct trauma to one side of the larynx.

The incidence of laryngeal injury reduced to 84% at the second assessment and the FLIS demonstrated an improvement in the severity from a median of 5.5 (moderate severity) to 4.0 (mild severity). The lack of significant improvement when assessing severity using PELLS

likely reflects its lack of sensitivity to small changes due to its broad categories. The auditory perceptual assessments also demonstrated significant improvement from moderate to mild dysphonia when using both CAPE-V and GRBAS. These findings are consistent with the literature where the majority of injuries and dysphonia resolve spontaneously within 4 weeks(Colice et al., 1989). However, as these patients are often discharged and the subset of patients who do not improve may be lost to follow up, the recommendation is for otolaryngology referral in those with worsening voice outcomes in those with recent prolonged intubation prior to discharge.

4.1.2 The use of voice assessments to identify laryngeal injury

There is a need for non-invasive methods to identify laryngeal injuries that may persist in this population. However, the results in this study showed that voice assessments using s/z ratio and auditory perceptual assessments were not able to reliably diagnose laryngeal injury after prolonged intubation or predict the progress of these injuries. Other studies that assessed the correlation of voice to other laryngeal pathology also found that voice assessments poorly reflect the endoscopic findings(Chang et al., 2012; Colice et al., 1989; Rzepakowska, Sielska-Badurek, Osuch-Wójcikiewicz, & Niemczyk, 2018). Chang et al reported assessing pre- and post-operative voice outcomes in 18 patients with severe dysplasia or early laryngeal cancer(Chang et al., 2012). They assessed the laryngeal lesions using videostroboscopy, intra-operative images and histology. They also identified the type of cordectomy performed. They did not utilise a formal validated voice assessment, however the parameters assessed correspond to that of CAPE-V - overall grade, roughness, breathiness, strain, pitch and loudness on a VAS. Chang et al found pre-operative overall dysphonia, roughness, strain and post-operative strain and pitch correlated moderately to more extensive cordectomies(Chang et al., 2012). However, they did not find any

correlation between voice outcomes and lesion appearances, location, inflammation, vibrational characteristics or histology. This suggested that those with significant pre-operative voice dysfunction may correlate with the intervention required for their presenting pathology but not with the pathology itself.(Chang et al., 2012). Rzepakowska et al also assessed the correlation between videostroboscopic examination and voice assessments (acoustic analysis, aerodynamic, VHI, dysphonia severity index, GRBAS) in benign, premalignant and malignant laryngeal pathology among 151 patients(Rzepakowska et al., 2018). A weighted score is assigned for different abnormalities seen on videostroboscopy – 1 for limited mobility, limited mucosal wave, dorsal glottal gap and decreased amplitude; 2 for absent vocal fold mobility, absent mucosal wave, glottal gap (oval, hourglass, irregular) and absent amplitude or inability to assess. They demonstrated a moderate to strong correlation between stroboscopic findings and grade, roughness, breathiness and asthenia in the groups with benign and premalignant lesions. In patients with malignant lesions, there was a positive correlation with breathiness, but an inverse correlation with MPT. This can be explained by the likely exophytic characteristics of malignant lesions, causing increased breathiness, reduced efficiency and reduced MPT. Interestingly, the group with malignant lesions was less likely to correlate with overall dysphonia, roughness, breathiness and asthenia compared to benign and premalignant groups despite having more abnormal findings on videostroboscopy. Potentially malignant lesions affect the vibratory function of the vocal fold in a different manner to those of benign or premalignant lesions. Therefore, the nature of the lesion is not reflected by the scoring system designed by the authors. Colice et al also reported the severity or type of laryngeal injury post prolonged intubation did not correlate with the development of chronic hoarseness (>12 weeks) in their population(Colice et al., 1989). A patient's ability to

compensate for their laryngeal pathology may also distort the perceived voice, further complicating the correlation between the voice produced by the patient and the objective laryngeal findings. Several compensatory mechanisms have been described after cordectomies and recurrent laryngeal nerve injuries using the remaining functional muscles(Dewan, Vahabzadeh-Hagh, Soofer, & Chhetri, 2017; Soliman, Hosny, El-Anwar, & Quriba, 2015). Laryngeal compensation may involve the contralateral vocal folds, the ventricular folds or the arytenoids(Soliman et al., 2015). It can reduce voice deviation but cordectomy patients were still unable to produce a voice comparable to those of normal controls (Rzepakowska et al., 2018; Soliman et al., 2015). It is not well understood how the laryngeal pathology disrupts the underlying mechanisms of voice production and how it affects our perception of it. The above studies illustrate that voice production is a much more complex process and cannot be simply correlated to the underlying pathology using the quality of the voice. This is further reinforced in this study when the laryngeal examination findings worsened in 5 patients at the follow up assessment however the voice outcomes improved.

The s/z ratio was used as a quick and simple tool to assess laryngeal pathologies on the vocal fold margins using a quotient of the voiceless /s/ and voiced /z/ phonemes. Those with vocal fold margin pathology will have difficult voicing /z/ due to decreased glottal efficiency, resulting in a larger s/z ratio(Gelfer & Pazera, 2006). The MPT for the longest /s/ and /z/ produced by this patient population is much shorter than the healthy population, even when assessed at the 5-7-day period. Maslan et al's study assessed the MPT in healthy adults with no upper aerodigestive, voice or neurological complaints in patients of a similar age. Their sample had a mean(SD) MPT of 22.27 (+/-1.56) seconds(Maslan, Leng, Rees,

Blalock, & Butler, 2011). Our patient population have all been critically ill and intubated for a median duration of 60 hours. This will have impacted on the respiratory and the neuromuscular system required for voice production. Furthermore, this group of patients were likely to have higher morbidity prior to intubation compared to the healthy sample in Maslan et al's study. Abnormal glottal closure was observed in 55-60% of patients in this study which may result in excessive air escape, reducing the MPT(Cantarella, Baracca, Pignataro, & Forti, 2011). While a statistical improvement was observed for the MPT of /s/ and /z/ between the first and second assessment, the disparity between these patients and the healthy baseline was still significant. Eckel and Boone described s/z ratios to be greater than 1.4 in 95% of dysphonic patients with laryngeal pathology (nodules or polyps). The reduction in /z/ is thought due to a decrease in efficiency and glottal resistance when there is a mass at the glottal margin therefore shortening phonatory duration when producing a voiced sound such as /z/(Eckel & Boone, 1981). At the first assessment in this study, patients had a median s/z ratio of 1.2 which improved to 1.0 at the second assessment, but this was not statistically significant. Even with the high incidence of laryngeal injury, the median s/z ratio did not exceed the threshold of 1.4. The formation of ulceration or granuloma over the vocal process as opposed to the anterior to middle third of the vocal fold where nodules or polyps usually occur is speculated to have less interference with the glottal resistance(Eckel & Boone, 1981; Wallis, Jackson-Menaldi, Holland, & Giraldo, 2004). The injuries to the supraglottis and subglottis are also less likely to have an effect on the s/z ratio. Furthermore, there was no correlation between the s/z ratio and the severity of endoscopic findings or specifically glottic injuries. Of all the patients, 15 patients (25%) had an s/z ratio equal or greater to 1.4 when assessed within 48 hours post extubation. This is marginally higher than Van der Meer's study that showed 19% of their patients had s/z

ratios greater than 1.4 at 24 hours after being intubated for a median of 40 hours(Van der Meer et al., 2010). Van der Meer reports s/z ratio has 100% sensitivity and 93% specificity of diagnosing vocal fold immobility 24 hours after a period of intubation. In this study, only one patient was found to have reduced vocal fold mobility at both assessments. The s/z ratio was 1.4 and 1.8 respectively at the first and second assessments. This is consistent with the 100% sensitivity proposed by Van der Meer. The specificity is 75% at 24 hours post-extubation and 83% at 5-7 days post-extubation, slightly lower than the specificity of 93% reported(Van der Meer et al., 2010).

4.1.3 Risk factors for laryngeal injury

Multiple studies have attempted to examine contributing risk factors to laryngeal injury in order to optimise the care provided. A number of factors influence the presence and severity of laryngeal injury reported - minimum duration of intubation, timing of assessment after extubation, quality of investigating instruments and validity of assessment tools. Patient characteristics (female, high BMI), medical history (smoking status, diabetes), history of voice overuse, intervention (NGT), medications (proton pump inhibitor, steroids), intubation details (number of attempts, size of tube, height tube ratio, Cormack Lehane score, mean cuff pressure) all failed to correlate with laryngeal injury scores. The lack of statistical significance is contradictory to many other studies and will be discussed further(Bishop, 1989; Brodsky et al., 2018; Santos et al., 1994; Whited, 1984). However, this result is similar to that presented by Colton House(Colton House et al., 2011). Interestingly, Colton House also presented a scoring system similar to that of FLIS (Table 9). Neither FLIS nor the scoring system from Colton House et al had weighted scoring for the more clinically severe injuries. This may underestimate the true severity of an injury and consequently affect the relationship of the risk factors to the true outcome. The argument provided by

Colton House et al for the lack of association with the above risk factors is the largest tube size used in their study (8.0 with an outer diameter of 10.7-10.9mm) could still easily fit into a female larynx which has been reported to be an average of 17mm in length (Bishop et al., 1984; Colton House et al., 2011). Improvement in the material of ETT, regular cuff monitoring, oral hygiene and overall advances in critical care medicine may have also reduced the contribution of these risk factors to laryngeal injury over time.

Given the mechanism of laryngeal injury secondary to prolonged intubation is due to ischaemia of mucosal tissue caused by the compression of the ETT, the duration of intubation and excessively large ETT are thought likely be significant contributors to laryngeal injury. However, many studies including this study have not shown this to be the case(Colton House et al., 2011; Kastanos et al., 1983; Scheel, Pisegna, McNally, Noordzij, & Langmore, 2016; Stauffer et al., 1981). In the systematic review on laryngeal injury post-prolonged intubation done by Brodsky et al, nine studies were identified with a mean (SD) intubation period of 8.2 (6.0) days. There was increased prevalence and severity of injury in those who were intubated for 5 days or more. This was consistent with other studies that have demonstrated duration being a risk factor(Santos et al., 1994). The median intubation time in this study was 2.5 days, therefore, the duration of intubation may not have been long enough in this patient cohort to demonstrate a statistically significant effect. When grouping the patients into those who have been intubated for less or more than 5 days, the laryngeal severity was not significantly different. However, the voice assessments demonstrated statistically worse dysphonia in those who have been intubated for more than 5 days (Table x).

Historically, the appropriate sizing was 9.0-10.0 ETT tube for males and 7.0-8.0 for females(Magill, 1930). However, as the tracheal diameter correlates with height and the reduction in ETT size did not affect airway resistance as much as previously thought, the up-to-date recommendation is 7.0-8.0 for male and 6.5-7.0 for female according to the average height(B. Benjamin, 1993; Coordes et al., 2011; Farrow, Farrow, & Soni, 2012). Coordes et al also developed a nomogram to guide selection of ETT tube size depending on height of the patient regardless of gender(Coordes et al., 2011). All male patients in this study were intubated with a size 8.0 tube and female with 7.0-7.5 tube. A smaller height tube ratio was suggested to be a risk factor of developing post-extubation stridor and vocal fold immobility(Tadié et al., 2010). Tadie et al investigated 138 patients who were intubated for a mean (SD) of 6.9(+/-8.6) days at 2.8(+/-3.7) hours post extubation with flexible laryngoscopy. Their study differed to ours as their assessment period fell within the immediate post extubation period, thus capturing a different set of complications, therefore the results were not fully comparable. Those who developed abnormal vocal fold mobility and post extubation stridor had a mean height tube ratio of 219.3(± 13.2) mm and 215.3 (± 13.1) mm respectively. They were both statistically different to the groups who did not develop those pathologies. However, the height tube ratio was not statistically different when comparing the group with laryngeal pathology (224.2 ± 13.7mm) to those with normal laryngeal examination (226.8 ± 16). The median height tube ratio in our study was 227 (219-233) mm and did not correlate with laryngeal injury either. The selection of ETT size in our institution was largely based on gender than height and has resulted in a height tube ratio larger than the values reported in Tadie et al's study. This suggests that size selection based on gender in our study was appropriate. However, extremes in height may still warrant consideration of an alternative size tube.

Studies have reported using steroids prior to extubation may increase the extubation success rate(Jaber, Jung, Chanques, Bonnet, & Marret, 2009). No steroids in this study were given to prevent post-extubation stridor or increase extubation success. Amongst the different types of steroids, only methylprednisolone given at least 12 hours prior to extubation had been shown to reduce the rate of re-intubation(François et al., 2007; Wittekamp et al., 2009). 33% of patients in this study received various steroids (methylprednisolone, dexamethasone, hydrocortisone, prednisolone) via either nasogastric or parenteral routes, with 70% being parenteral hydrocortisone. In this study, we have found no correlation between receiving steroids and the reduction in incidence or severity of laryngeal injury. Neuromuscular blocker is another advancement which have been demonstrated to facilitate intubation and reduce laryngeal injury(Mencke et al., 2003). 98% of patients received neuromuscular blockers during induction. One patient had no documentation of use, however, the standard practice in this institution is to administer neuromuscular blockers at induction. The different neuromuscular blockers used in this study were also not associated with the degree of injury. The majority of patients were intubated in the operating theatre using rocuronium. These were likely to be elective cases with an airway plan in place, conducted in a controlled environment with skilled staff available. The location of intubation along with the number of intubation attempts were not associated with the severity of laryngeal injury. Risk factors that were speculated to contribute to laryngeal injury but assessed to be non-significant in this study were BMI, smoking history, prior voice abuse and the presence of an NGT.

Gaynor and Greenberg suggested poorly controlled insulin dependent diabetic patients were at higher risk of developing respiratory distress after being intubated for 4 days or

more as they are more susceptible to infection(Gaynor & Greenberg, 1985). Their assessment was based on a retrospective case note review of 372 intubated patients. 5 of the 6 patients (which was 6% of their patient sample and 36% of all poorly controlled diabetic patients) who developed respiratory distress secondary to laryngeal injury had poorly controlled diabetes which led the authors to conclude that a diabetic patient is at significantly higher risk of laryngeal complications when intubated for more than 4 days and early tracheostomy was recommended. This recommendation should be interpreted carefully, as this was based on a retrospective chart review. Respiratory failure was the original indication for intubation for all their patients which may confound the outcome, as respiratory distress after extubation may not be solely attributed to laryngeal injury.

In this study, 21% of patients were reported to be dysphagic post-prolonged intubation requiring speech pathology input. The patients were documented to be dysphagic if there were clinical signs of aspiration or observed aspiration of secretions on endoscopic examination, raising awareness for further speech pathology assessment. In Brodsky's systematic review, half of all patients in their included studies experienced dysphagia(Brodsky et al., 2018). In the study performed by Scheel et al where a flexible endoscopic evaluation of swallow (FEES) was performed after a mean (SD) intubation of 9.4(6.1) days, 56.8% of their patients had either signs of penetration or aspiration consistent to that presented by Brodsky et al(Brodsky et al., 2018; Scheel et al., 2016). This study demonstrated lower incidence of dysphagia compared to the others which could be due to many reasons. One possible reason is the shorter median intubation duration of 2.5 days compared to the other studies. The injuries caused by the shorter duration of intubation may not be significant enough to impact on swallow. Without examining all patients using

FEES or videofluoroscopic swallow study (VFSS), those with penetration or silent aspiration may be missed. Scheel et al also reported only 22% of their study population qualified for dysphagia if only assessed for aspiration alone, which is similar to the results in our study(Scheel et al., 2016). The high incidence of dysphagia may also be related to the 20% of patients who experienced vocal fold immobility in their review(Scheel et al., 2016).

No risk factors were identified to contribute to laryngeal injury post prolonged intubation. This is an unexpected finding. The evaluation tool used, shorter intubation duration, optimisation of modifiable risk factors and the improvement in the care provided in the modern intensive care setting may have all contributed to this finding.

4.1.4 Difficulties encountered

Stroboscopy is a very useful tool for additional relevant diagnostic information and is currently deemed the gold standard for vocal fold evaluation(Bonilha, Focht, & Martin-Harris, 2015). As vocal fold vibration is too fast for human eye to appreciate, stroboscopy uses acoustic or electroglottographic signal to predict and sample consecutive cycles. However, in those with moderate to severe dysphonia the ability to predict the glottal cycle is limited which results in asynchronous images. This is not an uncommon occurrence and is reported as high as 17-63% in the literature(Powell et al., 2016). This group of patients may benefit from high speed videoendoscopy when it becomes more widely available. The VALI assessment form (Appendix 3) provides descriptive observations over several parameters rather than a severity index or a diagnosis(Poburka et al., 2017). It is useful to monitor a patient's progress over time but may be difficult to interpret as a once off assessment. Moderate supraglottic constriction also limits the evaluation of vocal fold with stroboscopy when phonating. Supraglottic constriction is thought to be due to excessive or imbalanced

use of laryngeal musculature(Stager, 2011). It is also a protective mechanism in those with vocal fold paresis and glottic gaps(Stager, 2011). However, the studies investigating the supraglottic constriction were in patients with functional dysphonia and not in the population who have been recently intubated. Injuries sustained from intubation may put additional strain on the supraglottis causing further constriction(Behrman, Dahl, Abramson, & Schutte, 2003). The supraglottis itself may also be more oedematous after recent intubation. These were all possible mechanisms resulting in excessive supraglottic constriction making the assessment of the vocal folds with stroboscopy more difficult.

No complications occurred as a result of this study. The use of flexible digital video transnasal endoscopy for investigation was largely uneventful for the majority of patients. Some patients reported mild discomfort associated with the taste of Co-Phenylcaine spray and the insertion of the endoscope. Five patients were referred early to the speech pathologists for further swallowing assessments due to large glottic gaps or aspiration of secretions seen on endoscopic examination. One patient reported worsening swallow following the second assessment with a subsequent normal VFSS. This patient had a laparotomy for ischaemic bowel, was intubated for 48 hours and had an NGT in situ for one week. She only reported difficulty after resuming a solid diet which coincided with her participation in this study. The subjective difficulty in swallowing is likely secondary to her admission indication and management.

4.1.5 Strengths and limitations

This is a difficult cohort of patients to recruit as they were all critically ill requiring prolonged intubation. The sample size is one of the largest to date and is representative of the Australian ICCU demographic. Loss to follow up at the second assessment is a potential

cause of bias, however, the 37 patients who completed both assessments had comparable characteristics to those who only completed the first assessment. This study provides the most comprehensive assessment of both the voice and the laryngeal examination so far, using several of the gold standard methods of assessment. The evaluation tools were selected for their simplicity of use (s/z) or validity (GRBAS, CAPE-V, VALI). Unfortunately, there were no validated tools for laryngeal assessment, but Study 2 discusses the development and validity of FLIS to address this gap. Several methods were employed to reduce the bias of subjectivity when using perceptual ratings. Both voice and laryngeal assessments followed a standard procedure. All the examinations were recorded and anonymised. All raters were blinded to the identity and history of the patient as outlined in the methods to reduce cognitive bias(Sauder & Eadie, 2018). Independent assessments were conducted by two experienced raters from each field, all with special interests in the larynx and voice.

There were several limitations in this study. Many patients were reluctant to participate in research studies after having been intubated for critical illness. Others were lost to follow up at the second assessment time point due to refusal or early discharge. Full cooperation is required from the patients in order to participate in the study, therefore all patients needed to consent for themselves and third-party consent was not appropriate. All the above reasons reduced the number of study participants and may have potentially contributed to our findings. This study did not capture all the patients who were extubated in this intensive care unit. As patients were assessed at approximately 24 hours post extubation, those who were re-intubated or converted to a tracheostomy due to laryngospasm, post-extubation stridor, or respiratory failure were excluded from recruitment as these presentations often

occur within minutes to hours after extubation. This, along with the other exclusion criteria introduced a selection bias. Patients with the most severe form of laryngeal injuries may have been excluded. These patients were likely to have a longer duration of intubation and may have resultant delirium, cognitive impairment, dysphasia or remained unstable. This study also made the assumption that there were no laryngeal injury or pre-existing unreported dysphagia and dysphonia prior to intubation, however, these would most likely have been identified when collecting data from the case notes. Given the high incidence of laryngeal injury at 96.6% and the majority of patients developing moderate dysphonia, there were not enough patients to form a comparative group which limited the statistical analysis that can be performed. The rationale behind choosing perceptual assessment tools in this study is for its practicality and ease of use by the bedside. Auditory perceptual assessments while subjective are considered gold standard as the voice is perceptual in nature(Oates, 2009). However, voice assessment is multi-dimensional and perhaps other tools requiring specialist analysis such as acoustic analysis, aerodynamics and patient reported outcomes may provide more insight into the relationship between voice and endoscopic findings of laryngeal injury after prolonged intubation.

4.1.6 Conclusion of the voice and laryngeal investigation standards post extubation

Laryngeal injury is very common, up to 96% in this patient population. It is also under recognised in those who have been intubated for more than 24 hours. Even though these patients demonstrate improvement clinically, the incidence of injury and presence of voice abnormality remained high after 5-7 days. Although dysphonia indicates underlying laryngeal injury, the current bedside voice assessment tools were not able to diagnose laryngeal injury or its severity. It is also difficult to stratify the risk of developing laryngeal injury using previously described risk factors as modern medical care has largely optimised

the ETT care they receive and reduced the morbidity of these patients. Despite both endoscopic and voice assessments demonstrate significant improvements by 5-7 days, voice assessments were not able to predict the laryngeal outcome and vice versa. Being aware of potential long-term side effects and life-threatening complications of prolonged intubation is important when looking after patients who have recently been intubated in the ICCU. Early referral to speech pathology or otolaryngology is required for further investigation if these patients present with red flag signs of persistent or worsening dysphonia, dysphagia and dyspnoea.

4.2 Validity and reliability of the Flinders Laryngeal Injury Score

The FLIS was designed for use in patients with translaryngeal injuries, which is most commonly due to endotracheal intubation. It was not designed to describe larynges with malignant lesions or the post-operative larynx. To assess these other pathologies, the scoring system will need to be expanded to include descriptions of lesions and their locations in further detail. A scoring system such as FLIS which assesses the type and severity of laryngeal injury was necessary in order to answer the questions being asked in Study 1. It can also be used to communicate between clinicians in the clinical setting and evaluate improvement in patients over time. A literature review identified many other studies have created their own scoring system when examining the post-intubated larynx, but these have been over-simplified or have never been validated(Antonaglia et al., 2010; Colton House et al., 2011). This study proposes that standardising the post-intubated laryngeal assessment with FLIS will provide consistency in reporting laryngeal injuries and allow comparison between research studies.

A good scoring system requires it to be as objective as possible with ways to reduce bias. It is critical to have good inter and intra-rater reliability. For it to be widely used it should follow the convention of existing clinical practice and needs to be easy to apply(Boateng et al., 2018). FLIS is an ordinal scale - the higher the score, the more severe the laryngeal injury. The scoring system was designed to not only identify the presence of an injury but also rate its severity. Subjectivity is introduced into the scale when using visuo-perceptual judgement to assess severity, however, it allows assessment of the larynx in greater detail. In order to allow interpretation of all ratings in the same way, photos of the described injury

pathology were presented at the education session for reference. This can be further enforced by providing a figure of the respective laryngeal injuries with the scoring system.

Validity is crucial to ensure the scale developed is able to measure the underlying construct(Boateng et al., 2018). Content validity is to ensure this scale has the relevance and representation for its use and can be assessed using content validity ratio (CVR)(Boateng et al., 2018; Zamanzadeh et al., 2015). CVR was assessed by five otolaryngology consultants of their opinions on the items in FLIS. There were two sets of items in this scoring system – one being the laryngeal injuries for each subsite, the other being the rating for each type of injury. All the experts expressed that the injuries assessed for each subsite were essential - when assessing a recently extubated larynx, each of the items would be considered. However, three of the five experts indicated they would not consider the severity rating for the injuries to be essential, each of which will be discussed further.

Concurrent validity assesses the correlation of the new scale to an existing gold standard(Boateng et al., 2018; Cook & Beckman, 2006). Given there is none available, concurrent validity was assessed by correlating FLIS to PELLS. PELLS is an easy 5-point ordinal scale with ascending severity. It demonstrated good correlation with FLIS providing it with concurrent validity. However, the simplicity of PELLS reduces its utility in assessing complex laryngeal injuries and makes it a less sensitive tool to small changes. This is reflected when FLIS demonstrated statistically significant improvement between the two assessment times in Study 1 and PELLS did not (Table 20). Figure 4 demonstrated the spread of severity when the injuries were assessed using FLIS, with a differently shaped distribution curve when assessed using PELLS (Figure 5). While the patients were skewed towards the lower FLIS, the majority of patients were in the moderately severe category of degree 2

when assessed using PELLS. Furthermore, the injuries described in PELLS do not necessarily correspond to the assigned severity. A small subglottic ulceration (degree 4) may have less clinical consequence than a large vocal process granuloma (degree 2). Other important laryngeal injuries, such as vocal fold immobility or stenosis, were also not included.

One of the feedbacks received was that there were too many severity ratings per item. For example, it has been suggested to simplify the items 'oedema' and 'erythema' and 'ulceration/granuloma' to a dichotomous scale being absent or present. It can be very subjective to evaluate the degree of oedema in the percentage format (<25%, 25-50%, 50%) and the lighting of the endoscope may also impair the ability to assess erythema accurately. However, there may be a significant difference in severity if a patient is to present with severe oedema as opposed to mild oedema, and a haematoma as opposed to hyperaemia. Changing the 4-point scale of to a 3-point scale with 0 being none, 1 being mild and 2 being severe for 'oedema' and 'ulceration/granuloma' may reduce the complexity but retain the details of the severity. There was also a suggestion that haematoma be its own category. As haematoma in this situation is most likely to be traumatic from the ETT, the effect of it is also likely to be that of obstruction similar to oedema. Whereas, erythema or hyperaemia is likely secondary to inflammation, and to a lesser extent an infectious process. While erythema is an observation important for clinical examination, erythema and oedema are both signs of inflammation. In Study 1, 91% of those with erythema also had oedema. To simplify the scale, erythema may be removed while keeping haematoma as a separate entity. Simplifying the scale may increase the inter-rater reliability for all the raters and broaden its use. However, changing severity scales to a dichotomous scale may impair the utility of the scoring system for evaluating progress over time and simply allow its use as a

diagnostic tool at one point in time. The other suggestion made was to change the rating scale for stenosis to one which is widely accepted and used such as the Myers-Cotton scale(Myer, O'Connor, & Cotton, 1994). A stenosis of greater than 50% was graded as the most severe as these patients are often symptomatic with a stenosis of this severity and may require treatment(Costantino & Mathisen, 2016).The rationale behind the initial design of <25% being grade I and 25-50% being grade II is that patients with subglottic stenosis less than 50% are still worth identifying for follow up of their subclinical disease as it can be progressive. However, as Myers-Cotton subglottic stenosis scale (stenosis between 0-50% is grade I, 51-70% is grade II, 71-99% as grade III) is well known and commonly applied, it will be easier for users who were already familiar with this system(Myer et al., 1994).

The less common pathologies such as stenosis and reduced mobility of the vocal folds have largely resulted in raters scoring 0 for the majority of the cases. It is also highly unlikely that a patient will have severe ratings for all injuries at all levels to reach the maximum score of 58. In study 1 where 97 videolaryngoscopies were assessed using the FLIS, the maximum score was 20, with the majority of the scores between 2-6. Few examinations of the larynx will result in a score above 20. One can argue whether uncommon injuries such as stenosis or vocal fold mobility are worth including in the scale. However, even though these injuries are uncommon, their presence can be significant and have therefore been kept on the scale. This has again been confirmed when assessing the scale's content validity with all the experts agreeing that all laryngeal injuries included were essential.

The total FLIS score is currently presented in a continuous format. There is the potential for further research to grouping the values into categories as mild, moderate and severe laryngeal injury depending on the score. The scale in the current format is able to

communicate a certain score out of 58, but with no guidance on the standing of the value in the distribution. Grouping the values will convey more useful information and increase ease of interpretation for the user(Hauser & Schwarz, 2019). Given the non-normal distribution of the scores which is skewed towards the lower scores, scaled-grouping with uneven intervals corresponding to the underlying distribution is most appropriate(Hauser & Schwarz, 2019). The distribution of laryngeal injury in Colice et al's study caused by intubation for more than 4 days was 6% none, 42% mild, 29% moderate, 23% severe(Colice et al., 1989). If we use the same distribution of severity to group the FLIS data collected from Study 1 into the 3 categories of mild, moderate and severe the proposal would be: mild being 1-4, moderate being 5-9 and severe being 9 and above. Further study with a larger range of pathology severity should be conducted to assess the outcome of different categories. This will not only allow grouping into categories depending on its outcome, but it can also provide predictive validity to the scale. It is also worth noting that the scores given do not necessarily indicate the same level of severity. The scores given are currently unweighted. For example, a maximum score of 2 given for immobile vocal fold does not clinically equate to the same severity of 2 given for a moderately sized granuloma. Currently there are no guidance in the literature on how each injury should be weighted. As reduced vocal fold mobility and severe stenosis are likely to be the most devastating injuries, a suggestion could be that they are weighted as double or triple the original score.

Another method of assessing the severity using this scoring system could be to calculate the total score for each subsite and group severity categories within each of the subsite. The most severe subsite then represents the overall laryngeal severity category. The rationale is a subglottic severe stenosis may score 3 which is potentially life threatening. However, if the

other subsites sustained minimal injury, the total score may be categorised into the mild-moderate group. To determine the severity category of each subsite, the lowest score that would indicate a clinically severe injury is chosen. For the supraglottis, bilateral haematoma (total of 4) could result in substantial swelling causing obstruction. Therefore, a score of 4 and above is deemed as severe. For the glottis, grade 3 stenosis (total of 3), or unilateral immobile vocal fold along with unilateral vocal fold with reduced mobility (total of 3) is defined as severe. For the subglottis, the lowest score possible for the most severe injury is grade 3 stenosis (total of 3). This will result in a categorisation as presented in Table 30.

Table 30 The proposal for severity categorisation within each subsite using the Flinders laryngeal injury score

	Supraglottis	**Glottis**	**Subglottis**
Mild	1-2	1	1
Moderate	3	2	2
Severe	4-16	3-23	3-19

This study assessed the inter-rater reliability in a heterogenous sample of the target population with raters of variable experiences. The highest inter-rater and intra-rater reliability are in the otolaryngology consultant group. The result would suggest that FLIS is most suitable for use in the consultant population who are experts in examining the larynx. Even though the trainee group had excellent inter-rater reliability, the difference between the trainee and the consultant group lowered the coefficient significantly. The use of this scale requires the user to have prior knowledge of the anatomy, types of pathology, and be familiar with the orientation of the obtained view through trans nasal endoscopy. They will also need to have a certain level of experience with the range of pathology in order to accurately rate its severity. While all the raters included in this study have several years of

experience in managing different functions of the larynx, the otolaryngology consultants with experience in managing laryngeal diseases and outcomes were considered to have the most valid rating. The median FLIS total scores of the trainee group are higher than the consultant group, suggesting the trainees are more cautious with their diagnosis. This is likely due to the difference in experiences as trainees have not yet observed the full spectrum of pathology and its severity and are more likely to result in over diagnosis and over calling the severity of laryngeal signs seen on the videos.

The laryngeal injury with the highest inter-rater reliability is erythema in the supraglottis with an ICC above 0.80 when assessed by the consultant group. Erythema in the glottis and subglottis however have lower inter-rater reliability. Despite the discussion above regarding the subjectivity of assessing erythema with FLIS, the assessment of erythema in the supraglottis by experienced users have proved to be very reliable. The difference in the reliability of the supraglottis and other subsites could be due to the location of the supraglottis being easier to examine with no obstruction by other structures. Whereas subtle erythema of the glottis or subglottis may easily be missed. Certain laryngeal injuries had lower than ideal ICC, such as supraglottic ulceration/granuloma, glottic stenosis and subglottic stenosis. In this study, the low ICC may be somewhat misleading given the uncommon nature of the pathology amongst the videos resulted in zero variances from some raters. This led to an ICC that may be artificially low which needs to be interpreted with caution. On the other hand, given the rarity of these pathology the raters may also have less experience assessing these types of injury resulting in reduced inter-rater reliability. To combat the statistical problem, more videos of post-intubated larynges covering all types of pathology in varying severity will be required in future studies. When

assessing the most common types of injuries (oedema, granuloma/ulceration, erythema) across all three subsites, oedema has consistently lower inter-rater reliability compared to the others. This reflects the need to change the rating responses for oedema as previously discussed.

When FLIS was first designed, ulceration and granuloma were listed as two separate items for scoring. Many studies have viewed these two pathologies as separate entities, defining ulceration as the loss of tissue and granuloma as protruding, inflamed fibrovascular tissue (Colton House et al., 2011). However, Hoffman et al and Shin et al have discussed them as one entity at different time points in their natural history(Hoffman, Overholt, Karnell, & McCulloch, 2001; Shin, Watanabe, Oda, Umezaki, & Nahm, 1994). Terms used to describe the same pathology include contact ulcer, contact ulcer granuloma, pyogenic granuloma, vocal process granuloma, vocal cord granuloma, peptic granuloma, peptic ulcers of the larynx, contact pachydermia and posterior hypertrophic pachydermia(Hoffman et al., 2001). Shin et al also described the histopathological classification of vocal cord granulomas. It consisted of different grades of injury and erosion of the overlying epithelium which is commonly understood as ulceration (Shin et al., 1994). In our experience with assessing 97 videos of post-intubation larynges, there were some examples when it may be difficult to differentiate vocal process ulceration from vocal process granuloma (Example figure 27). Given the evidence provided, it was decided to combine ulceration/granuloma as one item.

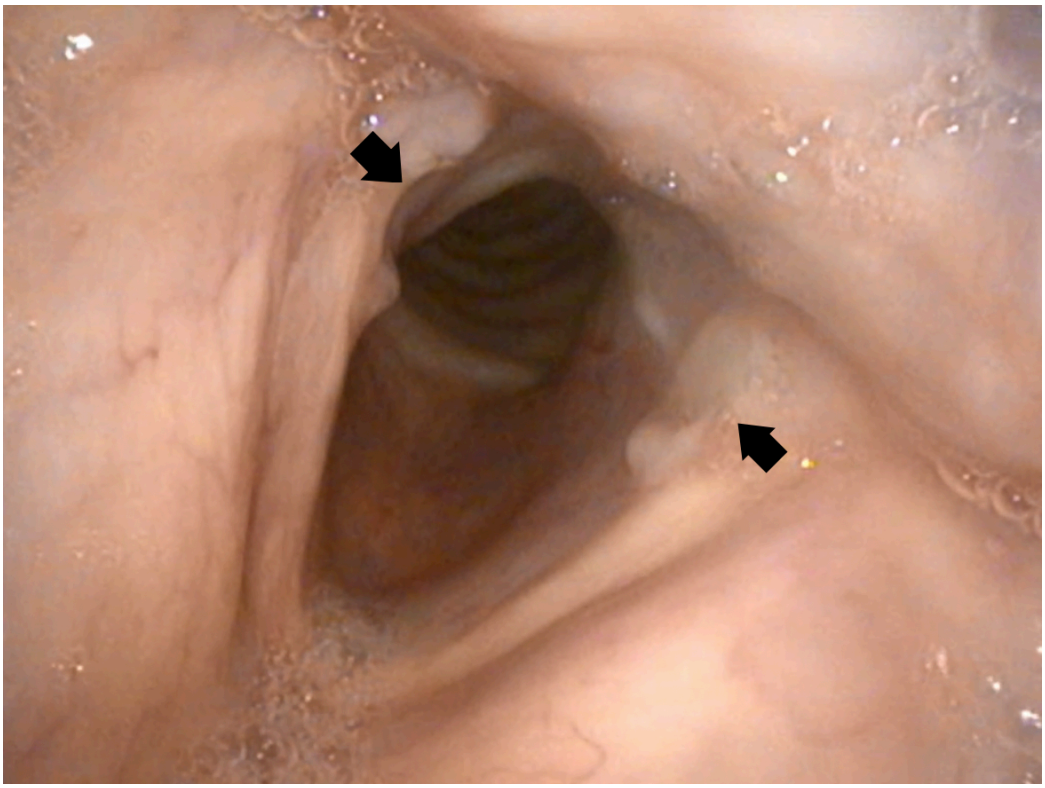

Figure 27 An example of a bilateral vocal process granuloma with overlying ulceration identified by black arrows where the endotracheal tube would have been situated.
(FLIS glottal ulceration/granuloma right: 1, left: 1)

Certain laryngeal injuries that have been described as a complication of intubation in the literature were not included due to their rarity and an effort to keep the scale simple. While stenosis can occur in all three subsites, supraglottic stenosis is by far the least common, only reported in 5.7% of all laryngeal stenosis(Nair, Nilakantan, Sood, Gupta, & Gupta, 2016). Arytenoid dislocation and vocal fold avulsion are both likely secondary to direct trauma during intubation with insufficient relaxation(Mikuni et al., 2006). Arytenoid dislocation or subluxation is reported to be extremely uncommon at 0.023% of all direct laryngoscopies(Senoglu, Oksuz, Ugur, Dogan, & Kahraman, 2008). Vocal fold avulsion is another uncommon complication which is more commonly reported in the paediatric population(Strychowsky, Adil, Licameli, & Rahbar, 2015).

4.2.1 Strength and limitation of the FLIS

A scoring system for this purpose has never been described in detail, validated or widely applied. FLIS ensures a systematic examination of the larynx and common pathologies. It also allows for documentation of overall laryngeal severity and for each individual subsite. It can be used in research settings to ensure a consistent way of reporting injuries. This will then allow comparison between studies in this population. This study has demonstrated FLIS has high inter-rater and intra-rater reliability when utilised by experienced users. As the target users for this scoring system is the otolaryngology consultants and trainees when assessing the post-intubated larynx, further refinement needs to be made to ensure the reliability within this group is acceptable.

Several improvements can be made to the scoring system. Reducing its complexity with less severity ratings may increase its ease of use. Consideration of the suggestions made may lead to further refinement. This scale is not all encompassing of laryngeal injuries sustained

post intubation. FLIS can be applied but may be somewhat limited in those with laryngeal injury after short-term intubation. The range of laryngeal injury after short-term intubation are often secondary to direct trauma from the insertion of the ETT. These patients are less likely to present with granuloma, stenosis and vocal fold immobility and will likely result in lower FLIS scores.

4.2.2 Conclusion

FLIS is a useful tool clinically for systemic examination and diagnosis of laryngeal injury post prolonged intubation. It's application in the recently extubated patients is not limited to the immediate post-extubated period but can be used as an assessment tool for subsequent follow up. Adopting it for further research will reduce heterogeneity in methods between studies when assessing the larynx. Revisions to the existing scoring system will improve the current version and likely increase its usability. With further research into the outcome of laryngeal injury, the FLIS score may be able to provide a patient with an expected recovery or outcome.

5 THESIS CONCLUSION

This study used the most comprehensive methods to assess laryngeal and voice outcomes after extubation in the modern-day intensive care. It demonstrated an extremely high incidence of laryngeal injury and dysphonia after intubation for at least 24 hours which was still highly prevalent prior to discharge from the hospital. The high incidence of injury resulted in the lack of a comparative group for statistical analysis. Bedside voice assessment tools were not able to identify these injuries or predict the severity and outcome. Known risk factors that contribute to laryngeal injuries have not demonstrated statistical significance potentially due to the small sample size and optimisation of the care provided for these patients. Otolaryngology referral is recommended for a transnasal endoscopy examination in these patients who have worsening or persistent dysphonia, dyspnoea and dysphagia prior to discharge. The Flinders laryngeal injury score introduced for assessing the larynx in these patients demonstrated to be an effective and valid tool when used by otolaryngology consultants. However, it needs to be further refined to allow extensive use in the research and clinical settings.

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Appendix 1: Human Research Ethics Approval

Office for Research

Flinders Medical Centre
Ward 6C, Room 6A219
Flinders Drive, Bedford Park SA 5042
Tel: (08) 8204 6453
E: Health.SALHNOfficeforResearch@sa.gov.au

Government of South Australia
SA Health
Southern Adelaide Local Health Network

Final Approval for Ethics Application

6 April 2018

Associate Professor Eng Ooi,
Room 5118,
Flinders Medical Centre,
Flinders Drive,
Bedford Park,
SA 5062

Dear Associate Professor Ooi,

OFR Number:	208.17
HREA application ID:	MS03322
Project title:	The VOiCe And Laryngeal Investigation Standards post Extubation (VOCALISE) Study
Chief Investigator:	Associate Professor Eng Ooi
Ethics Approval Period:	6th April 2018 – 6th April 2021

The Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC EC00188) have reviewed and provided approval for this application which meets the requirements of the *National Statement on Ethical Conduct in Human Research (2007).*

You are reminded that this letter constitutes **Ethics** approval only. **Ethics approval is one aspect of the research governance process**.

You must not commence this research project at any SA Health sites listed in the application until a Site Specific Assessment (SSA), or Access Request for data or tissue form, has been approved by the Chief Executive or delegate of each site.

Public health sites approved under this application:

- Flinders Medical Centre

The below documents have been reviewed and approved:

- HREA 19/05/2017
- HREA Project Description v3 13/03/2018
- Participant Information Sheet and Consent Form v3 13/03/2018
- Letter from Professor Ooi supporting application 07/07/2017
- Letter from Professor Bersten supporting application 03/07/2017
- Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) tool
- Digital Nasoendoscopy and Stroboscopy Assessment draft 05/07/2017
- Letter from Ms Tedesco supporting application 07/07/2017
- Voice Handicap Index 10 (VHI-100
- Researcher response to ethics committee 13/03/2018
- Researcher response to ethics committee query dated 29/03/2018

Terms And Conditions Of Ethics Approval:

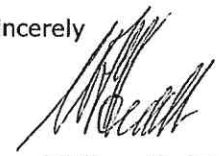
As part of the Institution's responsibilities in monitoring research and complying with audit requirements, it is essential that researchers adhere to the conditions below and with the *National Statement chapter 5.5.*

Final ethics approval is granted subject to the researcher agreeing to meet the following terms and conditions:

1. The approval only covers the science and ethics component of the application. A SSA will need to be submitted and authorised before this research project can commence at any of the approved sites identified in the application.
2. If University personnel are involved in this project, the Principal Investigator should notify the University before commencing their research to ensure compliance with University requirements including any insurance and indemnification requirements.
3. Compliance with the *National Statement on Ethical Conduct in Human Research* (2007) & the *Australian Code for the Responsible Conduct of Research* (2007).
4. To immediately report to SAC HREC anything that may change the ethics or scientific integrity of the project.
5. Report Significant Adverse events (SAE's) as per SAE requirements available at our website.
6. Submit an annual report on each anniversary of the date of final approval and in the correct template from the SAC HREC website.
7. Confidentiality of research participants MUST be maintained at all times.
8. A copy of the signed consent form must be given to the participant unless the project is an audit.
9. Any reports or publications derived from the research should be submitted to the Committee at the completion of the project.
10. All requests for access to medical records at any SALHN site must be accompanied by this approval email.
11. To regularly review the SAC HREC website and comply with all submission requirements, as they change from time to time.
12. Once your research project has concluded, any new product/procedure/intervention cannot be conducted in the SALHN as standard practice without the approval of the SALHN New Medical Products and Standardisation Committee or the SALHN New Health Technology and Clinical Practice Innovation Committee (as applicable). Please refer to the relevant committee link on the SALHN intranet for further information.

For any queries about this matter, please contact The Office for Research on (08) 8204 6453 or via email to Health.SALHNOfficeforResearch@sa.gov.au

Yours sincerely



Professor William Heddle
Acting Chair, SAC HREC

Appendix 2: Consensus Auditory Perceptual Evaluation of Voice (CAPE-V)

CAPE-V form has been removed due to copyright restriction.
Form is available online from the American Speech-Language-Hearing Association: https://www.asha.org/Form/CAPE-V/

Appendix 3: Voice-vibratory assessment with laryngeal imaging (VALI)

FIGURE 1. VALI rating form for stroboscopy. Voice-Vibratory Assessment with Laryngeal Imaging (VALI)—Stroboscopy (Poburka, B., Patel, R., and Bless, D. 2016).