Otolaryngologic Symptom Severity Post SARS-CoV-2 Infection

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PII: S0892-1997(23)00080-2
DOI: https://doi.org/10.1016/j.jvoice.2023.02.024
Reference: YMVJ 3862

To appear in: *Journal of Voice*

Accepted date: 20 February 2023

Please cite this article as: Emerson Bouldin , Shelly Sandeep , Amanda Gillespie , Andrew Tkaczuk Assistant Professor , Otolaryngologic Symptom Severity Post SARS-CoV-2 Infection, *Journal of Voice* (2023), doi: https://doi.org/10.1016/j.jvoice.2023.02.024

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Running Title: Symptoms Post SARS-CoV-2 Infection

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Acquisition, analysis, or interpretation of data: Tkaczuk, Shelly

Drafting of the manuscript: Tkaczuk, Shelly, Bouldin, Gillespie

Critical revision of the manuscript for important intellectual content: Tkaczuk, Shelly Bouldin, Gillespie

Study Supervision: Tkaczuk

This research was presented at the Fall Voice Meeting (2021)

Abstract

Objective(s): To assess laryngologic symptomatology following SARS-CoV-2 infection and determine whether symptom severity correlates with disease severity.

Methods: Single-institution survey study in participants with documented SARS-CoV-2 infection between March 2020 and February 2021. Data acquired included demographic, infection severity characteristics, comorbidities, and current upper aerodigestive symptoms via validated patient reported outcome measures. Primary outcomes of interest were scores of symptom severity questionnaires. COVID-19 severity was defined by hospitalization status. Descriptive subgroup analyses were performed to investigate differences in demographics, comorbidities, and symptom severity in hospitalized participants stratified by ICU status. Multivariate logistical regression was used to evaluate significant differences in symptom severity scores by hospitalization status.

Results: Surveys were distributed to 5300 individuals with upper respiratory infections. Ultimately, 470 participants with COVID-19 were included where 352 were hospitalized and 118 were not hospitalized. Those not hospitalized were younger (45.87 vs. 56.28 years), more likely female (74.17 vs. 58.92%), and less likely white (44.17 vs. 52.41%). Severity of dysphonia, dyspnea, cough, and dysphagia was significantly worse in hospitalized patients overall and remained worse at all time points. Cough severity paradoxically worsened in hospitalized respondents over time. Dyspnea scores remained abnormally elevated in respondents even 12 months after resolution of infection.

Conclusion: Results indicate that laryngologic symptoms are expected to be worse in patients hospitalized with COVID-19. Dyspnea and cough symptoms can be expected to persist or even worsen by one-year post infection in those who were hospitalized. Dysphagia and dysphonia symptoms were mild. Non-hospitalized participants tended to have minimal residual symptoms by one year after infection.

Introduction

The coronavirus disease of 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has remained an ongoing public health crisis since it was first declared a public health emergency of international concern on January 30, 2020.[1] Clinical manifestations of infection vary among patients, but commonly include fever, fatigue, and cough.[2] Less frequently sputum production, headache, hemoptysis, and diarrhea are reported.[2]

Laryngologic complications of COVID-19 have been observed and described, including voice changes, cough, dyspnea, and intubation-related injuries. What is now more clinically evident is longstanding manifestations of infection. A recent review of symptoms following COVID-19 infection revealed 32.6-87.4% of infected patients reported one or more persistent symptom, with fatigue and dyspnea listed as most common.[3] New research from October 2022 studied over 33,000 patients with COVID-19 and reported that 42% of them had not fully recovered to pre-infection symptom baseline.[4] That study used serial patient questionnaires and found breathlessness, chest pain, palpitations and confusion were the most reported long-lasting COVID-19 symptoms.

The goal of the current investigation was to determine the prevalence and severity of specific laryngologic and upper aerodigestive symptoms in participants following COVID-19 infection, with particular attention to differences between hospitalized and non-hospitalized patients. We aimed to contribute to the evolving evidence regarding long-term clinical manifestations of COVID-19 with the goal of improving patient management and counseling.

Materials and Methods

This single institution, cross-sectional survey study was approved by the Emory Institutional Review Board (STUDY00001054). All individuals who had contracted the novel SARS-CoV2 virus were eligible to participate regardless of hospitalization status or disease severity. Documented COVID-19 positive patients between March 2020 and Feb 2021 were identified via an Emory Healthcare patient database called Clinical Data Warehouse (CDW). The CDW is a repository that integrates data within Emory Healthcare including patient billing and collections, general ledger and budget information, patient visit data, provider information, diagnoses and procedures, clinical laboratory results, clinician documentation, pharmacy, and emergency department utilization and details.

Patients diagnosed with COVID-19 identified via the database were contacted via email to request their participation using a HIPAA-compliant Research Electronic Database Capture (REDCap) survey.[5] Surveys were distributed in May 2021. The included surveys were all completed between May 2021 to August 2021. The survey questions included self-reported comorbidities, smoking status, self-reported hospitalization status, quality of life post-infection questions, and responses on patient-reported quality of life and disease-severity questionnaires specific to laryngologic and upper aero-digestive symptoms. These validated symptom severity

instruments included Voice Handicap Index - 10 (VHI-10), Dyspnea Index (DI), Cough Severity Index (CSI), and Eating Assessment Tool - 10 (EAT-10).[6-10] Of note, all instruments are scored out of 40 points total and higher scores represent more severe symptoms. Abnormal scores for each questionnaire are defined as the following: VHI-10 > 11, DI > 10, CSI > 3.23, and EAT-10 ≥ 3.[6,9,11,12].

Statistical analysis was conducted using SAS 9.4 software (SAS, Cary, NC). The primary outcomes of interest were total scores of the symptom severity questionnaires. Univariate analysis was performed to evaluate the normality of the data. Student's T-test and Chi-square test were utilized to assess differences between demographics and disease severity status stratified by hospitalization status. Multivariate linear regression models were built to identify various participant characteristics, hospitalization status and time since infection associated with individual participant scores. Logistic regression was run to evaluate if the comorbidities differ for hospitalized, ICU and intubated participants.

Results

Surveys were distributed to 5300 individuals diagnosed with upper respiratory infections including COVID-19 and influenza. Given the small number of participants with influenza (n =6), a comparative analysis was not performed. Inclusion for analysis required reported diagnosis of COVID-19 and completion of at least one symptom severity questionnaire. 527 signed the consent and began the survey; 57 participants were excluded for lack of survey completion. Remaining 470 participants (81% completion rate) were then stratified based on hospitalization admission status, which was used as a surrogate marker for infection severity. A consort diagram representing exclusions and final participation is represented in Figure 1.

Significant differences among demographic variables and hospitalization status are depicted in Table I. Those not hospitalized tended to be younger (45.9 vs. 56.3 years; p = <.001), more likely female (74.2 vs. 58.9%; p = .003), and less likely white (44.2 vs. 52.4%). Overall non-smoking status was similar between both groups (80.0 vs. 82.2%). Comorbidities varied between hospitalized and non-hospitalized patients as seen in Table 2. Over seventy-seven percent (77.27%) stated they required supplemental O_2, 31.53% (111) were admitted to the intensive care unit and 11.93% (42) required intubation and mechanical ventilation. There was no statistically significant difference in the comorbidities between hospitalized, ICU and intubated participants except pulmonary diagnosis, which was greater in the intubated group (p-value = 0.03) (Table 3). Subgroup analysis of symptom severity scores was performed in hospitalized participants stratified by disease severity, which was defined as hospitalized but non-ICU admitted, ICU admitted but not intubated, and ICU admitted and intubated. All mean symptom severity scores were highest in those participants who reported being intubated during their ICU stay (Table 4). The largest differences were in DI, CSI, and VHI-10. VHI-10 scores were below the accepted abnormal threshold (<11) in all groups. Participants who were not intubated, regardless of ICU status, had overall very similar symptom severity scores.

Multivariable Linear Regression (MLR)

In assessing each symptom severity index, hospitalization status was added as the primary independent variable with age, gender, smoking status, and time since COVID-19 infection as covariates. Table 5 presents all mean scores, standard deviation, and sample size data for subgroups defined by time since infection (0-6 months, 6-12 months, and >12 months). Figure 2 provides a visual representation of the data in comparison to abnormal thresholds for each symptom questionnaire.

Voice Handicap Index – 10

Mean VHI-10 scores in both hospitalized and non-hospitalized groups were subclinical. They did not reach abnormal threshold, greater than 11, indicative of those more likely of having a voice disorder.[11] However, MLR showed that VHI-10 scores were statistically significantly greater in hospitalized compared to non-hospitalized participants. Average scores for hospitalized and non-hospitalized were 4.9 (SD 1.4) vs. 2.0 (SD 1.6), respectively (p = .001).

Figure 2 highlights the mean VHI-10 scores reported at varying times since infection. The highest mean score of voice handicap was reported by hospitalized patients >12 months since infection (mean 5.5, SD 8.7). The lowest mean score of voice handicap was reported at the same post-infection time point, but in non-hospitalized patients (mean 1, SD 1.58).

Dyspnea Index

The Dyspnea Index (DI) was significantly greater in the hospitalized participants than non-hospitalized. Mean DI score for the hospitalized cohort was 12.7 (2.2) compared to 8.1 (2.5) for non-hospitalized (p= 0.002). Of note, a clinically abnormal DI score is greater than 10.[7] DI scores were elevated above the clinical threshold for abnormal for all hospitalized participants at all time-points post COVID-19 infection (Figure 2). Hospitalized individuals continued to report high DI even after 12 months post infection (mean 11.8, SD 11.4).

Cough Severity Index

MLR analysis found overall Cough Severity Index (CSI) mean scores to be significantly elevated in those who were hospitalized (mean 7.0 (1.9)) compared to non-hospitalized (mean = 2.5 (2.2); p = <.001). A CSI score >3.23 is indicative of clinically significant cough symptoms.[12]

Mean reported scores were clinically abnormal at all time points in the post infectious period of those who were hospitalized. Of note, highest mean score in *hospitalized* patients was reported at >12 months since infection (mean 7.5, SD 10.2), while highest mean score in *non-hospitalized* patients was reported earlier at 0-6 months since infection (mean 4.9, SD 8.8).

Eating Assessment Tool - 10

Dysphagia symptoms captured by EAT-10 score were significantly greater in hospitalized (mean 3.6, SD 1.3) versus non-hospitalized participants (mean 1.7, SD 1.5) (p = 0.026), per MLR analysis. EAT-10 is considered clinically abnormal at a score of 3 or more.[9] Dysphagia was subclinical when assessed at varying time points post infection. At >12 months since infection, the mean EAT-10 score in hospitalized patients was 2.9 (5.7), compared to a mean score of 0.2 (0.7) in non-hospitalized patients at the same time post-infection.

Discussion

Our findings provide relevant and practical insight into the prevalence and severity of specific laryngologic COVID-19 symptoms, with particular focus on how symptomatology may be related to severity of infection and duration of symptoms post-infection. These results are generally consistent with emerging literature.

Laryngeal symptoms and complications of COVID-19 continue to be described in the literature as the pandemic has progressed. In a newly published study of long-COVID outcomes in over 33,000 patients, 33% of individuals reported symptom duration greater than four weeks.[4] Many of those symptoms assessed were laryngologic, including cough (54%), breathlessness (45%), sore throat (31%) and hoarseness (13%).[4] Allisan-Arrighi et al. found that non-intubated patients with COVID-19 were more likely to be diagnosed with muscle tension dysphonia and

laryngopharyngeal reflux.[13] In the recent study by Hastie and colleagues, 13% of participants reported dysphonia as a symptom during acute COVID-19 infection. That study used symptom checklists and not validated quality of life questionnaires so it is unknown if the dysphonia was long-term or how it affected participants' lives. Most recently, Shah et al. described long-term laryngeal complications post infection including dysphonia, dysphagia, COVID-related hypersensitivity and laryngotracheal stenosis.[14]

In our population of participants post-COVID-19 infection, voice handicap, as rated by the VHI-10, was worse in hospitalized than non-hospitalized respondents. The most critically ill participants who required intubation rated the greatest voice handicap post-infection, which is similar to another recent international cohort.[15] However, this score did not reach the defined and accepted threshold of clinically significant dysphonia.[6] In fact, all respondents, regardless of disease severity and time point post-infection did not reach this threshold. Other investigations have revealed dysphonia can be experienced in up to 20% of patients 6 months post-ARDS, where the voice disturbance is often attributable directly to the pathophysiology and management of the condition.[16] Intubation appears to be a key predictor of dysphonia after critical illness.[17,18] There is little literature to support any direct pathogenicity of SARS-CoV-2 on the glottis, however, reports on COVID-19 related dysphonia and laryngeal edema exist.[19-21] Dysphonia remains a minimized symptom, but is prevalent in 3-9% of the general population where it can impact quality of life and can contribute to lost wages.[22,23] Post-COVID-19 patients who experiencing significant dysphonia should be evaluated for hyperfunctional muscle-tension-related voice disorders, glottic insufficiency, and vocal manifestations of poor pulmonary function. Challenging diagnoses such as post intubation phonatory insufficiency or posterior glottis stenosis may be more frequently encountered in this population.[24,25] Laryngoscopy will

remain paramount and indicated at any time in the evaluation of a dysphonic patient, and recommended for vocal symptoms lasting longer than 4 weeks.[26]

Swallowing is a physiologic process that is frequently negatively impacted by systemic disease and critical illness. In large prospective observational studies of the critically ill, dysphagia is observed in 10% of patients at time of ICU discharge, where the majority of patients continue to have swallowing issues through the remainder of their hospitalization.[27] Heterogeneous data limits accurate estimates, but immediate post-extubation dysphagia rates vary widely in the literature from 3% to 62%.[28] Severe swallowing deficits after prolonged intubation, such as penetration and aspiration, are present in up to 35% of patients.[29] Longer periods of intubation increase the risk of aspiration as well as subsequent pneumonia.[30] A multi-institutional study in Ireland revealed in a group of post-COVID-19 patients referred for SLP evaluation that 84% required modified diets and 31% required alternative forms of nutrition.[15] The current study revealed that overall dysphagia symptoms post COVID-19 infection were mild. Only the hospitalized participant group reached clinically meaningful dysphagia symptom severity. Although subgroup analysis was not performed on our dataset, participants who may have suffered severe thromboembolic complications such as CVA or other neurologic insults would be expected to have worse swallowing outcomes than participants who did not.

Acute cough is a common and now stigmatizing symptom in COVID-19 infection, however, its presence may be less specific than fever in those infected, particularly with the Delta variant.[31,32] Preliminary studies have thus far indicated that persistent cough after SARS-CoV-2 infection at least 2 months post-infection ranges between 7 and 16%.[33-35] A recent review investigating cough in the setting of Post-COVID syndrome indicates a possible higher prevalence, and discusses potential neurotropism of this virus and the neuroinflammatory

mechanisms leading to a hypersensitive cough state.[36] The exact pathophysiologic mechanisms driving cough post-COVID infection are not completely known, but speculated to be due to parenchymal lung damage, the direct influence of infection of sensory neural tissues, and sensory hypersensitivity.[37-41] Post-infectious cough is not novel to SARS-CoV-2, where previous infection as an etiology for subacute cough lasting > 3 but less than 8 weeks ranges from 12 to 48%.[42-44] After H1N1 influenza, post-infectious cough was reported as high as 43%, and was objectively associated with 9-fold higher cough reflex sensitivity and worse quality of life when compared to those with no cough.[45] There may be cough predilection phenotypes where certain individuals can be susceptible to recurrent bouts of post-infectious cough, and also tend to have a predisposition to elevated cough sensitivity.[46] In this cohort, post-infectious cough severity symptoms appear to be dependent on disease severity. Critically ill and intubated participants had the worst cough scores at all time-points. Additionally, there was an inverse symptom course, with hospitalized participants more likely to have worsening scores over time versus improvement in the non-hospitalized participants. Non-hospitalized participants had near normal cough severity scores by 6 months. With these findings in mind, expectant management with cough suppressive therapies and reassurance may suffice for the majority of recovering patients post-COVID.

In its most severe form, COVID-19 infection results in significant aberrations in oxygenation with multi-lobar pneumonia and acute respiratory distress syndrome (ARDS) where even young individuals with minimal comorbidities have required extensive cardiopulmonary support including extracorporeal membrane oxygenation (ECMO).[47] In the current cohort, 31.5% of hospitalized respondents reported ICU admission and 6.8% required intubation and mechanical ventilation. Recent reports indicate that up to 74% of patients with severe pulmonary

manifestations of COVID-19 (requiring at least 6L of supplemental oxygen) experience dyspnea at one month after discharge.[48] Others have reported that 10% of patients experience significant dyspnea at 6 months post-infection, and those admitted to the ICU were more likely to endorse these symptoms than those hospitalized without ICU admission.[49] Average post-infection dyspnea scores in our cohort remained abnormally elevated at all time points in hospitalized participants with substantially higher mean scores in recovered mechanically ventilated participants. Although reported data are heterogeneous, the anticipated duration of mechanical ventilation once a patient is intubated for acute respiratory failure due to COVID-19 infection is > 9 days.[50-52] The consequences of ARDS, prolonged intubation, and mechanical ventilation can result in anatomic and physiologic abnormalities of the airway and lungs. Herridge et al. investigated post ARDS cohorts and commonly noted restrictive lung patterns and reduced diffusional capacity at 3 months post-illness, where median lung volumes and spirometric values approach 80% predicted by 6 months.[53] At 5 years, spirometry should be expected to be normal or near-normal in surviving patients, and chest CT findings are typically minor where even the extent of disease does not significantly correlate with subjective respiratory symptoms or pulmonary function.[54,55] Iatrogenic airway stenosis has been reported throughout the literature for decades with the risk of such sequelae often dramatically increasing after a week of orotracheal intubation.[56-59] In the setting of COVID-19, those with milder disease not requiring hospitalization can be reassured that dyspnea symptoms should resolve, while those who were critically ill would benefit from a thorough investigation to ensure no evidence of diminished pulmonary function or sequelae of prolonged intubation or other airway instrumentation such as laryngotracheal stenosis.

Survey studies are not without limitations where informational biases such as recall bias and response fatigue can be expected and can influence outcomes. In this particular study, the surveys were presented to participants in the same order. Despite so many questions, our study had a survey completion rate of 81%. Other possible biases include selection bias where non-responders could be older, sicker, or even deceased. Another consideration, more specific to this population, is cognitive impairment post-COVID.[60] Although we asked patients to report only their current symptoms, cognitive impairment could impact the accuracy of self-reported responses, especially comorbidities and estimated time since infection. Regarding the validity of the questionnaires, each symptom severity index queried is a validated and routinely used patient reported outcome measure. Survey responses were able to be stratified into different time periods since infection, which provides a glimpse of patient experience and recovery. Therefore, this data may provide some insight into the prevalence of specific symptoms and their severity post infection. However, a longitudinal cohort study would better assess the progression and severity of these symptoms post-infection. Of note, a key limitation of our results is sample size – particularly when assessing symptoms at different time points post infection. Table 5 presents sample sizes of each subgroup, which make direct comparisons difficult. Importantly, as this data was obtained via cross-sectional survey design, these results are observational and cannot predict causality.

Conclusion

In this population, those non-hospitalized with COVID-19 tended to be younger, female, and have less comorbidities than hospitalized participants. At all time-points, all upper aerodigestive symptom severities were worse in those hospitalized with COVID-19 versus not hospitalized. Based on these survey results, dyspnea and cough can be expected to linger or even

worsen post-infection in patients hospitalized with COVID-19. Dysphonia and dysphagia symptoms were found to be mild. Non-hospitalized participants tended to have minimal symptoms by one-year post-infection. These findings provide some practical and applicable data that can be clinically useful in counseling patients presenting with persistent complaints after recovering from infection with novel SARS-CoV2. Particularly, those who were hospitalized and critically ill could have sequelae of their illness and management that should warrant Otolaryngology referral.

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Figure Legend

Figure 1. Subject Acquisition, Exclusion, and Selection

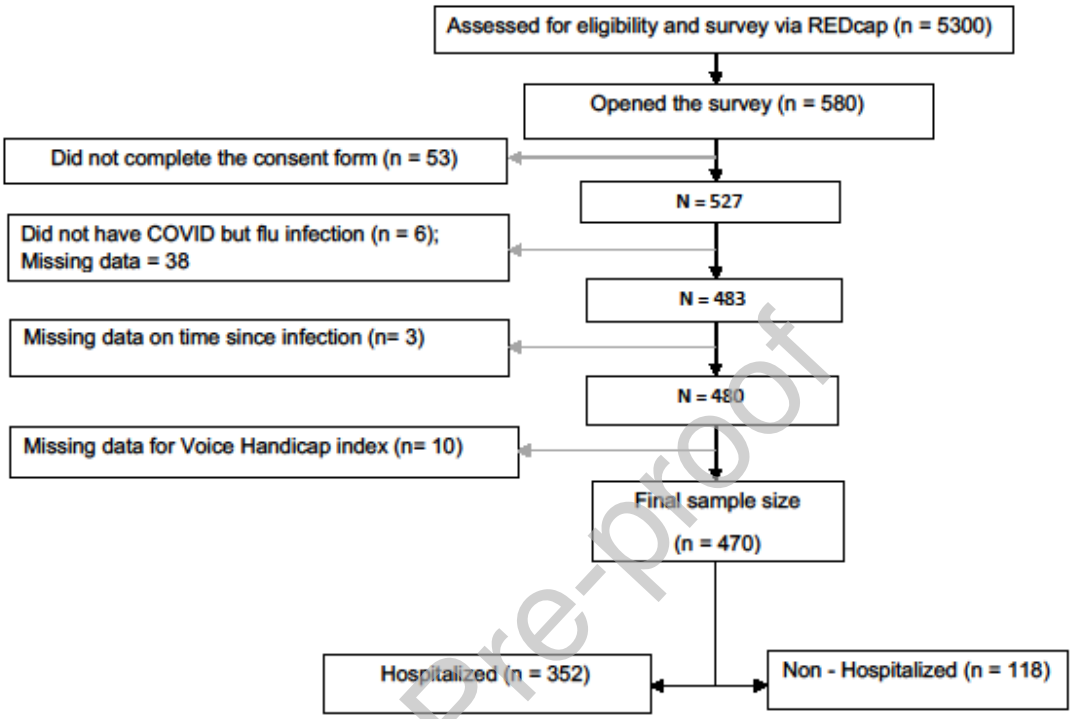
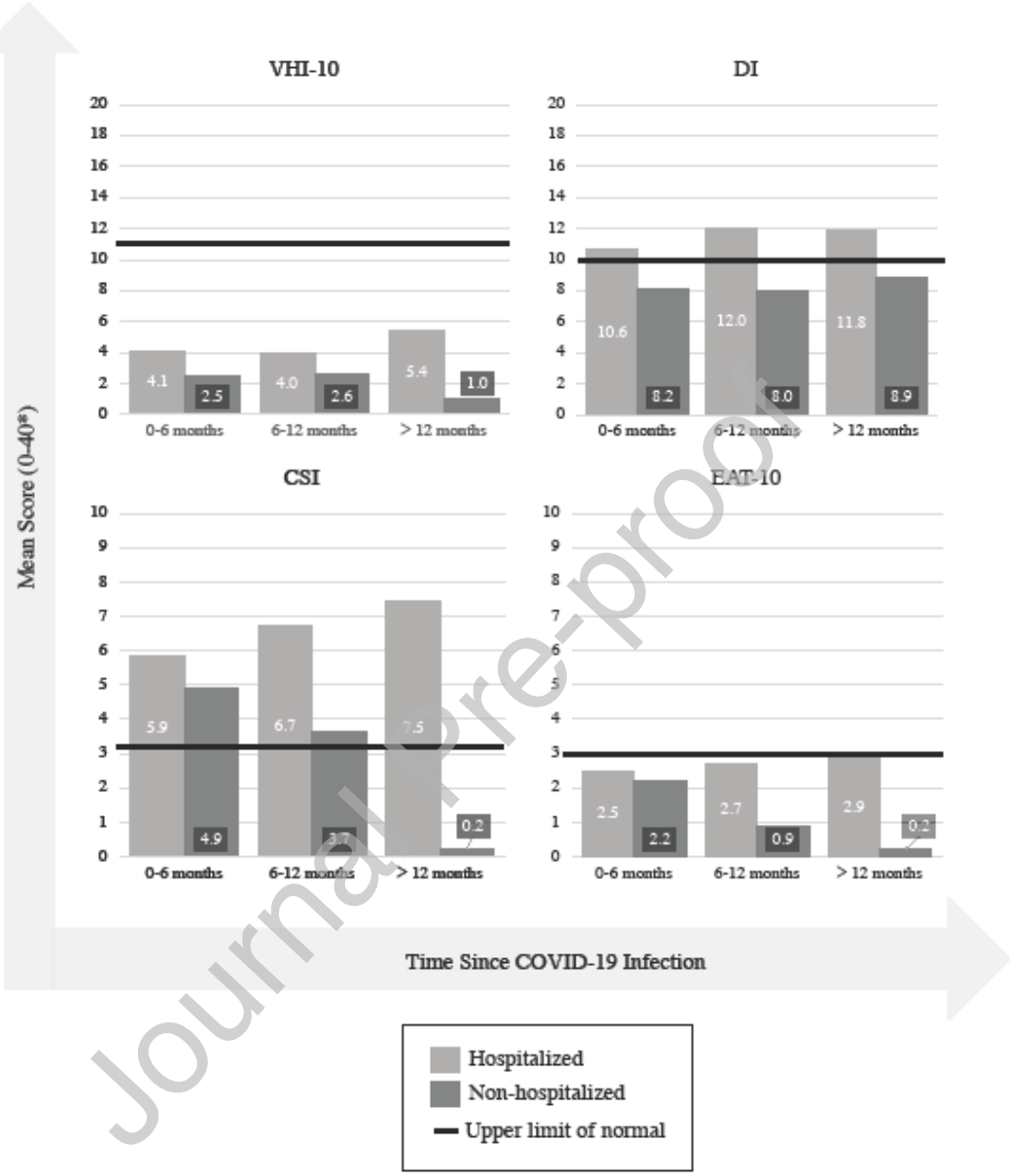


Figure 2. Severity of Upper Aerodigestive Symptoms Post COVID-19 Infection



*All questionnaires are scored from 0-40, yet abnormal thresholds vary. Higher scores are associated with more severe symptoms. The vertical axes have been adjusted for ease of viewing.

Please see **Table 5** for standard deviation and sample size details for each subgroup.

Table 1. Demographics Stratified by Hospitalization Status

	Not Hospitalized (N=118)	Hospitalized (n=352)	P-values

Age in years (Mean, SD)	45.87 (14.72)	56.28 (18.35)	<0.0001
Gender (%)			0.0028
Male	25.83%	41.08%	
Female	74.17%	58.92%	
Race (%)			0.07
Black or African American	47.5%	39.02%	
White	44.17%	52.41%	
More than one race	5.83%	2.55%	
Unknown/Not reported	2.50%	1.42%	
Smoking status (%)			0.5990
Smokers	20.00%	17.85%	
Non-Smoker	80.00%	82.15%	
Time since COVID infection (%)			0.1034
Less than 6 months	43.22%	39.2%	
6 to 12 months	49.15%	45.45%	
More than 12 months	7.63%	15.34%	

Table 2. Comorbidities, Vaccine Administration and Disease Severity

	Not Hospitalized	Hospitalized	
COVID Vaccine administrated (%)			0.027
Yes	67.5%	77.62%	

Comorbidity			<0.0001
Asthma	16.95%	19.89%	
Cardiac Disease	2.54%	11.65%	
Pulmonary Disease	0.85%	6.82%	
Diabetes Mellitus	8.47%	31.25%	
Hypertension	29.66%	40.91%	
None	38.14%	21.02%	
Severity			
Oxygen supplementation	0	272/352	
ICU admission	0	111/271	
Ventilation	0	42/111	

Cardiac disease includes individuals with reported coronary artery disease and congested heart failure. Pulmonary disease includes individuals with chronic obstructive pulmonary disease/emphysema, and pulmonary fibrosis.

Table 3. Percent Differences of Comorbidities in Patients Based on ICU and Intubation Status

	N	Hypertension	Diabetes Mellitus	Asthma	Cardiac Disease	Pulmonary Disease	None
Not ICU	241	38.17	24.90	19.09	9.13	4.98	21.16
ICU, not intubated	69	47.27	36.36	21.82	17.39	10.14	21.74
Intubated	42	54.76	42.86	30.95	16.67	14.29	19.05

Cardiac disease includes individuals with reported coronary artery disease and congested heart failure. Pulmonary disease includes individuals with chronic obstructive pulmonary disease/emphysema, and pulmonary fibrosis.

Table 4. Means and Standard Deviations of Symptom Severity Scores in Patients Based on ICU and Intubation Status.

		VHI-10	**DI**	**CSI**	**EAT-10**
Mean (SD)	**Not ICU**	3.40 (5.82)	10.33 (10.30)	5.91 (8.74)	2.59 (6.55)
		31	37	36	40

Range	**ICU, not intubated**	4.33 (6.84) 28	11.43 (9.76) 33	5.55 (8.69) 39	2.51 (4.66) 20
	Intubated	8.90 (8.77) 29	17.45 (12.24) 40	11.44 (11.45) 40	3.34 (5.79) 30

All questionnaires are scored from 0-40. Higher score indicates more severe symptoms.

Table 5. Means and Standard Deviations of Symptom Severity Scores in Patients Stratified By Time Since Infection

		0-6 months since infection		6-12 months since infection		>12 months since infection	
		Hospitalized	Non-hospitalized	Hospitalized	Non-hospitalized	Hospitalized	Non-hospitalized
VHI-10 (abnormal > 11)	*N*	*138*	*51*	*160*	*58*	*54*	*9*
	Mean (SD)	4.1 (6.6)	2.5 (5.3)	4.0 (5.9)	2.6 (4.5)	5.4 (8.7)	1 (1.6)
DI (abnormal > 10)	*N*	*136*	*48*	*158*	*57*	*53*	*9*
	Mean (SD)	10.6 (10.0)	8.2 (9.2)	12.0 (11.0)	8.0 (8.4)	11.8 (11.4)	8.9 (8.2)
CSI (abnormal > 3.23)	*N*	*136*	*47*	*157*	*56*	*53*	*9*
	Mean (SD)	5.9 (9.3)	4.9 (8.8)	6.7 (8.9)	3.7 (5.8)	7.5 (10.2)	0.2 (0.7)
EAT-10 (abnormal ≥ 3)	*N*	*156*	*45*	*136*	*56*	*53*	*9*
	Mean (SD)	2.5 (5.7)	2.2 (6.5)	2.7 (6.7)	0.9 (2.3)	2.9 (5.7)	0.2 (0.7)

All questionnaires scored 0-40