Pandian, V., Cherukuri, S. P. S., Koneru, M., Karne, V., Tajrishi, F. Z., Aloori, S., Kota, P., Dinglas, V., Colantuoni, E., Akst, L., Hillel, A. T., Needham, D. M., Brodsky, M. B., & PALSS study team†. (2024).Post-extubation Assessment of Laryngeal Symptoms and Severity (PALSS) in the Intensive Care Unit: Protocol of a prospective cohort study. *ORL - Head and Neck Nursing, 42*(1), 8-21.

Feature Article

Post-extubation Assessment of Laryngeal Symptoms and Severity (PALSS) in the Intensive Care Unit: Protocol of a Prospective Cohort Study

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Keywords: Intubation, airway extubation, larynx, voice, deglutition, deglutition disorders, laryngoscopy, artificial respiration

ORL - Head and Neck Nursing

Abstract

Aims

The Post-extubation Assessment of Laryngeal Symptoms and Severity (PALSS) study systematically evaluates patient symptoms related to endotracheal intubation with mechanical ventilation, assesses laryngeal injury and voice function after extubation, and develops a screening tool to identify patients with clinically important, post-extubation laryngeal injury.

Design

Single-center, prospective observational cohort study conducted in 6 intensive care units (ICU).

Methods

Patients ≥18 years old who are orally intubated and mechanically ventilated in an ICU and meet eligibility criteria will undergo flexible laryngoscopy, with a sample size goal of 300 completed

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laryngoscopies. Primary outcome measures include signs and symptoms of laryngeal injury, including voice symptoms and alterations in swallowing, measured using the Laryngeal Hypersensitivity Questionnaire-Acute and Voice Symptom Scale questionnaires respectively. Data will be collected within 72 hours post-extubation and at 7-day follow-up or hospital discharge (whichever occurs first). Data will be analyzed using descriptive statistics, regression models, and predictive modeling using machine learning.

Discussion

The findings of this study will describe the clinical signs and symptoms of laryngeal injury post-extubation.

Conclusion

The PALSS study will provide insights for future studies that explore laryngeal injuries using flexible laryngoscopy after endotracheal intubation.

Implications for patient care

Identifying signs and symptoms of laryngeal injury after endotracheal intubation will facilitate the development of a screening tool that will assist in early identification of post-extubation laryngeal injury, and aid in decreasing short- and long-term complications of endotracheal intubation.

Reporting Method

SPIRIT

Patient or Public Contribution

Patients were study participants; and family members provided informed consent when the patient lacked decision-making capacity.

What does this paper contribute to the wider global clinical community?

1. This study protocol aims to present important insights into the effects of endotracheal tubes on the larynx, voice and swallowing, which have significant implications for patient outcomes and clinical practice.

2. The development of a screening tool for laryngeal injury will be a critical contribution to the global clinical community with its aim of improving patient care and preventing short- and long-term complications by enabling bedside nurses, speech-language pathologists, laryngologists, and other clinicians to screen patients more accurately and efficiently for potential laryngeal injuries.

3. This paper provides a valuable methodological example for future studies exploring the assessment of laryngeal symptoms after endotracheal intubation and mechanical ventilation in the intensive care unit setting.

INTRODUCTION

Endotracheal intubation with mechanical ventilation in an intensive care unit (ICU) is a life-sustaining intervention for approximately 20 million critically ill patients worldwide each year (Adhikari et al., 2010; Ambrosino & Vitacca, 2018). In the United States alone, nearly one million patients per year are intubated, with approximately 40% requiring intubation for more than 96 hours (Mehta et al., 2015). This life-sustaining intervention, however, can lead to laryngeal injury affecting as many as 83% of patients (Bishop et al., 1984; Brodsky et al., 2018, 2021). Despite the well-established association between intubation and laryngeal injury, patients-reported symptoms of laryngeal injury are often overlooked, and there is no standard of practice or evidence-based pathway for referral and evaluation by speech-language pathologists (SLPs) or laryngologists after extubation.

Patients with laryngeal symptoms, including hoarseness, loss of voice, throat clearing, sore throat, vocal fatigue, and difficulty swallowing (Krisciunas et al., 2020; Shinn et al., 2019) are not often identified as high-risk for laryngeal injury. In fact, before 2018, patients extubated from mechanical ventilation who presented with hoarseness were often subject to a "wait and see" approach that deferred assessment for one week to three months or even longer (Schwartz et al., 2009; Stachler et al., 2018). This approach led to some patients experiencing serious long-term consequences (e.g., stenosis, compromised breathing), with some laryngeal injuries resulting in chronic conditions (e.g. dysphagia, dysphonia) that may have been avoidable with early assessment and intervention (Kelly et al., 2023; Lowery et al., 2021). Furthermore, laryngeal injury can cause significant healthcare burden because patients with such injuries require longer hospital stays, increased healthcare utilization, and higher healthcare costs (Bhatti et al., 2010; Brodsky et al., 2018; Saeg & Alnori, 2021).

Investigating laryngeal injury and voice/communication is a research priority among several professional societies, including the American Association of Critical Care Nurses and the Society of Critical Care Medicine (Needham et al., 2012). Recent studies are emerging with larger sample sizes. Furthermore, clinical practice and clinical guidelines have shifted towards targeting patient wakefulness during mechanical ventilation via an endotracheal tube, creating an important opportunity to interact with patients and evaluate their symptoms during intubation and soon after extubation (Bassett et al., 2015; Page & McKenzie, 2021; Wøien, 2020).

Given the significant impact of laryngeal injury on patient outcomes and the lack of a standard approach to identifying and managing this condition, this study protocol aims to explore the role of patient symptoms in identifying laryngeal injury and to propose an evidence-based pathway for identification and referral by nurses and other clinicians, and diagnostic evaluation by SLPs and otolaryngologists after extubation, with ultimate goal of reducing long-term sequelae of endotracheal intubation.

Purpose

The Post-extubation Assessment of Laryngeal Symptoms and Severity (PALSS) study systematically investigates the impact

of endotracheal intubation on mechanically ventilated ICU patients. Specifically, the PALSS study will determine the prevalence, characteristics, and severity of patient symptoms associated with endotracheal intubation and mechanical ventilation by assessing patient symptoms, laryngeal injury and voice function after extubation in the setting of critical care and develop a screening tool to identify patients with clinically significant post-extubation laryngeal injury.

Aims and hypotheses

Aim 1: Systematically evaluate patient laryngeal symptoms and standard clinical bedside assessments, both during intubation and post-extubation, and determine patient and ICU variables associated with these findings.

Hypothesis 1a: Patient reports of laryngeal symptoms are common during intubation and post-extubation, and will be associated with routine clinician bedside assessments, reflecting these discomforts.

Hypothesis 1b: Specific patient variables (e.g., age, sex) and ICU variables (e.g., duration of intubation and endotracheal tube (ETT) size) are associated with laryngeal symptoms and related clinical bedside assessments.

Aim 2: After extubation, prospectively evaluate evidence of laryngeal injury using 3 types of laryngoscopy (i.e., white light, digital image enhanced processing, and stroboscopy) and voice measures (i.e., perceptual, acoustic) to determine associations with patient symptoms and clinical bedside assessments (Aim 1), along with patient and ICU variables (Aim 1).

Hypothesis 2a: Specific patient and ICU variables (e.g., age, sex, duration of intubation, ETT size) and patient symptoms are associated with laryngeal injury and voice measures.

Hypothesis 2b: Findings from routine clinical bedside assessments are associated with laryngeal injury and voice measures.

Aim 3: Construct a screening tool to assist in timely identification of patients with clinically important, post-extubation laryngeal injury.

Hypothesis 3a: Patient and ICU variables, patient symptoms and bedside assessments (Aim 1), that are associated with laryngeal injury and voice measures (Aim 2), can be used to create a sensitive clinical screening tool for laryngeal injury.

METHODS

Design and Setting

This is a prospective, observational, cohort study conducted in the 6 adult ICUs of a large tertiary academic institution in the United States, Johns Hopkins Medical Institution.

Eligibility criteria

The inclusion and exclusion criteria are reported in **Table 1**. All eligible patients would be included in the study and there will be no exclusion based on sociodemographic factors.

Outcomes

Primary Outcome Variables

The primary outcome is the occurrence of laryngeal injury, evaluated from both the patient and clinician perspectives. Patient symptoms will be assessed using questionnaires that evaluate laryngeal and voice symptoms. Clinical signs will be evaluated through anatomic and physiological assessments related to both voice and swallowing, including perceptual and acoustic voice assessments, as well as a screening for tracheal aspiration.

Patient assessment (symptoms)

Laryngeal symptoms: The presence of an ETT may result in physical sensations that are associated with laryngeal injury. After extubation, patients often report laryngeal symptoms such as abnormal sensations of mucus in the throat; pain; sensation of blockage, tightness, irritation or something pushing/pressing on the throat; constriction; tickle; or itch (Borders et al., 2019; Park et al., 2017; Su et al., 2015). The presence and severity of these laryngeal symptoms will be assessed using the Laryngeal Hypersensitivity Questionnaire-Adult (LHQ-A) (Brodsky et al., in press).

Voice symptoms: Voice symptoms, such as roughness, hoarseness, breathiness, and variability, are commonly reported by patients after extubation (Sørensen et al., 2016; Van der Meer et al., 2010). However, it is widely recognized that the severity of voice disorders may not necessarily correspond to the impact they have on patients' quality of life. To assess the presence and severity of voice symptoms, the Voice Symptom Scale (VoiSS) will be utilized (Deary et al., 2003; Webb et al., 2007; Wilson et al., 2004).

Clinician assessment (signs)

Anatomic signs of laryngeal injury: Laryngeal injury can manifest via various signs, such as erythema, edema, hematoma, granulation tissue, and ulceration of anatomical structures including the pharynx, base of tongue, epiglottis, vocal folds, and vocal processes (Benjamin, 1993; Colton House et al., 2011; Dubick & Wright, 1978; Shinn et al., 2019; Stauffer et al., 1981; Whited, 1985). Additionally, there may be pooling of secretions in the pharyngeal and laryngeal spaces (Brodsky et al., 2021). The presence and severity of laryngeal injury signs are evaluated through laryngoscopy.

Physiologic signs of laryngeal injury

Alterations in voice: Changes in voice quality can serve as an important indicator of laryngeal injury, with manifestations including irregular fluctuations in fundamental frequency and/or amplitude, breathiness from incomplete glottic closure, weakness or lack of intensity from reduced breath support, and strain from increased muscle tension. To assess these physiological changes, we will employ both subjective and objective measures. Using Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V) stimuli (Kempster et al., 2009; Zraick et al., 2011), perceptual voice parameters will be gauged using the GRBAS scale (Aghadoost et al., 2022; Dejonckere et al., 1996; Hirano, 1989) and acoustic voice parameters will be analyzed using the Multi-Dimensional Voice Program (MDVP) (Keung et al., 2022; Lovato et al., 2016) and Analysis of Dysphonia in Speech and Voice (ADSV) (Wei et al., 2022) software. Additionally, we will utilize the All Voiced Sentence protocol with CAPE-V sentences to generate the Cepstral Spectral Index of Dysphonia (CSID) (Awan et al., 2010).

Alterations in swallowing: Disordered swallowing (i.e., dysphagia) that results in aspiration can have serious consequences for patients' health and well-being (Leder et al., 2001; Leder & Ross, 2010; Plowman et al., 2023). We will use the Yale Swallow Protocol in combination with Flexible Endoscopic Evaluation of Swallowing (FEES), a widely validated instrumental assessment of swallowing (Amathieu et al., 2012; Garuti et al., 2014; Leder et al., 2001; Leder & Ross, 2010; Suiter et al., 2014; Suiter & Leder, 2008). In addition, the Functional Oral Intake Scale (FOIS) will be used to assess the level of functional independence in oral intake.

Secondary Outcome Variables

Tongue strength

Impairments in speech can result from the weakening of tongue strength. In order to ascertain that alterations in voice are not caused by a tongue weakness, we will measure peak tongue strength using the Iowa Oral Performance Instrument (IOPI) (IOPI

Table 1. Inclusion and Exclusion Criteria

Inclusion	Exclusion
≥18 years Required mechanical ventilation via an oral endotracheal tube in intensive care unit (ICU) Anticipated intubation duration in an ICU of ≥8 hours	Pre-existing dysphonia or dysphagia Pre-existing central nervous system, neuromuscular, or connective tissue disease* Tracheostomy prior to study enrollment History of major thoracic surgery (e.g., sternotomy, thoracotomy) prior to the current hospital admission Head and/or neck disease* Head and/or neck surgery other than tonsillectomy Known or suspected anatomical abnormalities or pre-intubation trauma of the oral cavity, pharynx, larynx, or esophagus Unlikely to be extubated (e.g. expected death)

* Exclusion is specific to any condition that may be associated with pre-existing impairment in phonation or swallowing

Medical, Carnation, WA). (Crow & Ship, 1996; Solomon et al., 2008; Su et al., 2015).

Hand grip strength

Hand grip strength provides a measure of distal muscle strength that has important functional implications in critically ill patients. Isometric hand grip strength will be measured using a Jamar Preston hand dynamometer (Jackson, MI) (Massy-Westropp et al., 2004).

Predictors of laryngeal injury

In order to identify the predictors of laryngeal injury, we plan to measure a range of patient, intubation, medication, and critical illness-associated risk factors. An overview of these factors is provided in Table 2.

Participant timeline

In accordance with the study protocol, patients are evaluated at three time-points during their hospital stay (Figure 1). The first as-sessment is conducted within 48 hours prior to the anticipated ex-tubation, the second assessment is conducted within 72 hours af-ter the extubation, and the third assessment is conducted at 7 days (±2 days) following extubation or at the time of hospital discharge, whichever occurs first. Delays in extubation will result in repeat assessments every 48 hours until extubation. Data collection dur-ing the first assessment is expected to take approximately 20 min-utes. For the second assessment, which includes administration of assessments and setup/breakdown time for the endoscopy equip-ment, 40 minutes is estimated. Finally, the third assessment is es-timated to take approximately 25 minutes.

Sample size

The study endeavors to design and evaluate a screening tool to identify laryngeal injury. The sample size was calculated based on a precision of performance of the novel screening tool. Prelimi-nary data for the sample size calculation were obtained from 19 orally intubated patients recruited from The Johns Hopkins Hos-pital, who met eligibility criteria similar to this study protocol. Laryngoscopy was performed on these 19 patients using white light and digital image-enhanced processing. The median age of the patients was 63 (interquartile range (IQR): 54-71) years, with males having a median ETT size of 8.0 (range: 7.0 - 8.5) and fe-males 7.0 (range: 6.5 - 8.0). The median duration of intubation was 5 days (IQR: male 3 - 6 days; female 3 - 8 days). All 19 (100%) patients displayed evidence of laryngeal injury, with 7/19 (37%) exhibiting multiple levels of injury. Grade 2 injury (i.e., requir-ing follow-up and indicative of non-self-limiting short-term harm) (Eckerbom et al., 1986; Lindholm, 1970; Thomas et al., 1995) was observed in 8/19 (42%) patients. Grade 3 injury (i.e., a serious injury necessitating the attention of a laryngologist and carrying the potential for long-term or chronic consequences) was observed in 8/19 (42%) patients.

A predictive model for injury was created using logistic regression models with primary terms for patient and intubation characteristics, in addition to the interaction of gender and ETT size, based on preliminary data from the 19 patients. Injury was defined as any non-self-limiting injury (Grade 2 or 3) or severe injury (Grade 3). The estimated sensitivity for non-self-limiting and severe injury was 81% and 75%, respectively, using this model. Hypothetical studies were then simulated with samples sizes ranging from 100 to 1000 patients to evaluate the precision (i.e., margin of error) for estimating the true sensitivity of the screening tool. A sample size of 300 patients was deemed adequate for this study, with a margin of error of 10% and 13% for non-self-limiting and severe injury, respectively. A sample size of 1000 patients reduced the margin of error to 5% and 7% for any injury and severe injury, respectively. The proposed sample size of 300 patients will enable us to detect significant correlations of ≥0.16 in Aims 1 and 2, with a power of 80%, which was deemed appropriate for this study.

Recruitment

Consecutive ICU patients will be screened daily over a period of approximately five years. Each patient is eligible to participate in the research study only once. Once an appropriate patient has been identified through the screening process, the study team seeks permission from the clinical team to approach the patient/proxy for informed consent. All research activities are conducted during the patient's hospital admission at the study institution; no outpatient research is conducted. Patients are followed longitudinally until hospital discharge. Their participation in the study ends at hospital discharge, upon withdrawal of consent by the patient or his/her proxy or at the request of the patient's attending physician.

Blinding

Each laryngoscopy recording will be reviewed and evaluated by two laryngologists independently. The laryngologists will be blinded to patient information. SLPs will evaluate the perceptual voice recordings in duplicate, with each SLP blinded to the other's rating and limited to only knowing the patient's age and sex/gender. Acoustic voice recordings will be completed by one SLP with patient data limited age and sex/gender. All other assessments (e.g., questionnaires, delirium screening) are not blinded as they are performed by research staff or clinicians directly involved in conduct of the study or clinical care, respectively.

Table 2. Independent study variables

Symptoms inventory/assessment	Instrument	Scale
Patient Factors		
Age	Medical record	Continuous
Sex	Medical record	Binary
Race	Medical record	Categorical
Ethnicity (Hispanic/Non-Hispanic)	Medical record	Binary
Height/Weight/body mass index	Medical record	Continuous
Smoking status (never/prior/current)	Patient/proxy interview	Categorical
Tobacco use (pack years)	Patient/proxy interview	Continuous
Comorbidities: Charlson & Functional Comorbidity Indexes	Medical record	Ordinal
Intubation Factors		
Reason for mechanical ventilation	Medical record	Categorical
Setting of intubations (e.g., pre-hospital, ED, ICU, surgery)	Medical record	Categorical
Nature of intubation (e.g., emergent, non-emergent)	Medical record	Binary
Number of attempts at intubation	Medical record	Continuous
Size/position of endotracheal tube	Medical record	Continuous
Unplanned extubation (e.g. self-extubation)	Medical record	Binary
Duration of oral intubation (days)/mechanical ventilation	Medical record	Continuous
Medication		
Sedatives and Analgesics	Medical record	Continuous
Systematic corticosteroids/immunosuppressants	Medical record	Continuous
Antibiotics	Medical record	Continuous
Critical Illness Risk Factors		
COVID-19 status	Medical record	Binary
ICU admitting diagnosis	Medical record	Categorical
Severity of illness: APACHE II score	Medical record	Continuous
Daily Sedation status (RASS score)	Medical record	Categorical
Daily Organ failure status (SOFA score)	Medical record	Continuous

ED: Emergency Department; ICU: Intensive Care Unit
APACHE II: Acute Physiology and Chronic Health Evaluation II score, considers age, pre-existing medical conditions and acute physiology within the first 24 hours of ICU admission; CAM-ICU: The *Confusion Assessment Method for the Intensive Care Unit* (CAM-ICU) is a valid, reliable and recommended delirium assessment instrument for mechanically ventilated patients in the ICU; RASS: Richmond Agitation Sedation Score is a valid, reliable and recommended measure of sedation and agitation status in the ICU; SOFA: Sequential Organ Function Assessment. For medications, we collected drug name and total dose recorded daily during the study.

Instruments and data collection methods

Laryngeal Hypersensitivity Questionnaire-Acute (LHQ-A)

LHQ-A is a 13-item questionnaire that evaluates laryngeal sensations in three domains, namely obstruction (7 items), pain/thermal (3 items), and irritation (3 items) (Brodsky, 2023). The responses are given on a 4-point Likert scale, with scores ranging from 1 (all of the time) to 4 (none of the time). The total score possible is 52, with lower scores suggesting greater laryngeal impairment. The LHQ-A takes less than 10 minutes to complete. This assessment is conducted at all three assessment time points. Depending on the patient's ability, non-verbal gestures, such as head nodding/shaking, eye movement/tracking, finger pointing, or written responses are used to record patients' laryngeal symptoms during intubation (within 48 hours of expected extubation). Patients will provide responses within 72 hours post-extubation and at 7-day follow-up or hospital discharge (whichever occurs first) in written form on the study-specific paper case report form or verbally for written recording by study personnel.

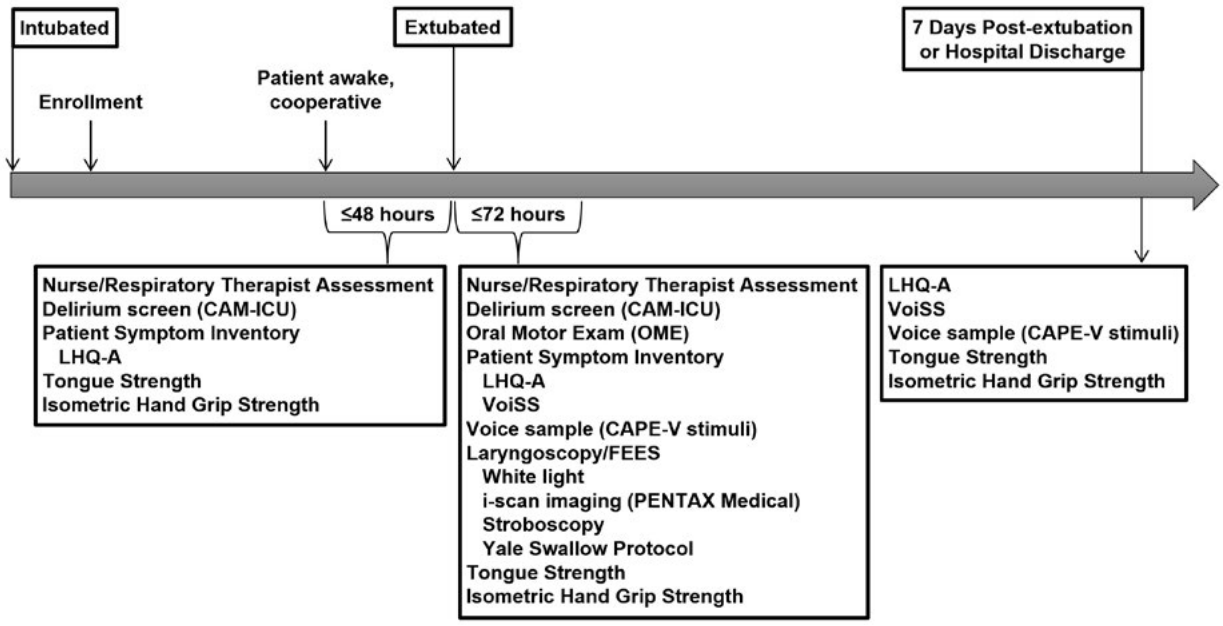
Voice Symptom Scale (VoiSS)

VoiSS is a 30-item questionnaire that measures voice impairment, physical symptoms, and emotional response using a 4-point scale (Deary et al., 2003; Webb et al., 2007; Wilson et al., 2004). The items are scored as never, occasionally, some of the time, most of the time, or always, with scores ranging from 0 to 4, respectively. The maximum possible score is 120, with higher scores indicating more significant voice impairment (without any established threshold for binary analysis of this measure). It takes approximately 15 minutes to complete the VoiSS. This assessment is administered within 72 hours post-extubation and at 7-day follow-up or hospital discharge (whichever occurs first). Responses are recorded on study-specific paper case report forms.

Laryngoscopy

The anatomical integrity of the larynx is evaluated via video recording of a laryngoscopy performed by credentialed nurse practitioner or SLP. The video recording is assessed by a board-certified laryngologist assessed using a 4-point categorical scale that considers both the type and location of the injury. The post-

Figure 1. Study Timeline



CAM-ICU: Confusion Assessment Method-Intensive Care Unit; LHQ-A: Laryngeal Hypersensitivity Questionnaire-Acute; OME: Oral Motor Exam; VoiSS: Voice Symptom Scale; CAPE-V: Consensus Auditory-Perceptual Evaluation of Voice; FEES: Flexible Endoscopic Evaluation of Swallowing

extubation laryngoscopy is completed as part of the research protocol, not as a routine clinical care procedure. Whenever possible, the laryngoscopy is combined with FEES within a 72-hour window post-extubation if an SLP consultation is requested by the patient's primary clinical team.

The PENTAX Medical Laryngoscopy Tower (PENTAX Medical, Montvale, NJ) (Figure 2) is used to digitally capture laryngo-scopic evaluations by appropriately trained and credentialed clin-ical personnel involved with this study. This recording system is strictly used for research purposes. Laryngoscopic evaluations are standardized using the study institution's Voice Center proto-col. The study laryngoscopy is completed using three sources of light—white light, digital image enhanced processing, and stro-boscopy. Each light type is independent and is performed sequen-tially during a single pass of the endoscope.

White light endoscopy allows for viewing of all structures as they appear typically. Digital image enhanced processing, as part of the Workstation (i-scan), is a real-time virtual chromoen-doscopy technology that enhances the views of the mucosa and vascularity beneath surface tissues (Neumann et al., 2013). Strobe lighting technique uses flashes of light to sample motion at dif-ferent times, effectively creating a slow-motion "movie" of move-ments. Laryngeal stroboscopy is, therefore, used to slow down the high-speed vibratory pattern of the vocal folds (i.e., males ~125 Hz, females ~230 Hz) during voicing, so that movements of the vocal folds can be observed (Colton et al., 2005; Goy et al., 2013; Schaeffer et al., 2015). Whereas white light and i-scan assess the integrity of all anatomy, stroboscopy assesses the vibratory pat-tern, movement, and function of the vocal folds.

Voice assessments

Perceptual assessment

Voice samples will be recorded at a sampling rate of 48 kHz using a condenser microphone positioned at a fixed distance (~3 cm) from the patients' lips. We will attempt to minimize environmen-tal noises in accordance with established guidelines (Deliyski et al., 2005; Titze & Palaparthi, 2014). Recordings will be made post-extubation at the time of laryngoscopy using stimuli from the CAPE-V (Kempster et al., 2009; Zraick et al., 2011). The same voice samples from the CAPE-V recordings will be rated by two skilled SLPs using a perceptual rating scale—the GRBAS scale (Aghadoost et al., 2022; Dejonckere et al., 1996; Hirano, 1989). The GRBAS scale measures: 1) Grade (degree of hoarseness or voice abnormality), 2) Roughness (irregular fluctuations in fundamental frequency and/or amplitude of the sound), 3) Breathiness (air leakage through the glottis), 4) Asthenia (weakness, lack of power, lack of intensity in the voice) and 5) Strain (hyperfunction; related to an abnormally high fundamental frequency, noise in the high frequency range, and/or richness in high frequency harmonics). The two SLPs, blinded to patient details other than age and sex/gender, and blinded to each other's scores will independently score these parameters. Any discrepancies with a difference of ≥ 2 severity levels will be reconciled by consensus after a re-review of the audio file.

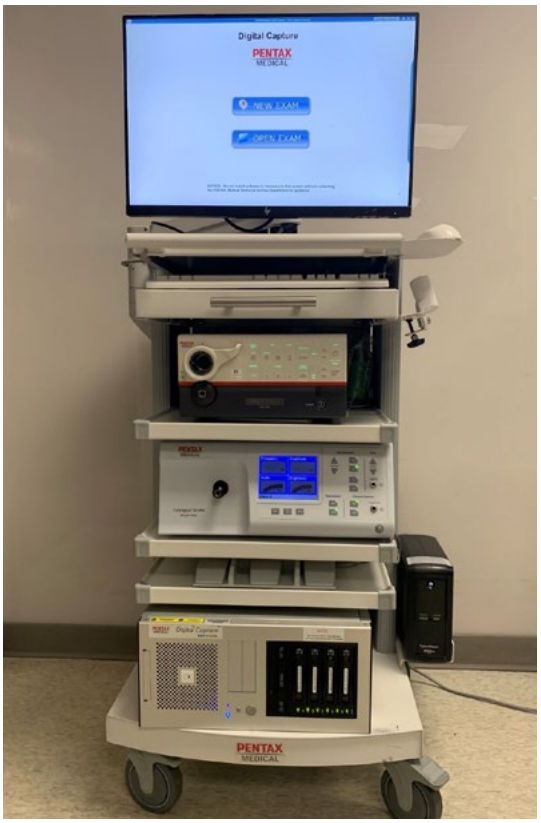
Acoustic assessments

The Computerized Speech Lab (CSL), developed by PENTAX Medical (Montvale, NJ, USA), represents an advanced acoustic analysis system that has been thoroughly tested and validated in previous studies (Keung et al., 2022; Lovato et al., 2016; Wei et al., 2022). Comprising advanced hardware and software, the CSL is capable of measuring as many as 33 different parameters of the voice utilizing the Multi-Dimensional Voice Program (MDVP). In this study, voice samples collected from participants were segmented into three distinct tasks using the CAPE-V and analyzed independently. A skilled speech-language pathologist (SLP) is responsible for parsing and completing all acoustic analyses, generating full reports containing all available parameters for comparison.

Swallow Test

The Yale Swallow Protocol, a widely accepted and validated screening tool for aspiration (Leder & Suiter, 2014; Suiter et al., 2014; Suiter & Leder, 2008; Ward et al., 2020), is implemented in this study. Following administration of six cognitive screening questions, a cup containing 3 oz. (90 ml) of water is pro-

Figure 2. Study Laryngoscopy Tower



vided to the patient, or held for them if necessary, for continuous uninterrupted consumption via cup or straw. The screening is deemed "failed" if the patient experiences any of the following: interruptions in consumption (such as stopping or resting), or coughing, choking, throat clearing, or changes in vocal quality (i.e., a wet, "gurgly" quality after consumption has been completed). The screening is deemed "passed" in the absence of all of these responses. This screening is conducted only at the time of the post-extubation assessment and responses are recorded on study-specific, paper case report forms. Furthermore, two SLPs independently review the laryngoscopy videos to determine the presence of aspiration, blinded to each other and without knowledge of patient details. Disparities with a difference of ≥ 2 levels of severity in the ratings will be resolved by consensus following video review.

Functional oral intake scale

The FOIS is a widely used outcomes rating scale that assesses the degree of functional independence in oral intake among patients with dysphagia (Crary et al., 2005). The scale comprises seven levels ranging from nothing by mouth (Level 1) to total oral diet with no restrictions (Level 7). FOIS is a simple and practical tool that is easy to administer and score, making it suitable for use in both clinical and research settings. FOIS can be used to track changes in oral intake over time, and it has been shown to have good inter-rater reliability and validity (Crary et al., 2005). FOIS assessments will be performed twice, once to establish baseline (prior to hospitalization (self-report) and at ICU discharge (clinical determination of level).

Iowa Oral Performance Instrument

The assessment of peak tongue strength will be conducted by placing the IOPI bulb, attached to the IOPI device, in the patient's oral cavity behind the upper incisors and against the alveolar ridge of the hard palate, followed by comparison with established norms (Crow & Ship, 1996; Solomon et al., 2008; Su et al., 2015). Patients will be given clear instructions and encouraged to exert maximum pressure on the bulb using their tongue. The IOPI device will register the peak pressure; three measurements will be taken with 60 second rest break between each measurement. Standardized verbal encouragement will be the sole form of feedback provided to patients. Peak tongue strength will be determined as the highest value among the three measurements.

Isometric hand grip strength

To measure grip strength, the Jamar Preston hand dynamometer will be used for each hand, following established research practices. This device has been shown to be valid and reliable according to guidelines from the American Society of Hand Therapists (Massy-Westropp et al., 2004). The average of three consistent measurements will be compared with published norms (Mathiowetz et al., 1985).

Data management

The paper case report forms containing subject data will be entered into a secure relational database (Microsoft Access, Redmond, WA, USA) that adheres to strict physical and electronic data security measures. Additional data privacy measures include locked offices and filing cabinets for paper records and computers, with encryption and password protection for computers, computer files and electronic data storage in strict accordance with the U.S. Office of Management and Budget and University data security guidance. Subject-identifying information will be eliminated from datasets prior to analyses and only research study personnel who are essential for direct interaction with the medical record and/or the subject will be privy to the linkage between the unique identifier and identifying information.

Statistical methods

Primary analysis

Aim 1: We will explore the relationships between primary outcome variables and patient, intubation, and critical illness factors. Descriptive statistics, such as means, standard deviations, and quantiles for continuous variables, and proportions for binary/categorical/ordinal variables, will be used to summarize patients' laryngeal injury symptoms and patient/ICU variables. Graphical displays, including scatterplots with locally weighted scatterplot smoothing (LOWESS) curves, side-by-side boxplots, or cross-tabulations, will aid in visualizing the pairwise associations among patient symptoms and between symptoms and patient/ICU variables. In instances where continuous patient/ICU variables exhibit non-linear relationships with patient symptoms, we will discretize them (binary or categorical) for subsequent analyses. To quantify the pairwise associations among patient symptoms, we will utilize correlation coefficients, such as Spearman rank correlation and phi-coefficient. To understand the independent associations of patient symptoms and patient/ICU variables with outcomes, we will employ separate multivariable linear and logistic regression models for continuous and binary patient symptoms, respectively. Due to the large number of patient/ICU variables under consideration, we will only include those with standardized coefficients (Vittinghoff et al., 2005) or differences ≥0.1 in the models (Austin, 2011), with gender included in all models due to its potential importance as a risk factor for laryngeal injury. Furthermore, we will use variance inflation factors (VIFs) to exclude variables that exhibit high collinearity (VIF > 10), and standard regression diagnostics will evaluate the fit of the models.

Aim 2: We will examine the relationship between laryngeal injury types, severity, perceptual and acoustic measures, and the symptoms identified in Aim 1. Descriptive statistics will be used

to summarize the measures of laryngeal injury obtained via laryngoscopy and voice measures, as described in Aim 1. To quantify the association among these measures and between them and patient symptoms and variables, similar graphical displays and measures of association as per Aim 1 will be utilized (Table 2). To construct multivariable regression models, the statistical methods described in Aim 1 will be employed. For analyses of acoustic voice outcomes, separate regression models will be created for males and females due to inherent differences in this outcome measure between sexes.

Aim 3: A predictive screening tool based on patient variables (such as age and sex), intubation variables (including ETT size and du-ration of intubation), patient symptoms, and voice characteristics (including routine clinician assessment and acoustic features from audio voice recordings) will be constructed using a supervised machine learning algorithm (Quinlan, 1987). To achieve this, we will employ the conditional inference tree approach (Hothorn et al., 2006), a recursive binary partitioning algorithm that tests the null hypothesis of no association between laryngeal injury and the variables, identifies the variable with the strongest association with laryngeal injury, and applies a binary split of the variable to maximize identification of patients with laryngeal injury. This process is repeated until the global test for association is not re-jected. The conditional inference tree approach includes a multiple comparisons adjustment to account for the possible multiple tests performed. Within each branch of the regression tree, the classification error is computed and can be used to summarize the predictive ability of the regression tree. Sensitivity, or the proportion of patients identified to have laryngeal injury among those with laryngeal injury, will also be evaluated to assess the predictive ability of the regression tree. The R statistical package partykit (Hothorn et al., 2006) with procedure ctree will be used to implement the conditional inference tree approach. One of the benefits of this approach is that the predictive model can be easily coded and incorporated into the electronic medical record.

Secondary analysis

Secondary analysis will involve repeating the laryngeal and voice questionnaires and analyses, tongue strength measure, and hand grip strength measure within 72 hours post-extubation and at 7-day follow-up or hospital discharge (whichever occurs first) and evaluating association of time and perceptual/acoustic voice, tongue strength, and grip strength recovery.

Monitoring

Data Monitoring: The three multiple principal investigators (PIs) will be responsible for data safety and monitoring issues on an ongoing basis throughout the study as per approval from the institutional review board (IRB) and the study sponsor.

Interim Analysis: In this non-randomized prospective cohort study, there are no early stopping rules.

Harms

This is a single-center, 6 ICU prospective cohort study that is closely supervised by three multiple PIs and trained study personnel who will monitor safety throughout the project. The PIs oversee patient eligibility screening, informed consent process, and patient assessments. Any adverse events that may occur will be immediately reported to the PIs, who will, in turn, report them in accordance with IRB and study sponsor guidelines. Pregnant and incarcerated people are excluded from participation in this study. All subjects have the right to decline participation in any or all of the research protocol or withdraw from the study at any time without any consequence to their clinical care.

Survey burden

The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (Ely, Inouye, et al., 2001; Ely, Margolin, et al., 2001), Laryngeal Hypersensitivity Questionnaire-Acute (LHQ-A) (Brodsky et al., in press), Voice Symptom Scale (VoiSS) (Deary et al., 2003), and CAPE-V (Awan et al., 2010; Zraick et al., 2011) are non-invasive questionnaires/rating scales and minimal risk. All of the questionnaires/surveys will be administered according to the timeline presented in Figure 1, as feasible based on patient clinical status.

Risks associated with Laryngoscopy/FEES

Although rare, potential risks of FEES include discomfort, epistaxis (nose bleeding: 0.3%-1.1% of all procedures), vasovagal response (brief fainting: 0%-0.06%), laryngospasm (closure of the vocal folds with acute breathing difficulty: 0%-0.03%), and mucosal laceration (extremely rare) (Aviv et al., 2000; Nacci et al., 2008). In a study of 1340 patients who underwent a Fiberoptic Endoscopic Evaluation of Swallowing with Sensory Testing (FEEST), a procedure similar to laryngoscopy and FEES, 172 (12.8%) were in the ICU. Epistaxis requiring nasal cauterization occurred once (0.07%), and heart rate measures before and after the procedure were not significantly changed. Overall, 81% of patients had no or mild discomfort, and 80% stated they would repeat the examination with referral from their physician (Aviv et al., 2005). For this study, laryngoscopy will follow an established protocol for routine clinical laryngoscopic evaluation per the study institution's Voice Center. The protocol will not be modified for any subject as a result of participation in the study. The risks associated with the procedure will be minimized by the experienced and credentialed clinicians from the study team performing the procedure and the close proximity of hospital clinicians who also will monitor the patient. While in the ICU setting, patients will have routine cardiac and pulmonary monitoring.

Risks associated with Yale Swallow Protocol

No adverse events have been documented from completing this swallow screening (Leder et al., 2012; Leder & Suiter, 2014; Ward et al., 2020). The greatest risk associated with the YSP is aspiration. If a subject's physician consults an SLP for bedside swallowing evaluation, the YSP will not be repeated for research purposes to avoid duplication of testing. Only credentialed study personnel, SLPs, and nurses will be responsible for administering the YSP.

Data Auditing: Study personnel will regularly conduct data audits during study start-up and intermittently thereafter, such that approximately 10% of all records will be audited by the end of the study. The principal investigators will meet with research staff, on a weekly basis, to track progress, recruitment, and data quality/completeness. The study sponsor will not take part in design or conduct of the study; collection, management, analysis or interpretation of the data, or preparation, review and approval of scientific manuscripts.

Ethics

Research ethics approval: The study sponsor is the NIH/NINR and we have obtained IRB approval from Johns Hopkins Medicine IRB (IRB00151643).

Protocol amendments: Protocol amendments will only be made by the study team after obtaining IRB approval. Any death or life-threatening serious adverse events (SAEs) will be reported by the Principal Investigator to the study sponsor Program Officer by telephone, fax, or email within 24 hours, with a written report to the IRB within 3 business days for unexpected deaths/SAEs and within 10 business days for expected deaths and SAEs due to the participant's underlying disease or condition or those caused by a possible risk of the study procedure/intervention as outlined in the protocol and informed consent process. Other SAEs will be re-

ported to the IRB within 7 days, followed by a written report to the IRB within 10 days. The study sponsor does not require reporting of deaths due to the participant's underlying disease or condition or those caused by a possible risk of the study procedure/intervention as outlined in the protocol and consent form. All other SAE report submissions to the study sponsor will follow the timeline described above.

Informed consent or assent: Potential study participants will be identified by screening current medical records of patients in the ICU via a health insurance portability and accountability act (HIPAA) waiver as approved by the IRB. Because many eligible patients will be critically ill and unable to provide informed consent initially, an IRB-approved consent process will be used to obtain consent from the appropriate substitute decision-maker. Once enrolled, participants who regain decision-making capacity will be asked to provide their own informed consent to remain enrolled. The principal investigator or an IRB-approved consent designee, with permission from the patient's attending physician, will approach each subject or substitute decision-maker to explain the study and obtain informed consent. The informed consent process will adhere to IRB policies and procedures. All consents will be appropriately documented via an IRB-approved process and entered into the medical record using the institution's Clinical Research Management System to ensure that all hospital clinicians are aware of the patient's participation.

Confidentiality: All subject data will be confidential and secured via physical and electronic data security measures, including locked offices and filing cabinets for records and computers, and encryption and password protection for computers, computer files, and electronic data storage in accordance with the U.S. Office of Management and Budget. Only de-identified data will be used for analysis.

Declaration of interests: This study is funded by the National Institute of Nursing Research of the National Institute of Health, Bethesda, United States.

Access to data: Aggregate data will be published based on data access by the study team.

Ancillary and post-study care: The study team will not provide ancillary or post-study care, nor will they offer compensation to participants who may suffer harm as a result of their involvement. However, given that the study participants are hospitalized patients and that participation in the research investigation does not require a clinical referral, it is possible that clinical findings discovered during the study may have relevance to the participant's care. To this end, all laryngoscopy procedure findings will be communicated to the study's laryngologists and reported to the medical team in the usual manner for standard clinical care, including documentation in the patient's electronic medical record. The findings will be shared solely for the purpose of informing and optimizing the participant's clinical care, rather than for research purposes.

Dissemination

The results of this study will be disseminated through peer-reviewed scientific publications, ensuring accessibility to healthcare professionals and the public. Authorship and authorship rank in publications will be determined based on the scientific contributions of all key personnel and research staff, in conjunction with thorough discussion among the three principal investigators.

PATIENT AND PUBLIC CONTRIBUTION

This study will involve patients as participants, and in cases where patients are unable to provide consent, their legal authorized representative will provide it on their behalf. The contribution of patients in dedicating their time and effort to participate in this study is highly valued and appreciated. We recognize their altruistic act of contributing to this research and understand that their involvement is essential to achieving the study's objectives. Participants' valuable insights and feedback will inform the study's outcomes and ensure that the research is focused on addressing their needs and concerns.

DISCUSSION

The current clinical studies on laryngeal injury after endotracheal intubation and mechanical ventilation in an ICU provide limited insight into essential patient symptoms and physical findings. Furthermore, some prior studies are limited by small sample sizes, methodological heterogeneity, and/or the absence of replicable methods. This study protocol aims to help address these challenges through a rigorous and comprehensive approach that considers patient-reported symptoms as well as planned, prospective outcome measures that can be independently replicated. This novel investigation addresses the interrelationships of patient symptoms, critical illness, endotracheal intubation with mechanical ventilation, serious laryngeal injury.

Standard practice in the study site's ICUs involves patient referral to an SLP for cognitive, speech, language, and swallowing evaluations following extubation from endotracheal intubation. The only opportunity for these SLPs to identify laryngeal injury during or immediately after extubation is when an instrumental swallowing evaluation, specifically FEES, is indicated after extubation. Bronchoscopy that may be completed while a patient is intubated traverses the lumen of the ETT, greatly limiting visualization of the larynx. After extubation, the integrity of the larynx must be assessed while the patient is awake to assess function. Additionally, a systematic evaluation of current variations in ICU practice patterns indicates that most patients who are extubated and may have severe laryngeal injury are not referred to an SLP or a laryngologist (Brodsky et al., 2018, 2021). This lack of referral can be attributed to the absence of high-quality research to identify patients who are most susceptible to serious laryngeal injury. Furthermore, even with bedside/clinical evaluations, false-negative findings may occur. The presence of a "hoarse voice" after extubation is not necessarily indicative of laryngeal injury, but certainly requires further investigation. This study aims to systematically evaluate all subjects for laryngeal injury, allowing for immediate sharing of clinical results with the study SLPs, laryngologists and clinical teams. Patients who are not identified with serious laryngeal injury will receive standard care.

This protocol aims to provide a greater understanding of critical care patients' conditions and enable appropriate referrals, assessments, and treatment plans based on study findings. Aim 1 of this investigation protocol specifically focuses on patient symptoms and the accuracy of standard clinical bedside assessments pre- and post-extubation. This aim seeks to determine patient and ICU variables associated with these findings. Aim 2 focuses on evaluating laryngeal injury after extubation and determining associations with patient symptoms and standard clinical assessments (Aim 1) along with patient and ICU factors. It is expected that patient symptoms, such as hoarseness, voice abnormalities, throat clearing, throat pain, vocal fatigue, and dyspnea, combined with laryngoscopic assessment, will enable the development of a reliable, valid, and feasible clinical screening tool for use by clinicians, particularly nurses (Aim 3).

CONCLUSION

We highlight the high prevalence of laryngeal injury after endotracheal intubation with mechanical ventilation in critically ill patients, and the lack of a standard approach for identifying and managing this condition. The purpose of this study protocol is to investigate the impact of endotracheal intubation in mechanically ventilated ICU patients, evaluate patient symptoms and clinical bedside assessments during intubation and post-extubation, and prospectively evaluate evidence of laryngeal injury after extubation using laryngoscopy and voice measures. On the basis of

these assessments, the study aims to construct a screening tool for identifying patients with clinically significant post-extubation laryngeal injury. The findings of this study could help to improve patient outcomes and reduce short- and long-term consequences associated with laryngeal injury in critically ill patients.

RELEVANCE TO OTOLARYNGOLOGY NURSING PRACTICE

This proposed study directly addresses the often-underestimated laryngeal injury and related functional impairments of patients who have undergone endotracheal intubation with mechanical ventilation. The intricate risk factors that contribute to laryngeal damage in mechanically ventilated ICU patients in under-studied, highlighting the importance of this protocol. By conducting a prospective, multi-ICU observational investigation in Aims 1 and 2, we will establish the much-needed foundation to develop strategies that helps ensure timely identification, treatment, and prevention of laryngeal injury in this growing patient population. The invaluable benefits to patients and society far exceed the minimal risks associated with the study. Participation in such investigation will contribute to critical insights into improving the care of future patients, thus underscoring its significance.

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Conflict of Interest Statement

No conflict of interest

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Acknowledgements

We would like to express our deepest gratitude to the patients and their family members who participated in this study. Without their willingness to share their experiences, this research would not have been possible. We also extend our appreciation to the dedicated nurses who provided compassionate care to our patients and helped facilitate integrating the research team into clinical care. Additionally, we would like to acknowledge the invaluable contribution of the speech-language pathologists who provided their expertise in the evaluation and treatment of our participants. Finally, we would like to thank all of the individuals who supported this study in various capacities, including data collection, analysis, and manuscript preparation. Their tireless efforts are deeply appreciated.

Funding

NIH/NINR **R01NR017433-01A1**
ClinicalTrials.gov: NCT03726086

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E-ISSN: 1064-3842