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The Relationship between Post-Stroke Depression and Post-Stroke Dysphagia

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THE RELATIONSHIP BETWEEN POST-STROKE DEPRESSION AND POST-STROKE DYSPHAGIA

BY

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A dissertation submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirement for the degree Doctor of Philosophy in the College of Health Professions

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Body of Abstract

Background: Post-stroke dysphagia and post-stroke depression (PSD) can have devastating effects on stroke survivors and substantial financial impacts on the healthcare system; however, there is a dearth of research examining this patient population. Thus, we studied the incidence, risk, and cost of PSD in patients with post-stroke dysphagia.

Methods: We conducted a retrospective, cross-sectional study of individuals with a primary diagnosis of acute ischemic stroke and secondary diagnoses of dysphagia and/or depression using administrative claims data from the 2017 Medicare 5% Limited Data Set. Additionally, we developed a novel dysphagia severity index for use with administrative data and applied it to our data sets.

Results: Persons with post-stroke dysphagia were as, or slightly more, likely to have PSD compared to the general stroke population. Those with dysphagia (irrespective of severity) had greater odds and hazard of diagnosis of PSD in the 90 days after discharge, and those with dysphagia and PSD incurred higher healthcare costs.

Conclusion: Our results supported an association between post-stroke dysphagia and PSD and that the presence of PSD in patients with post-stroke dysphagia increased post-discharge cost. Thus, future research is warranted to further explore the effects of PSD on post-stroke dysphagia.

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CHAPTER 1: INTRODUCTION

Background and Significance

Stroke

Stroke is one of the leading causes of morbidity, mortality, and long-term disability worldwide, impacting more than 795,000 people per year in the United States, with approximately 75% of strokes occurring in people over the age of 65 (Centers for Disease Control, 2020). Many stroke survivors experience serious physical and psychological consequences after stroke, such as dysphagia (difficulty swallowing) and depression (Kumar et al., 2010; National Stroke Association, n.d.). These common stroke sequelae often delay functional recovery and are associated with poor patient outcomes, increased hospital length of stay (LOS), and increased healthcare costs (Kumar et al., 2010).

Post-Stroke Dysphagia

Dysphagia is a significant impairment that can occur in up to 78% of stroke survivors (Martino et al., 2005). This condition has many negative consequences, including increased burden on caregivers and healthcare providers, increased healthcare costs due to prolonged hospitalizations and readmissions, institutionalization after discharge,

decreased quality of life (QOL), and increased mortality (Altman et al., 2010; National Stroke Association, n.d.). Many dysphagic patients experience improvement in swallow function within the first two to four weeks after stroke (Bahcecı et al., 2017); however, some patients continue with persistent dysphagia resulting in long-lasting disability (Kumar et al., 2010). Dysphagia is also associated with serious complications and comorbidities, such as malnutrition, dehydration, aspiration pneumonia, compromised overall health (American Speech-Language-Hearing Association [ASHA], n.d.) and depressive symptoms (Dziewas, et al., 2017; Holland, 2011; Verdonschot et al., 2013, 2017). Furthermore, dysphagia has serious psychosocial impacts, with dysphagic patients reporting disinterest in eating, embarrassment, reduced self-esteem, and social isolation (ASHA, n.d.; Ekberg et al., 2002).

Post-Stroke Depression

Post-stroke depression (PSD) is the most common stroke-related neuropsychiatric disorder, affecting approximately one-third of stroke survivors (Hackett & Pickles, 2014; Towfighi et al., 2017). PSD is a major predictor of negative outcomes after stroke due to its association with cognitive and social impairments, reduced treatment efficacy, disability, poor functional and rehabilitative outcomes, poor QOL, and high mortality (Bucur & Papagno, 2018; Bhogal et al., 2004; Cole et al., 2001; Das & Rajanikant, 2018; Towfighi et al., 2017). Though a large number of risk factors for PSD have been investigated, such as demographics (e.g., age, gender, race), social factors (e.g., marital status, social support), and medical history (e.g., history of stroke, premorbid

cardiovascular risk factors, biomarkers), results from the literature remain controversial (Babkair, 2017). Despite the substantial prevalence and serious consequences of PSD, it remains under-recognized and, therefore, underidentified by healthcare providers (Ibrahimagic et al., 2019; Kumar et al., 2010).

Problem Statement

It is known that both post-stroke dysphagia and PSD can have devastating effects on patients' physical, psychological, and social well-being as well as substantial financial impacts on patients, caregivers, and the healthcare system (Dziewas et al., 2017; Paolucci et al., 2019); however, because of the dearth of research specifically examining PSD in post-stroke dysphagic patients, the degree to which these condition are associated, how they impact stroke survivors, and their combined effects of post-stroke recovery are not known. Furthermore, there is a lack of clinical guidelines to direct clinical practice and treatment in this patient population. For these reasons, there is a great need for research to examine the role of PSD in patients with post-stroke dysphagia. Thus, this study will provide essential information about the association between PSD and post-stroke dysphagia and propose a novel methodology for classifying dysphagia severity for use in administrative data research, which may lead to future studies to examine the influence of PSD on post-stroke dysphagia recovery, establish protocols for early identification of post-stoke dysphagic patients with PSD, and develop treatment strategies to address PSD in post-stroke dysphagic patients to maximize recovery and improve outcomes.

Research Questions

1. What is the rate of PSD in patients with post-stroke dysphagia?
2. How can dysphagia severity in a post-stroke population be categorized using dysphagia-specific ICD-10 diagnosis and procedure codes to determine if dysphagia severity impacts diagnosis of PSD?
3. What are the mean healthcare costs for post-stroke dysphagic patients with and without PSD?

CHAPTER 2: REVIEW OF THE LITERATURE

Section 1: Normal Swallowing

Anatomy, Physiology and Neurologic Control

The act of swallowing is an integrated, dynamic, and complex mechanism, involving a series of sequential, coordinated sensorimotor events, including a combination of volitional and reflexive movements of more than 30 nerves and muscles (Malandraki & Robbins, 2013; Matsuo & Palmer, 2008; Sasegbon & Hamdy, 2017). The neural control of swallowing recruits from all levels of the nervous system, including the cerebral cortex (e.g., primary sensorimotor cortex, prefrontal cortex, sensorimotor integration areas, and parieto-occipital region), subcortical regions (e.g., insula and frontal operculum, anterior cingulate cortex, basal ganglia, thalamus, hypothalamus, amygdala, cerebellum, and supplementary motor areas), brainstem, and peripheral nervous system (PNS) (Dehaghani et al., 2016; Malandraki & Robbins, 2013; Matsuo & Palmer, 2008; Mistry & Hamdy, 2008; Sasegbon & Hamdy, 2017). The brainstem swallowing center, which is considered the core of the swallowing system, contains the central pattern generators (CPGs) that – along with the premotor circuitry and motor neurons – control and coordinate the phases of swallowing (Lang, 2009; Mistry & Hamdy, 2008). With regard to cortical control, the literature indicate that cortical representation involved in swallowing

is bilateral, though asymmetric, with some studies suggesting greater activity in the right hemisphere (Ertekin & Aydogdu, 2003; Mistry & Hamdy, 2008; Sasegbon & Hamdy, 2017). Mosier and Bereznaya (2001) describe cortical control of swallowing as five clusters of independent brain regions, with the regions within each cluster working in excitatory and inhibitory coordination (Cichero & Murdoch, 2006). The clusters are organized as follows: A – primary motor, sensory, and supplementary cortices and cingulate gyrus; B – inferior frontal gyrus, secondary sensory cortex, corpus callosum, basal ganglia, and thalamus; C – premotor and posterior parietal cortices; D – cerebellum, and E – insula (Cichero & Murdoch, 2006; Mosier and Bereznaya, 2001). The authors also suggest that certain clusters influence others. For example, the cortical regions of Cluster A are involved in volitional motor behavior, planning, and execution; sensory, motor, and cognitive processing; and are thought to act as sensorimotor output that affect Cluster B, which facilitate sensory information integration about the bolus (Cichero & Murdoch, 2006; Mosier and Bereznaya, 2001). Furthermore, excitation of Cluster B provides an inhibitory effect on Cluster D, while Cluster C has the opposite (excitatory) effect on Cluster A, potentially involving motor planning and implementation (Cichero & Murdoch, 2006; Mosier and Bereznaya, 2001). Cluster D (cerebellum) controls motor coordination, timing, sequencing, and proprioception, which modulates the internal representation for swallowing versus the actual execution of swallowing, impacting both Clusters A and B (Cichero & Murdoch, 2006; Mosier and Bereznaya, 2001). Finally, Cluster E (insula) affects Clusters A and C, potentially for the purpose of movement synchronization (Cichero & Murdoch, 2006; Mosier and Bereznaya, 2001).

The swallowing process is divided into three phases: oral, pharyngeal, and esophageal, with the oral stage containing two phases: oral preparatory and oral transport (ASHA, n.d). The volitional actions during the oral phase, such as the stereotypic motor pattern of mastication, are controlled by discrete areas of the cerebral cortex and CPGs in the reticular formation and trigeminal nucleus of the brainstem (Jean, 2001; Lang, 2009). The events of the semi-reflexive pharyngeal phase are triggered and controlled by the activation of cortical and subcortical brain regions, primarily the CPG in the nucleus tractus solitarius located in the medulla oblongata of the brainstem (Jean, 2001; Lang, 2009; Mistry & Hamdy, 2008). The involuntary or reflexive esophageal phase is also coordinated by the swallowing CPG located in the nucleus tractus solitarius of the medulla oblongata (Jean, 2001; Lang, 2009; Mistry & Hamdy, 2008).

In the oral stage of swallowing, saliva, teeth, and three main muscle groups are responsible for the execution of oral acceptance, containment, mastication, manipulation, and bolus formation (Malandraki & Robbins, 2013; Sasegbon & Hamdy, 2017). The first muscle group needed for the oral preparatory and oral transport phases includes the lips and cheeks, which are comprised of the orbicularis oris, buccinator, risorius, lip elevators, and lip depressors, and are innervated by the Facial Nerve (CN VII) (Sasegbon & Hamdy, 2017). The second muscle group is the tongue, which includes the transverse, vertical, superior, and inferior longitudinal muscles; genioglossus; hyoglossus; styloglossus; and palatoglossus and are innervated by the Facial (CN VII) (taste), Glossopharyngeal (CN IX) (taste), Vagus (CN X) (innervates palatoglossus, taste and

sensation for base of tongue), and Hypoglossal (CN XII) (muscle contractions) nerves (Sasegbon & Hamdy, 2017). The third muscle group is the mandibular muscles, comprised of the temporalis, masseter, lateral pterigoids, and medial pterigoids, and innervated by the Facial nerve (CN VII) and the mandibular branch of the Trigeminal nerve (CN V_3) (Sasegbon & Hamdy, 2017).

The oral phase of swallowing begins with the sensory recognition of food or liquid, as the olfactory and taste systems work in concert, which causes salivation triggered by olfaction and taste via sensory fibers in the oropharynx that respond to temperature and/or touch-pressure and chemoreceptors that respond to smell and taste (Malandraki & Robbins, 2013). Saliva is produced in anticipation of and throughout eating. Saliva is an important component of the swallowing process because it aids in mastication (by softening and breaking down food), formation of a bolus, and lubrication (for bolus passage into the pharynx) (Sasegbon & Hamdy, 2017). From the oropharyngeal sensory fibers, the Trigeminal (CN V), Facial (CN VII), Glossopharyngeal (CN IX), and fibers shared by the Vagus (CN X) and Accessory (CN XI) nerves receive sensory and taste information, which is transmitted to groups of nuclei in the brainstem (e.g., regions of the nucleus tractus solitarius, nucleus ambiguus, and reticular formation of both these groups of nuclei) (Malandraki & Robbins, 2013). These nuclei receive supramedullary input and transmit motor commands via the Trigeminal (CN V), Facial (CN VII), Glossopharyngeal (CN IX), fibers shared by the Vagus (CN X) and Accessory (CN XI), and the Hypoglossal (CN

XII) nerves to the terminal organs (i.e., nearly 40 pairs of oropharyngeal muscles) (Malandraki & Robbins, 2013).

Teeth, which are innervated by the maxillary and mandibular branches of the Trigeminal nerve (CN V), are also important structures in the swallowing process because they physically crush and grind food during mastication, allowing for bolus formation (Sasegbon & Hamdy, 2017). After food is introduced into the oral cavity and the lips, teeth, and tongue take the bolus from the utensil, oral containment via labial seal prevents anterior spillage out of the oral cavity and mastication, using rotary lateral mandibular movement, occurs while lingual manipulation positions food on the molars for crushing and grinding. Mastication is a volitional motor task controlled by the brainstem CPG and supplemented by the motor cortex; however, once initiated, it becomes largely automatic relying on preprogrammed movement patterns (Mistry & Hamdy, 2008). During this time, sensory feedback prevents tongue injury during mastication and indicates when the bolus has been adequately masticated. These oral preparatory actions are performed through labial, buccal, lingual, mandibular, and velar movements, which form the bolus (Malandraki & Robbins, 2013). Regarding liquids, the oral phase is much simpler and faster than with solid foods as mastication is not required. In normal swallowing, the liquid bolus is introduced through the lips where it is contained behind closed lips (i.e., labial closure), held in the anterior floor of the mouth or between the dorsal lingual surface and hard palate, and then is pulled together into a bolus prior to the initiation of the pharyngeal swallow (Matsuo & Palmer, 2008).

During the oral transport phase, the tongue initiates the anterior to posterior propulsion of the bolus from the oral cavity to the pharynx. At the beginning of this phase, the bolus is on the anterior tongue. The tip of the tongue either tips up or down (e.g., “tipper” versus “dipper”) positioning the bolus on the superior lingual surface while the posterior tongue lowers, which occurs via intrinsic lingual muscles (i.e., attached to other muscles in the tongue, including the superior and inferior longitudinal, vertical and transverse muscles) and extrinsic lingual muscles (i.e., attached to structures [like the hyoid bone], including the hyoglossus, styloglossus, genioglossus, and palatoglossus) (Malandraki & Robbins, 2013; Sasegbon & Hamdy, 2017). The tongue sequentially squeezes against the hard palate causing anterior to posterior flexion that forces the bolus posteriorly toward the pharynx (Sasegbon & Hamdy, 2017). As the bolus progresses posteriorly, the sensory fibers in the oropharynx and tongue that respond to temperature and/or touch-pressure are stimulated and trigger the initiation of the pharyngeal swallow (Malandraki & Robbins, 2013; Sasegbon & Hamdy, 2017). While this process is occurring, the velum elevates, contacts the nasopharynx, and seals the nasopharynx preventing food/liquid from entering (Sasegbon & Hamdy, 2017).

The pharyngeal phase of swallowing involves numerous sensorimotor and physiologic behaviors that occur simultaneously between the hypopharynx and the larynx to transport the bolus from the oropharynx to the esophagus (Logemann, 1998). At the initiation of the pharyngeal phase, the velum is elevated and in contact with the lateral and posterior pharyngeal walls, providing complete closure of the velopharyngeal port

(Matsuo & Palmer, 2008). Lingual-palatal contact propels the bolus against the posterior pharyngeal wall, which contributes to the positive pressure that pushes the bolus downward (Malandraki & Robbins, 2013). Laryngeal elevation and anterior hyoid movement, via the extrinsic laryngeal muscles and thyrohyoid muscles, contribute to airway protection and opening of the upper esophageal sphincter (UES) - comprised of the inferior pharyngeal constrictor muscles, cricopharyngeus muscle, and the most proximal part of the esophagus - for passage of the bolus from the pharynx to the esophagus (Malandraki & Robbins, 2013). Adequate laryngeal closure is critical for airway protection; therefore, it occurs at three anatomical levels: the true vocal folds, the false vocal folds, and the epiglottis (Malandraki & Robbins, 2013). While all of this is occurring, the pharyngeal constrictors begin contracting in a descending arrangement, the laryngeal framework is pulled upward, the epiglottis inverts to seal the laryngeal vestibule, pharyngeal stripping waves and pharyngeal contraction propel the bolus, and finally the UES (closed at rest by tonic muscle contraction) opens, via relaxation of the cricopharygeus muscle, to allow the bolus to pass from pharynx to the esophagus (Malandraki & Robbins, 2013; Sasegbon & Hamdy, 2017).

The esophageal phase begins upon entry of the bolus through the UES. Afferent neurons transmit the sensation of the arrival of the bolus in the esophagus to the neurophysiological swallowing centers, which activate vagal efferent fibers producing a proximal to distal sequence of contractions or peristaltic wave (i.e., “primary peristalsis”) that propels the bolus toward the stomach (Malandraki & Robbins, 2013). When

peristalsis is initiated, the lower esophageal sphincter (LES) relaxes and the bolus moves into the stomach via peristalsis and gravity (Malandraki & Robbins, 2013).

Section 2: Abnormal Swallowing (Dysphagia)

Stroke-Related Changes in Anatomy, Physiology, and Neurologic Control

Because swallowing is an extremely complex neuromechanism, involving the integration of many coordinated sensorimotor events, including that of several brain regions (such as the cortex, subcortical regions, and brainstem), more than 30 nerves and muscles, and neural control from the peripheral nervous system (PNS) (Malandraki & Robbins, 2013; Matsuo & Palmer, 2008; Sasegbon & Hamdy, 2017; Wilmskoetter et al., 2019b), it is clear that a disruption in this process caused by stroke could result in serious impairments in swallow (Wilmskoetter et al., 2020), thus, impacting a patient's ability to safely and efficiently eat and drink, potentially affecting nutrition and hydration. Neurologic insults can disrupt neuronal transmission of information to and from the central nervous system, resulting in impaired muscle and sensory function in the oropharyngeal system (Malandraki & Robbins, 2013). In addition, patients with neurogenic (or post-stroke) dysphagia frequently present with concomitant language and/or cognitive deficits, which may further exacerbate symptoms and outcomes (Malandraki & Robbins, 2013). Understanding not only the symptomatology but also the neurophysiological underpinnings of post-stroke dysphagia is important because the trajectory of recovery and clinical outcomes vary depending on brain lesion sites, severity, and complexity (Logemann, 1998).

The literature posits that swallowing is modulated by a complex bilateral neural network (Wilmskoetter et al., 2019b). In addition, studies have shown that pharyngeal

musculature is represented bilaterally (yet asymmetrically) in the cerebral cortex; therefore, a lesion the ‘‘dominant swallowing hemisphere’’ may result in dysphagia following a unilateral hemispheric stroke (Cohen et al., 2016). Furthermore, several scientific studies have revealed that right hemisphere stroke lesions are associated with greater pharyngeal involvement, including longer pharyngeal transit times, greater risk for penetration or aspiration, and/or more severe dysphagia (Malandraki & Robbins, 2013; Robbins et al., 1993; Suntrup-Krueger et al., 2017; Wilmskoetter et al., 2019b), while left hemisphere lesions are associated with oral phase impairments, particularly decreased lingual coordination and oral apraxia (Malandraki & Robbins, 2013). It is reported that several different lesion locations can potentially cause dysphagia in stroke patients, including the somatosensory and motor cortices, anterior cingulate, thalamus, insula, internal capsule, brainstem, cerebral cortex (including insula, posterior central gyrus, precentral gyrus, cingulate gyrus, supramarginal gyrus, angular gyrus), and subcortical structures (including basal ganglia; Liu et al., 2017; Wilmskoetter et al., 2019b).

The knowledge that stroke lesion location can influence the type and severity of dysphagia is beneficial for clinicians diagnostically, to facilitate more accurate predictions of physiological swallow impairments after stroke, and for treatment planning as well. For example, strokes in the cerebral cortex have been shown to result in both oral and pharyngeal dysphagia; however, their impact on the oral phase, such as reduced labial closure, reduced oral containment, and lingual incoordination, is theorized to be due to

the loss of cortical modulation of the oral swallow neurons (Sasegbon & Hamdy, 2017). Understanding information about lesion location and how it relates to swallowing impairment is important for clinicians initiating intervention because although symptom onset is acute in patients with post-stroke dysphagia, and some recovery is expected due to the cortical reorganization that generally occurs after stroke (Cohen et al., 2016; Malandraki & Robbins, 2013), patients still benefit from intervention and management for transient dysphagia symptoms. Furthermore, even though many stroke patients recover swallowing function spontaneously during the acute phase (up to 90% of patients after two weeks) and a number of patients continue to recover at four weeks, 11–50% of patients present with persistent dysphagia at six months with a small proportion of patients remaining with dysphagia longer than six months (Bahcecı et al., 2017; Cohen et al., 2016). The reason is not frequently obvious why some patients experience persistent dysphagia and others do not, though there may be other contributing factors, including comorbidities, that may prolong a patient's swallow recovery.

Section 3: Post-Stroke Depression

Stroke-Related Changes in Anatomy, Physiology, and Neurologic Control

PSD is defined as a "prominent and persistent period of either depressed mood or markedly diminished interest or pleasure in most or all activities that (1) is believed to be the direct physiologic consequence of stroke, (2) is not better explained by another psychiatric illness or as a feature of delirium, and (3) causes clinically significant distress or impairment (Nemani & Gurin, 2021, p. 87). The etiology of PSD is not well-understood; therefore, there is currently no consensus among experts regarding its cause or exactly what areas of the brain are associated with PSD. However, researchers believe that PSD is multi-factorial, involving biological and psycho-social factors, such as inflammation, response to ischemia (as with stroke), genetic susceptibility, neurogenesis, and involvement of the hypothalamo-pituitary-adrenal (HPA) axis (Das & Rajanikant, 2018; Towfighi et al., 2018). Furthermore, it is suggested that the role of proinflammatory cytokines in (stroke-induced) neuroinflammation and neurodegeneration is a major factor in PSD (Das & Rajanikant, 2018; Towfighi et al., 2018). Multiple scientific studies have identified brain regions, including the prefrontal cortex, dorsolateral prefrontal cortex, amygdala, thalamus, hippocampus, anterior cingulate cortex, and basal ganglia, that may be involved in the neuromechanism of PSD (Douven et al., 2017; Robinson & Jorge, 2016; Shi et al., 2017b). Additionally, investigators have demonstrated that left hemisphere lesions are linked with a higher incidence of depression, and location of subcortical lesions have a greater influence on PSD (Das & Rajanikant, 2018). Recent research has also shown that damage to the areas associated with PSD can decrease

activity of the underlying neural networks, resulting in poorer patient prognosis (Shi et al., 2017b). For example, a stroke lesion in the prefrontal cortex, which has dense axonal connections to the limbic system, may result in disrupted transmission of information pertaining to emotions, behavior, and motivation (associated with the limbic system; Shi et al., 2017b). A study by Wilmskoetter et al. (2019a) performed neuroimaging mapping of stroke lesions and revealed that brain lesions in cortical structures connected to the limbic system are associated with reduced improvement in oral intake in dysphagic patients after stroke. Since there is currently no known literature related to PSD in post-stroke dysphagic patients, it may be possible that PSD in post-stroke dysphagic patients with brain lesions in regions connected to the limbic system is an under-diagnosed comorbidity that negatively affects stroke recovery, specifically swallow function recovery, in this patient population.

Although the relationship between PSD and post-stroke swallow function recovery has not yet been investigated, there have been a number of studies examining PSD and general functional recovery after stroke. The literature suggest that PSD negatively affects patients in many ways, including decreased neuroplasticity; physical, social, and cognitive function; participation in rehabilitation therapies; and ability to perform activities of daily living (ADLs; Bhogal et al., 2004; Parikh et al., 1990; Towfighi et al., 2017; Žikić et al., 2014). The majority of studies suggest significantly greater functional disability in patients with PSD versus non-depressed patients (Žikić et al., 2014). Accordingly, PSD is associated with poorer functional outcomes and QOL and increased

healthcare utilization and mortality rates (Bhogal et al., 2004; Parikh et al., 1990; Towfighi et al., 2017).

There has been much research in the neurology literature examining PSD and functional recovery, specifically motor recovery. For example, in a randomized controlled trial (RCT), Chollet et al. (2011) compared fluoxetine (a selective serotonin reuptake inhibitor (SSRI) antidepressant) to placebo in acute, ischemic stroke patients with PSD and moderate to severe hemiplegia. The study findings revealed significantly improved motor function in the fluoxetine group, suggesting that fluoxetine has (or SSRIs in general have) a positive effect on motor recovery (Chollet et al., 2011). Similarly, a meta-analysis by Mead et al. (2012) was conducted to determine if SSRIs improve recovery (i.e., reduce dependency and disability) after stroke. The researchers found evidence that SSRI use after stroke may improve dependence, disability, neurological impairment, anxiety, and depression (Mead et al., 2012). Despite promising evidence in the literature, however, it is not yet fully understood whether improvements in function from SSRIs are due to the role of pharmacotherapy on neuroplasticity or if PSD impedes motor function recovery and pharmacotherapy reverses those effects (Towfighi et al., 2017). Further research is needed to examine the role of PSD in post-stroke recovery and to determine the factors influencing whether PSD worsens functional outcomes (Chollet et al., 2011; Towfighi et al., 2017). Likewise, additional research is warranted to explore the role of PSD in post-stroke swallow recovery to determine what influence (if any) it has on patient outcomes.

CHAPTER 3: METHODOLOGY

Specific Aims

Aim 1: Determine the rate of PSD in patients with post-stroke dysphagia.

- Hypothesis 1: The rate of PSD in patients with post-stroke dysphagia is at least as high as the rate of PSD in the general stroke population.

Aim 2: To categorize dysphagia severity in an inpatient post-stroke population using dysphagia-specific ICD-10 diagnosis and procedure codes and to determine if dysphagia severity impacts diagnosis of PSD.

- Hypothesis 1: A stable subset of dysphagia diagnosis and procedure codes will identify groups of patients with distinct dysphagia severity characteristics.
- Hypothesis 2: Patients who fall in different dysphagia severity groups will have different risk of PSD diagnosis after discharge.
    - *Hypothesis 2a*: Post-stroke patients with more severe dysphagia will have a greater proportion of PSD diagnosis within the 90 days after discharge.
    - *Hypothesis 2b*: Post-stroke patients with more severe dysphagia will have greater odds of being diagnosed with PSD within the 90 days after discharge.

- *Hypothesis 2c*: Post-stroke patients with more severe dysphagia and a diagnosis of PSD will have a shorter time to first depression diagnosis.

Aim 3: Compare the mean healthcare costs in post-stroke dysphagic patients with and without PSD.

- Hypothesis 1: Dysphagic patients with PSD will incur greater healthcare costs than dysphagic patients without PSD.

Study Design

We conducted a retrospective, cross-sectional study of individuals with a primary diagnosis of acute ischemic stroke (AIS) using administrative data from the 2017 Medicare 5% Limited Data Set (LDS), the most recent data set available at the start of this study. Per the university Institutional Review Board, this study was not considered human subject research.

Description of Administrative Database

The Centers for Medicare & Medicaid Services (CMS) provide LDS files for research. LDS files include de-identified (i.e., no specific direct identifiers as defined in the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (CMS.gov, 2020), patient-level claims data for a nationally representative random sample of all Medicare beneficiaries.

Data Coding

For this study, we used several medical code sets, including International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM); International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS); Healthcare Common Procedure Coding System (HCPCS); and Current Procedural Terminology (CPT). (See Appendices 1-3 for tables containing all codes used in this study.) ICD-10-CM and ICD-10-PCS codes are U.S. versions of the International Classification of Disease, Tenth Revision (ICD-10), which was developed by the World Health Organization (WHO) to classify

mortality and morbidity (Steindel, 2010). ICD-10-CM is used for diagnostic coding while ICD-10-PCS is used for inpatient procedures (LaPointe, 2018). HCPCS is used to code procedures, services, supplies, and materials and has three levels: Level I CPT codes, Level II National codes, and Level III Local codes (not nationally accepted and rarely used) (PMIC, 2019). HCPCS Level I CPT (simplified as "CPT") codes are used to code physician and allied healthcare professional procedures and services. HCPCS Level II codes are used for supplies, equipment, materials, and services not represented in CPT codes.

Patient Population

We included Medicare beneficiaries 65 years of age and older who were discharged from the hospital with a primary diagnosis of AIS. Within this population, we examined patients with diagnosis of dysphagia and/or depression during inpatient hospitalization and within 90 days after discharge. Individuals with a history of dysphagia or depression within 90 days prior to stroke were excluded.

Outcome Measures

Our outcomes of interest included diagnosis of dysphagia and/or depression during the inpatient hospitalization or within a 90-day follow-up window after discharge; dysphagia severity (indicated by feeding status [e.g., feeding tube use], nutrition [e.g., diagnosis of malnutrition], and respiratory compromise [e.g., aspiration pneumonia, intubation, etc.]; see Appendix 4); hospital length of stay (LOS); time from stroke to depression; and healthcare costs.

Aim 1: Data Set Construction

We constructed the data set for Aim 1 in four steps (Figure 1). First, we identified ICD-10-CM diagnosis codes relevant to our diagnoses of interest (e.g., AIS, dysphagia, depression). Second, we pulled claim-level diagnosis, procedure, Diagnosis Related Groups (DRGs), dates of service, reimbursement amounts, and provider data from Standard analytic files (SAFs) and patient demographic data from Denominator files for relevant outcomes of interest. Third, we extracted outpatient claims data less than or equal to 90 days prior to stroke, removed patients who had a diagnosis of dysphagia or depression prior to stroke, and pulled data relevant to our outcomes of interest. Finally, we reviewed discharge dates, extracted claims data within a 90-day follow-up window after discharge, and identified patients with dysphagia and/or depression.

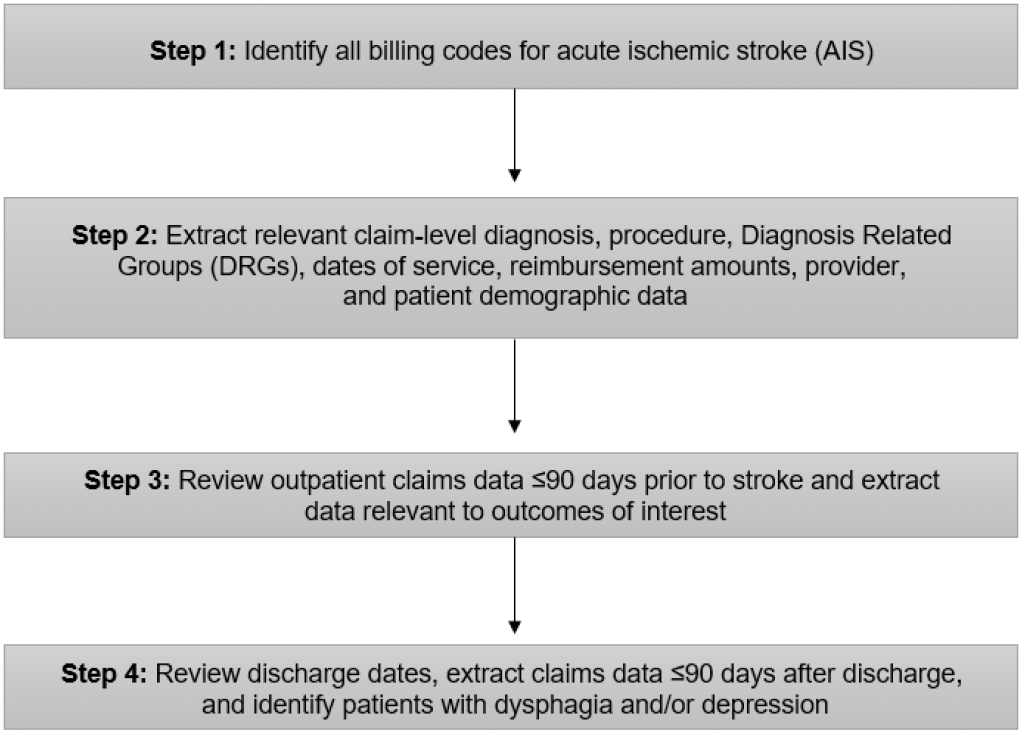

Figure 1. Flow chart of the construction of the Aim 1 data set.

Aim 2: Data Set Construction

For Aim 2, we studied a population of patients diagnosed with post-stroke dysphagia during two different time points: (1) during acute hospitalization and (2) within the 90-day time period after discharge from the acute hospital. For inpatient data set construction, first, we extracted all AIS survivors with a diagnosis of dysphagia and NIHSS score (a measure of stroke severity) (N=445) from our original (Aim 1) data set. We limited our analysis to this group of patients to ensure that we would have a valid measure of stroke severity (the NIHSS score) for external construct validity of our dysphagia groups. The selection of this patient subgroup for the development of a severity grouping also helps assure that the population represents patients seen in hospitals that have adopted the most recent recommendations for the ICD-10 coding for AIS severity, which minimizes variations due to coding conventions. Second, we compiled ICD-10-CM and ICD-10-PCS codes relevant to dysphagia (Appendix 4), based on the literature (Cohen et al., 2020; Gonzalez-Fernandez et al., 2009; Pu, et al., 2017) and clinical expertise. Third, we created dichotomous variables that represented common dysphagia sequelae, subgroup diagnoses, and procedures using the compiled codes (Appendix 4) to identify post-stroke patients in the acute hospital with specific dysphagia-related outcomes. For example, the variable Respiratory Problems included ICD-10-CM codes for respiratory conditions such as acute respiratory distress syndrome (ARDS), respiratory failure, dyspnea, and acute respiratory distress. Fourth, we programmed individual array coding schemes in SAS for each type of code set (ICD-10-CM and ICD-10-PCS). For the post-discharge data set, we examined the same patient sample from the

previous Aim 2 data set and pulled additional post-discharge data, including Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes relevant to dysphagia (Appendix 4) and outpatient visits (e.g., first visit coded with depression). We also removed patients who had died, were discharged to hospice, and/or had missing follow-up data (final N=359).

Aim 3: Data Set Construction

The Aim 3 data set was constructed using the post-discharge Aim 2 data set of AIS survivors who had received a diagnosis of post-stroke dysphagia while in the acute hospital and had a documented NIHSS score (a measure of stroke severity) in their electronic record (n=359). We extracted each patient's Medicare administrative claims data for the 90 days after discharge from the Index hospital admission to summarize healthcare costs from the perspective of the medical care system (measured as claims paid by Medicare plus the coinsurance and deductible amounts paid by patients, in United States dollars [USD]). We used claims data from the Medicare service-specific data tables to calculate total costs (defined as payments) for the 90-day post-discharge period. Data sets used were (1) inpatient costs after discharge (e.g., inpatient rehabilitation admission or admission to an acute hospital), (2) outpatient costs, (3) home health costs, (4) skilled nursing facility (SNF) costs, and (5) Part B (carrier) costs. Data from each service table were aggregated at the patient level by summing total payments for the service type. Patients who did not use a service were then assigned $0 cost for

that service. Total cost for 90 days post-discharge was the sum of cost across all service types.

Statistical Approaches and Data Analysis

All statistical analyses were conducted using SAS statistical software (version 9.4, released 2016, SAS Institute, Inc., Cary, N.C., USA). Univariate analyses for demographics and clinical characteristics were conducted. Frequency tables were used for categorical variables to determine proportions (frequency and percentages) while mean, standard deviation, and range were computed for continuous variables. P-values were considered statistically significant for $\alpha<0.05$.

Variable Definitions

Variables were defined as follows:

- Dysphagia: Patient administrative data contained billing codes related to dysphagia (Cohen et al., 2020; Gonzalez-Fernandez et al., 2009; Appendix 1); dichotomous.
- Depression: Patient administrative data contained billing codes related to depression (Appendix 1); dichotomous.
- Cognitive decline: Patient administrative data contained billing codes related to cognitive decline (Appendix 1); dichotomous.
- Days to depression: Number of days from admission date for AIS to first visit coded for depression; continuous.
- Charlson Comorbidity Index (CCI): A validated index for predicting the outcome and risk of mortality from many comorbid diseases (Charlson et al., 1987; Quan et al., 2005; Quan et al., 2011); continuous.

- Stroke Administrative Severity Index (SASI): A validated measure of stroke severity at hospital discharge (Simpson et al., 2018); continuous.
- National Institutes of Health Stroke Scale (NIHSS): A reliable 15-item scale used to identify the severity of neurological symptoms after stroke, estimate prognosis, and predict recovery in acute stroke patients (Brott et al., 1989); continuous.
- Length of stay (LOS): Period of a single hospitalization; continuous. Longer hospitalizations are considered a marker for poor outcomes.
- Dual eligibility: Beneficiary of both Medicare and Medicaid, which indicates low socioeconomic status (Moon & Shin, 2006); dichotomous.
- Tissue plasminogen activator (tPA) administration: Treatment for ischemic stroke that dissolves the clot and improves blood flow; dichotomous. Used as proxy for better quality of care in research and a marker for better expected outcomes.

Aim 1 Data Analysis

For Aim 1, we calculated proportions using frequency tables to determine the rate of PSD in patients with post-stroke dysphagia. We compared demographics and clinical characteristics using t-tests for continuous variables and chi-square for categorical variables. In addition, we estimated regression coefficients and adjusted odds ratios (OR) using logistic regression to determine if PSD is associated with post-stroke dysphagia and if patients diagnosed with post-stroke dysphagia are more likely to be diagnosed with PSD. Finally, we performed time-to-event (survival) analyses (including the Cox proportional hazards model) to assess the time to depression after stroke and estimate

the hazard (hazard ratio, HR) for being diagnosed with PSD in dysphagic versus non-dysphagic patients.

Student's T-Test

The two-sample t-test is a widely used parametric test that compares the means of two data sets to determine if they are equal, which indicates no difference (Winters et al., 2010). We compared the means of the continuous variables age, CCI, SASI, and LOS in dysphagic and non-dysphagic patients to determine if differences were significant between groups.

Chi-Square Test for Independence

The chi-square test is a nonparametric test used to determine if there is a significant association between categorical variables, testing the distributions of independent data sets against a theoretical distribution (Winters et al., 2010). A larger chi-square statistic indicates that distributions are more alike or related, with a value of 0 suggesting no relationship (Winters et al., 2010). We tested relationships between the categorical variables gender, race, depression, cognitive decline, tPA administration, and dual eligibility in dysphagic and non-dysphagic patients to determine if associations were significant between groups.

Logistic Regression

Logistic regression is used to describe the relationship between a dichotomous outcome variable and one or more predictor variables (covariates; Hosmer et al., 2013). In logistic regression, multiple covariates can be included in a single model, which allows for simultaneous adjustment of multiple potential confounders (Wiest et al., 2015).

In our first step to build a logistic regression model (Proc Logistic in SAS), we used purposeful selection to include clinically relevant predictor variables (Hosmer et al., 2013; Stoltzfus, 2011) in our initial model, such as age (in years); gender (male/female); race (white, black, Hispanic, or other); CCI (score); SASI (score); tPA (yes/no); LOS (in days), and dual eligibility (yes/no). Next, for model building, we used a direct approach, simultaneously placing all predictor variables identified for inclusion with equal importance into a multivariable model (Hosmer et al., 2013; Stoltzfus, 2011). Then we checked for multicollinearity between predictor variables by examining several values, including variables with high correlation (>0.8 indicating multicollinearity), a Variance Inflation Factor (VIF) greater than 10, tolerance values greater than 0.1, and small Eigenvalues (close to 0) with large corresponding condition values (indicating multicollinearity; Schreiber-Gregory, 2017). Given that multicollinearity was not detected, we continued with model building, using a less stringent variable inclusion criterion (alpha of <0.25) so as not to exclude potentially important variables at this initial stage of model development (Hosmer et al., 2013; Mickey & Greenland, 1989; Stoltzfus, 2011). Variables that were not significant at $p<0.25$ were manually removed one at a time, and

the model was refit using the traditional level of statistical significance ($p<0.05$) until a parsimonious model was constructed.

To determine how well the final model fit the data, we took a random 10% sample of the population and applied the Hosmer–Lemeshow (HL) goodness-of-fit (GOF) test, which is a chi-square-based test that divides the population into subgroups based on estimated probability of success and assesses if observed event rates match expected event rates (Hosmer et al., 2013; Montgomery et al., 2012; Stoltzfus, 2011). If the model fit is good, then the HL statistic will follow a chi-square distribution; however, a small p-value (< 0.05) indicates a poor fit (Hosmer et al., 2013; Montgomery et al., 2012). A criticism of the HL GOF test is that it has low power (Stoltzfus, 2011); however, in our case, low power is not a concern because of our large data set (N=9,163). The concern would be that because power increases as sample size increases, small deviations from the model in a large data set will appear significant (Paul et al., 2013). We have addressed this limitation by conducting the HL GOF test with a smaller 10% random sample of our data set (n=917).

Time-to-Event (Survival) Analysis

Time-to-event (survival) analysis refers to statistical procedures that analyze the time until a well-defined endpoint (event) occurs (Schober & Vetter, 2018). These specific analyses are required because of the unique features of time-to-event data. For example, not all individuals will experience the event of interest during the study observation

period, resulting in unknown/incomplete observations for some individuals (called "censoring"), which must be resolved through the application of appropriate statistical techniques (Schober & Vetter, 2018).

Cox Proportional Hazards Model

The Cox proportional hazards model (Cox, 1972) is a common semiparametric method for analyzing time-to-event data that does not makes assumptions about the distribution of survival times (Schober & Vetter, 2018). It is a regression model used to assess the relationship among multiple predictors to a time-to-event outcome (Vittinghoff et al., 2005). The Cox model provides the hazard ratios (HRs) (and 95% confidence intervals (Cis)) of an individual experiencing an event given a set of covariates and assumes a relationship between covariates and the hazard function (Fisher & Lin, 1999; Schober & Vetter, 2018). In this study, the starting point was admission to the hospital with a primary diagnosis of AIS, and the terminal event was the first post-stroke visit coded for depression.

First, we used time-to-event analysis (Proc Lifetest in SAS) to estimate the unadjusted time to diagnosis of depression (event) from the initial diagnosis of stroke (in days) by dysphagic versus non-dysphagic groups without controlling for covariates. Second, we constructed conventional Cox proportional hazards models (Proc Phreg in SAS) to determine which covariates (age, gender, race, CCI, SASI, tPA, LOS, or dual eligibility) significantly affect the time of PSD diagnosis using adjusted HRs. Third, we manually

removed each covariate if it did not meet inclusion criteria defined as adequate model fit statistic, likelihood ratio tests, and statistical significance (<0.05). Fourth, we tested for interaction effects between covariates, and last, we included all significant covariates in the final parsimonious model. After the final model was constructed, we performed diagnostics to check for adequacy of the model.

A fundamental assumption of Cox regression is that hazards between groups are constant (or proportional) over time (Bellera, et al., 2010; UCLA: Statistical Consulting, n.d.-a; Schober & Vetter, 2018). If this assumption of proportionality is violated, biased and/or incorrect estimates may be derived resulting in misleading interpretations (Bellera, et al., 2010; UCLA: Statistical Consulting, n.d.-a). Thus, we assessed the proportionality of the hazards using graphical checks for categorical covariates by which Kaplan-Meier survival curves are plotted for each level of categorical covariate, and then the survival function graphs were judged as to whether or not the survival curves appear parallel (with a parallel graph indicative of proportionality) (Bellera, et al., 2010; Fisher & Lin, 1999; UCLA: Statistical Consulting, n.d.-a). Typically, graphical checks alone are not sufficient to assess proportionality due to their subjectivity (Bellera, et al., 2010); however, it was evident that survival function graphs for all categorical covariates we assessed (dysphagia, gender (female), race (white), dual eligibility) were not parallel (displayed crossed curves). This was suggestive of non-proportionality, meaning there was an interaction between these covariates and time (Bellera, et al., 2010; UCLA: Statistical Consulting, n.d.-a). For the continuous covariate (age), we applied the

empirical score process using a transform of the martingale residuals as a diagnostic for proportionality (Lin et al., 1993). Then we inspected the simulation graph for an aberrant observed pattern and checked the corresponding supremum test results for significance ($p<0.05$), indicative of a violation of the proportional hazards assumption (Allison, 2010; Introduction to Survival, n.d.; Lin et al., 1993). No violation was detected for the continuous covariate (age).

To account for the non-proportionality of four of the covariates (dysphagia, female, white, dual eligibility), we created time-dependent variables that explicitly introduced covariate-by-time interactions into the Cox model, which generalizes the model to permit the use of non-proportional hazards, thereby addressing the proportionality violation (Allison, 2010; Bellera, et al., 2010; Cox, 1972; UCLA: Statistical Consulting, n.d.-a). After running the Cox models again with each covariate-by-time interaction term, we found that the interaction covariates for dysphagia and white remained significant, indicating non-proportionality; however, our use of the method for extending the Cox model by including covariate-by-time interactions as predictors allowed for the incorporation of non-proportionality in the Cox model (Allison, 2010; UCLA: Statistical Consulting, n.d.-a).

Aim 2 Data Analysis

For Aim 2, we developed a novel dysphagia severity index for use with administrative data to categorize patients with similar dysphagia severity during acute hospitalization (hypothesis 1) and then used the severity index to examine the risk for receiving a

diagnosis of depression after discharge in patients diagnosed with post-stroke dysphagia (hypothesis 2). We described demographics and clinical characteristics using frequencies and proportions, comparing results for categorical variables using chi-square or Fisher's exact test, and we calculated means and standard deviations for continuous variables, comparing means using t-tests. Bivariate comparisons were performed using one-way analysis of variance (ANOVA) for continuous, normally distributed variables; Kruskal-Wallis for non-normally distributed variables; and chi-square test or Fisher's exact for dichotomous variables.

Billing data does not contain clinical details about disease severity or treatment response; therefore, a proxy for severity is needed in order to adequately utilize and analyze claims data (Gonzalez-Fernandez et al., 2009; VanDerwerker et al., 2020). There is currently no universal standard for dysphagia severity classification in post-stroke patients for use with administrative data in the literature; therefore, we developed a novel proxy index for dysphagia severity in administrative data with key clinical variables using cluster analysis.

Aim 2 Hypothesis 1

Cluster Analysis

Cluster analysis is a data exploration technique for organizing data into homogenous groups (or clusters) such that objects or individuals grouped together in one cluster resemble one another and are distinctly different from objects or individuals grouped in

other clusters (Everitt et al., 2010). Cluster analysis facilitates improved understanding of the underlying characteristics that define each cluster (Lu, 2018). Unsupervised *K*-means cluster analysis is a method by which a partitioning algorithm divides observations into a specified number (*k*) of clusters (chosen a priori) and then randomly selects *k* points as initial cluster means (centroids), called "cluster seeds" (Frades & Matthiesen, 2010; King, 2015; MacQueen, 1967). Next, each observation is assigned iteratively to the cluster with the closest centroid, based on the minimum Euclidean squared distance, and the centroids of the newly formed clusters are recalculated (Abbas, 2008; Everitt et al., 2010; Frades & Matthiesen, 2010; King, 2015; Lu, 2018). This process is repeated until the centroids have stabilized – allocation of the same or similar observations to each cluster occurs in successive rounds (Frades & Matthiesen, 2010) or the sum of the distances between the observations and their respective centroids is minimized (Abbas, 2008; King, 2015).

We performed *K*-means cluster analysis to categorize patients with dysphagia based on indicator dysphagia groups constructed from ICD-10 diagnosis and procedure codes for patients during acute hospitalization for AIS. First, we ran a correlation analysis using Pearson correlation coefficients (Proc Corr in SAS) to determine if any variables were highly correlated. Codes with strong correlation were combined. Next, we performed a cluster analysis (Proc Fastclus in SAS) to group billing codes into their respective disjoint clusters (SAS Institute, 1999). Using an iterative process, we started with a large number of clusters (*k*=7) and repeatedly estimated the *k*-means algorithm while reducing *k*

clusters by one for each new iteration until an optimal number of clusters was identified. Criteria for the optimal number of clusters was defined as estimated consensus among graphical representations of the clusters (SAS Institute, 2015), cubic cluster criterion (CCC) (Sarle, 1983), pseudo-F statistic (PSF) (Caliński & Harabasz, 1974), and maximal R-square value (King, 2015; Lu, 2018; SAS Institute, 2015). Once the final number of clusters was agreed upon, the codes were appraised for clinical significance and relevance within the clusters, and irrelevant codes (for which very few or no patients were diagnosed) and/or codes that yielded poor statistical results (e.g., over-powering R-square value, negative CCC, etc.) were removed.

We performed cluster validation to assess the quality of the clustering generated by our algorithm (Frades & Matthiesen, 2010). For validation, we tested cluster stability by running the algorithm on three random samples of 60% of the data set and compared the cluster means of key outcomes to the means of those key outcomes from the initial cluster analysis to determine if the algorithm produced similar results (structures) with different data sources (Frades & Matthiesen, 2010). Once we concluded that our algorithm was valid, we used the algorithm, now referred to as the "Administrative Data Dysphagia Severity Scale" (ADDSS), to examine the risk for receiving a diagnosis of depression after discharge from the acute hospital in patients with a post-stroke dysphagia diagnosis.

Aim 2 Hypothesis 2

We calculated frequencies and proportions to determine if patients with more severe dysphagia have a greater proportion of PSD diagnosis within the 90 days after discharge (hypothesis 2a). In addition, we used logistic regression to determine if post-stroke patients with more severe dysphagia have greater risk of being diagnosed with PSD within the 90 days after discharge (hypothesis 2b). Finally, we performed time-to-event (survival) analyses to assess the time to depression after stroke to determine if post-stroke patients with more severe dysphagia and a diagnosis of PSD have a shorter time to first depression diagnosis after discharge from the acute hospital (hypothesis 2c).

Logistic Regression

Logistic regression is used to describe the relationship between a dichotomous outcome variable and one or more predictor variables (covariates; Hosmer et al., 2013). In logistic regression, multiple covariates can be included in a single model, which allows for simultaneous adjustment of multiple potential confounders (Wiest et al., 2015).

In our first step to building our logistic regression models (Proc Logistic in SAS), we used purposeful selection to include clinically relevant predictor variables (Hosmer et al., 2013; Stoltzfus, 2011), in addition to our primary independent variable of interest, PSD, in our initial models, such as age (in years); CCI (score); female (yes/no); race (white, black, Hispanic, or other); tPA (yes/no); dual eligibility (yes/no); and dysphagia severity cluster (mild, moderate, severe). We checked for multicollinearity between predictor variables

(Proc Corr and Proc Reg in SAS) by examining several values, including variables with high correlation (>0.8 indicating multicollinearity), a Variance Inflation Factor (VIF) greater than 10, tolerance values greater than 0.1, and small Eigenvalues (close to 0) with large corresponding condition values (indicating multicollinearity; Schreiber-Gregory, 2017). Given that multicollinearity was not detected, we continued with model building. Next, we fit logistic regression models with key covariates judged to have potentially strong impacts on the data. Variables that were not significant at $p<0.25$ were manually removed one at a time, and the models were refit using the traditional level of statistical significance ($p<0.05$). Typically, we would refit the models until a parsimonious model was constructed; however, we were unable to fit a parsimonious model because none of the covariates reached statistical significance ($p<0.05$). (Details in the Aim 2 Results section.)

Time-to-Event (Survival) Analysis

Time-to-event (survival) analysis refers to statistical procedures that analyze the time until a well-defined endpoint (event) occurs (Schober & Vetter, 2018). These specific analyses are required because of the unique features of time-to-event data. For example, not all individuals will experience the event of interest during the study observation period, resulting in unknown/incomplete observations for some individuals (called "censoring"), which must be resolved through the application of appropriate statistical techniques (Schober & Vetter, 2018). For our Aim 2 time-to-event analysis, we used Proc Lifetest in SAS to model the underlying survival distribution function of our time-to-event

data (Allison, 2010) and estimate the unadjusted time to diagnosis of depression (event) from the initial diagnosis of stroke (in days) by dysphagia severity groups. Then we compared Kaplan-Meier survival curves between dysphagia severity groups.

Aim 3 Data Analysis

For Aim 3, we calculated means and standard deviations for continuous variables and frequencies and proportions for categorical variables. We compared demographics and clinical characteristics for normally distributed data using t-tests for continuous variables and chi-square or Fisher's exact for categorical variables. We used nonparametric Wilcoxon Rank Sum/Mann Whitney U and Kruskal-Wallis for non-normally distributed variables. For the cost analysis, we performed gamma-distributed generalized linear modeling with a log-transformed link function. To analyze cost by dysphagia severity clusters/groups, we applied the ADDSS, created in Aim 2, to this data set.

Cost Analysis

First, we graphically assessed the normality of the distributions of the cost data using histograms, and we also used the Shapiro-Wilk test (Shapiro & Wilk, 1965) to determine if the data were normally distributed. Next, we assessed for homoscedasticity via the White test (White, 1980), which tests for constant variance in a regression model. Once we confirmed the data were non-normally distributed and that heteroscedasticity was present, we applied generalized linear models (GLMs) to compare healthcare costs in post-stroke dysphagic patients with and without a diagnosis of depression. We used

gamma-distributed GLMs (Proc Genmod in SAS) with logarithmic transformation based on the right-skewed distribution and presence of heteroscedasticity in our cost data. GLMs with gamma distribution are known for being an appropriate statistical approach for analysis of cost data, which typically have a right-skewed distribution (Manning et al., 2005). We chose the natural log transformation (log link) because it is known to stabilize variance (approximate homoscedasticity) and result in improve distribution symmetry in cost data (Blough & Ramsey, 2000). Next, in addition to our primary independent variable of interest (post-stroke depression [PSD]), we determined which clinically relevant covariates would be included in our initial models to control for potential population differences. We chose age, NIHSS score, CCI score, female gender, race (white, black, Hispanic, other), tPA administration, dual eligibility, and dysphagia severity cluster (mild, moderate, severe) as covariates to be included one at a time in each of our individual GLMs. We did not include discharge location (home, inpatient rehabilitation [IPR] facility, skilled nursing facility [SNF], transferred to another facility [from the acute hospital]) as a covariate in the models because this is an in-hospital designation that is endogenous to post-discharge cost values. Finally, covariates that were not significant at $p<0.25$ were manually removed one at a time, and the models were refit using the traditional level of statistical significance ($p<0.05$) until a parsimonious model was constructed.

We determined the goodness of fit (GOF) of our final models via the deviance to degrees of freedom (DF) ratio, which posits that if the model is a good fit for the data, the deviance to DF ratio value will be close to one (UCLA: Statistical Consulting, n.d.-b). Our

gamma-distributed GLMs met this criterion; therefore, they were judged to have adequate goodness of fit for our data.

CHAPTER 4: RESULTS

Aim 1 Results

To determine the rate of PSD in patients with post-stroke dysphagia, we analyzed a data set of Medicare beneficiaries who had been diagnosed with AIS from the 2017 Medicare 5% LDS. We used descriptive statistics to show trends in the data set and hypothesis testing to address our hypothesis: The rate of PSD in patients with post-stroke dysphagia is at least as high as the rate of PSD in the general stroke population. Our results supported our hypothesis. We found that the rate of PSD in post-stroke dysphagic patients is slightly higher than the rate in non-dysphagic patients.

Patient Characteristics

Our data set of 9,163 patients had a mean age of 78.66 years (SD 8.56) with a range of 65-98 years. Fifty-three percent of patients were women and 82% were white, which is in line with the demographic makeup of the overall Medicare beneficiary population in which 54% are women and 75% are white ("Medicare Beneficiary," 2017). (Patient characteristics and descriptive data are summarized in Table 1.) Of the patients in the general stroke population, 1,440 (15.72%) were diagnosed with dysphagia during their inpatient hospitalization. Compared to patients not diagnosed with dysphagia, those with

a dysphagia diagnosis had higher CCI and SASI scores, though they were not significantly higher. Furthermore, there were no significant differences in age, gender, or race between patients diagnosed with dysphagia and patients not diagnosed with dysphagia. In contrast, those diagnosed with dysphagia demonstrated significantly higher rates of depression diagnosis than those not diagnosed with dysphagia during acute hospitalization, 12.01% versus 9.52%, respectively (p=0.003). Patients diagnosed with dysphagia also demonstrated greater incidence of cognitive decline (p <.0001) at 29.24% compared to 18.93% for patients not diagnosed with dysphagia. The mean LOS for patients with a dysphagia diagnosis was 7.99 days (SD 5.76, p<.0001), which on average was approximately three days longer than patients without a dysphagia diagnosis. Fewer patients diagnosed with dysphagia received tPA (3.47%) as compared to patients not diagnosed with dysphagia (5.31%, p=0.003). Those with a dysphagia diagnosis were also more likely to have dual eligibility (p =0.0042).

Table 1. Baseline characteristics and descriptive data for Aim 1

Characteristics	General Stroke Population N=9,163 (100%)	Stroke with Dysphagia N=1,440 (15.72%)	Stroke without Dysphagia N=7,723 (84.28%)	*p*-value
	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	
Age, years	78.66 (8.56) 65-98	80.46 (8.76) 65-98	78.33 (8.48) 65-98	0.099
CCI max possible 24	3.82 (2.18) 1-17	4.35 (2.19) 1-15	3.72 (2.16) 1-17	0.589
SASI max possible 56	6.04 (6.84) 0-48	9.31 (6.60) 0-45	5.44 (6.71) 0-48	0.423
LOS, days	5.33 (4.24) 1-93	7.99 (5.76) 1-56	4.83 (3.69) 1-93	<.0001
Time to depression, days	35.88 (30.46) 3-246	40.16 (30.69) 3-182	33.96 (30.18) 3-246	0.729
	N (%)	N (%)	N (%)	
Female	4901 (53.49)	780 (54.17)	4121 (53.36)	0.573
Race				0.115
White	7532 (82.20)	1157 (80.35)	6375 (82.55)	--
Black	1042 (11.37)	171 (11.88)	871 (11.28)	--
Hispanic	132 (1.44)	25 (1.74)	107 (1.39)	--
Other	457 (4.99)	87 (6.04)	370 (4.79)	--
Depression	908 (9.91)	173 (12.01)	735 (9.52)	0.003
Cognitive decline	1883 (20.55)	421 (29.24)	1462 (18.93)	<.0001
tPA	460 (5.02)	50 (3.47)	410 (5.31)	0.003
Dual eligibility	1616 (17.64)	292 (20.28)	1324 (17.14)	0.004

Footnote: N=population size, SD=standard deviation, CCI=Charlson Comorbidity Index, SASI=Stroke Administrative Severity Index, tPA=tissue plasminogen activator, LOS=length of stay

Odds of PSD

We used multivariable logistic regression to examine the relationship between PSD and post-stroke dysphagia. All predictor variables were included in the initial model (Table 2). After insignificant variables were manually removed and collinearity was verified, we ran the final parsimonious model (Table 3). The HL GOF test of a random 10% sample of the population (n=917) demonstrated that the model was a good fit with an insignificant *p*-value >0.05 (*p*=0.7984).

Table 2. Initial multivariable logistic regression model to determine association between PSD and post-stroke dysphagia with all potential covariates included.

Variable	Coefficient	SE	OR	95% CI	*p*-value
Post-stroke dysphagia	0.9904	0.0828	2.692	2.289-3.167	<.0001
Age	-0.2714	0.0441	0.762	0.699-0.831	<.0001
Female	0.5438	0.0759	1.722	1.484-1.999	<.0001
Race[a]					
White	0.5722	0.1421	1.850	1.435-2.384	<.0001
Hispanic	-0.7632	0.3858	0.487	0.174-1.358	0.048
Other	0.2339	0.1815	1.319	0.884-1.967	0.198
CCI	-0.00407	0.0172	0.996	0.963-1.030	0.813
SASI	-0.00876	0.00573	0.991	0.980-1.002	0.126
tPA	0.2426	0.1546	1.275	0.941-1.726	0.117
LOS	0.0145	0.00783	1.015	0.999-1.030	0.065
Dual eligibility	0.3497	0.0917	1.419	1.185-1.698	0.0001
Intercept	-1.2083	0.3661	--	--	0.001

Footnote: SE=standard error, OR=odds ratio, CI=confidence interval, CCI=Charlson Comorbidity Index, SASI=Stroke Administrative Severity Index, tPA=Tissue plasminogen activator, LOS=length of stay in acute hospital. [a]Reference group was black patients.

Table 3. Final multivariable logistic regression model with significant covariates included and Hosmer-Lemeshow Goodness-of-Fit test.

Variable	Coefficient	SE	OR	95% CI	*p*-value
Post-stroke dysphagia	0.9972	0.0804	2.711	2.315-3.174	<.0001
Age	-0.2714	0.0441	0.762	0.699-0.831	<.0001
Female	0.5383	0.0757	1.713	1.477-1.987	<.0001
Race[a]					
White	0.5684	0.1419	1.818	1.413-2.340	<.0001
Hispanic	-0.7677	0.3857	0.478	0.171-1.333	0.047
Other	0.2289	0.1814	1.295	0.868-1.931	0.207
Dual eligibility	0.3553	0.0912	1.427	1.193-1.706	<.0001
Intercept	-1.1812	0.3587	--	--	0.001
	n	Percent of population	X^2	DF	*p*-value
HL[b]	917	10	4.6094	8	0.7984

Footnote: n=sample size, SE=standard error, OR=odds ratio, CI=confidence interval, X^2=chi-square statistic, DF=degrees of freedom. [a]Reference group was black patients. [b]Hosmer-Lemeshow Goodness-of-Fit test applied to a 10% random sample of the population.

We conducted multivariable logistic regression analysis on the entire population (N=9,163), which revealed that patients who were diagnosed with post-stroke dysphagia were 2.7 times more likely to be diagnosed with PSD within 90 days after discharge (adjusted OR, 2.711; 95% CI, 2.315-3.174; *p*<.0001) compared to patients who were not diagnosed with post-stroke dysphagia. White patients were 81.8% more likely to be diagnosed with PSD than black patients (adjusted OR, 1.818; 95% CI, 1.413-2.340; *p*<.0001). Furthermore, white patients were shown to be the only race significantly more likely to be diagnosed with depression after stroke. The odds of being diagnosed with

PSD increased in women by 71.3% (adjusted OR, 1.713; 95% CI, 1.477-1.987; *p*<.0001) and in individuals who qualified for dual eligibility by 42.7% (adjusted OR, 1.427; 95% CI, 1.193-1.706; *p*<.0001). The odds of depression diagnosis decreased by 23.8% with age (adjusted OR, 0.762; 95% CI, 0.699-0.831; *p*<.0001).

Unadjusted Time to Depression

Without covariate adjustment, the unadjusted estimation of mean time from diagnosis of AIS to diagnosis of depression was 40 days (SD ± 30.69) for patients diagnosed with dysphagia and 34 days (SD ± 30.18) for patients not diagnosed with dysphagia (Table 1). Although patients who had a diagnosis of post-stroke dysphagia demonstrated greater mean days to depression diagnosis than patients who did not have a diagnosis of post-stroke dysphagia, these results were not significant (p=0.729). The unadjusted survival plot (Figure 2) illustrated the differences in time to depression diagnosis between those who were diagnosed with dysphagia and those who were not diagnosed with dysphagia. It showed that both groups had an equally high probability of survival (not being diagnosed with PSD) soon after discharge, and as the 90-day post-discharge time period progressed, patients without a dysphagia diagnosis demonstrated better survivability (less likelihood of being diagnosed with depression) than patients with a dysphagia diagnosis. Furthermore, patients who were diagnosed with dysphagia appeared to experience a steady increase in diagnosis of PSD compared to those not diagnosed with dysphagia over the 90-day post-discharge time period, with the dysphagic group

demonstrating an approximately 1.5-fold higher probability of being diagnosed with PSD during the last 15 days of follow-up.

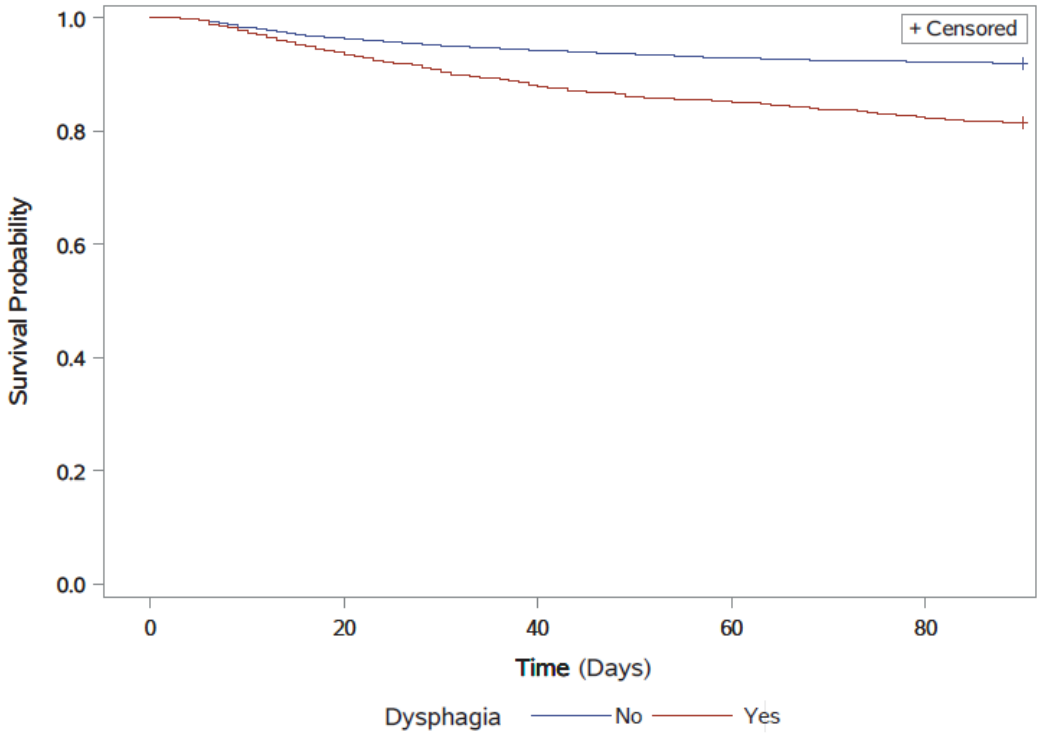

Figure 2. Survival curve for PSD during 90-day post-discharge follow-up period by presence of dysphagia diagnosis, Kaplan-Meier method.

Unadjusted initial Cox proportional hazards models were run on each covariate separately to determine potential influence on time to depression. We found a significant effect for dysphagia, age, gender (female), race (white), LOS, and dual eligibility. Unadjusted Cox models showed that the hazard for depression diagnosis in patients who have been diagnosed with post-stroke dysphagia was 2.4-fold greater (HR, 2.420; 95% CI,

2.099-2.790; *p*<.0001) than the hazard of depression diagnosis in those without a dysphagia diagnosis. Conversely, with each increase in year of age after discharge from the hospital, the hazard for diagnosis of PSD decreased by 1.5% (HR, 0.985; 95% CI, 0.978- 0.993; *p*=0.0002). The hazard for women was approximately 54% (HR, 1.541; 95% CI, 1.345- 1.766; *p*<.0001) great than the hazard for men, while the hazard of depression diagnosis for white patients was 37% (HR, 1.37; 95% CI, 1.087- 1.727; *p*=0.0077) greater than the hazard for depression diagnosis for non-white patients. For each one-day increase in LOS, the hazard of PSD diagnosis increased by 2.2% (HR, 1.022; 95% CI, 1.010-1.034; *p*=0.0002). The hazard of PSD diagnosis for those who qualified for dual eligibility was about 41% (HR, 1.414; 95% CI, 1.210- 1.652; *p*<.0001) greater than the hazard for those who did not qualify for dual eligibility. No significant effects were observed for Hispanic or "other" race, CCI, SASI, or tPA.

Adjusted Time to Depression

Results from the extended Cox model with covariate adjustment (Table 4) were comparable to unadjusted results. Based on the model, having a diagnosis of dysphagia, being female, being white, and having dual eligibility significantly increased the risk of being diagnosed with depression after stroke, while every year of age significantly decreased the risk of depression diagnosis. The dysphagia-by-time interaction covariate that we incorporated into the extended Cox model allowed the effect of dysphagia (our covariate of greatest interest) to change with time (Allison, 2010), and its significance suggested that the dysphagia effect did, in fact, vary over time since discharge from the

hospital. This is illustrated by the adjusted cumulative hazard plot (Figure 3), which showed that when controlling for significant covariates, the hazard for diagnosis of PSD was initially low (<0.01) until about the tenth day after discharge and then consistently increased throughout the duration of the 90-day follow-up period for both patients with and without a diagnosis of post-stroke dysphagia. On average and on any given day in the 90 days after discharge, the hazard for diagnosis of depression for patients who had a dysphagia diagnosis was approximately 76% greater (HR, 1.755; 95% CI, 1.368-2.251; p<.0001) than the hazard for patients who did not have a dysphagia diagnosis. In addition, the hazard of PSD diagnosis for women was about 67% higher than (HR, 1.666; 95% CI, 1.449-1.915; p<.0001) the hazard for men, while the hazard of depression diagnosis for individuals with dual eligibility was approximately 40% higher than (HR, 1.404; 95% CI, 1.193-1.654; p<.0001) the hazard for those who did not have dual eligibility. In contrast, hazard decreased significantly by 2.5% (HR, 0.975; 95% CI, 0.967-0.982; p<.0001) with each year of age, suggesting that older stroke survivors are less likely to be diagnosed with depression. When controlling for significant covariates, we found that the hazard of PSD diagnosis for white patients was 71% higher than (HR, 1.708; 95% CI, 1.401-2.082; p<.0001) the hazard for non-white patients, placing white patients at greater risk for diagnosis of depression than any other race. We ran additional Cox models to determine if there were any significant interaction effects between dysphagia and other significant covariates (age, gender (female), race (white), LOS, dual eligibility) for time to depression and found none.

The adjusted cumulative hazard plot (Figure 3) showed that when controlling for significant covariates, there was a low immediate hazard for depression diagnosis followed by a steady increase in hazard for both groups, people with and without a diagnosis of dysphagia, over time, continuing until the end of the follow-up period. The group with a diagnosis of dysphagia demonstrated a higher hazard for depression diagnosis almost immediately after discharge and for the duration of the 90-day follow-up period compared to the group without a diagnosis of dysphagia. Furthermore, those diagnosed with post-stroke dysphagia demonstrated an approximately 1.75-fold higher hazard for PSD diagnosis than those not diagnosed with post-stroke dysphagia, suggesting that at any given time in the 90 days after discharge, the hazard for depression diagnosis is higher for patients diagnosed with dysphagia compared to patients not diagnosed with dysphagia.

Table 4. Final parsimonious Cox proportional hazards model with significant covariates.

Variable	Coefficient	SE	HR	95% CI	*p*-value
Post-stroke dysphagia	0.56246	0.56246	1.755	1.368-2.251	<.0001
Female	0.51049	0.07109	1.666	1.449-1.915	<.0001
Race, white	0.53525	0.10101	1.708	1.401-2.082	<.0001
Dual eligibility	0.33958	0.08341	1.404	1.193-1.654	<.0001
Age (years)	-0.02581	0.00412	0.975	0.967-0.982	<.0001

Footnote: SE=standard error, HR=hazard ratio, CI=confidence interval

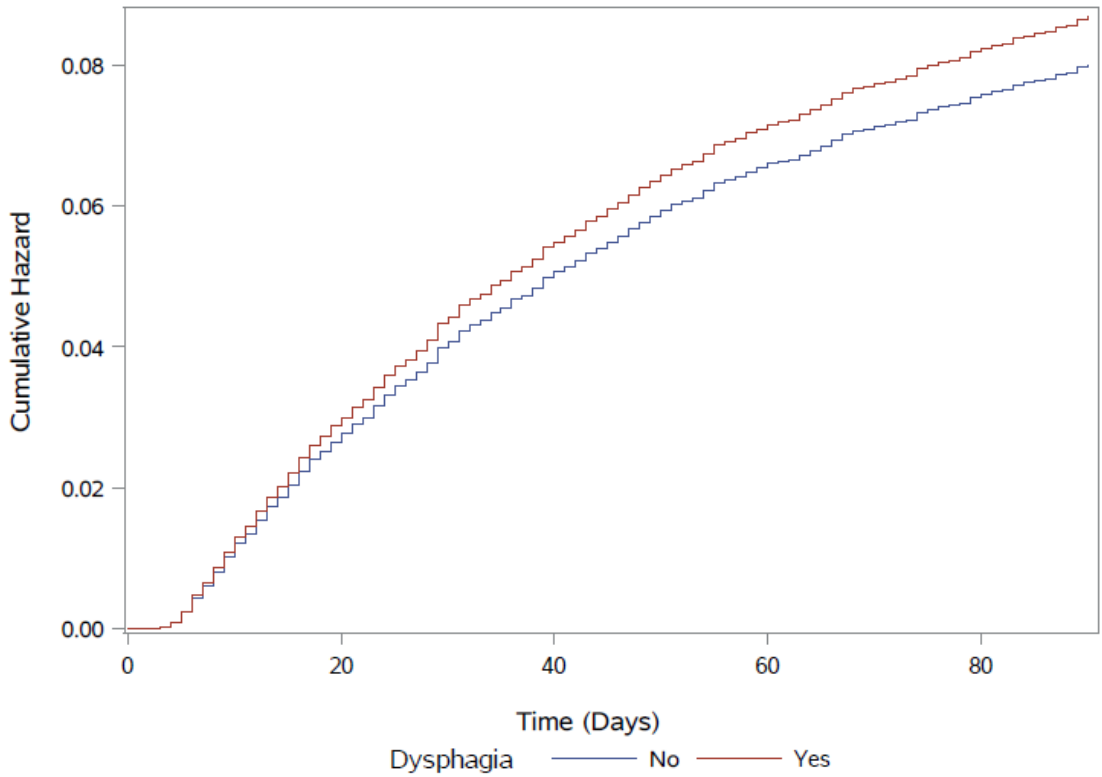

Figure 3. Hazard curve for PSD during 90-day post-discharge follow-up period by presence of dysphagia diagnosis with covariates.

Aim 2 Results

For Aim 2, we developed a novel proxy index of dysphagia severity for use with administrative data – ADDSS – to identify patients with similar dysphagia and stroke severity during acute hospitalization (hypothesis 1). Then we used the ADDSS to examine the proportion of, risk of, and time to depression diagnosis by dysphagia severity group after discharge (hypothesis 2). Our results supported hypothesis 1 in that we created the ADDSS using a stable subset of ICD-10 dysphagia diagnosis and procedure codes to identify groups of patients with distinct dysphagia severity characteristics. Our results were not supportive of hypothesis 2, given that we did not find a statistically significant difference in risk of PSD diagnosis after discharge by dysphagia severity, nor did the evidence support our hypothesis 2 sub-hypotheses (2a, 2b, or 2c).

Patient Characteristics

In our NIHSS data set of 445 post-stroke patients with a diagnosis of dysphagia in the acute hospital, the mean age of the sample was 80 years (8.96) with a range of 65 to 98 years (Table 5 for baseline characteristics and descriptive data of the population). Fifty-five percent of patients were female and 83% were white, which is similar to the demographic makeup of the overall Medicare population in which 54% are female and 75% are white ("Medicare Beneficiary," 2017). On average, patients in this sample presented with moderate stroke severity, indicated by a mean NIHSS score of 11.46 (8.25). The mean SASI score was 10.44 (6.92), or severe (Simpson et al., 2018), and the mean CCI score was 4.45 (2.29), suggestive of high comorbidity (Goldstein et al., 2004).

The mean LOS in this population was 7.88 days (5.17), which is slightly higher than the average six-day LOS among ischemic stroke patients (Koton et al., 2010) and lower than the average LOS of post-stroke dysphagic patients, considering that a diagnosis of dysphagia may result in almost five additional days in the acute hospital (Atrill et al., 2018). In addition, the mean cost of the inpatient stay was $84,620 ($89,510). Approximately 5% of patients received tPA, 27% presented with cognitive decline, and 13% were diagnosed with depression during inpatient hospitalization. The majority of patients were discharged from the acute hospital to a SNF (33%) or an IPR facility (30%), and about 7% died in the hospital.

Table 5. Baseline characteristics and descriptive data for Aim 2

Stroke with Dysphagia, N=445 (100%)		
Characteristics	Mean (SD)	N (%)
Age, years	80.06 (8.96) 65-98	
Female		243 (54.61)
Race		
White		371 (83.37)
Black		45 (10.11)
Hispanic		6 (1.35)
Other		23 (5.17)
NIHSS max possible 42	11.46 (8.25) 0-38	
SASI max possible 56	10.44 (6.92) 0-45	
CCI max possible 24	4.45 (2.29) 1-15	
LOS, days	7.88 (5.17) 1-36	
Cost incurred	$84,620 ($89,510) $7,196-$911,378	
tPA		22 (4.94)
Cognitive decline		120 (26.97)
Depression		59 (13.26)
Dual eligibility		91 (20.45)
Discharge location		
Home		31 (6.97)
IPR		135 (30.34)
SNF		147 (33.03)
HH		36 (8.09)
Trans		13 (2.92)
Other		53 (11.91)
Died in hospital		30 (6.74)

Footnote: N=population size, SD=standard deviation, NIHSS=National Institutes of Health Stroke Scale, SASI=Stroke Administrative Severity Index, CCI=Charlson Comorbidity Index, LOS=length of stay, tPA=tissue plasminogen activator, IPR=inpatient rehabilitation, SNF=skilled nursing facility, HH=home health, Trans=transferred to another facility

Hypothesis 1: Development of ADDSS

Cluster Analysis

Through the previously described procedure, we used *K*-means cluster analysis to group dysphagia-related variables into clusters to infer dysphagia severity. All variables (Appendix 4) were included in the initial algorithm (Table 6). Through a trial-and-error process during each iteration, we manually removed any variables that were judged to overwhelm the explanatory power of the other variables (high R-square value) and/or were not clinically meaningful and then re-ran the algorithm until the resulting statistics were considered optimal (Table 6). Based on the estimated criteria for the ideal number of clusters, we considered three clusters to be optimal for this data set. The three distinct clusters each characterized a disparate level of dysphagia severity (i.e., mild, moderate, or severe). The cluster means and distributions of variables across the three clusters are shown in Table 7.

Table 6. *K*-means cluster analysis iterations and statistics

Iteration	Cluster (*k*)	Overall R-Square	Pseudo F Statistic	Approx. Expected Overall R-Squared	Cubic Clustering Criterion
1st	7	0.65	138.29	0.49	28.04
2nd	6	0.59	124.49	0.47	18.07
3rd	5	0.58	152.05	0.44	22.72
4th	4	0.57	199.11	0.40	27.65
5th	3	0.38	135.17	0.32	7.38

Table 7. Cluster means by variable

Variable	Cluster 1	Cluster 2	Cluster 3
Aspiration pneumonia	0.33	0.04	0.38
Cognitive impairment	0.29	0.29	0.15
Dehydration	0.06	0.04	0.05
Feeding device placement	1.00	0	0.38
Intubation	0.02	0.01	0.34
Malnutrition	0.16	0.03	0.08
Respiratory problems	0	0	0.98
Tracheotomy/Tracheostomy	0	0	0.09

Description of Clusters

Clinical classifications of the clusters were assessed via the means of each of the eight variables (attributes) (Table 7) across clusters and graded into three qualitative categories. Cluster 1 showed evidence of dysphagia severity in the setting of alternative nutrition with the highest means for feeding device placement, malnutrition, and dehydration. Using feeding device placement as the primary marker of dysphagia severity and given that the mean for feeding device placement in Cluster 1 was 1.0 versus 0 and 0.38 for Clusters 2 and 3, respectively, patients in Cluster 1 were judged to have severe dysphagia severity. Patients in this cluster also showed evidence of aspiration pneumonia and cognitive impairment and contained six out of eight (75%) of the total attributes (dysphagia indicator variables constructed from dysphagia-related ICD-10 diagnosis and procedure codes in the cluster analysis), suggesting that patients in this group had substantial stroke-related illness; therefore, patients in Cluster 1 were also judged to have moderate overall stroke severity. Thus, Cluster 1 represented moderate stroke with *severe dysphagia severity* with an emphasis on alternative nutrition.

Cluster 2 had the lowest means of all attributes, except cognitive impairment, which was the only notable attribute in this cluster. Cases in this group had little evidence of active feeding, nutrition, or respiratory problems; hence, patients in Cluster 2 had mild dysphagia severity (with more cases of cognitive impairment compared to feeding, nutrition, or respiratory problems). Cluster 2 also contained 63% of the total attributes, suggesting that (like patients in Cluster 1) patients in Cluster 2 had substantial stroke-related illness and, as such, were determined to have had moderate overall stroke severity. Thus, Cluster 2 represented moderate stroke with *mild dysphagia.*

Cluster 3 demonstrated evidence of dysphagia severity with more cases of respiratory compromise than any other clusters and the highest means for respiratory problems, aspiration pneumonia, intubation, and tracheotomy/tracheostomy. Because it is known that aspiration pneumonia is difficult to differentiate from other pneumonia types and, consequently, is often misdiagnosed (Son et al., 2017), feeding device placement, not aspiration pneumonia, was used as the most important (and reliable) marker for dysphagia severity. Additionally, intubation in this cluster was likely driven by diagnoses of respiratory conditions, not dysphagia severity; therefore, given that the mean for feeding device placement (0.38) was the second highest out of all of the clusters, we determined that patients in Cluster 3 had moderate dysphagia severity. Cluster 3 also contained 100% of the total attributes, indicating that patients in this cluster were very ill compared to those in the other clusters; therefore, these patients were judged to have

moderate/severe overall stroke severity. Thus, Cluster 3 represented moderate/severe stroke with *moderate dysphagia sev*erity with respiratory complications.

Cluster Validation

We conducted a subgroup sensitivity analysis by applying the three-cluster solution (algorithm) to three 60% random samples of the data set to assess cluster stability (Table 8). We compared the cluster means of key outcomes that are indicators of stroke severity (NIHSS, LOS, and CCI) to their means from the initial cluster analysis and determined that, overall, they were stable and demonstrated a good fit. In the Mild dysphagia severity with moderate stroke cluster (Cluster 2), mean NIHSS scores were 10.08 in the initial 100% sample and 10.67, 11.60, and 10.32, respectively, across 60% random samples, and in the Moderate dysphagia severity with moderate/severe stroke cluster (Cluster 3), NIHSS scores were 16.23 in the initial 100% sample and 15.52, 16.53, and 16.64, respectively, across the three 60% random samples. In the Severe dysphagia severity with moderate stroke cluster (Cluster 1), mean NIHSS scores were 13.51 in the initial 100% sample and 13.97, 12.69, and 11.12, respectively, across all three 60% random samples. The validation of cluster distribution for mean NIHSS score by severity showed very small differences in patient characteristics, indicating consistency and stability.

In the Mild dysphagia severity with moderate stroke cluster (Cluster 2), mean CCI scores were 4.27 in the initial 100% sample and 4.21, 4.36, and 4.12, respectively, across 60% random samples. The mean CCI score in the initial 100% sample for the Moderate

dysphagia severity with moderate/severe stroke cluster (Cluster 3) was 5.11, and across the first, second, and third 60% random samples, mean CCI scores were 4.96, 4.76, and 5.05, respectively. Mean CCI scores in the Severe dysphagia severity with moderate stroke cluster (Cluster 1) were 4.65 in the initial 100% sample, and in the first, second, and third 60% random samples, they were 5.08, 4.76, and 5.00, respectively. Mean CCI scores were very similar (close) across clusters and samples, demonstrating excellent consistency and stability.

In the initial 100% sample for the Mild dysphagia severity with moderate stroke cluster (Cluster 2), mean LOS was 6.22 days, and across the 60% random samples, it was 6.32, 6.58, and 7.42 days, respectively. For the Moderate dysphagia severity with moderate/severe stroke cluster (Cluster 3), in the initial 100% sample, mean LOS was 10.51 days and 10.72, 12.41, and 10.43 days, respectively, across the 60% random samples. Mean LOS in the initial 100% sample for the Severe dysphagia severity with moderate stroke cluster (Cluster 1) was 13.52 days, and across the first, second, and third 60% random samples, mean LOS was 12.74, 13.06, and 7.75 days, respectively. The cluster distribution for mean LOS demonstrated the greatest stability across all samples in the Mild dysphagia severity with moderate stroke cluster (Cluster 2), which comprised the largest proportions of the 100% and three 60% samples, respectively. The most notable disparities in mean LOS were observed in the third 60% random sample of the Severe dysphagia severity with moderate stroke cluster (Cluster 1) and the second 60% random sample of the Moderate dysphagia severity with moderate/severe stroke cluster

(Cluster 3), which could be explained by the small sample sizes in those clusters (n=74 and n=16, respectively), yielding more unstable results (which is typical of means in small samples). In addition, mean LOS is known for being sensitive to outliers and, thus, could have been affected by unknown outliers not included in the original cluster analysis. Despite this, mean NIHSS scores demonstrated overall adequate stability.

Table 8. Subgroup sensitivity analysis for cluster validation

Cluster[a]	Variable	Initial 100% sample (mean)	1st 60% sample (mean)	2nd 60% sample (mean)	3rd 60% sample (mean)
1	NIHSS	13.51	13.97	12.69	11.12
	CCI	4.65	5.08	4.76	5.00
	LOS	13.52	12.74	13.06	7.75
	% in cluster	14%	15%	18%	28%
2	NIHSS	10.08	10.67	11.60	10.32
	CCI	4.27	4.21	4.36	4.12
	LOS	6.22	6.32	6.58	7.42
	% in cluster	71%	76%	75%	56%
3	NIHSS	16.23	15.52	16.53	16.64
	CCI	5.11	4.96	4.76	5.05
	LOS	10.51	10.72	12.41	10.43
	% in cluster	15%	9%	6%	16%

Footnote: NIHSS=National Institutes of Health Stroke Scale, LOS=length of stay, CCI=Charlson Comorbidity Index. Three-cluster algorithm applied to three separate 60% random samples of the data set.
[a]Cluster 1=severe dysphagia severity with moderate stroke; Cluster 2=mild dysphagia severity with mild stroke; Cluster 3=moderate dysphagia severity with severe stroke.

Composition of Clusters

The demographics and characteristics of patients in each cluster are shown in Table 9. The distributions of gender and race proportions in each cluster were similar to the distributions in the overall sample, with the Mild dysphagia severity cluster containing

the oldest group (mean, 80.66; SD, 9.06) and the Moderate dysphagia severity cluster containing the youngest group (mean, 77.62; SD, 8.37). We found statistically significant differences in age, NIHSS score, SASI score, LOS, acute hospital costs, dual eligibility, and discharge disposition among the three clusters.

Mild Severity

The Mild dysphagia severity cluster, which also represented patients with moderate stroke severity, comprised the largest proportion of patients (71%) out of all of the clusters and had patients with the lowest severity. This cluster consisted of 54% women. Although patients in the Mild cluster were the oldest, they had the lowest mean NIHSS score (10.08 ±7.93), SASI score (9.26 ±6.19), CCI score (4.27 ±2.26), and LOS (6.22 ±3.34) compared to patients in the other clusters. Furthermore, the Mild cluster had the second highest proportion of tPA administration (5%), highest proportion of patients who were discharged home (9%) and to IPR (32%), and lowest proportion of patients who died in the acute hospital (3%) compared to patients in the other clusters. They also incurred the lowest costs (mean, $59,571; SD, $53,326) compared to patients in the other clusters.

Moderate Severity

The Moderate dysphagia severity cluster, which represented patients with moderate/severe stroke severity, contained 15% of the sample and, overall, had patients with the greatest severity, indicated by stroke-related outcomes, such as the highest mean NIHSS, SASI, and CCI scores (16.23 ±8.18, 16 ±8.87, 5.11 ±2.24, respectively) and

highest costs (mean, $155,309; SD, $145,766) among all clusters. Similar to the other two clusters, about 55% of patients in this cluster were women. Patients in the Moderate dysphagia severity with moderate/severe stroke cluster had the lowest proportion of tPA administration (0%), highest proportion of patient mortality in the acute hospital (20%), and lowest proportion of patients to discharge home (0%). Patients in the Moderate dysphagia severity with moderate/severe stroke cluster stayed in the acute hospital (mean, 10.51; SD, 5.75) longer than patients in the Mild cluster on average but had a shorter mean LOS than those in the Severe dysphagia severity cluster. The majority of the patients in the Moderate dysphagia severity cluster discharged to IPR (30%) versus all other discharge locations.

Severe Severity

The Severe dysphagia severity cluster, which represented patients with moderate stroke severity, was comprised of 14% of the sample. Fifty-six percent of patients in this cluster were women, which is a similar proportion to the Mild and Moderate dysphagia severity clusters. Out of the three clusters, patients in the Severe dysphagia severity with moderate stroke cluster demonstrated mean NIHSS (13.51 ±7.78), SASI (10.63 ±5.12), and CCI scores (4.65 ±2.38) that were higher than patients in the Mild dysphagia severity with moderate stroke cluster but lower than patients in the Moderate dysphagia severity with moderate/severe stroke cluster. Similarly, the proportion of patients who died in the acute hospital (10%) in the Severe dysphagia severity with moderate stroke cluster was higher than that of patients in the Mild dysphagia severity cluster but lower than those in

the Moderate dysphagia severity cluster. Patients in the Severe dysphagia severity cluster also had the longest mean LOS (13.52 ±6.82) and greatest proportion of patients who were discharged to SNF (56%). Their hospital costs (mean, $137,728; SD, $98,165) were higher than costs incurred by patients in the Mild dysphagia severity with moderate stroke cluster but lower than those in the Moderate dysphagia severity with moderate/severe stroke cluster. Surprisingly, they had the highest proportion of tPA administration (8%).

Table 9. Demographic and characteristic composition of clusters

	Cluster[a]			
Demographics / Characteristics N=445 (100%)	Mild Dysphagia *Emphasis on cognitive impairment* n=317 (71%)	Moderate Dysphagia *Emphasis on respiratory compromise* n=65 (15%)	Severe Dysphagia *Emphasis on alternative nutrition* n=63 (14%)	*p*-value
	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	
Age, years	80.66 (9.06) 65-98	77.62 (8.37) 65-94	79.59 (8.69) 66-98	0.0280
NIHSS max possible 42	10.08 (7.93) 0-38	16.23 (8.18) 1-38	13.51 (7.78) 1-33	<.0001
SASI max possible 56	9.26 (6.19) 0-36	16 (8.87) 0-45	10.63 (5.12) 0-31	<.0001
CCI max possible 24	4.27 (2.26) 1-15	5.11 (2.24) 1-13	4.65 (2.38) 1-12	0.1395
LOS, days	6.22 (3.34) 1-24	10.51 (5.75) 3-27	13.52 (6.82) 5-36	<.0001
Cost incurred	$59,571 ($53,326) $7,196-$474,099	$155,309 ($145,766) $18,853-$911,378	$137,728 ($98,165) $16,697-$628,341	<.0001
	n (%)	n (%)	n (%)	
Female	172 (54.26)	36 (55.38)	35 (55.56)	0.7548
Race				0.7082
White	270 (85.17)	53 (81.54)	48 (76.19)	--
Black	30 (9.46)	7 (10.77)	8 (12.70)	--
Hispanic	4 (1.26)	0 (0)	2 (3.17)	--
Other	13 (4.10)	5 (7.69)	5 (7.94)	--
tPA	17 (5.36)	0 (0)	5 (7.94)	0.1246
Depression	45 (14.20)	10 (15.38)	4 (6.35)	0.2847
Dual eligibility	56 (17.67)	20 (30.77)	15 (23.81)	0.0144
Discharge disposition				<.0001
Home	30 (9.46)	0 (0)	1 (1.59)	--
IPR	102 (32.18)	19 (29.23)	14 (22.22)	--
SNF	98 (30.91)	14 (21.54)	35 (55.56)	--

HH	34 (10.73)	1 (1.54)	1 (1.59)	--
Trans	5 (1.58)	8 (12.31)	0 (0)	--
Other	37 (11.67)	10 (15.38)	6 (9.52)	--
Died in hospital	11 (3.47)	13 (20.00)	6 (9.52)	--

Footnote: N=population size, n=sample size, SD=standard deviation, NIHSS=National Institutes of Health Stroke Scale, SASI=Stroke Administrative Severity Index, CCI=Charlson Comorbidity Index, LOS=length of stay, tPA=tissue plasminogen activator, IPR=inpatient rehabilitation, SNF=skilled nursing facility, HH=home health, Trans=transferred to another facility

[a]Mild dysphagia severity with moderate stroke; Moderate dysphagia severity with moderate/severe stroke; Severe dysphagia severity with moderate stroke.

Hypothesis 2: Application of ADDSS

Proportion of PSD Diagnosis After Discharge by Dysphagia Severity

We applied the ADDSS to our post-discharge sample. Then we calculated frequencies and proportions of dysphagic patients with a diagnosis of PSD, stratified by dysphagia severity cluster, and used the chi-square test to determine statistical significance. We found that the proportions of PSD diagnosis across all three dysphagia severity groups were very similar (17%, 14%, and 16%, p=0.9016, respectively), revealing no statistically significant difference in proportions of PSD diagnosis in the 90 days after discharge by dysphagia severity (Table 10). Thus, we concluded that the evidence was not supportive of hypothesis 2a.

Table 10. Proportion of and time to PSD diagnosis by dysphagia severity

Variable N=359 (100%)	Cluster[a] Mild Dysphagia *Emphasis on cognitive impairment* n=266 (74%)	Moderate Dysphagia *Emphasis on respiratory compromise* n=42 (12%)	Severe Dysphagia *Emphasis on alternative nutrition* n=51 (14%)	*p*-value
	n (%)	n (%)	n (%)	
Depression	45 (16.92)	6 (14.29)	8 (15.69)	0.9016
	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	
Time to depression, days	39.31 (39.00) 5-91	63 (71.50) 9-96	70.88 (73.50) 12-124	0.0218

Footnote: N=population size, n=sample size, SD=standard deviation
[a]Mild dysphagia severity with moderate stroke; Moderate dysphagia severity with moderate/severe stroke; Severe dysphagia severity with moderate stroke.

Risk of PSD Diagnosis After Discharge by Dysphagia Severity

We performed multivariable logistic regression to (1) examine the relationship between PSD and post-stroke dysphagia by dysphagia severity levels and (2) test hypothesis 2b to determine if post-stroke patients with more severe dysphagia had greater risk of being diagnosed with PSD within the 90 days after discharge. In addition to our primary independent variable of interest, PSD, we included key predictor covariates, including dysphagia severity (by ADDSS clusters), age, CCI score, and dual eligibility, in our initial individual logistic regression models; however, we found none of the covariates to be statistically significant. Thus, no significant effect was found between dysphagia severity and risk of PSD diagnosis in the 90 days after discharge. Nonetheless, we observed that

compared to patients in the mild dysphagia cluster, those in the moderate and severe dysphagia severity groups were less likely to be diagnosed with PSD after discharge, but these results did not reach statistical significance. Thus, the evidence was not supportive of hypothesis 2b.

Time to PSD Diagnosis After Discharge by Dysphagia Severity

The unadjusted estimated mean time from diagnosis of AIS to diagnosis of depression was 39 days (SD ±39.00) for patients with mild dysphagia, 63 days (SD ±71.50) for patients with moderate dysphagia, and 70 days (SD ±73.50) for patients with severe dysphagia (Table 10). These results were statistically significant (p=0.0218) and demonstrated that those with mild dysphagia had the shortest mean time to PSD diagnosis within the 90-day period after discharge compared to patients in the other severity groups. Patients who had moderate dysphagia were diagnosed with depression, on average, sometime in between those in the mild and severe dysphagia severity groups, and those with severe dysphagia demonstrated the longest mean time to PSD diagnosis.

We created a dichotomous variable for dysphagia severity: “mild” (patients classified as having mild dysphagia severity) and “not mild” (patients classified as having moderate or severe dysphagia severity) and performed a time-to-event (survival) analysis to generate an unadjusted survival plot (Figure 4). The survival plot illustrates the differences in time to depression diagnosis between patients with mild dysphagia and patients with

moderate and severe dysphagia. Patients in both groups had an equally high probability of not being diagnosed with PSD soon after discharge, with the likelihood of being diagnosed with depression steadily increasing in both groups as the 90-day post-discharge period progressed (shown as descending survival curves in Figure 4). The median time to depression was 39 days (IQR, 44) for patients in the mild dysphagia severity group and 72.5 days (IQR, 48) for patients in the moderate or severe dysphagia severity group (p=0.0124). This means that 50% of patients with mild dysphagia had a diagnosis of depression a little more than one month after discharge, while 50% of patients with moderate or severe dysphagia had a diagnosis of depression almost at the end of the 90-day post-discharge follow-up period. Overall, patients with mild dysphagia demonstrated a greater likelihood of being diagnosed with depression in the 90 days after discharge compared to patients with moderate or severe dysphagia severity. These findings were not supportive of hypothesis 2c in which we hypothesized that patients with more severe dysphagia would have a shorter time to first depression diagnosis after discharge from the acute hospital.

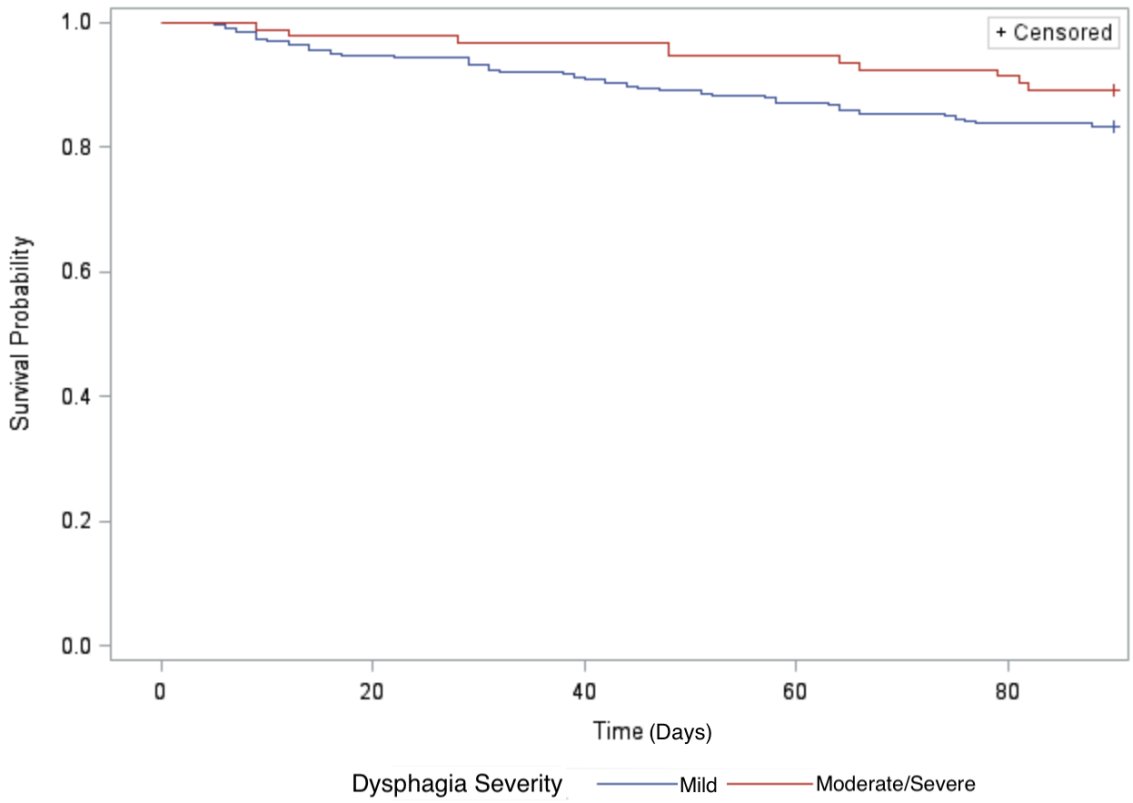

Figure 4. Survival curves for PSD during 90-day post-discharge follow-up period by dysphagia severity (mild vs. moderate/severe), Kaplan-Meier method.

Aim 3 Results

To determine if dysphagic patients with a PSD diagnosis incurred greater healthcare costs than dysphagic patients without a PSD diagnosis, we performed a cost analysis on a data set of post-discharge Medicare beneficiaries with a primary diagnosis of AIS who had been diagnosed with dysphagia during their inpatient acute hospitalization. We found that our results supported our hypothesis that patients who were diagnosed with dysphagia and PSD did, in fact, incur higher healthcare costs in the 90 days after discharge than those diagnosed with dysphagia alone.

Patient Characteristics

Our data set of 359 post-stroke patients diagnosed with dysphagia was stratified by dysphagia severity cluster according to the ADDSS (Table 11). There were no significant differences in gender or race among patients in all three dysphagia severity groups. The group with Mild dysphagia severity (and moderate stroke) contained 74% of the sample and had a mean age of 80.15 years (SD 8.94) with a range of 65-98 years. Patients in the Mild dysphagia cluster also had the lowest statistically significant mean NIHSS (8.53 ±6.87, p<.0001), SASI (9.16 ±6.34, p<.0001), and CCI (4.18 ±2.12, p=0.0276) scores; mean LOS (6.20 ±3.16, p<.0001); and proportion of dual eligibility (16%, p=0.0144) compared to those in the Moderate and Severe dysphagia clusters. Patients in the Mild group had the second highest proportion of tPA administration (6%, p=0.1306), lowest proportion of feeding tube placement (0%, p<.0001), and while they also had the highest proportion of depression diagnosis after discharge (17%), this result was not statistically significant

(p=0.3894). Those in the Mild cluster were discharged home (23%, p<.0001) more than patients in the higher severity clusters, and the proportions discharged to IPR and SNF (37% and 38%, p<.0001, respectively) were in-between those in the Moderate and Severe dysphagia clusters.

The Moderate dysphagia severity (with moderate/severe stroke) group contained 12% of the sample and had the youngest patients, with a mean age of 76.43 years (SD 8.09) and a range of 65-98 years. Patients in the Moderate dysphagia cluster had the highest mean NIHSS (16.02 ±7.47, p<.0001), SASI (14.67 ±7.45, p<.0001), and CCI (4.86 ±1.83, p=0.0276) scores of all the clusters. The mean LOS (11.52 ±5.84, p<.0001) was higher in the Moderate dysphagia group than in the Mild group and lower than the Severe group. Patients in the Moderate dysphagia group received the lowest proportion of tPA administration (0%, p=0.1306), though not statistically significant, and they also had the lowest proportion of discharge home (2%, p<.0001) and the highest discharge to IPR (45%, p<.0001). Twelve percent of patients in this group received a depression diagnosis after discharge, which was in-between those in the Mild and Severe dysphagia clusters; however, this finding was not statistically significant. Half of all patients in the Moderate dysphagia group had feeding tube placement (p<.0001), which was in-between the proportions for the Mild and Severe groups.

The Severe dysphagia (with moderate stroke) group contained 14% of the sample and had a mean age of 78.57 years (SD 8.22) with a range of 65-95 years. Patients in the

Severe dysphagia cluster had mean NIHSS (12.53 ±7.99, p<.0001), SASI (10.69 ±5.57, p<.0001), and CCI (4.41 ±2.20, p=0.0276) scores that were in-between those of patients in the Mild and Moderate dysphagia clusters. Patients in the Severe dysphagia cluster also had the longest mean LOS (13.57 ±3.16, p<.0001) and the greatest proportion of patients who discharged to SNF (69%, p<.0001) compared to those in the Mild and Moderate clusters. They also had the lowest proportion of depression diagnosis after discharge (10%); however, this finding was not statistically significant. Patients in the Severe group also had the highest proportion of feeding tube use at 100% (p<.0001).

Table 11. Baseline characteristics and descriptive data for Aim 3

Demographics / Characteristics N=359 (100%)	Cluster[a] Mild Dysphagia *Emphasis on cognitive impairment* n=266 (74%)	Moderate Dysphagia *Emphasis on respiratory compromise* n=42 (12%)	Severe Dysphagia *Emphasis on alternative nutrition* n=51 (14%)	*p*-value
	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	
Age, years	80.15 (8.94) 65-98	76.43 (8.09) 65-98	78.57 (8.22) 65-95	0.0280
NIHSS max possible 42	8.53 (6.87) 0-29	16.02 (7.47) 3-31	12.53 (7.99) 1-33	<.0001
SASI max possible 56	9.16 (6.34) 0-36	14.67 (7.45) 0-41	10.69 (5.57) 0-31	<.0001
CCI max possible 24	4.18 (2.12) 1-15	4.86 (1.83) 1-11	4.41 (2.20) 1-12	0.0276
LOS, days	6.20 (3.16) 2-21	11.52 (5.84) 3-27	13.57 (6.22) 5-34	<.0001
	n (%)	n (%)	n (%)	
Female	142 (53.38)	22 (52.38)	30 (58.82)	0.7548
Race				0.3361
White	223 (83.83)	35 (83.33)	39 (76.47)	--
Black	29 (10.90)	5 (11.90)	7 (13.73)	--
Hispanic	2 (0.75)	0 (0)	1 (1.96)	--
Other	12 (4.51)	2 (4.76)	4 (7.84)	--
Depression	44 (16.54)	5 (11.90)	5 (9.80)	0.3894
Feeding tube	0 (0)	21 (50)	51 (100)	<.0001
tPA	16 (6.02)	0 (0)	5 (9.80)	0.1306
Dual eligibility	43 (16.17)	13 (30.95)	15 (29.41)	0.0144
Discharge location				<.0001
Home	61 (22.93)	1 (2.38)	2 (3.92)	--
IPR	99 (37.22)	19 (45.24)	14 (27.45)	--
SNF	100 (37.59)	14 (33.33)	35 (68.63)	--
Trans	6 (2.26)	8 (19.05)	0 (0)	--

Footnote: N=population size; n=sample size, SD=standard deviation, NIHSS=National Institutes of Health Stroke Scale, SASI=Stroke Administrative Severity Index, CCI=Charlson Comorbidity Index, LOS=length of stay, tPA=tissue plasminogen activator, IPR=inpatient

rehabilitation, SNF=skilled nursing facility, HH=home health, Trans=transferred to another facility
[a]Mild dysphagia severity with moderate stroke; Moderate dysphagia severity with moderate/severe stroke; Severe dysphagia severity with moderate stroke.

Cost of Care

Unadjusted Cost

Using univariate analysis to examine total 90-day post-discharge cost, we found that, on average, dysphagic patients (irrespective of severity) with a depression diagnosis had $12,667 higher mean total costs after discharge than those without depression, these results are statistically significant, p<.0001 (Table 12). When comparing the fully adjusted cost estimate from the multivariable model, there is some overlap in the 95% confidence intervals (CIs) which is not surprising given the small sample size used for this estimate. The mean unadjusted total 90-day post-discharge costs by dysphagia severity clusters show that patients with Mild and Severe dysphagia with a depression diagnosis had higher mean total costs ($15,914 and $11,680, respectively) than those without a depression diagnosis in the same dysphagia severity groups, while patients with Moderate dysphagia with a depression diagnosis had $316 lower mean total costs compared to those with Moderate dysphagia without a depression diagnosis (Table 12).

We also found that patients in the Moderate dysphagia group (with moderate/severe stroke severity) had statistically significant unadjusted higher mean inpatient costs after discharge than those with Mild or Severe dysphagia severity (Figure 5 and Appendix 5). Patients with Moderate dysphagia had more inpatient rehabilitation admissions and/or

readmissions to the acute hospital after discharge than those with more or less severe dysphagia (and less severe stroke severity). These results are consistent with the medical characteristics of the patients in the Moderate dysphagia group, in that they demonstrated the highest stroke severity, likely resulting in greater impairment and disability and requiring more intensive rehabilitation, which is why they also had the largest proportion of discharge to IPR facilities. Furthermore, patients in the Moderate dysphagia group were the most ill and had the most serious respiratory comorbidities, such as aspiration pneumonia, intubation, and tracheotomy/tracheostomy, out of all groups; thus, readmissions to the acute hospital are expected in this group. In contrast, we found that those with the least dysphagia severity (Mild) were overwhelmingly discharged home (23%) compared to patients with Moderate (2%) and Severe (4%) dysphagia severity, respectively (Table 11), and, as expected, patients discharged home had the lowest unadjusted mean total 90-day post-discharge costs, inpatient costs, and carrier costs after discharge ($p<.0001$, respectively) (Appendix 6).

Table 12. Estimated mean total 90-day post-discharge costs and 95% confidence intervals for patients with and without depression diagnosis by overall dysphagia and dysphagia severity clusters

		Cluster[a]		
Cost[b]	Overall Dysphagia[c] N=359 (100%)	Mild Dysphagia[d] *Emphasis on cognitive impairment* n=266 (74%)	Moderate Dysphagia[d] *Emphasis on respiratory compromise* n=42 (12%)	Severe Dysphagia[d] *Emphasis on alternative nutrition* n=51 (14%)
	Mean (SD), 95% CI *p*-value	Mean (SD), 95% CI *p*-value	Mean (SD), 95% CI *p*-value	Mean (SD), 95% CI *p*-value
Depression				
Yes	44,613 (21,820) 34,417-57,829 <.0001	43,074 (22,458) 32,526-57,042 <.0001	54,177 (17,388) 23,549-124,644 <.0001	48,588 (20,597) 21,119-111,785 <.0001
No	31,946 (26,559) 28,642-35,631 <.0001	27,160 (21,688) 23,968-30,778 <.0001	54,493 (39,186) 40,116-74,021 <.0001	36,908 (25,895) 28,043-48,576 <.0001

Footnote: N=population size, n=sample size, SD=standard deviation, CI=confidence interval

[a]Mild dysphagia severity with moderate stroke; Moderate dysphagia severity with moderate/severe stroke; Severe dysphagia severity with moderate stroke.

[b]Cost in United States dollars (USD).

[c]Column values are unadjusted

[d]Column values are adjusted

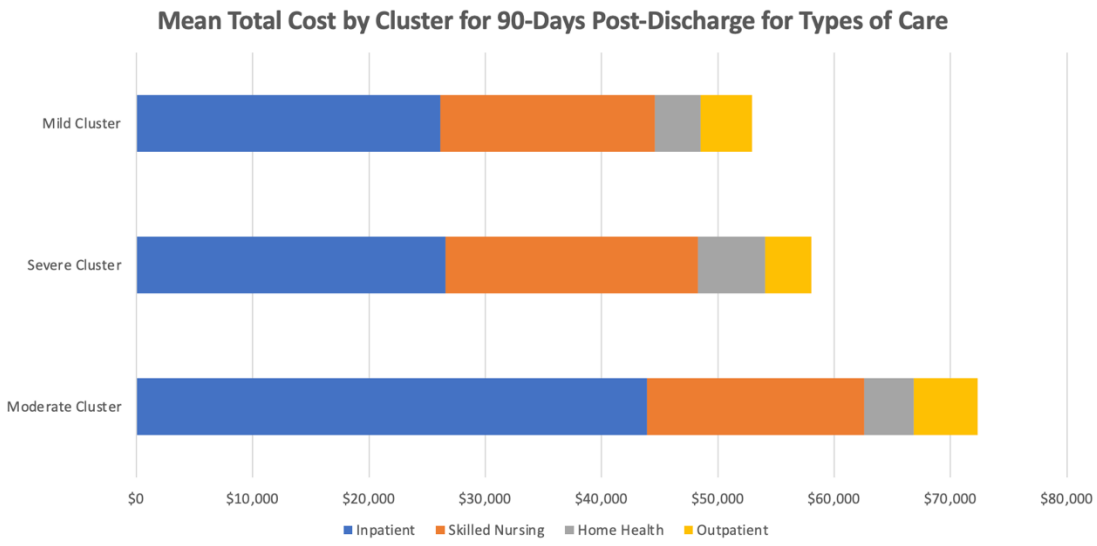

Figure 5. Mean total cost for types of care by dysphagia severity for 90 days post-discharge.

Adjusted Cost

We used multivariable analysis via gamma-distributed GLMs with logarithmic transformation to compare healthcare costs across dysphagia severity groups, with our main independent variable being PSD diagnosis. We included clinically relevant predictor variables in each of our initial individual models to determine if they were statistically significant as potential confounding factors (Table 13).

Table 13. Regression parameters for 90-day post-discharge cost for each univariable model to identify significant covariates for inclusion in the multivariable model

Variable	Parameter Estimate	*p*-value
Depression	0.3340	0.0201
Dysphagia severity		0.0002
Mild	Reference	--
Moderate	0.6031	--
Severe	0.2447	--
Age	-0.0124	0.0442
NIHSS	0.0278	<.0001
Female	0.0102	0.9214
CCI	0.0252	0.3399
tPA	-0.0920	0.6761
Dual eligibility	0.1921	0.1377
Race		0.6490
White	-0.2014	0.2160
Black	Reference	--
Hispanic	-0.1716	0.7690
Other	-0.1287	0.6413

Footnote: NIHSS=National Institutes of Health Stroke Scale, CCI=Charlson Comorbidity Index, tPA=tissue plasminogen activator, Reference=reference group in the model

Controlling for the statistically significant covariates from our initial models, we fit our final parsimonious cost model measuring the effect of PSD on total 90-day post-discharge cost (Table 14). The results showed that a diagnosis of PSD was associated with increased mean total healthcare costs in the 90 days following discharge from the acute hospital. It also showed that stroke severity (NIHSS score) and dysphagia severity (moderate) significantly contributed to the variations in cost. This is illustrated in the increase in marginal cost difference between dysphagic patients with and without a diagnosis of

depression, for which the unadjusted difference was $12,667 and now, controlling for dysphagia severity and stroke severity, the cost difference has increased to $15,556.

Table 14. Estimated mean 90-day post discharge cost for patients with and without depression, controlling for effects of differences in dysphagia severity and stroke severity

Variable	Parameter Estimate	SE	95% CI	*p*-value
Depression				
Yes	0.3599	0.1419	0.0819 – 0.6379	0.0112
No	Reference	--	--	--
Dysphagia severity				
Mild	Reference	--	--	--
Moderate	0.5108	0.1687	0.1801 – 0.8414	0.0025
Severe	0.2243	0.1475	-0.0647 – 0.5134	0.1282
NIHSS	0.0167	0.0074	0.0021 – 0.0312	0.0246

Footnote: SE=standard error, CI=confidence interval, NIHSS=National Institutes of Health Stroke Scale, Reference=reference group in the model

In order to estimate the adjusted mean costs for the dysphagia severity groups with and without PSD, we created a variable that represented dysphagia severity by cluster (mild, moderate, or severe) in the presence or absence of PSD ("Mild/No PSD," "Mild/PSD," "Mod/No PSD," "Mod/PSD," "Sev/No PSD," "Sev/PSD"). The "combination" independent variable was then used in a multivariable cost estimation model to measure the effect of PSD and dysphagia severity on total 90-day post-discharge cost. The results showed that having a PSD diagnosis and being in the mild dysphagia severity cluster were associated with higher 90-day costs (p=0.0089) (Table 15). We also found that stroke severity had a

significant effect on cost (p=0.0259). The marginal cost difference was $15,914 higher for patients with Mild dysphagia severity with a diagnosis of depression compared to patients with Mild dysphagia severity without a diagnosis of depression, controlling for stroke severity. This finding supports our hypothesis that dysphagic patients with PSD will incur greater healthcare costs than dysphagic patients without PSD.

Table 15. Estimated mean 90-day post discharge cost for patients in three different dysphagia severity groups with and without depression, controlling for effects of differences in stroke severity

Variable	Parameter Estimate	SE	95% CI	*p*-value
Dysphagia severity & PSD				
Mild/No PSD	Reference	--	--	--
Mild/PSD	0.4119	0.1575	0.1032 – 0.7206	0.0089
Moderate/No PSD	0.5604	0.1786	0.2105 – 0.9104	0.0017
Moderate/PSD	0.5228	0.4342	-0.3282 – 1.3737	0.2286
Severe/No PSD	0.2427	0.1556	-0.0623 – 0.5478	0.1189
Severe/PSD	0.5049	0.4289	-0.3356 – 1.3455	0.2390
NIHSS	0.0165	0.0074	0.0020 – 0.0311	0.0259

Footnote: SE=standard error, CI=confidence interval, NIHSS=National Institutes of Health Stroke Scale, PSD=post-stroke depression, Reference=reference group in the model

To contrast cost differences between patients with mild dysphagia and those with moderate or severe dysphagia, we constructed a dichotomous variable for dysphagia severity – “mild” (patients classified as having mild dysphagia severity) or “not mild” (patients classified as having moderate or severe dysphagia severity). This approach

helped create more proportionate sample sizes per cluster (n=266 and n=93, respectively), which is helpful to understand the effect of small cluster samples on the variation in the adjusted cost estimates. Multivariable analysis results from this model (Table 16) were very similar to results from our other models (Tables 14 and 15) in that depression had a significant effect on cost, as did dysphagia severity (in this case, moderate or severe) and stroke severity (Figure 6), with a marginal cost difference between dysphagic patients with and without a diagnosis of depression of $10,745, controlling for dysphagia severity and stroke severity.

Table 16. Estimated mean 90-day post discharge cost for patients with and without depression, controlling for effects of differences in dysphagia severity (by dichotomous dysphagia severity variable) and stroke severity

Variable	Parameter Estimate	SE	95% CI	*p*-value
Depression				
Yes	0.3541	0.1421	0.0755 – 0.6327	0.0127
No	Reference	--	--	--
Dysphagia severity				
Mild	Reference	--	--	--
Not mild	0.3530	0.1229	0.1122 – 0.5938	0.0041
NIHSS	0.0165	0.0074	0.0020 – 0.0311	0.0259

Footnote: SE=standard error, CI=confidence interval, NIHSS=National Institutes of Health Stroke Scale, Not mild= patients classified as having moderate or severe dysphagia severity, Reference=reference group in the model

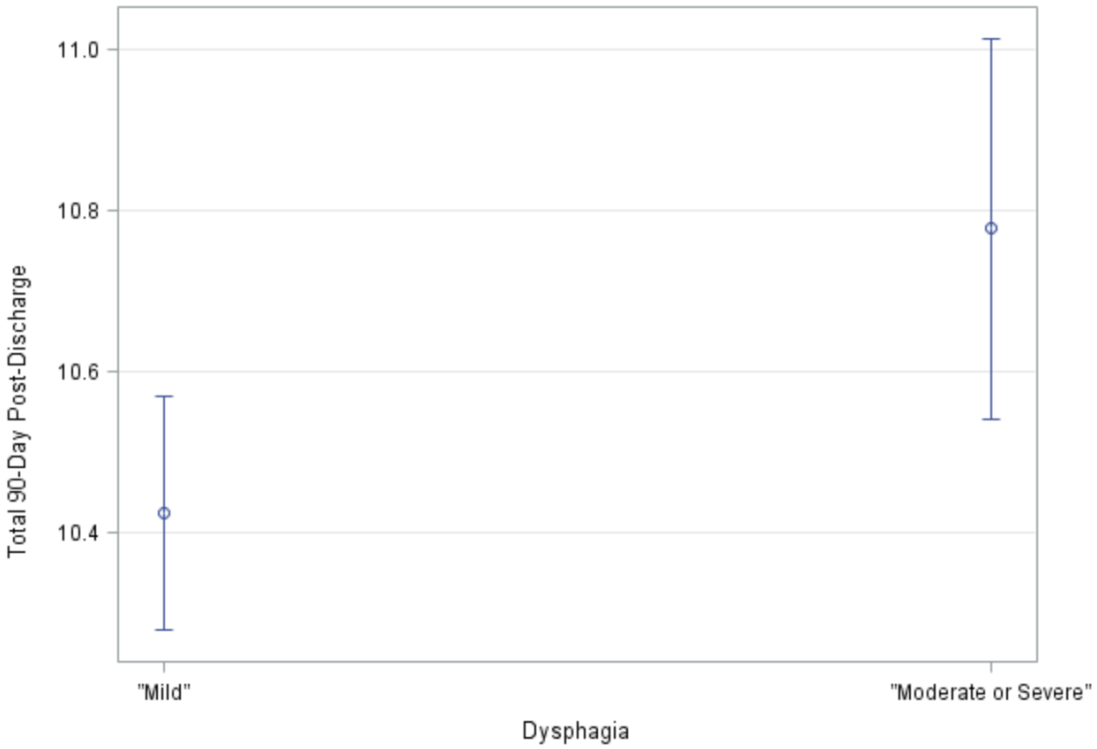

Figure 6. Effect of depression on 90-day post-discharge cost by mild dysphagia severity vs. moderate or severe dysphagia severity.

Overall, results from this cost analysis consistently showed that not only does depression diagnosis significantly increase healthcare costs in the 90 days after discharge, so do stroke severity and dysphagia severity. We found that patients with dysphagia and depression (regardless of dysphagia severity) incur higher healthcare costs in the 90 days after discharge than dysphagic patients without depression, an unadjusted effect size of $12,667. Furthermore, we found that the presence of depression resulted in a 36% increase (β, 0.3599; 95% CI, 0.0819-0.6379; *p*=0.0112) in cost after controlling for dysphagia severity and stroke severity (adjusted effect size). We also found that

dysphagia severity cluster is an important covariate in explaining variations in post-discharge cost for patients diagnosed with both post-stroke dysphagia and PSD, which is supportive of our Aim 2 Hypothesis 1 (i.e., development of the ADDSS) – that these dysphagia severity clusters are useful and clinically meaningful predictors in administrative data analyses.

CHAPTER 5: DISCUSSION

Aim 1 Discussion

Section 1: Brief Summary of Results

Objectives

The objectives for Aim 1 were to not only examine the rate of diagnosis of PSD in patients with a diagnosis of post-stroke dysphagia but also to determine if it is at least as high as the rate of diagnosis of PSD in the general stroke population. Furthermore, we studied the relationship between PSD and post-stroke dysphagia, evaluated the odds and hazard of being diagnosed with depression after stroke, and estimated the time to depression from the initial stroke diagnosis in patients with and without a diagnosis of dysphagia.

Hypothesis and Results

Consistent with our hypothesis, the results from Aim 1 demonstrated that the rate of diagnosis of PSD in patients with a diagnosis of post-stroke dysphagia is at least as high as the rate of diagnosis of PSD in the general stroke population. In fact, patients diagnosed with dysphagia demonstrated slightly higher proportions of depression diagnosis during acute hospitalization (12%) compared to patients not diagnosed with dysphagia (approximately 10%). We also found that PSD diagnosis was significantly affected by

dysphagia diagnosis during the 90-day post-discharge follow-up period as well, with those who had been diagnosed with dysphagia being almost three times more likely to be diagnosed with depression than patients who had not been diagnosed with dysphagia and the patients diagnosed with dysphagia demonstrating an approximately 1.75-fold higher hazard for PSD diagnosis than the patients not diagnosed with dysphagia. The mean time from stroke to depression diagnosis was higher for patients diagnosed with dysphagia compared to those not diagnosed with dysphagia (40 days versus 34 days, respectively), signifying that patients with a dysphagia diagnosis were diagnosed with depression later than patients without a dysphagia diagnosis; however, these results were not significant. Additional results are discussed in detail in the following sections.

Section 2: PSD in Patients with Post-Stroke Dysphagia

Related Research

Dysphagia is a common consequence of stroke (Dziewas, et al., 2017; Gonzalez-Fernandez et al., 2013; Labeit et al., 2018; Martino et al., 2005; Rofes et al., 2011, 2013), as is depression (Broomfield et al., 2014; Gillen et al., 1999; Saxena et al., 2007; Stein et al., 2020; Towfighi et al., 2017; Williams, 2005). It is believed that dysphagia has a substantial effect on mental health and is linked to depression (Dziewas, et al., 2017; Holland, 2011; Verdonschot et al., 2013, 2017); however, the incidence of PSD in post-stroke dysphagic patients is not known. To our knowledge, there is no literature that specifically examines PSD in post-stroke dysphagic patients as a primary outcome. There are some incidental reports of dysphagia in stroke survivors with depression (Ayerbe et

al., 2011; Kang et al., 2012; Harris et al., 2017; Saxena et al., 2008); however, establishing rates of PSD in dysphagic patients and elucidating the relationship between PSD and post-stroke dysphagia were not the main objectives in these studies. For example, Kang et al. (2012) examined the effects of a dysphagia exercise program on swallow function and its indirect effect on depressive symptoms in subacute stroke patients with dysphagia (onset of stroke within six months) in a rehabilitation hospital. Although PSD was not their primary outcome of interest, the researchers reported that post-stroke dysphagic patients in both the control and experimental groups had severe (score of >29) mean Beck Depression Inventory (BDI) (Beck & Steer, 1993) scores before dysphagia treatment (Kang et al., 2012; Smarr & Keefer, 2011). After two months of treatment, the control group's mean BDI scores remained severe (score of >29), and the mean BDI scores of the experimental group, who demonstrated significant improvement in (oral phase) swallow function, significantly decreased to scores in the moderate range (score of 20-28) (Kang et al., 2012; Smarr & Keefer, 2011). While improvement in mean BDI scores was observed in the experimental group, patients continued to experience moderate depressive symptoms, which could be due to the fact that their swallow function improvement (in oral phase only), though statistically significant, was not clinically meaningful (Kang et al., 2012). The researchers noted that there was no meaningful difference in proportions of patients with aspiration pneumonia or transitioning from tube feeding to oral feeding between groups (Kang et al., 2012); therefore, it is feasible that patients who continued to have pharyngeal phase dysphagia, particularly severe enough to result in aspiration pneumonia and/or the need for non-

oral nutrition (tube feeding), would also continue to experience depressive symptoms. Harris et al. (2017) examined the prevalence of PSD and its association with functional status among African American stroke survivors in an inpatient rehabilitation setting. Although the researchers did not primarily study dysphagia in this patient population, they reported that individuals with depression had a significantly higher proportion of dysphagia compared to those without depression (60% versus 44.1%, p=0.014), suggesting that dysphagia is more common in those with depression during the subacute stroke period (Harris et al., 2017).

Incidence of PSD Diagnosis

One of the main findings in the present study was that patients diagnosed with post-stroke dysphagia are at least as likely as those not diagnosed with post-stroke dysphagia to be diagnosed with PSD. There is a slightly higher proportion of PSD diagnosis in patients who had been diagnosed with post-stroke dysphagia compared to those who had not, 12% versus about 10%, respectively; however, the difference in proportions as well as the actual proportions of post-stroke dysphagia and PSD were much lower than expected, considering the substantially higher incidence of both diagnoses reported in the literature. Notwithstanding, our findings coincide with Harris et al.'s (2017) results (but with our proportions much lower than theirs). There are no other studies for direct comparison; however, our findings are still lower than expected if compared to studies that have reported incidence of PSD and post-stroke dysphagia separately. For example, our results showed that 10% of the general stroke population were diagnosed with

depression during acute hospitalization, which is substantially lower than the approximately 33% of stroke survivors who are reportedly diagnosed with depression at any one time after stroke (Hackett & Pickles, 2014; Kutlubaev & Hackett, 2014; Towfighi et al., 2017; Zhang et al., 2020). Similarly, our results demonstrated that 16% of the general stroke population had a diagnosis of dysphagia, which is remarkably low compared to Martino et al.'s (2005) systematic review report of 37-80% of stroke survivors experiencing dysphagia (depending on type of dysphagia screen and/or assessment used, timing of assessment after stroke, and lesion location).

Section 3: The Problem of Underdiagnosis and Undercoding

Underdiagnosis and Undercoding of Dysphagia

We found that 16% of post-stroke patients have dysphagia in the acute hospital setting. The difference in our findings compared to those in the literature can be primarily explained by underdiagnosis and undercoding (Cohen et al., 2020; Dziewas, et al., 2017; Gonzalez-Fernandez et al., 2008; Labeit et al., 2018; Rofes et al., 2011; Takizawa et al., 2016). Despite its high prevalence, post-stroke dysphagia is frequently underdiagnosed because of a number of factors, including restricted availability of dysphagia experts (speech-language pathologists [SLPs]) in hospitals, limited access to costly instrumental diagnostic equipment or other material resources in certain medical settings, and lack of consensus for which patients require dysphagia screening (Dziewas, et al., 2017; Labeit et al., 2018; Rofes et al., 2011). Furthermore, various methods for dysphagia evaluation are reported in studies examining post-stroke dysphagia, including patient report, screening

tools, bedside swallow assessment, and modified barium swallow study – all with varying levels of sensitivity for detecting dysphagia (Takizawa et al., 2016); therefore, depending on the evaluation method used, dysphagia may be missed in some stroke patients. For example, silent aspiration can occur in up to 67% of post-stroke patients with dysphagia (Daniels et al., 1998; Martino et al., 2012), and if the diagnostic tool to evaluate dysphagia does not have adequate sensitivity to detect silent aspiration (like patient report, screening tools, or bedside swallow assessments), then a potentially large proportion of individuals with dysphagia will go undiagnosed. In addition, underdiagnosis and undercoding of dysphagia are known limitations in administrative data analysis (Cohen et al., 2020; Gonzalez-Fernandez et al., 2008; Takizawa et al., 2016). Nevertheless, there is high specificity in dysphagia diagnosis within medical billing data; therefore, we can confidently assume that the patients who are diagnosed with dysphagia do, in fact, have dysphagia (Cohen et al., 2020). Conversely, we cannot assume that just because a patient does not have a diagnosis of dysphagia that dysphagia is not present; therefore, interpretations of the findings from this study should be made with caution.

Underdiagnosis and Undercoding of PSD

Correspondingly, PSD is an often underestimated and underdiagnosed sequela of stroke (Dar et al., 2017). It is underdiagnosed for a variety of reasons, including difficulties evaluating depression in patients with cognitive and/or language disorders (which are common after stroke), misattributing common symptoms of stroke and depression (such

as fatigue, poor sleep, and emotional lability) resulting in misclassification by healthcare providers, and use of screening tools with inadequate sensitivity for detecting depression (Conroy et al., 2020; Starkstein & Robinson, 1989; Williams, 2005). In addition, patients may not report depressive symptoms because of the social stigma associated with mental health disorders (Alaghehbandan & MacDonald, 2013). Due to the risk of mortality and number of serious co-occurring conditions that may present after stroke, it is feasible that healthcare providers in the acute hospital are more focused on basic life-sustaining functions as opposed to assessing for neuropsychiatric manifestations in acute stroke patients, resulting in overlooked diagnoses of PSD. Dar et al. (2017) and VanItallie (2005) recommended that healthcare professionals be adequately trained to recognize depressive symptoms, use appropriate diagnostic rating scales, and be able to discriminate signs of depression from other disorders (e.g., dementias and normal grief reactions). Furthermore, like post-stroke dysphagia, PSD is also known to be undercoded in administrative billing data, resulting in questionable accuracy of diagnostic information and underreporting of diagnostic procedures (Alaghehbandan & MacDonald, 2013), which may misrepresent the true proportion of medical conditions and level of care received by patients. To address the issue of undercoding, researchers have developed promising case-finding algorithms with adequate sensitivity and specificity for the detection of PSD in administrative databases; thus, the utilization of administrative data for PSD research remains useful (Alaghehbandan & MacDonald, 2013; Damush et al., 2008; West et al., 2000). Nevertheless, as with dysphagia, we should not assume that

depression is not present just because there is no diagnosis of PSD in the medical record. For this reason, the results from this study should be interpreted cautiously.

Addressing Underdiagnosis and Undercoding

Underdiagnosis and undercoding are alarming problems in healthcare because they not only demonstrate that patients who have serious medical conditions may not be identified or may be identified but their diagnosis not adequately coded, but it also means that these patients may not receive treatment for potentially critical conditions. For example, we know that post-stroke dysphagia can lead to serious complications if not managed, such as malnutrition, dehydration, aspiration pneumonia, and death (Labeit et al., 2018), and we also know that PSD is a predictor of negative outcomes after stroke, including disability; poor physical, social, and cognitive function; lower quality of life; and high mortality (Towfighi et al., 2017). Because of the prevalence and seriousness of these medical conditions, medical providers need to be alert to the issues of underdiagnosis and undercoding and be trained in not only identifying these patients but also properly coding for their respective medical diagnoses. As another example, increased surveillance for recognizing symptoms of dysphagia and depression in post-stroke patients and targeted and repeated (respective) dysphagia and depression screenings early in the acute post-stroke phase using appropriate diagnostic instruments are necessary to adequately detect high risk patients. Then providers can assign timely interventions and/or referrals as needed, potentially mitigating the risks of morbidity and mortality in this patient population.

As a result of the probable undercoding of post-stroke dysphagia and PSD in this study, our findings are likely grossly underestimated and more conservative than the true population incidences. Nonetheless, because of our large, representative sample size (N=9,163), our results may be more generalizable than other studies with smaller, less representative samples, and, to our knowledge, they establish the first reported incidence of PSD in Medicare patients with dysphagia who are 65 years of age and older after AIS.

Section 4: Likelihood of PSD Diagnosis

In the present study, fewer patients who received tPA administration were diagnosed with post-stroke dysphagia, which is expected given that tPA is known to reduce the severity of stroke. Those with a dysphagia diagnosis demonstrated significantly higher proportions of cognitive decline and had increased LOS (by about three days longer) than patients without a dysphagia diagnosis. We found that having a diagnosis of dysphagia, being female, being white, and having dual eligibility were positively associated with depression diagnosis after stroke, while age was negatively associated with PSD diagnosis. Compared to patients without a diagnosis of post-stroke dysphagia, those with a diagnosis of dysphagia were 2.7 times more likely to be diagnosed with depression after discharge from the acute hospital. In addition, white patients were 82% more likely to have a PSD diagnosis after discharge than black patients and were overall more likely to have a PSD diagnosis than any other race; however, due to the disproportionate number of white patients in this study (>80%), these results should be interpreted with caution.

The odds of being diagnosed with depression increased in women by 71%, and for those with dual eligibility, which is indicative of low socioeconomic status (SES), the odds increased by 43%. Age was the only factor for which the odds of PSD diagnosis were reduced (by 24%).

Although there were very few studies by which to compare our findings, we found that our results were similar to Ayerbe et al.'s (2011) findings that at three months post-stroke, dysphagic patients were almost twice as likely to have depression than non-dysphagic patients; however, Saxena et al. (2008) found no significant association between PSD and dysphagia at six months after stroke (in multivariate analyses). The reason for the disparity may be due to variations in study methodology, sample sizes, diagnostic assessments and time frames, etc., which are discussed in detail below. Despite the discordance with Saxena et al.'s (2008) results, our findings are supported by other non-stroke dysphagia literature, which posit that dysphagia is associated with affective complaints (Verdonschot et al., 2013, 2017). In a systematic review by Verdonschot et al. (2017), the researchers found that all 24 articles they appraised suggested that depressive symptoms were significantly and positively associated with dysphagia. Furthermore, dysphagia is known to have severe social and psychological impacts that reduce quality of life, such as embarrassment, isolation, and loss of self-esteem due to swallowing difficulties and anxiety, panic, and avoidance of meals due to fear of food sticking in the throat and choking (Ekberg et al., 2002). For these reasons, it is plausible that dysphagia is not only associated with PSD but also increases the odds of

PSD in post-stroke patients, as we found in the present study. Furthermore, these dysphagia-related psychological impacts may exacerbate or be exacerbated by similar psychosocial impacts of PSD, such as social withdrawal, social deterioration, and social discontentment (Dar et al., 2017). Given that the nature of association between post-stroke dysphagia and PSD is not understood, it is feasible to consider that both could potentially contribute to, cause, or affect each other.

Sienkiewicz-Jarosz et al.'s (2010) results revealed that stroke patients with more depressive symptoms had lower income, which was comparable to our findings with patients who had dual eligibility (an indicator of low SES), as were Khedr et al.'s (2020) results that PSD is significantly associated with lower SES. It is known that low SES is a determinant of poor health status, and the combination of low SES and high levels of psychological distress has been shown to have a multiplicative effect in which low SES magnifies the negative effects of psychological distress (Lazzarino et al., 2013a, 2013b). Furthermore, it is believed that those with lower SES possess fewer financial, social, and psychological resources to manage adverse events (Lazzarino et al., 2013a, 2013b; Matthew & Gallo, 2011); therefore, our findings that individuals with dual eligibility (an indicator of low SES) have increased odds of PSD compared to those who do not have dual eligibility are in line with the literature.

With regard to gender differences, we found that women were more likely to be diagnosed with PSD than men, which was similar to Goldmann et al.'s (2016) findings that

the odds of PSD were higher in women. Conversely, our results contradicted Ayasrah et al.'s (2018) findings in which gender was not found to predict PSD. In the 15 studies examining prevalence of depression that Appelros et al. (2010) reviewed, most reported that PSD was more common in women than men, while others found no difference between women and men, and one study found a higher prevalence of PSD in men. The authors concluded that whether or not being a woman is a risk factor for PSD remains ill-defined (Appelros et al., 2010). Even so, we know that there are gender-related differences in depression outside of the setting of stroke, with women almost twice as likely than men to become depressed during their lifetime (Kuehner, 2017; Salk et al., 2017). The reasons for this "gender gap" in depression remain unclear; however, there is evidence to support several possible factors, including genetic susceptibility, hormonal influences, psychological stress responsiveness, coping styles, and social roles (Kuehner, 2017). For example, studies have shown that women may be more likely to develop depression after a stressful life event (Cohen et al., 2019) and, due to gender socialization and cultural ideals about women, feel more comfortable seeking help when experiencing symptoms of depression. Additional reasons for the "gender gap" may be clinician bias and stereotypes about gender, in which clinicians' diagnostic priorities tend to skew more toward assessing women for depressive symptoms versus men. Furthermore, clinician assessment methods (e.g., informal patient interview) may be biased toward depressive symptoms that are more characteristic in women (Sigmon et al., 2005), such as sadness or crying, and may not capture depressive symptoms more characteristic in men, such as

anger or substance abuse. For these reasons, it is plausible that after stroke, women are more likely to be diagnosed with depression than men, as we found in the present study.

We found the odds of PSD diagnosis decreased with age, which is in agreement with Goldmann et al.'s (2016) findings that older patients demonstrated lower odds of PSD; however, our findings differed from Ayasrah et al.'s (2018) results in which age was not found to predict PSD. McCarthy et al. (2016) reported that at three months post-stroke, patients between 25-64 years of age had significantly greater depressive symptoms than those 65 years and older, with the 25-54 age group demonstrating the highest risk for depression out of all age groups examined, which is in line with our findings that older patients have lower odds of PSD diagnosis. The authors noted, however, that their results were in accordance with some similar studies but contradicted the results of others and suggested that these disparities were due to variability in study methods, such as using age as a dichotomous, instead of continuous, variable and restricting age groups in study samples (McCarthy et al., 2016). Furthermore, McCarthy et al. (2016) proposed that the association between age and PSD may be curvilinear as opposed to linear, meaning that risk of PSD is greatest between the ages of 25 and 54, attenuating through midlife and early old age, and then increasing again in late old age. Another potential reason for the inconsistent findings in studies examining age and PSD could be the underdiagnosis of depression in older individuals as a result of age-related clinician bias in which depression is assumed to be a normal response to a serious medical event, disease diagnosis, or even advancing age (Stewart, 2004). Clinicians may observe symptoms of depression but

not diagnose or refer an older patient for intervention if these symptoms are assumed an expected reaction in this particular patient age group.

We found that white patients were more likely to be diagnosed with PSD than any other race within the three-month time period after discharge from the acute hospital; however, it should be noted that we had a disproportionately large number of white patients in our population (>80%), which can bias results. Accordingly, our findings should be interpreted with caution. Nevertheless, our results were similar to Goldmann et al.'s (2016) findings from their prospective study that comprised an adequate representation of Hispanic patients (50.8% Hispanic, 25.7% non-Hispanic white, and 17.5% non-Hispanic black) that non-Hispanic white post-stroke patients had greater odds of depression one month after stroke compared to other races; however, no significant differences were found in diagnosis of PSD between non-Hispanic white and Hispanic patients after a year. In Jia et al.'s (2010) retrospective study of Veterans Affairs patients utilizing administrative data, researchers found that post-stroke non-Hispanic white patients had higher odds of PSD than Hispanic and non-Hispanic black patients one year after stroke, which is in agreement with our findings; however, Jia et al.'s (2010) study population was also comprised of disproportionately greater number of white patients versus patients of other races/ethnicities (65.54% white, 21.9% black, 7% Hispanic, and 5.55% other), which could potentially bias results. In contrast to these and our findings, Sienkiewicz-Jarosz et al. (2010), Ayerbe et al. (2011), and Saxena et al. (2008) did not find any significant associations between PSD and race/ethnicity. Furthermore, they found no significant

associations between PSD and other demographic variables, such as age and gender, either. We found that our results were both consistent with and in contradiction to results from other studies examining variables associated with PSD, which is common in this area of research, especially for demographic variables (De Ryck et al., 2014; Kutlubaev & Hackett, 2014; Towfighi et al., 2017; Zhang et al., 2020). For example, in Shi et al.'s (2017a) meta-analysis, the investigators found that demographic factors, such as female gender and age (<70 years) were risk factors for PSD during the acute and subacute (≤ three months) phases, while in Babkair's (2017) integrative systematic review, the investigator found that significant associations for demographic variables, such as gender and age, were inconsistent across studies. Several researchers who have conducted systematic reviews and meta-analyses have reported that because of varying and conflicting results in the numerous studies evaluating predictors of PSD, there are no consistent associations between PSD and demographic variables, such as age and gender (Babkair, 2017; De Ryck et al., 2014; Kutlubaev & Hackett, 2014; Towfighi et al., 2017). Moreover, they reported limited comparison and generalizability in most studies due to differences in inclusion/exclusion criteria, settings, assessment timing, and depression diagnostic criteria and tools; disparate variables that may be poorly quantified; methodological variations; and inadequate sample sizes with underpowered analyses as the reasons for disparities across study results (Babkair, 2017; Kutlubaev & Hackett, 2014; Towfighi et al., 2017). As such, our ability to make direct comparisons to analogous studies is limited; however, we believe that we have addressed many of the authors' criticisms of previous studies and, therefore, are confident that this study makes a

meaningful contribution to the literature by elucidating the association between the diagnosis of PSD and patients diagnosed with post-stroke dysphagia.

Section 5: Hazard of PSD Diagnosis

The results of our survival analyses revealed that, when controlling for significant covariates, the hazard for PSD diagnosis in patients with and without a diagnosis of dysphagia was initially low after discharge and consistently increased for the duration of the 90-day follow-up period; however, the group with a dysphagia diagnosis demonstrated an approximately 1.75-fold higher hazard for PSD diagnosis than the group without a dysphagia diagnosis during the 90 days after discharge, suggesting that patients diagnosed with dysphagia were more likely to be diagnosed with depression than patients not diagnosed with dysphagia. We found that on average and on any given day in the 90 days after discharge, the hazard for diagnosis of depression for patients diagnosed with dysphagia was approximately 76% greater than that for patients not diagnosed with dysphagia. The hazard of PSD diagnosis for women was about 67% higher than for men, while the hazard of diagnosis of depression for individuals with dual eligibility was approximately 40% higher than for those who did not have dual eligibility. Conversely, hazard decreased significantly by 2.5% with each year of age, suggesting that older stroke survivors are less likely to be diagnosed with depression. Finally, we found that the hazard of PSD diagnosis for white patients was 71% higher than for non-white patients, suggesting that white patients are at greater risk for diagnosis of depression than any other race; however, because of the imbalance in racial demographics in our

study population (white patients make up >80%), these findings should be interpreted cautiously.

We are unable to directly compare these results to analogous studies because, to our knowledge, there are no studies that have examined the hazard of PSD diagnosis in patients diagnosed with post-stroke dysphagia; therefore, our findings may be the first to establish that diagnosis of dysphagia has a highly significant effect on the hazard of diagnosis of depression after AIS during the first 90 days after discharge from the hospital. Nevertheless, we can compare our findings to the few published studies that have assessed hazard. For example, Aben et al. (2003) included female gender and age in their Cox regression analyses to assess the effect of cohort (stroke versus myocardial infarction) on the cumulative incidence of depression, and though they did not discuss the hazard of these variables explicitly, their results showed that, similar to our findings, the hazard of depression in the stroke cohort was significantly higher (about 60%) in women versus men. Contrary to our findings that with every year of age, the hazard of PSD diagnosis significantly decreased, age was not found to be a significant covariate in Aben et al.'s (2003) study. Likewise, Leentjens et al.'s (2006) findings that female gender was not significant contradicted our results that being female significantly increased the hazard of being diagnosed with depression after stroke. As with studies reporting the odds of PSD diagnosis, our findings are consistent with some results from studies examining hazard, yet contrary to others. As previously discussed in detail, the reasons

for these disparities may be variations in methodology, sample size, inclusion/exclusion criteria, diagnostic timing and tools, etc.

Section 6: Time to Depression Diagnosis

With regard to time to depression diagnosis, to our knowledge, there have been no previous studies that have examined time from initial stroke diagnosis to depression diagnosis in patients diagnosed with post-stroke dysphagia; thus, the present study appears to be the first on this specific topic. We found the mean time to depression diagnosis after stroke was 40 days for patients diagnosed with dysphagia and 34 days for patients not diagnosed with dysphagia. Although patients with a dysphagia diagnosis were diagnosed with depression later than patients without a dysphagia diagnosis on average, these findings were not significant. Nonetheless, we also found that patients with a post-stroke dysphagia diagnosis had a 1.5-fold higher likelihood of being diagnosed with depression in the last 15 days of the 90-day post-discharge follow-up period compared to those without a post-stroke dysphagia diagnosis.

Later Onset of PSD versus Later Diagnosis of PSD

The reason for our findings that patients with a diagnosis of dysphagia were diagnosed with depression later than those without a diagnosis of dysphagia could be that depression actually developed during the subacute, as opposed to the acute, phase after stroke, which is feasible given that the literature suggests the timing of PSD is variable among individuals and initial onset can occur between several days to years after stroke

(Conroy et al., 2020). Most studies report the highest rates of PSD within the first month to a year after stroke, with a decline in the subsequent 12 to 24 months thereafter (Conroy et al., 2020; Ostir et al., 2011; Towfighi et al., 2017). Additionally, patients with a diagnosis of post-stroke dysphagia often have higher stroke severity (Arnold et al., 2016) and greater functional limitations (Castagna et al., 2019) than those not diagnosed with post-stroke dysphagia, requiring continuation of care at an IPR facility or SNF after discharge. As a result, these patients could potentially develop later-onset PSD when transitioning from a medical facility where they received 24-hour care, to home, where they experience an abrupt discontinuation of constant care and reduced socialization.

Conversely, it is possible that PSD was present in patients diagnosed with dysphagia earlier than detected, but the diagnosis was delayed due to the previously stated reasons for underdiagnosis of PSD, such as barriers diagnosing patients with concurrent cognitive and/or language disorders and misclassification of depressive symptoms as stroke symptoms. Because PSD is associated with worse functional outcomes, increased disability, and higher mortality after stroke (Towfighi et al., 2018; Zhang et al., 2020), the timing of depression diagnosis is important for early identification and prompt intervention; however, optimal screening time after stroke is not known (Towfighi et al., 2018). Nevertheless, it is plausible that early and recurrent depression screenings starting during acute hospitalization would benefit those at risk for PSD.

Section 7: Aim 1 Limitations

Although retrospective, "big data" studies have many advantages, the use of large data sets with medical administrative data also have disadvantages and carry potential bias (Kaplan et al., 2014), which are the main reasons for the limitations of this study. First, because administrative data consists of medical and billing code sets and were not collected specifically for research purposes, crucial information and details about patients may be omitted, such as premorbid level of function (e.g., disability, dependence); diagnostic methods and severity (of dysphagia and depression); and behavioral, environmental, and social factors (Kaplan et al., 2014). For example, although we removed patients with a diagnosis of dysphagia or depression within 90 days prior to stroke from the data set, we cannot be sure that those patients did not have a prior history of or undiagnosed dysphagia or depression before our 90-day pre-stroke cutoff. Second, sampling bias limits the generalizability of the study results to the population actually represented in the data set (Kaplan et al., 2014), which in our case, limits generalizability to those 65 year of age and older who receive Medicare benefits and excludes stroke survivors younger than 65 and those who do not have Medicare. Third, coding errors and misclassification bias are recognized limitations in the use administrative data (Cohen et al., 2020), and since undercoding of dysphagia and depression is well-known (Cohen et al., 2020; Gonzalez-Fernandez et al., 2009), our findings may be conservative and the true population values are likely underestimated.

Aim 2 Discussion

Section 1: Brief Summary of Results

Objectives

Because claims data lack clinical details about disease severity, a proxy for severity is needed to adequately utilize and analyze administrative data (Gonzalez-Fernandez et al., 2009). To our knowledge, there is currently no method for post-stroke dysphagia severity classification for use with administrative data. Thus, we saw an opportunity to address this gap in the literature. Accordingly, our first objective for Aim 2 was to create a novel proxy index for dysphagia severity for use with administrative data (called the ADDSS). The second objective was to use this novel proxy index to stratify our sample based on inferred dysphagia severity and determine if post-stroke dysphagic patients with varying degrees of dysphagia severity had different PSD-related outcomes. Therefore, we examined if dysphagia severity, via the ADDSS, was related to differences in PSD diagnosis as well as time to PSD diagnosis within a 90-day post-discharge follow-up period in post-stroke dysphagic patients.

Hypotheses and Results

For hypothesis 1, we used a stable subset of ICD-10 dysphagia diagnosis and procedure codes to develop a clinically relevant, novel dysphagia severity index for use with administrative data – the ADDSS. Cluster validation subsequent to the development of the ADDSS revealed an interesting and unanticipated finding that dysphagia severity categories were not the same as stroke severity (NIHSS score) categories. (Additional

details in Section 3.) Then we applied the ADDSS to our data set to test hypothesis 2 and its sub-hypotheses, which we found were not supported by our data. We did not find that patients in different dysphagia severity groups had significantly different risk of PSD diagnosis after discharge (hypothesis 2), nor did we find a statistically significant difference in proportions of PSD diagnosis across dysphagia severity groups within the 90 days after discharge (hypothesis 2a). Furthermore, no significant effect was found between dysphagia severity and the odds of receiving a PSD diagnosis in the 90 days after discharge (hypothesis 2b). Lastly, the data did not support that post-stroke patients with a diagnosis of PSD and more severe dysphagia had a shorter time to first depression diagnosis compared to those with a diagnosis of PSD and less dysphagia severity (hypothesis 2c). These results are discussed in detail in Sections 4 and 5.

Section 2: Construct Validity of the ADDSS

Utility of the ADDSS

Large administrative databases are being used more often in dysphagia research, especially in studies of stroke (Bartlett & Thibeault, 2018). In a recent review by Bartlett and Thibeault (2018), the authors examined research articles that used administrative datasets or clinical registries to study dysphagia, and almost half of the articles focused on stroke. Thus, there is great value and importance in developing instruments specifically for use in administrative-level post-stroke dysphagia research (such as the ADDSS).

Because the ADDSS algorithm was shown to be valid and produced stable dysphagia severity clusters, it can be used in post-stroke dysphagia research when stratification by dysphagia severity is desired. It could also potentially be helpful in other aspects of post-stroke dysphagia research, such as epidemiologic post-stroke dysphagia incidence and prevalence reporting, identifying dysphagic subgroups (e.g., patients with dysphagia-related sequelae), and capturing the burden of post-stroke dysphagia (e.g., healthcare utilization and cost). Additionally, we developed the ADDSS and performed a subsequent subgroup sensitivity analysis with an inpatient population and then applied the ADDSS to an outpatient population – all of which revealed similar results. Therefore, we believe that the ADDSS may have utility in grouping post-stroke patients into disparate dysphagia severity groups in both inpatient and outpatient stroke populations as well; however, this should be further explored in future studies.

Other Administrative-Level Instruments

There are no other administrative-level post-stroke dysphagia severity classification instruments available to compare to the ADDSS; however, there other stroke severity instruments designed to be used with U.S. administrative data for which we may conduct indirect comparisons. For example, the Stroke Administrative Severity Index (SASI; Simpson et al., 2017) is a valid measure of stroke severity at hospital discharge for use with administrative claims data. Like the ADDSS, the SASI was developed using similar source data (the Medicare 5% LDS) and methods. That is, exploratory cluster analysis was used to group together patients who had similar International Classification of Diseases

[ICD] diagnosis and procedure codes (ICD-9 for the SASI and ICD-10 for the ADDSS) into distinct clusters – three stroke severity clusters for the SASI (mild, moderate, and severe) and three dysphagia severity clusters for the ADDSS (mild, moderate, and severe). Additionally, both the SASI and the ADDSS were based on the NIH Stroke Scale (NIHSS), which was used as the theoretical framework and for internal and external validation for the SASI and for construct validation of the dysphagia severity groups for the ADDSS.

Additional examples of stroke severity instruments for use with administrative data in stroke research are the Administrative Data Stroke Scale (ADSS) and the Administrative Stroke Outcome Variable (ASOV; Patel et al., 2021). The ADSS and ASOV were designed for use in population-wide studies – the ADSS measuring stroke severity at admission and the ASOV as an estimate for 90-day modified Rankin Scale (mRS). The ADSS was developed using the National Inpatient Sample (NIH), an all-payer U.S. national and regional inpatient database. Similar to our instrument (ADDSS) design, Patel et al. (2021) also used the NIHSS as a template for their ADSS and selected variables based on ICD-9 diagnostic and procedural codes as indicators of stroke severity. Instead of cluster analysis, the researchers used forward selection stepwise multivariable logistic regression to develop the ADSS. Then they used the ADSS model to predict poor functional outcome, which was defined using the ASOV as “good outcome” versus “bad outcome” to differentiate patients with minimal-to-moderate post-stroke disability from those with severe disability (Patel et al., 2021). To validate their instruments, the researchers used two separate cohorts for external validation.

These stroke severity instruments have similarities to our ADDSS in their implementation with administrative data, some comparable development methods, and their (potential) utility. The SASI, ADSS, and ASOV were designed to categorize stroke severity and can also be used to predict and answer questions about comorbidities. They have great utility in addressing the challenges of studying administrative claims data for stroke patients from which valuable information may be absent, such as admission and discharge NIHSS scores and 90-day mRS outcomes. They adjust for stroke severity differences in population-wide stroke studies to not only allow for comparisons with studies that do not use administrative data (e.g., clinical trials) but also to limit confounding of stroke severity in administrative-level studies. The ADDSS is a dysphagia-specific instrument for use with AIS patients with the purpose of categorizing patients into disparate dysphagia severity clusters. It also has potential for being used as a prediction tool and for answering questions about comorbidities. In future research, we not only plan to conduct reliability and validation studies with the ADDSS, but we also plan to further explore the utility of the ADDSS for predicting depression diagnosis in post-stroke dysphagic patients, such as how the ADDSS severity groups could be used to predict swallow function recovery in the acute hospital setting. For example, perhaps individuals with mild post-stroke dysphagia (per the ADDSS classification) may spontaneously recover swallow function without intervention, while those with moderate dysphagia may recover swallow function with minimal therapy, and individuals with severe dysphagia will recover swallow function with maximum therapeutic intervention (or recover only some swallow function or none at all). Although future studies are promising, currently, the

ADDSS is not yet a validated instrument. Thus, an important question is: Since there are already validated administrative-level stroke severity instruments available, could we use those to estimate dysphagia severity, instead of developing a dysphagia-specific index?

Section 3: Why is a Dysphagia-Specific Index Needed?

Association Between Stroke Severity and Dysphagia Severity

There is evidence in the literature that stroke severity is not only associated with dysphagia, but it is also predictive of dysphagia severity (De Stefano et al., 2021; Jeyaseelan et al., 2015; Khedr et al., 2021; Otto et al., 2016; Takizawa et al., 2016). Jeyaseelan et al. (2015) conducted a retrospective study of stroke patients in an inpatient acute rehabilitation unit to determine the utility of the NIHSS as a predictor for post-stroke dysphagia (via modified barium swallow study [MBSS] and/or radiographic evidence of aspiration pneumonia). The researchers found that the presence of dysphagia was significantly correlated with stroke severity, with the proportion of dysphagic patients generally increasing as NIHSS score increased (Jeyaseelan et al., 2015). An NIHSS score with a cut-off of >9 demonstrated sensitivity of 75%, specificity of 62%, positive predictive value (PPV) of 46%, and negative predictive value (NPV) of 85% and, therefore, was determined to be moderately predictive of dysphagia (Jeyaseelan et al., 2015). In a retrospective study at a tertiary hospital, De Stefano et al. (2021) examined factors that contributed to the severity and persistence of dysphagia in subacute stroke patients. The researchers found that an admission NIHSS score of >12 was significantly predictive of moderate or severe dysphagia (measured by the American Speech-

Language-Hearing Association (ASHA) National Outcome Measurement System (NOMS) score) after 60 days (De Stefano et al., 2021). Otto et al.'s (2016) cross-sectional, prospective study of acute stroke patients demonstrated a statistically significant correlation between stroke severity (NIHSS score) and dysphagia severity (via the Protocol for Investigation of Oropharyngeal Dysphagia in Adults), with an NIHSS score of 0-6 (minor stroke, per the researchers' definition) correlated with normal swallowing and mild dysphagia and an NIHSS score of ≥16 (severe stroke, per the researchers' definition) correlated with severe dysphagia. Although there is some evidence to support the NIHSS being potentially predictive of post-stroke dysphagia severity, adequate sensitivity, validity, and reliability have not yet been demonstrated for its use as a prediction tool for dysphagia severity. For these reasons, there is not sufficient evidence to support the use of a stroke severity instrument to estimate dysphagia severity in research with administrative data at this time.

Discordance Between Stroke Severity and Dysphagia Severity

In discordance with the aforementioned literature, our study results showed that dysphagia severity (ADDSS) did not coincide with stroke severity (NIHSS score). That is, our dysphagia severity cluster classification did not extend to stroke severity classification. For example, we found that patients in the mild ADDSS group primarily had cases of cognitive impairment but showed little evidence of feeding or nutrition problems (important indicators of dysphagia) and demonstrated almost no indication of respiratory compromise. Accordingly, we presumed that patients in the mild ADDSS group would

also present with mild stroke; however, that was not supported by the data. Conversely, the mild ADDSS group contained 63% of the total attributes (dysphagia indicator variables constructed from dysphagia-related ICD-10 diagnosis and procedure codes in the cluster analysis), which are suggestive of stroke-related illness. Additionally, patients in this group had NIHSS scores indicative of moderate stroke (mean, 10.08; SD, 7.93). Thus, we determined that patients in the mild ADDSS group actually had moderate stroke.

Patients in the moderate ADDSS group had the most cases of respiratory compromise compared to the other clusters, including such attributes as respiratory problems, aspiration pneumonia, intubation, and tracheotomy/tracheostomy; however, dysphagia severity was judged not by aspiration pneumonia, which is known to be difficult to differentiate from other pneumonia types and is often misdiagnosed (Son et al., 2017), but by feeding device placement, which is a (reliable) key marker for dysphagia severity. Because the feeding device placement mean (the metric by which we graded the clusters into qualitative categories) was the second highest out of all three clusters, we determined that patients in this group had moderate dysphagia severity. Again, we presumed that patients in the moderate ADDSS group would also present with moderate stroke; however, that was not supported by the data. This group contained 100% of the total attributes, suggesting that patients were very ill, and patients had NIHSS scores indicative of moderate/severe stroke (mean, 16.23; SD, 8.18). Thus, we determined that patients in the moderate ADDSS group actually had moderate/severe stroke. It seemed

that stroke severity indicators captured respiratory issues associated with respiratory compromise and aspiration pneumonia in these patients but not dysphagia. This is further supported by intubation in this cluster being likely driven by diagnoses of respiratory conditions, not dysphagia severity, given the overwhelming presence (and higher means) of respiratory compromise attributes versus feeding/nutrition attributes.

Patients in the severe ADDSS group demonstrated dysphagia severity in the setting of alternative nutrition with the highest means for feeding device placement (primary marker for dysphagia), malnutrition, and dehydration compared to the other clusters. Accordingly, we presumed that patients in the severe ADDSS group would also present with severe stroke; however, that was not supported by the data. This group also showed evidence of aspiration pneumonia and cognitive impairment and contained 75% of the total attributes, suggesting that patients in this group had substantial stroke-related illness; however, patients in the severe ADDSS group had NIHSS scores indicative of moderate stroke (mean, 13.51; SD, 7.78). Thus, we determined that patients in the severe ADDSS group actually had moderate, not severe, stroke.

Because of the incongruity between NIHSS scores and ADDSS clusters found in this study, it is important to recognize that stroke severity and dysphagia severity are not synonymous. For this reason, when conducting (administrative-level) dysphagia severity research, general stroke severity instrument instruments should not be used when the outcome of interest is dysphagia-specific.

General Versus Disease-Specific Instruments

There are advantages and disadvantages to both general (generic) and disease-/condition-specific instruments that measure health-related outcomes. For example, in QOL scales used to measure health related QOL (HRQOL), which may include outcome measures like patient perception, presence/absence of symptoms, and/or functional limitations (e.g., physical, psychosocial, etc.; Timmerman et al., 2014), general instruments are advantageous because of their broader content and applicability across diverse clinical populations. This allows for comparisons across diseases/conditions; however, because general instruments were designed to allow for generalizability, they lack specificity. Conversely, disease-specific instruments, which are designed for use with specific patient populations, have the benefit of measuring more specific symptoms, resulting in increased responsiveness and clinical utility compared to general QOL instruments (Hobart et al., 2002; Ware et al., 2016). The main disadvantage of disease-specific instruments is that they cannot be used or compared across diseases/conditions.

An example of a general (generic) instrument is the Centers of Disease Control and Prevention HRQOL 14-Item Measure (CDC HRQOL–14 Measure), which is a population measure for HRQOL that consists of broad questions, such as perceived health status, activity limitations, pain, depression, anxiety, sleeplessness, etc. (Hennessy et al., 1994; Moriarty et al., 2003), and can be used with a variety of populations. Although it has many beneficial applications for general use, its utility is not adequate when assessing diagnostic specific HRQOL. An example of a disease-/condition-specific instrument is the

Stroke Specific Quality of Life scale (SS-QOL), which is a well-known assessment of HRQOL for patients with stroke (Williams et al., 1999). The SS-QOL can be used across patients with various types of stroke; however, it was not designed for use to measure outcomes about specific stroke-related diagnoses. It measures post-stroke HRQOL using 12 domains, including energy, upper extremity function, work/productivity, mood, self-care, social roles, family roles, vision, language, thinking, and personality. Although this instrument was specifically designed for use with stroke survivors, there is no domain for dysphagia, which is a common sequela of stroke. The only items that are remotely related to dysphagia are under the Self-Care domain; however, those items involve assistance preparing or cutting food, not the act of eating, drink, or swallowing. Thus, even though SS-QOL is a disease-/condition-specific instrument designed for use in stroke patients, its use would not be appropriate for post-stroke dysphagic patients if the outcomes of interest are dysphagia-specific. Another QOL instrument that was developed based on the SS-QOL is the Stroke and Aphasia Quality of Life Scale (SAQOL-39), which was designed for stroke survivors with long-term aphasia (Hilari et al., 2003). The disease-/condition-specific SAQOL-39 has four domains, including physical, psychosocial, communication, and energy, with items adapted from the original SS-QOL specifically for individuals with aphasia. To improve content validity, the SAQOL-39 also has four additional items (not part of the SS-QOL) related to speech, language, and cognitive difficulties. Similar to the SAQOL-39, there is a dysphagia-specific QOL scale called the Swallowing Quality of Life (SWAL-QOL), which is a measure of QOL in individuals with swallowing disorders (McHorney et al., 2000a, 2000b, 2002). The SWAL-QOL has 10

domains, including burden, eating duration, eating desire, food selection, communication, fear, mental health, social, sleep, and fatigue, that are specific to swallowing/dysphagia.

We know that it is vital to use appropriate clinical assessments in patient populations for which they were designed to maintain the validity and interpretability of the instrument. For instance, in clinical research, investigators would not use a general QOL assessment to examine QOL in dysphagic patients, given that there is a swallowing-specific scale available, such as the SWAL-QOL. Likewise, in research involving administrative data, disease-specific instruments should be utilized (when available) over general instruments to ensure the most rigorous results.

Need for Dysphagia-Specific Instruments for Administrative Data

Administrative claims data reflect clinical practice; however, crucial information required to discern dysphagia severity in post-stroke patients, such as dysphagia diagnostic instrument results, oral health status, and diet texture and liquid consistency levels, is not captured. For this reason, it is compulsory that an appropriate administrative-level, dysphagia-specific instrument be developed for use with post-stroke patients. To this end, we have proposed the ADDSS in lieu of the few other general stroke severity administrative-level instruments available.

The ADDSS also has potential for utility in research that combines administrative data with clinical data. For example, the ADDSS severity levels could be used adjunctively with data collected clinically from the Functional Oral Intake Scale (FOIS), which measures change in functional eating abilities over time in post-stroke patients (Crary et al., 2005). The categorization of the seven levels of the FOIS lend themselves to the ADDSS severity levels, such that FOIS levels 1-2 (nothing by mouth to feeding tube dependent with minimal attempts with food/liquid) correspond to ADDSS severe dysphagia severity, FOIS levels 3-4 (feeding tube dependent with consistent oral intake to total oral diet of single consistency) correspond to ADDSS moderate dysphagia severity, and FOIS levels 5-7 (total oral diet with multiple consistencies, requiring special preparation or compensations to total oral diet with no restrictions) correspond to ADDSS mild dysphagia severity. The ADDSS severity levels may also be suitable in conjunction with clinical data from the International Dysphagia Diet Standardisation Initiative (IDDSI) levels (Cichero et al., 2017), such that IDDSI 7 (regular/easy to chew), 6 (soft and bite size), 0 (thin), and 1 (slightly thick) correspond to ADDSS mild severity; IDDSI 5 (minced & moist) and IDDSI 2 (mildly thick) correspond to ADDSS moderate severity; and IDDSI 3 (liquidised/moderately thick) and IDDSI 4 (pureed) correspond to ADDSS severe severity. The ADDSS could also potentially have applicability for use with clinical data from the Eating Assessment Tool (EAT-10), which estimates initial dysphagia severity and monitors treatment response (Belafsky et al. 2008). The next steps in this line of research are to conduct validity and reliability testing of the ADDSS for its use in administrative data research to classify post-stroke dysphagia severity.

Section 4: Diagnosis of PSD by Dysphagia Severity

To our knowledge, there have been no previous studies that have examined the association between dysphagia severity and depression diagnosis in patients diagnosed with post-stroke dysphagia; thus, the present study appears to be the first on this specific topic. We hypothesized that patients in different dysphagia severity groups would have different risk of PSD diagnosis after discharge (hypothesis 2); however, our results were not supportive of this hypothesis. We found no statistically significant difference in risk of PSD diagnosis after discharge by dysphagia severity. Thus, our hypothesis that post-stroke patients with more severe dysphagia would have greater odds of PSD diagnosis within the 90 days after discharge (2b) was also not supported. Additionally, we hypothesized that post-stroke patients with more severe dysphagia would have a greater proportion of PSD diagnosis within the 90 days after discharge (2a); however, we found that the proportions of patients diagnosed with PSD across all three dysphagia severity groups were very similar (17%, 14%, and 16%, p=0.9016, respectively), revealing no statistically significant difference. Thus, the evidence was not supportive of this hypothesis either.

Although we were unable to directly compare our results to analogous studies because, to our knowledge, there are no other administrative-level studies of post-stroke dysphagia and PSD in the literature, we were able to make general comparisons to the few non-stroke clinical studies that have examined dysphagia severity and depression. For example, Nguyen et al. (2005) conducted a retrospective study of patients treated for

head-and-neck cancer (HNC) with dysphagia at a Veterans Affairs (VA) hospital and found that dysphagia severity (measured by MBSS) was significantly and positively correlated with depression (measured by the Hospital Anxiety-Depression Scale-Depression [HADS-D]), with patients with moderate to severe dysphagia demonstrating greater depression scores than those with mild dysphagia. Our results that post-stroke dysphagia severity was not significantly associated with depression diagnosis were dissimilar to Nguyen et al.'s (2005) findings. The discordance in findings is primarily a result of the limitations in comparing prospective versus retrospective studies (e.g., study methodology, sample sizes, diagnostic assessments used, timing of assessments, etc.) and comparing disparate patient populations (stroke versus HNC). In a prospective study of patients with HNC and dysphagia at an outpatient clinic, Krebbers et al. (2020) found that the presence of aspiration during fiberoptic endoscopic evaluation of swallowing (FEES), signifying increased dysphagia severity, was significantly associated with lower depression scores (measured by the HADS-D). That is, patients who presented with more severe dysphagia reported fewer symptoms of depression than those who presented with less severe dysphagia. Our findings were contradictory to Krebbers et al.'s (2020) results in that we found no significant association between dysphagia severity and depression. The reasons for discordance between Krebbers et al.'s (2020) and our findings are likely the same as with Nguyen et al.'s (2005) study findings. Additionally, the discrepancy in our respective results could also be heavily influenced by our disparate patient populations and time intervals. Krebbers and colleagues (2020) examined patients at least six months after their HNC treatments who were in total remission. It is feasible that, in time, patients

who are medically stable and disease-free may adjust to their dysphagia symptoms or limitations (Krebbers et al., 2020), such as the patients who had HNC, and experience/report fewer symptoms of depression. In another prospective study, Verdonschot et al. (2016) studied patients with dysphagia at an otorhinolaryngology outpatient clinic to determine the relationship between dysphagia severity and affective symptoms. The patient sample included individuals with HNC at least six months post-treatment, patients with a neurologic diagnosis (e.g., Parkinson's disease, stroke) considered stable and/or who had received stable medication management for at least three months, and patients with other medical diagnoses (e.g., Zenker's diverticulum, cervical spine degeneration; Verdonschot et al., 2016). The researchers did not find any significant associations between dysphagia severity via FEES and clinically relevant symptoms of depression (measured by HADS-D; Verdonschot et al., 2016), which was consistent with our findings. Nevertheless, there were limitations to Verdonschot et al.'s (2016) study that could have affected their results. For example, the researchers used FEES to measure dysphagia severity; however, they proposed that if another diagnostic instrument had been used, such as MBSS, manometry, or electromyography, dysphagia severity results may have been different (Verdonschot et al., 2016). Furthermore, some literature suggests that the use of the HADS-D to measure depressive symptoms has disadvantages, such as low sensitivity and specificity for detecting depressive symptoms in certain populations of older adults (Edelstein et al., 2010). Other study limitations reported by Verdonschot et al. (2016) included methodologic issues, such as heterogeneity of the study sample and a small sample size, resulting in small subgroup

sizes, which limited the types of subgroup analyses that could be conducted. Finally, because of the underlying association between HNC and neurologic diseases with affective symptoms, researchers could not definitively attribute depressive symptoms to dysphagia alone (Verdonschot et al., 2016). For these reasons, the results of Verdonschot et al.'s (2016) study should be interpreted with caution.

There is evidence in the literature, and from Aim 1 of this study, to support that dysphagia is associated with depression (Dziewas, et al., 2017; Holland, 2011; Verdonschot et al., 2013, 2017); however, there is a paucity of studies examining the relationship between dysphagia severity and depression. For this reason, we cannot yet draw definitive conclusions from the results of this study. We can, however, consider the reasons why we may have found no association between post-stroke dysphagia severity and diagnosis of PSD in the 90 days after discharge from the hospital. The first possibility is that there may not be a relationship between dysphagia severity and depression, which is consistent with Verdonschot et al.'s (2016) findings, and that the association between dysphagia and depression is irrespective of dysphagia severity. That is, having dysphagia is what matters most in relation to depression, despite severity. The second potential explanation of our findings is timing. Our study time period was limited to the 90 days after discharge, and we know from the literature that timing of PSD is variable among individuals, with initial onset occurring between several days to years after stroke (Conroy et al., 2020). Therefore, it is feasible that patients without a depression diagnosis presented with depression at a later time that occurred outside of this study, which we

were not able to capture. The third possible reason for our results is that there is, in fact, an effect of dysphagia severity on PSD diagnosis, which would be consistent with Nguyen et al.'s (2005) and Krebbers et al.'s (2020) findings; however, underdiagnosis and undercoding of dysphagia and PSD, which are well-documented phenomena, could have been barriers in detecting the true proportions of patients with diagnoses of post-stroke dysphagia and PSD (Cohen et al., 2020; Dar et al., 2017; Gonzalez-Fernandez et al., 2008).

Section 5: Diagnosis of PSD by Dysphagia Severity and Time

With regard to time to depression diagnosis, to our knowledge, there have been no previous studies that have examined time from initial stroke diagnosis to depression diagnosis stratified by dysphagia severity in patients diagnosed with post-stroke dysphagia; thus, the present study appears to be the first on this topic. We hypothesized that post-stroke patients with more severe dysphagia and a diagnosis of PSD would have a shorter time to first depression diagnosis (2c); however, found the (statistically significant) mean time to depression diagnosis after stroke was 39 days for patients with mild dysphagia, 63 days for patients with moderate dysphagia, and 70 days for patients with severe dysphagia. Patients with mild dysphagia were diagnosed with PSD sooner on average than the patients with more severe dysphagia; thus, the evidence was not supportive of our hypothesis (2c). Additionally, we found that 50% of patients with mild dysphagia had a diagnosis of depression a little more than one month after discharge, while 50% of patients with moderate or severe dysphagia had a diagnosis of depression almost at the end of the 90-day post-discharge follow-up period.

A reason for our findings that patients with mild dysphagia were diagnosed with PSD sooner than those with more severe dysphagia after discharge could be due to healthcare providers' focus on medical, not psychological, conditions in patients with greater dysphagia severity, given the risks of serious complications, such as malnutrition, dehydration, aspiration pneumonia, compromised overall health, and mortality (ASHA, n.d.). Thus, providers could potentially overlook the symptoms of depression in these more severely dysphagic patients, while depressive symptoms in patients with less dysphagia severity, who may be considered at lower risk for complications, more easily attract the attention of healthcare providers. Another explanation of our findings could be a result of clinician training and experience compounded by discharge disposition. Depressive symptoms can be challenging to recognize by untrained and/or inexperienced healthcare providers because they typically present as somatic (e.g., fatigue) and/or other affective symptoms (e.g., guilt, worthlessness, lack of interest) in older adults, not depressed mood, which may be mistakenly attributed to stroke or cognitive impairment, instead of PSD (Dar et al., 2017; Lökk & Delbari, 2010; VanItallie, 2005). Furthermore, discharge disposition may also play a role in our results in that patients with mild dysphagia may be discharged to a location (e.g., IPR facility, home with home health) where they may receive attention from healthcare providers who have adequate training to recognize the symptoms of PSD, such as physical medicine and rehabilitation (PM&R) physicians or neuropsychologists at an IPR facility or a patient's primary care physician who knows their baseline function if discharged home. Conversely, patients with more severe dysphagia, potentially requiring alternative nutrition via feeding tube, may be

discharged to a SNF where there may not be healthcare providers trained in recognizing symptoms of PSD, which may explain why these patients were not diagnosed with depression on average until the end of the 90-day post-discharge follow-up period.

Another reason for our findings could be the time interval of this study, which was within the 90 days after discharge from the acute hospital. Since “early” onset of PSD is defined as symptoms of PSD within the first three months after stroke, and “late” onset is considered any time subsequently (Lökk & Delbari, 2010), it is possible that patients in this study who were not diagnosed with depression experienced late onset PSD outside of the study time frame, in which case, their diagnoses were not captured.

The final reason for our study results could be the well-known problem of undercoding and underdiagnosis of dysphagia and depression in administrative data (Cohen et al., 2020; Conroy et al., 2020; Dziewas, et al., 2017; Gonzalez-Fernandez et al., 2008; Labeit et al., 2018; Rofes et al., 2011; Takizawa et al., 2016; Starkstein & Robinson, 1989), which may underestimate the true population values. Undercoding and underdiagnosis of dysphagia are due to a number of factors, including lack of available dysphagia specialists (speech-language pathologists [SLPs]), limited access to diagnostic equipment or resources in certain medical settings, lack of consensus for which patients require dysphagia screening, and use of inappropriate diagnostic tools with varying sensitivities for detecting dysphagia (Dziewas, et al., 2017; Labeit et al., 2018; Rofes et al., 2011; Takizawa et al., 2016). Similarly, undercoding and underdiagnosis of depression are due

to factors, such as lack of healthcare provider training/experience, misclassification of symptoms of depression in the setting of post-stroke cognitive and/or language impairments and use of screening tools with inadequate sensitivity for detecting depression (Conroy et al., 2020; Starkstein & Robinson, 1989; Williams, 2005).

Section 6: Aim 2 Limitations

We had the same limitations for Aim 2 as we had for Aim 1, with another example of key information missing from administrative data being the lack specific medical codes for important dysphagia-related considerations, such as diet texture, liquid consistency, edentulous status, etc., which would be advantageous in a more robust classification of dysphagia severity clusters. Additionally, using a subset of patients who had documented NIHSS scores for Aim 2 had disadvantages in that (1) it substantially reduced our sample size for Aim 2, and (2) it introduced bias, as not all facilities record the NIHSS in practice, particularly not the smaller community or rural hospitals; therefore, patient data containing NIHSS scores may disproportionately represent patients from large, comprehensive stroke centers. Furthermore, cluster analysis is typically conducted on large sample sizes, but our NIHSS sample size was much smaller than our original sample size, potentially yielding less robust results. A future ADDSS validation study should be conducted with a larger sample size.

Aim 3 Discussion

Section 1: Brief Summary of Results

Objectives

Our objective was to compare the mean healthcare costs in post-stroke dysphagic patients with and without a depression diagnosis in the 90-day follow-up period after discharge from the acute hospital. Additionally, we applied the ADDSS to our data set to analyze post-discharge costs in patients diagnosed with depression, stratified by dysphagia severity.

Hypotheses and Results

We studied 359 Medicare beneficiaries hospitalized for AIS with a secondary diagnosis of post-stroke dysphagia and examined their healthcare costs over a 90-day post-discharge period in 2017. Fifteen percent of post-stroke dysphagic patients had a diagnosis of depression. Consistent with our Aim 3 hypothesis, we found that dysphagic patients with a PSD diagnosis had greater total healthcare costs in the 90 days after discharge than dysphagic patients without a PSD diagnosis. Stratifying for dysphagia severity using the ADDSS revealed the same results, that patients with depression and dysphagia (irrespective of dysphagia severity) incurred higher total healthcare costs in the 90 days after discharge compared to dysphagic patients without depression, with an unadjusted additional cost of $12,667. Furthermore, we found that stroke severity and dysphagia severity significantly contributed to the variations in cost, as seen in an increase in unadjusted marginal cost difference from $12,667 to $15,556 (after controlling for

dysphagia severity and stroke severity). Additionally, we found that the presence of depression resulted in a 36% increase in cost after controlling for dysphagia severity and stroke severity. These results are discussed in detail below.

Section 2: Cost Analysis

Unadjusted Cost

When examining unadjusted total cost by dysphagia severity groups and depression diagnosis, we found that patients with mild and severe dysphagia with a depression diagnosis incurred higher mean total costs ($15,914 and $11,680, respectively) than those without a depression diagnosis in the same dysphagia severity groups, while those with moderate dysphagia and a depression diagnosis incurred $316 lower mean total costs compared to patients with moderate dysphagia without a depression diagnosis. We also found that patients with moderate dysphagia had higher unadjusted mean inpatient costs after discharge than those with mild or severe dysphagia, meaning that patients with moderate dysphagia had more post-discharge readmissions to the acute hospital and/or inpatient rehabilitation admissions.

Although counterintuitive at first glance, these findings are compatible with the medical characteristics of patients in the moderate dysphagia severity group. These patients had moderate/severe stroke severity (the highest stroke severity of the three dysphagia groups) and were very ill as evidenced by the many comorbidities/complications in this group, including cognitive impairment, malnutrition, dehydration, and feeding tube use.

In addition, patients in the moderate dysphagia group demonstrated the highest proportions of respiratory comorbidities, including intubation and tracheotomy/tracheostomy. Thus, the higher post-discharge inpatient costs for acute hospital readmissions were likely driven by their stroke severity (with greater stroke severity a predictor for worse outcomes; Adams et al., 1999) and serious respiratory issues. Furthermore, because this group had moderate/severe stroke severity, likely resulting in greater impairment and disability, they presumably required more intensive rehabilitation. Accordingly, this group had the largest proportion of discharge to IPR facilities compared to the mild and severe dysphagia groups, which also contributed to their higher post-discharge inpatient costs. Conversely, we did not find a notable difference in mean total costs between patients with and without depression in the moderate dysphagia group. The reason for this is likely due to cost of care being primarily dictated by moderate/severe stroke severity and respiratory complications, which may have obscured any depression-related costs.

Adjusted Cost

When measuring the effect of PSD and dysphagia severity in combination on total 90-day post-discharge cost, we found that having mild dysphagia with a PSD diagnosis was significantly associated with higher total 90-day costs and that stroke severity had a significant effect on cost. Controlling for stroke severity, the marginal cost difference was $15,914 higher for patients with mild dysphagia and a diagnosis of depression compared to those with mild dysphagia without a diagnosis of depression, which supported our

hypothesis that patients with post-stroke dysphagia and PSD with incur greater healthcare costs than post-stroke dysphagic patients without PSD. These findings are also in line with our findings from Aim 2 in which patients with mild dysphagia were diagnosed with PSD sooner than those with moderate or severe dysphagia. Thus, it is logical that patients with mild dysphagia, who were diagnosed with PSD early in the 90-day post-discharge follow-up window and likely received treatment for depression earlier in the post-discharge follow-up period, would incur higher post-discharge costs than those with mild dysphagia without the addition disease burden and those with more severe dysphagia severity, who were not diagnosed with PSD until much later in the 90-day post-discharge window. It is important to note that the dysphagia severity groups had an unequal number of observations for each cluster (mild: n=266, moderate: n=42, and severe: n=51), which could explain why associations between depression diagnosis and moderate and severe dysphagia severity, respectively, did not reach statistical significance, despite having similar directionality as the significant result.

To moderate the effect of the small number of observations in the moderate and severe dysphagia severity clusters and better understand the cost differences between the mild dysphagia and moderate and severe dysphagia groups, we “collapsed” the moderate and severe categories into one group, creating a dichotomized variable, “mild” (patients classified as having mild dysphagia severity) versus “not mild” (patients classified as having moderate or severe dysphagia severity), which resulted in 266 observations for the “mild” group and 93 observations for the “not mild” group. For our final result, when

assessing the cost differences between patients stratified by two severity groups (mild versus not mild), we found that depression, moderate or severe dysphagia severity, and stroke severity all had significant effects on cost. When we controlled for dysphagia severity and stroke severity, the marginal cost difference for dysphagic patients with a diagnosis of depression was $10,745 higher than for those without depression. These finding may be more intuitive than our previous findings in that it may be more feasible for patients with both greater dysphagia severity and greater stroke severity, along with their respective comorbidities and complications, to incur higher mean total healthcare costs than patients with mild dysphagia.

Related Research

Although there are no other studies that have examined 90-day post-discharge costs in dysphagic patients with PSD, there are similar studies by which to make general comparisons. For example, in a recent systematic review by Marin et al. (2020), the authors examined healthcare costs associated with post-stroke dysphagia and related complications and found evidence that patients diagnosed with dysphagia after stroke incurred higher costs than patients not diagnosed with dysphagia after stroke. There were very few studies that assessed post-discharge cost; however, the authors found two that examined healthcare costs after discharge from the acute hospital. One study by Bonilha and colleagues (2014) examined the one-year cost associated with post-stroke dysphagia, while the other study by Gomes and colleagues (2016) examined the predictive ability of the Malnutrition Universal Screening Tool (MUST) on stroke

outcomes, including risk of malnutrition and hospitalization costs. Gomes et al. (2016) prospectively recruited patients over the age of 18 with a diagnosis of ischemic or hemorrhagic stroke from two hyperacute stroke units in London and assessed all hospitalization costs during a six-month period after stroke (Gomes et al., 2016). Gomes et al. (2020) found an increase in costs from patients with low risk of malnutrition (via MUST) to patients with high risk of malnutrition, from £4,920 (approximately $8,780 [USD, 2019]) to £8,720 (approximately $15,560 [USD, 2019]), respectively (Marin et al., 2020, p. 11). Furthermore, the researchers reported 77% higher median costs for patients with high risk of malnutrition compared to those with low risk of malnutrition (Gomes et al., 2020). Gomes et al. (2020) did not directly link malnutrition risk to post-stroke dysphagia as they did not formally assess dysphagia; however, results of "inadequate swallow" from a bedside nursing swallow screen were reported. The researchers found that patients with high risk of malnutrition were more likely to have "inadequate swallow" (Gomes et al., 2020), indicating possible dysphagia. Thus, even though higher malnutrition costs were not directly attributed to dysphagia, it is feasible that because malnutrition in patients after stroke is a common (and serious) complication of post-stroke dysphagia (Foley et al., 2009), higher healthcare costs could have potentially been a consequence of dysphagia-related malnutrition. Although we cannot directly compare our results to Gomes et al.'s (2020) findings, there appears to be a similar inclination in directionality of the association between post stroke dysphagia-related diagnoses and higher healthcare costs.

With regard to depression, stroke survivors with PSD generally have greater healthcare utilization (Jia et al., 2006); therefore, higher healthcare costs would be expected in this patient population. Again, to our knowledge, there are no other studies that examined 90-day post-discharge costs in dysphagic patients with PSD; however, we can make general comparisons to similar studies. Husaini, et al. (2013) conducted a study retrospectively examining the effect of depression on hospitalization costs in stroke patients using data from the 2008 Tennessee Hospital Discharge Data System and found that depressive symptoms were associated with increased healthcare costs. The researchers reported that stroke patients with depression had approximately 63% higher mean hospitalization costs compared to the stroke only cohort ($77,864 versus $47,790, respectively; Husaini, et al., 2013). In another study, Chinthammit et al. (2017) retrospectively examined the impact of co-occurring conditions on total and component healthcare expenditures (e.g., inpatient, outpatient, emergency room (ER), prescription drugs, home health, and other) in stroke survivors versus a non-stroke matched control group using 2002-2012 Medical Expenditure Panel Survey (MEPS) data. The researchers found that total expenditures were significantly higher in stroke patients with certain concurrent conditions, such as depression, compared to matched controls ($23,122 versus $19,705, respectively; Chinthammit et al., 2017). They also found that stroke patients with depression had significantly greater inpatient expenditures compared to matched controls ($8,878 versus $6,736, respectively; Chinthammit et al., 2017).

Although differences in methodologies, patient populations (i.e., stroke type), study timeframes, and primary outcomes among the studies discussed do not allow for direct comparisons with our study results, there is a clear trend in higher healthcare costs associated with the two separate stroke sequelae, dysphagia and depression, respectively. Thus, it is reasonable to suggest that post-stroke dysphagic patients with PSD would also incur higher healthcare costs than post-stroke dysphagic patients without PSD, which is what we found in this study. The increase in healthcare costs is likely due to increased healthcare utilization as a result of the higher healthcare utilization by patients diagnosed with depression after stroke, which have previously not been examined. This study is a starting point towards understanding the healthcare costs associated with both post-stroke dysphagia and PSD. Its value is not only in establishing these costs but also in highlighting the need for earlier detection and intervention for patients with post-stroke dysphagia and PSD with the goals of providing appropriate care for patients and potentially easing the economic burden of these co-occurring conditions.

Section 3: Aim 3 Limitations

We had the same limitations for Aim 3 as we had for Aims 1 and 2, with some additions. First, the administrative files from which we extracted our claims data did not provide itemized cost; therefore, we did not have access to medication cost and could not assess the cost of pharmacological treatment for PSD. Second, the small sample sizes in our moderate and severe dysphagia severity subgroups could have been prohibitive in observing an effect in those groups, thus, biasing our findings.

CHAPTER 6: CONCLUSION

This research has contributed to the existing dysphagia body of knowledge by examining a rarely studied population, post-stroke dysphagic patients with depression, and revealing new insights into the relationship between post-stroke dysphagia and PSD. Furthermore, this study has addressed a gap in the literature by providing a novel method for dysphagia severity classification in stroke patients for use with administrative-level data, which previously did not exist.

Results of this study demonstrated evidence of an association between PSD and post-stroke dysphagia. That is, patients with post-stroke dysphagia had significantly greater odds and hazard of being diagnosed with PSD within 90 days after discharge, and patients diagnosed with both dysphagia and PSD incurred higher post-discharge healthcare costs. In the application of our novel dysphagia severity index (the ADDSS), we found that patients with less dysphagia severity were diagnosed with PSD sooner after discharge than patients with greater dysphagia severity, which highlighted the need for early and recurrent depression screening for post-stroke patients, particularly, with greater dysphagia severity. We also found that (counterintuitively) greater dysphagia severity did not increase the odds of PSD diagnosis after discharge, which we proposed could be due to several reasons, one of which could be that having dysphagia matters the most in

relation to PSD, regardless of severity. Another reason could be due to the well-known problems of underdiagnosis and undercoding of dysphagia and depression, which could have been barriers in detecting the true proportions of patients with diagnoses of post-stroke dysphagia and PSD, especially in patients with more severe dysphagia, in which depressive symptoms can be more challenging to detect and also due to healthcare providers' focus on life-sustaining functions over psychological manifestations in the acute post-stroke setting. Furthermore, we discovered an interesting and unexpected finding that (in discordance with some literature) dysphagia severity categories were not the same as stroke severity categories, which has implications for administrative-level post-stroke dysphagia related research and the methodologies used to classify dysphagia severity. These findings also highlight the importance of not using stroke severity as a proxy for dysphagia severity in stroke research.

The foundational knowledge gained from this study is a starting point to understanding the influence of PSD on post-stroke dysphagia in pursuit of improved identification of and earlier intervention for dysphagic patients with depression after stroke. Furthermore, the glaring problems of underdetection and underdiagnosis of dysphagia and PSD discussed in this study underscore the importance of active and continued monitoring for depressive symptoms in this patient population and the need for implementation of adjunctive screening for depressive symptoms along with post-stroke dysphagia screening and/or assessment. Additionally, the potential utility for use of the ADDSS not only in administrative-level research but also in conjunction with additional data sources,

such as randomized clinical trials or prospective cohort studies, guides the next steps in this line of research, which is to validate the ADDSS. Finally, despite the prevalence of this patient population, the cost of care in patients with post-stroke dysphagia and depression has not been examined prior to this study; therefore, future studies to quantify healthcare costs of acute and chronic post-stroke dysphagic patients with depression are warranted.

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APPENDICES

Appendix 1: ICD-10-CM Codes

Variable	ICD-10 Code	Description
Aspiration pneumonia	J13, J14, J15.0, J15.1, J15.20, J15.211, J15.212, J15.29, J15.3, J15.4, J15.5, J15.6, J15.8, J18.9, J69.0	Due to: Streptococcus pneumoniae; Hemophilus influenzae; Klebsiella pneumoniae; Pseudomonas; Staphylococcus, unspecified; Methicillin susceptible Staphylococcus aureus; Methicillin resistant Staphylococcus aureus; Other staphylococcus; Streptococcus, group B; Other streptococci; Escherichia coli; Other Gram-negative bacteria; Other specified bacteria; Unspecified organism; Pneumonitis due to inhalation of food and vomit
Aspiration of food	T17.220, T17.320, T17.520, T17.820, T17.920, T17.420	Food in pharynx causing asphyxiation; Food in larynx causing asphyxiation; Food in bronchus causing asphyxiation; Food in other parts of respiratory tract causing asphyxiation; Food in respiratory tract, part unspecified, causing asphyxiation; Food in trachea causing asphyxiation
Cognitive impairment	I69.01, I69.11, I69.21, I69.31, I69.81, I69.91, G31.84, G31.9, R41.4, R41.81, R41.82, R41.9, S06, F01, F02, F03, F68.8	Cognitive deficits following: Nontraumatic subarachnoid hemorrhage; Nontraumatic intracerebral hemorrhage; Other nontraumatic intracranial hemorrhage; Cerebral infarction; Other cerebrovascular disease; Unspecified cerebrovascular disease; Mild cognitive impairment; Degenerative disease of nervous system, unspecified; Neurologic neglect syndrome; Age-related cognitive decline; Altered mental status, unspecified; Unspecified symptoms and signs involving cognitive functions and awareness; Intracranial injury; Vascular dementia; Dementia in other diseases classified elsewhere; Unspecified dementia; Other specified disorders of adult personality and behavior
Dehydration	E86.0	Dehydration
Depression	F32.x, F33.x	Major depressive disorder, single episode; Major depressive disorder, recurrent

Dysphagia	R13.x I69.091, I69.191, I69.291, I69.391, I69.891, I69.991	Aphagia or Dysphagia Dysphagia following nontraumatic subarachnoid hemorrhage; Dysphagia following nontraumatic intracerebral hemorrhage; Dysphagia following other nontraumatic intracranial hemorrhage; Dysphagia following cerebral infarction or stroke NOS; Dysphagia following cerebrovascular disease, specified NEC; Dysphagia following cerebrovascular disease, unspecified
Edentulous	K08.1a, K08.10a, K08.101, K08.102, K08.103, K08.104, K08.109, K08.11a, K08.111, K08.112, K08.113, K08.114, K08.119, K08.12a, K08.121, K08.122, K08.123, K08.124, K08.129, K08.13a, K08.131, K08.132, K08.133, K08.134, K08.139, K08.19a, K08.191, K08.192, K08.193, K08.194, K08.199	Complete loss of teeth; Complete loss of teeth, unspecified cause; Complete loss of teeth, unspecified cause, class I; Complete loss of teeth, unspecified cause, class II; Complete loss of teeth, unspecified cause, class III; Complete loss of teeth, unspecified cause, class IV; Complete loss of teeth UC, unspecified class; Complete loss of teeth due to trauma; Complete loss of teeth due to trauma, class I; Complete loss of teeth due to trauma, class II; Complete loss of teeth due to trauma, class III; Complete loss of teeth due to trauma, class IV; Complete loss of teeth due to trauma, unspecified class; Complete loss of teeth due to periodontal disease; Complete loss of teeth due to periodontal disease, class I; Complete loss of teeth due to periodontal disease, class II; Complete loss of teeth due to periodontal disease, class III; Complete loss of teeth due to periodontal disease, class IV; Complete loss of teeth due to periodontal disease, unspecified class; Complete loss of teeth due to caries; Complete loss of teeth due to caries, class I; Complete loss of teeth due to caries, class II; Complete loss of teeth due to caries, class III; Complete loss of teeth due to caries, class IV; Complete loss of teeth due to caries, unspecified class; Complete loss of teeth due to other specified cause; Complete loss of teeth due to other specified cause, class I; Complete loss of teeth due to other specified cause, class II; Complete loss of teeth due to other specified cause, class III; Complete loss of teeth due to other specified cause, class IV; Complete loss of teeth due to other specified cause, unspecified class

Esophageal disorder	K20.80, K20.81, K20.90, K20.91, K21.00, K21.01, K22.0, K22.5	Other esophagitis, specified NEC without bleeding; Other esophagitis with bleeding; Esophagitis, unspecified without bleeding; Esophagitis, unspecified with bleeding; Gastro-esophageal reflux disease with esophagitis without bleeding; Gastro-esophageal reflux disease with esophagitis with bleeding; Achalasia of cardia; Diverticulum of esophagus, acquired
Feeding problems	R63.3, R63.4, R63.6, R63.8, Z93.1	Problem with feeding; Abnormal weight loss (cause unknown); Underweight; Other symptoms and signs concerning food and fluid intake; Presence of gastrostomy
Malnutrition	E44.1, E44.0, E43.0, E46	Mild protein-calorie malnutrition; Moderate protein-calorie malnutrition; Unspecified severe protein-calorie malnutrition; Unspecified protein-calorie malnutrition
Paralysis of vocal cords and larynx	J38.0, J38.00, J38.01, J38.02	Paralysis of vocal cords and larynx; Paralysis of vocal cords and larynx, unspecified; Paralysis of vocal cords and larynx, unilateral; Paralysis of vocal cords and larynx, bilateral
Respiratory problems	J80, J96, R06.0, R06.00, R06.03	Acute respiratory distress syndrome; Respiratory failure NEC; Dyspnea; Dyspnea, unspecified, Acute respiratory distress
Tracheostomy status	Z93.0	Tracheostomy status
Stroke (ischemic)	I63.x	Cerebral infarction

Footnote: [a]=non-billable code, NEC=not elsewhere classified, NOS=not otherwise specified

Appendix 2: ICD-10-PCS Codes

Variable	ICD-10 Code	Description
Feeding device, insertion	0DH90UZ, 0DH93UZ, 0DH94UZ, 0DH97UZ, 0DH98UZ, 0DH50UZ, 0DH53UZ, 0DH54UZ, 0DH57UZ, 0DH58UZ, 0DHB0UZ, 0DHB3UZ, 0DHB4UZ, 0DHB7UZ, 0DHB8UZ, 0DH80UZ, 0DH83UZ, 0DH84UZ, 0DH87UZ, 0DH88UZ, 0DHA0UZ, 0DHA3UZ, 0DHA4UZ, 0DHA7UZ, 0DHA8UZ, 0DH60UZ, 0DH63UZ, 0DH64UZ, 0DH67UZ, 0DH68UZ	Insertion of device in: Duodenum, open approach; Duodenum, percutaneous approach; Duodenum, percutaneous endoscopic approach; Duodenum, via natural or artificial opening; Duodenum, via natural or artificial opening endoscopic; Esophagus, open approach; Esophagus, percutaneous approach; Esophagus, percutaneous endoscopic approach; Esophagus, via natural or artificial opening; Esophagus, via natural or artificial opening endoscopic; Ileum, open approach; Ileum, percutaneous approach; Ileum, percutaneous endoscopic approach; Ileum, via natural or artificial opening; Ileum, via natural or artificial opening endoscopic; Small intestine, open approach; Small intestine, percutaneous approach; Small intestine, percutaneous endoscopic approach; Small intestine, via natural or artificial opening; Small intestine, via natural or artificial opening endoscopic; Jejunum, open approach; Jejunum, percutaneous approach; Jejunum, percutaneous endoscopic approach (PEJ); Jejunum, via natural or artificial opening; Jejunum, via natural or artificial opening endoscopic; Stomach, open approach; Stomach, percutaneous approach; Stomach, percutaneous endoscopic approach (PEG); Stomach, via natural or artificial opening; Stomach, via natural or artificial opening endoscopic
Feeding device, removal	0DP50UZ, 0DP53UZ, 0DP54UZ, 0DPD0UZ, 0DPD3UZ, 0DPD4UZ, 0DP00UZ, 0DP03UZ, 0DP04UZ, 0DP60UZ, 0DP63UZ, 0DP64UZ	Removal of device from: Esophagus, open approach; Esophagus, percutaneous approach; Esophagus, percutaneous endoscopic approach; Lower intestinal tract, open approach; Lower intestinal tract, percutaneous approach; Lower intestinal tract, percutaneous endoscopic approach; Upper intestinal tract, open approach; Upper intestinal tract, percutaneous approach; Upper intestinal tract, percutaneous endoscopic approach; Stomach, open approach; Stomach, percutaneous approach; Stomach, percutaneous endoscopic approach

Intubation	0BH17EZ	Insertion of endotracheal airway into trachea via natural or artificial opening
Swallowing assessment	F00ZHZZ, F00ZJWZ, F00ZJTZ, F00ZJYZ	Bedside swallowing and oral function assessment; Instrumental swallowing and oral function assessment using swallowing equipment; Instrumental swallowing and oral function assessment using aerodynamic function equipment; Instrumental swallowing and oral function assessment using other equipment
Swallowing treatment	F06ZDZZ, F06ZDMZ, F06ZDTZ, F06ZDVZ, F06ZDYZ	Swallowing dysfunction treatment; Swallowing dysfunction treatment using augmentative/alternative communication equipment; Swallowing dysfunction treatment using aerodynamic function equipment; Swallowing dysfunction treatment using speech prosthesis; Swallowing dysfunction treatment using other equipment
Tracheotomy	0B110F4, 0B113F4, 0B114F4	Bypass trachea to cutaneous with tracheostomy device, open approach; Bypass trachea to cutaneous with tracheostomy device, percutaneous approach; Bypass trachea to cutaneous with tracheostomy device, percutaneous endoscopic approach;
Tracheostomy device removal	0BP10FZ, 0BP13FZ, 0BP1XFZ, 0BP14FZ, 0BP17FZ, 0BP18FZ	Removal of tracheostomy device from trachea, open approach; Removal of tracheostomy device from trachea, percutaneous approach; Removal of tracheostomy device from trachea, external approach; Removal of tracheostomy device from trachea, percutaneous endoscopic approach; Removal of tracheostomy device from trachea, via natural or artificial opening; Removal of tracheostomy device from trachea, via natural or artificial opening
Ventilator use	5A1935Z, 5A1945Z, 5A19557	Respiratory ventilation, <24 consecutive hours; Respiratory ventilation, 24-96 consecutive hours; Respiratory ventilation, >96 consecutive hours

Appendix 3: Level I CPT and Level II HCPCS Codes

Variable	CPT Code	Description
Swallowing assessment	92610, 74230[a], 92611[a], 92612, 92616	Evaluation of oral and pharyngeal swallowing function; Swallowing function, with cineradiography/videoradiography (modified barium swallow study); Motion fluoroscopic evaluation of swallowing function by cine or video recording (modified barium swallow study); Flexible fiberoptic endoscopic evaluation of swallowing by cine or video recording (FEES); Flexible fiberoptic endoscopic evaluation of swallowing and laryngeal sensory testing by cine or video recording (FEESST)
Swallowing treatment	92526, 92508	Treatment of swallowing dysfunction and/or oral function for feeding; Group dysphagia therapy
Variable	**HCPCS Code**	**Description**
Enteral feeding	B4081, B4082, B4083, B4087, B4088 B4102, B4149, B4150, B4152-B4155, B4157	Nasogastric tubing with stylet; Nasogastric tubing without stylet; Stomach tube levin; Gastrostomy/Jejunostomy tube, standard; Gastrostomy/Jejunostomy tube, low-profile Formulas
Food thickener	B4100[b]	Food thickener, administered orally
Speaking valve	L8501	Tracheostomy speaking valve
Suction	A4628, A4605, A4624	Oropharyngeal suction catheter; Tracheal suction catheter, closed system; Tracheal suction catheter, any type other than closed system
Ventilator, home use	E0465	Home ventilator, any type, used with invasive interface, (e.g., tracheostomy tube)

Footnote: [a]74230 (radiology) + 92611 (speech-language pathology) should be billed together, [b]=non-billable code

Appendix 4: Dysphagia-related variables for cluster analysis

Variable	Code
Aspiration pneumonia	J13, J14, J15.0, J15.1, J15.20, J15.211, J15.212, J15.29, J15.3, J15.4, J15.5, J15.6, J15.8, J18.9, J69.0
Aspiration of food	T17.220, T17.320, T17.520, T17.820, T17.920, T17.420
Cognitive impairment	I69.01, I69.11, I69.21, I69.31, I69.81, I69.91, G31.84, G31.9, R41.4, R41.81, R41.82, R41.9, S06, F01, F02, F03, F68.8
Dehydration	E86.0
Edentulous	K08.1, K08.10, K08.101, K08.102, K08.103, K08.104, K08.109, K08.11, K08.111, K08.112, K08.113, K08.114, K08.119, K08.12, K08.121, K08.122, K08.123, K08.124, K08.129, K08.13, K08.131, K08.132, K08.133, K08.134, K08.139, K08.19, K08.191, K08.192, K08.193, K08.194, K08.199
Enteral feeding	B4081[b], B4082[b], B4083[b], B4087[b], B4088[b], B4102[b], B4149[b], B4150[b], B4152[b]-B4155[b], B4157[b]
Esophageal disorder	K20.80, K20.81, K20.90, K20.91, K21.00, K21.01, K22.0, K22.5
Feeding device, insertion (placement)	0DH90UZ, 0DH93UZ, 0DH94UZ, 0DH97UZ, 0DH98UZ, 0DH50UZ, 0DH53UZ, 0DH54UZ, 0DH57UZ, 0DH58UZ, 0DHB0UZ, 0DHB3UZ, 0DHB4UZ, 0DHB7UZ, 0DHB8UZ, 0DH80UZ, 0DH83UZ, 0DH84UZ, 0DH87UZ, 0DH88UZ, 0DHA0UZ, 0DHA3UZ, 0DHA4UZ, 0DHA7UZ, 0DHA8UZ, 0DH60UZ, 0DH63UZ, 0DH64UZ, 0DH67UZ, 0DH68UZ
Feeding device, removal	0DP50UZ, 0DP53UZ, 0DP54UZ, 0DPD0UZ, 0DPD3UZ, 0DPD4UZ, 0DP00UZ, 0DP03UZ, 0DP04UZ, 0DP60UZ, 0DP63UZ, 0DP64UZ
Feeding problems	R63.3, R63.4, R63.6, R63.8, Z93.1
Food thickener	B4100b
Malnutrition	E44.1, E44.0, E43.0, E46
Intubation	0BH17EZ

Paralysis of vocal cords and larynx	J38.0, J38.00, J38.01, J38.02
Respiratory problems	J80, J96, R06.0, R06.00, R06.03
Speaking valve	L8501b
Suction	A4628b, A4605b, A4624b
Swallowing assessment	F00ZHZZ, F00ZJWZ, F00ZJTZ, F00ZJYZ, 92610a, 74230a, 92611a, 92612a, 92616a
Swallowing treatment	F06ZDZZ, F06ZDMZ, F06ZDTZ, F06ZDVZ, F06ZDYZ, 92526a, 92508a
Trachectomy/ Tracheostomy	0B110F4, 0B113F4, 0B114F4, Z93.0
Tracheostomy device removal	0BP10FZ, 0BP13FZ, 0BP1XFZ, 0BP14FZ, 0BP17FZ, 0BP18FZ
Ventilator use	5A1935Z, 5A1945Z, 5A19557, E0465b

Footnote: [a]CPT codes, [b]HCPCS codes

Appendix 5: Healthcare costs by dysphagia severity

Variable N=359 (100%)	Cluster[a] Mild Dysphagia *Emphasis on cognitive impairment* n=266 (74%)	Moderate Dysphagia *Emphasis on respiratory compromise* n=42 (12%)	Severe Dysphagia *Emphasis on alternative nutrition* n=51 (14%)	*p*-value
	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	
Cost[b] Incurred				
IP	26,159 (15,282) 0-73,484	43,933 (31,554) 6,578-134,407	26,580 (16,707) 4,960-83,053	<.0028
OP	1,758 (3,545) 3- 26,838	1,358 (1,851) 29-8,778	1,063 (1,253) 22-4,747	0.9189
HH	3,944 (2,133) 0-14,559	4,225 (2,134) 0-6,714	5,746 (2,088) 2,454-8,994	0.0881
SNf	18,431 (10,883) 0-56,641	18,662 (11,330) 2,295-45,994	21,721 (11,331) 0-42,891	0.2131
Carrier	2,658 (2,601) 0-19,703	4,136 (3,411) 212-15,152	2,955 (2,254) 0-11,005	0.0051

Footnote: N=population size, n=sample size, SD=standard deviation, IP=inpatient costs after discharge, OP=outpatient costs, HH=home health costs, SNf=skilled nursing facility costs, Carrier=carrier costs

[a]Mild dysphagia severity with moderate stroke; Moderate dysphagia severity with moderate/severe stroke; Severe dysphagia severity with moderate stroke.

[b]Cost in United States dollars (USD).

Appendix 6: Healthcare costs by discharge location

	Discharge Location				
Cost[a] incurred	Home n=64 (18%)	IPR n=132 (37%)	SNF n=149 (41%)	Trans n=14 (4%)	*p*-value
N=359 (100%)	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	
Total 90	10,114 (11,217) 24-46,601	46,528 (21,480) 276-148,772	28,367 (20,604) 55-119,188	81,207 (41,766) 11,129-149,559	<.0001
IP	13,831 (6,649) 6,290-25,666	32,047 (14,720) 0-109,993	19,076 (15,912) 0-83,053	61,136 (35,344) 6,819-134,407	<.0001
OP	1,226 (1,798) 10-7,675	1,801 (3,991) 3-26,838	1,608 (2,880) 28-19,424	1,583 (1,320) 85-3571	0.4951
HH	3,962 (2,575) 372-14,559	4,408 (1,831) 0-8,994	3,829 (2,020) 0-6,787	1,841 (974) 858-2,806	0.0671
SNf	13,393 (10,475) 1,434-30,390	19,339 (9,834) 233-56,641	19,391 (11,556) 0-6,542	17,929 (12,809) 3,852-45,994	0.5003
Carrier	1,765 (1,963) 0-13,251	3,516 (2,512) 0-19,703	2,357 (2,424) 0-11,061	7,133 (4,137) 1,981-15,152	<.0001

Footnote: N=population size, n=sample size, SD=standard deviation, IPR=inpatient rehabilitation, SNF=skilled nursing facility, Trans=transferred to another facility, Total 90=total healthcare related costs during 90-day period after discharge, IP=inpatient costs after discharge, OP=outpatient costs, HH=home health costs, SNf= skilled nursing facility costs, Carrier=carrier costs.

[a]Cost in United States dollars (USD)