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Study of the healthcare costs of oropharyngeal dysphagia after stroke and its nutritional and respiratory complications, and cost-effectiveness of a therapeutic intervention

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Doctoral thesis presented by **SERGIO MARIN RUBIO** to obtain the PhD degree

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DOCTORAL PROGRAM IN MEDICINE

Department of Medicine

Universitat Autònoma de Barcelona

2025

ACKNOWLEDGEMENTS

A la Laia, pel seu recolzament incondicional i per estar sempre al meu costat. Per celebrar els èxits junts, i per poder compartir els moments difícils. Per haver respectat en tot moment qui soc i quin és el meu camí, ajudant-me a continuar.

Al meu pare, per ser el meu exemple de constància i fortalesa, recordant-me la importància de la formació acadèmica i facilitant-me la seva ajuda en tot moment. A la meva mare, qui sempre ha confiat en mi i ha estat al meu costat, podent compartir els moments difícils i celebrant orgullosa les meves fites. Al meu germà i al meu cosí per haver estat referents a seguir en les vessants acadèmica, laboral i familiar.

Als meus directors, per haver-me il·lustrat en la vessant investigadora, i haver confiat en mi recolzant la meva formació i desenvolupament, respectant en tot moment les meves capacitats i el meu temps. Als meus tutors, per haver donat suport a aquest projecte i per la confiança depositada.

A la Unitat de Recerca de l'Hospital de Mataró pel seu recolzament en aquestes investigacions i per la seva ajuda i expertesa en l'anàlisi estadístic. A la Jane Lewis per la seva ajuda i col·laboració en l'escriptura dels articles científics d'aquesta tesi doctoral. Als companys de l'Hospital de Mataró, de l'Hospital Universitari Germans Trias i Pujol i del grup de Motilitat de l'Hospital de Mataró per haver-me acompanyat durant aquests anys. Als companys de residència de l'Hospital de Mataró, per haver estat referents en el dia a dia, tant a nivell professional com personal, i per aquesta amistat tan sincera. Finalment, vull agrair als meus amics de la universitat i de l'escola per estar sempre tan a prop durant tants anys.

Gràcies

Sergio

LIST OF ABBREVIATIONS

AI: artificial intelligence

AIMS-OD: Artificial Intelligence Massive Screening of Oropharyngeal Dysphagia

AHA/ASA: American Heart Association/American Stroke Association

AUC: area under the curve

BI: Barthel Index

BUN: blood urea nitrogen

BUN/Cr ratio: blood urea nitrogen to creatinine ratio

CBSE: clinical bedside swallowing evaluation

CCI: Charlson Comorbidity Index

CHEERS 2022: Consolidated Health Economic Evaluation Reporting Standards 2022

CEA: Cost Effectiveness Analysis

CSdM: Consorci Sanitari del Maresme

EAT-10: Eating Assessment tool-10

EF: enteral feeding

EFT: enteral tube feeding

ESO: European Stroke Organisation

ESPEN: European Society for Enteral and Parenteral Nutrition

ESSD: European Society for Swallowing Disorders

EQ-5D: European Quality of Life-5 Dimensions

FEES: Flexible Endoscopic Evaluation of Swallowing

GBP: sterling pounds (=£)

GUS: Gugging Swallow Screen

ICD: International Classification of Diseases

ICU: intensive care unit

ICUR: incremental cost-utility ratio

ID: identification

IQR: interquartile range

LES: lower esophageal sphincter

LOS: length of hospital stay

MeSH: Medical Subject Headings

MMI: minimal massive intervention

MNA: Mini Nutritional Assessment

MNA-sf: Mini Nutritional Assessment short-form
mRS: modified Rankin scale
MUST: Malnutrition Universal Screening Tool
NA: not available/not applicable
NGT: nasogastric tube
NIHSS: National Institutes of Health Stroke Scale
NMES: motor-level transcutaneous electrical stimulation
NHS EED: National Health Service-Economic Evaluation Database
NICE: National Institute for Health and Care Excellence
NS: nutritional supplementation
OD: Oropharyngeal dysphagia
PAS: penetration-aspiration scale
PLN: Polish zloty
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: The International Prospective Register of Systematic Reviews of the Center for Reviews and Dissemination
PS-OD: post-stroke oropharyngeal dysphagia
QALY: Quality Adjusted Life Years
QoL: Quality of Life
RCP: routine clinical practice
RoM: risk of malnutrition
rTMS: repetitive transcranial magnetic stimulation
SD: standard deviation
SES: sensory transcutaneous electrical stimulation
SSQ: Sydney Swallow Questionnaire
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
tDCS: transcranial direct current stimulation
SFr: Swiss Francs
TES: transcutaneous electrical stimulation
TOR-BSST: Toronto Bedside Swallowing Screening Test
TRP: transient receptor potential
TF: tube feeding
UES: upper esophageal sphincter
UK: United Kingdom

USA: United States of America

USD: United States Dollars (= *US$*)

VAS: visual analogue scale

V-VST: volume-viscosity swallowing test

VFS: videofluoroscopy

WHO: World Health Organization

WST: water-swallowing test

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ABSTRACT

Oropharyngeal dysphagia (OD) affects 40-78% of acute stroke patients. OD impairs swallow efficacy and safety, causing complications such as dehydration, malnutrition and aspiration, leading to respiratory infections and poorer quality of life (QoL) and clinical prognosis. Few studies have assessed the health-economic costs associated with post-stroke OD (PS-OD) and its complications, and the efficiency of its management. This doctoral thesis has the following objectives: (a) to assess and synthesise evidence on the costs associated with OD and its complications (malnutrition and respiratory infections); (b) to assess the acute, subacute (3 months) and long-term (12 months) costs of PS-OD and its complications; (c) to assess and synthesise the available evidence on the cost-effectiveness of PS-OD management; (d) to assess the cost and cost-utility of adding neurostimulation strategies with sensory (SES) or motor (NMES) transcutaneous electrical stimulation (TES) to compensatory management of chronic PS-OD.

This research project includes three studies with the following methodology and results. Study 1: Systematic review of the costs of OD and its complications after stroke. Main findings were (a) higher hospitalisation costs in patients requiring tube feeding in the United States of America (USA), in patients with ischaemic stroke (France and Switzerland), and in patients with OD and haemorrhagic stroke transferred to a rehabilitation centre in Taiwan; (b) independent cost increase in patients with OD during the first year after stroke in the USA, and (c) increase in hospitalisation costs associated with pneumonia (different countries), and with a higher risk of malnutrition in England. Study 2: Observational study of 395 patients consecutively admitted with acute stroke at Mataró Hospital without prior OD. OD caused a significant and independent increase in costs during hospitalisation (€789.68, p=0.011) and significantly higher costs at 3 and 12 months after stroke compared with patients without OD (3 months: €8242.0 ± €5376.0 vs. €5320.0 ± €4053.0, $p < 0.0001$; 12 months: €11,617.58 ± €12,033.58 vs. €7242.78 ± €7402.55, $p < 0.0001$). These costs independently and significantly increased in patients whose nutritional status declined (€2303.38, $p = 0.001$) and those that suffered at least one episode of respiratory infection (€3034.08, $p < 0.011$) at 12-months follow-up. Study 3: Systematic review of economic evaluation of OD management after stroke. Main findings were (a) reduction in hospitalisation costs with: early assessment of OD in Denmark; protocolised OD management after thrombolysis in Australia, and use of commercially prepared thickened

fluids in the USA, (b) cost-effectiveness: of videofluoroscopy as a screening method through model-based analysis; of rehabilitation programs that included the management of OD in Thailand, and of home enteral nutrition in the United Kingdom and, (c) favourable incremental cost-utility ratio (ICUR) of modified texture diets using a gum-based thickener in Poland. Additionally, the cost and the cost-utility of adding TES (SES or NMES) to the compensatory management of chronic PS-OD were assessed from the hospital perspective. The mean treatment cost of TES at 12 months was €1096.79 ± €346.87, mainly attributed to healthcare facilities and specialised personnel requirements. Bivariate analysis showed a significantly higher incremental QoL for those patients in the SES group compared to the control group at 12 months (SES: 12.17 ± 35.57, and control: -2.07 ± 23.77, *p*=0.027), but non-significant differences for incremental quality-adjusted life-years (QALYs) (SES: 0.0321 ± 0.1608, control: 0.0047 ± 0.1681, *p*=0.192 vs. control, and NMES: 0.0416 ± 0.1274, *p*=0.138 vs. control), nor when adjusted for confounders.

The main conclusions are that (a) healthcare costs were higher in those patients who developed OD and its complications after stroke, (b) OD caused significantly higher and independent economic costs during stroke hospitalisation that were significantly increased with the worsening of nutritional status and development of respiratory infections at long term, (c) therapeutic interventions aimed at preventing OD complications tend to be cost-effective and save costs and, (d) healthcare facilities and the need for specialised personnel were the main contributors to TES costs that improved swallow biomechanics and safety.

RESUM

La disfàgia orofaríngia (DO) afecta un 40-78% dels pacients amb ictus agut. La DO empitjora l'eficàcia i la seguretat de la deglució, causant complicacions com deshidratació, malnutrició i aspiracions que porten a desenvolupar infeccions respiratòries i a pitjor qualitat de vida i pronòstic. Pocs estudis han avaluat els costos associats a la DO després de l'ictus i les seves complicacions, i l'eficiència del seu maneig. Els objectius d'aquesta tesi són: (a) avaluar i sintetitzar l'evidència disponible en els costos associats a la DO i les seves complicacions (malnutrició i infeccions respiratòries); (b) avaluar els costos aguts, subaguts (3 mesos) i a llarg termini (12 mesos) de la DO després de l'ictus i les seves complicacions; (c) avaluar i sintetitzar l'evidència disponible sobre el cost-efectivitat del maneig de la DO després de l'ictus; (d) avaluar el cost i el cost-utilitat d'afegir una estratègia neurorestimuladora amb estimulació elèctrica transcutània (EET) sensorial (SES) o motora (NMES) al maneig compensador en pacients amb DO crònica després de l'ictus.

Aquest projecte de recerca inclou 3 estudis amb la següent metodologia i resultats. Estudi 1: Revisió sistemàtica sobre els costos de la DO després de l'ictus i les seves complicacions. Es van observar (a) majors costos d'hospitalització en pacients nodrits per sonda als Estats Units d'Amèrica (EUA), en pacients amb DO i ictus isquèmic (França i Suïssa), i en aquells amb ictus hemorràgic i DO traslladats a un centre de rehabilitació a Taiwan; (b) increment independent del cost en pacients amb DO durant el primer any després de l'ictus als EUA, i (c) increment en els costos d'hospitalització associats amb la pneumònia (diversos països), i amb risc de malnutrició major a Anglaterra. Estudi 2: Estudi observacional en 395 pacients ingressats de forma consecutiva a l'Hospital de Mataró amb ictus agut sense DO prèvia. La DO va suposar un increment significatiu i independent dels costos sanitaris durant l'hospitalització (€789.68, p=0.011) i costos significativament majors als 3 i als 12 mesos comparat amb aquells pacients sense DO (3 mesos: €8242.0 ± €5376.0 enfront €5320.0 ± €4053.0, p<0.0001; 12 mesos: €11,617.58 ± €12,033.58 enfront €7242.78 ± €7402.55, p<0.0001). Aquests costos van incrementar de forma significativa i independent amb l'empitjorament de l'estat nutricional (€2303.38, p=0.001) i al patir almenys un episodi d'infecció respiratòria (€3034.08, p<0.011) a l'any de seguiment. Estudi 3: Revisió sistemàtica sobre avaluacions econòmiques en el maneig de la DO després de l'ictus. Es van observar (a) reducció en els costos d'hospitalització amb: l'avaluació precoç de la DO a Dinamarca; protocol·litzant el seu maneig després de la trombòlisi a Austràlia, i utilitzant

fluids espessits preparats comercialment als EUA, (b) cost-efectivitat de: la videofluoroscòpia com a mètode de cribratge segons un model de decisió; de programes de rehabilitació que van incloure l'atenció a la DO a Tailàndia, i de la nutrició enteral domiciliària al Regne Unit i, (c) rati cost-utilitat incremental (ICUR) favorable de les dietes de textura modificada utilitzant un espessidor a base de gomes a Polònia. Addicionalment, es va avaluar el cost i el cost-utilitat d'afegir l'EET (SES o NMES) al maneig compensador de la DO en pacients amb DO crònica després de l'ictus. El cost mitjà del tractament amb l'EET als 12 mesos va ser de €1096.79±346.87, majoritàriament atribuït al cost de les instal·lacions sanitàries i del personal especialitzat. L'anàlisi bivariat va mostrar una qualitat de vida incremental major per aquells pacients en el grup tractat amb SES comparat amb el grup control als 12 mesos (SES: 12.17 ± 35.57, i control: -2.07 ± 23.77, p=0.027), però no diferències significatives en el cas dels anys de vida ajustats per qualitat (AVAQ) incrementals (SES: 0.0321 ± 0.1608, control: 0.0047 ± 0.1681, p=0.192 enfront control, i NMES: 0.0416 ± 0.1274, p=0.138 enfront control), ni ajustant per factors de confusió.

Les principals conclusions són: (a) majors costos en aquells pacients que van desenvolupar DO i les seves complicacions després de l'ictus, (b) la DO comporta costos econòmics significativament majors i independents durant l'hospitalització per ictus que s'incrementen significativament amb el desenvolupament de malnutrició i infeccions respiratòries a llarg termini, (c) les intervencions terapèutiques destinades a prevenir les complicacions de la DO tendeixen a ser cost-efectives i estalviar costos i, (d) les instal·lacions sanitàries i els requisits de personal especialitzat van ser els principals contribuents als costos de l'EET que va millorar la biomecànica i la seguretat de la deglució.

1 INTRODUCTION

1.1 Swallowing: an overview

1.1.1 The physiology of swallowing

Swallowing is a physiological process that involves the transfer of food (solids and liquids) from the oral cavity to the esophagus, passing through the pharynx. It is a complex process, given that it involves the passage of food through different anatomical structures. It simultaneously requires coordination between the digestive, respiratory, and central nervous systems. The process of swallowing requires the coordinated and rapid participation of more than 30 pairs of muscles of the mouth, pharynx, larynx, and esophagus, both to be effective and to ensure the safety of the respiratory system.[1]-[4]

1.1.2 Anatomy of swallowing

-Oral cavity

The oral cavity and the tongue comprise the first portion of the digestive tract. These anatomical structures are involved in the processes of mastication, tasting, salivation and swallowing, and the articulation and resonance of speech. The following paragraphs explain the main anatomical structures present in the oral cavity: the vestibule, the buccal cavity and the tongue.

<u>Vestibule</u>

The vestibule is a peripheral area of the oral cavity located between the lips, cheeks and gingivodental arches. Its entrance opens to the outside through the upper and lower lips and their union forms the labial seal.

<u>Buccal cavity</u>

The buccal cavity is divided into different areas with specific functions that contribute to the ingestion and preparation of food for digestion. These structures, located in the central part of the mouth, are anatomically and structurally complex and work together to facilitate essential functions such as mastication, salivation and swallowing of food.

The buccal cavity is delimited as follows: (a) anteriorly and laterally by the gingivodental arches, which include the gums and teeth, (b) upward by the palatal vault, (c) downward by the base of the mouth and, (d) backwards with the pharynx through the isthmus of the throat.

The palate is comprised of two distinct parts: (a) the hard palate or palatal vault, which occupies the anterior two-thirds of this anatomical structure, and which is formed by the maxillary and the palatine bones, covered by a mucous layer and another glandular layer and, (b) the soft palate, which is a muscle-membranous structure positioned in its posterior third and which separates the nasopharynx from the oropharynx. At the posterior part of the soft palate, there is a central prolongation called the uvula, and four lateral prolongations. These lateral structures of the soft palate include: (a) the palatoglossal arches (or anterior pillars, which form the first row of arches in the mouth and are located anterior to the tonsils) and, (b) the palatopharyngeal arches (or posterior pillars, structures that form the second row of arches, located behind the tonsils and which are responsible for delimiting the posterior part of the oral cavity). [5]

Tongue

The tongue, located in the central part of the base of the mouth, is composed of striated muscle covered with mucosa. The tongue is an organ with a great capacity for movement. Its main movements can be classified into three categories: retraction, projection and articulation. These characteristics allow the tongue to form and propel the alimentary bolus. In addition, the tongue contains the taste buds, which allow the perception of tastes.

Anatomically, the terminal sulcus separates the tongue in the root and the body. The root constitutes the anterior part of the oropharynx and is connected to the soft palate and epiglottis by the palatoglossal arches and the glossoepiglottic folds, respectively. In addition, it has alimentary canals on both lateral sides that lead the alimentary bolus to the pharynx. The body constitutes the mobile section of the tongue and occupies most of the oral cavity. The dorsal side of the tongue is coated with a specialised mucosa comprising the taste buds, responsible for the perception of tastes (sweet, salty, sour, bitter and umami). [4]-[6]

-Pharynx

The pharynx is the second section of the digestive tract and acts as a crossing between the respiratory system and the digestive system. It is a tubular structure that begins just behind the nasal cavities and mouth and extends to connect with the larynx, trachea and esophagus. Anatomically it is divided into 3 parts: the nasopharynx, the oropharynx and the laryngopharynx or hypopharynx.

Nasopharynx

The nasopharynx extends from the base of the skull to the velum of the palate. Its main functions are respiratory and phonetic. At the same time, the nasopharynx plays an important role in the swallowing process by preventing nasal regurgitation of the alimentary bolus. During this process, the velum of the palate rises and comes into contact with the posterior wall of the pharynx forming the velopharyngeal seal, and closing the communication between the oropharynx and nasopharynx.

Oropharynx

The oropharynx is located between the isthmus of the pharynx and the hyoid bone and communicates with the oral cavity. The oropharynx allows the transfer of air through the larynx and the alimentary bolus through the pharynx, performing respiratory and digestive functions.

Laryngopharynx or hypopharynx

The laryngopharynx or hypopharynx is the anatomical region at the posterior end of the pharynx, immediately above the esophagus. This essential structure for the human digestive and respiratory system is located between the hyoid bone and the lower end of the cricoid cartilage, at the level of the sixth cervical vertebra. It has the shape of a funnel and is located behind and parallel to the larynx (through which the air passes to the trachea). The piriform sinus is the continuation of the alimentary canals of the tongue and through which food passes on its way to the esophagus. The laryngopharynx has three layers: (a) the inner mucous layer, (b) the intermediate fibrous layer and (c) the outer muscular layer. The muscular wall contains five pairs of striated muscles: three constrictor or intrinsic muscles (superior, middle and inferior), which have transverse and oblique fibbers, and narrow the pharynx as the food bowl passes causing peristaltic movements and two elevator or extrinsic muscles that raise and shorten the pharynx during swallowing. [4], [5], [7]

-Larynx

The larynx is located between the laryngopharynx and the trachea, and it lies anterior to the esophagus. The larynx is a fundamental structure of the respiratory system that houses the organ of phonation. It is a complex structure formed of a cartilaginous skeleton, joints, and ligaments that connect the cartilages, as well as the muscles that facilitate their movement, all covered by a mucosal lining covering its interior. The main cartilages of the larynx include: (a) the thyroid cartilage, the largest of all; (b) the cricoid cartilage, located just below the thyroid cartilage; (c) the arytenoid cartilages, two small cartilages that rest on the upper edge of the cricoid cartilage; and (d) the epiglottis, connected to the thyroid cartilage by the thyroepiglottic ligament, with its upper part free.

The epiglottis performs an essential function during the swallowing process by protecting the airways. The epiglottis acts as a valve with a mechanism that prevents the alimentary bolus from entering the airways, diverting the bolus into the esophagus. During swallowing, the epiglottis moves backwards due to contraction of the aryepiglottic muscle, pressure from the base of the tongue, and upward and forward displacement of the hyoid bone. This movement closes the entrance to the respiratory tract and guides the alimentary bolus towards the hypopharynx, preventing the aspiration of food or liquids that could cause respiratory complications.

The muscles of the larynx are formed by a set of muscles that work in a coordinated way to control its position and shape. These muscles can be grouped into two main groups: (i) the intrinsic muscles (posterior cricoarytenoid muscles, cricothyroid muscle, thyroarytenoid muscles and vocalis muscle) and the extrinsic muscles (laryngeal elevators and laryngeal depressors). The intrinsic muscles play an important role in phonation, allowing the tone and intensity of the voice to be varied by adjusting the tension, length and position of the vocal cords. In addition, they also play an important role in protecting the airways during swallowing, collaborating with other structures to close the glottis, and preventing the passage of food and liquids into the airways. The oblique arytenoid muscles help by approximating the arytenoid cartilages, contributing to the closure of the larynx and the aryepiglottic muscles participate in the movement that closes the larynx during swallowing, moving the aryepiglottic folds and arytenoid cartilages towards the epiglottis to protect the airway. On the other hand, the thyroepiglottic muscles, which extend from the thyroid cartilage to the epiglottis, help to raise the epiglottis through its contraction and thus facilitate the opening of the larynx after swallowing. [4], [8], [9]

Laryngeal vestibule, laryngeal ventricle and infraglottic cavity

The laryngeal vestibule begins at the larynx and concludes at the vestibular folds or false vocal cords. The laryngeal ventricle is the following section, bounded superiorly by the vestibular folds and inferiorly by the true vocal cords or buccal folds. The final section is the infraglottic cavity, between the oral folds and the trachea. [8]

-Esophagus

The esophagus connects the larynx and the stomach and has as its main function the transport of food and liquids to the stomach. It is formed by a layer of smooth muscle covered by mucosa. Once the food enters the esophagus, the muscles in the muscular layer begin to contract causing peristaltic waves that drive the alimentary bolus into the stomach. The esophagus contains two well-differentiated sphincters that regulate the passage of food and liquids and prevent reflux: the upper esophageal sphincter (UES) and the lower esophageal sphincter (LES).

Upper esophageal sphincter (UES)

Located in the neck region, at the height of the fifth or sixth cervical vertebra, it is located at the junction between the pharynx and the esophagus. It is a muscle band that includes the cricopharyngeal muscle and fibers of the inferior constrictor muscle of the pharynx. This anatomical structure prevents the entry of air into the digestive tract during breathing and reflux from the esophagus to the pharynx and opens allowing the entry of the bolus or the exit of vomit and air.

Lower esophageal sphincter (LES)

Located at the junction between the esophagus and the stomach, just above the diaphragm. It is a region of smooth and circular muscle that surrounds the distal part of the esophagus. It is not a clearly defined anatomical structure; it is a physiological sphincter that works like a valve. Its main function is to prevent the reflux of gastric contents into the esophagus, closing when food passes into the stomach. [6], [7], [10]

1.1.3 The swallowing process

During the swallowing process, food passes from the mouth to the stomach where it arrives in the form of an alimentary bolus and undergoes a series of chemical and physical transformations starting the digestion process. It is a complex physiological function that requires a voluntary part and an involuntary part in the form of an automatic reflex. [11], [12] This process is divided into three phases controlled by specific sensory and motor nerve structures: the oral phase, the pharyngeal phase and the esophageal phase. [3]

-Oral phase

The oral phase of swallowing includes the processes of mastication, salivation, containment, formation and storage of the alimentary bolus and initiation of the swallowing reflex. This phase requires precise nerve control involving: (a) the cerebral cortex, (b) cranial pairs V (trigeminal), VII (facial) and XII (hypoglossal) and (c) the nerves that innervate the salivary glands and the orolingual muscles. This phase is divided into two parts, the preparatory oral phase and the oral propulsion phase. During the oral preparation phase, the ingestion of solids and liquids must be explained separately. These are voluntary actions that include mastication and the formation of the alimentary bolus. Mastication is a synchronized mandibular cyclic process that allows food to be transported to the molars. During this process, the saliva hydrates, lubricates and begins the digestion of the food due to the enzyme α-amylase forming the alimentary bolus. In the case of liquids, the bolus is sealed in the oral cavity by the tongue (anteriorly) and by the hard palate (posteriorly). In the case of solids, the bolus is not sealed in the oral cavity since it is processed through mastication and manipulation. The oral propulsion phase is also voluntary and has as its main function the lingual propulsion of the bolus towards the oropharynx. During the oral propulsion phase, the tongue rises to move the bolus posteriorly into the oropharynx. This bolus remains in the oropharynx until it is aggregated in repeated cycles or until the pharyngeal phase begins. [3]

-Pharyngeal phase

The pharyngeal phase of swallowing occurs after the oral phase and is completely involuntary. This phase includes the oropharyngeal motor response and the process that takes place between the entry of the alimentary bolus into the pharynx and its exit through the UES. Stimulation of the pharyngeal mechanoreceptors initiates this phase by sending information to the central nervous system and initiating the oropharyngeal motor response of swallowing. During this process, a temporary adaptation of the oropharyngeal architecture takes place, with the transition from being a respiratory tract to a digestive tract (coordinated opening and closing of structures such as the glossopalatine seal, the velopharyngeal seal, the laryngeal vestibule and the UES), allowing the propulsion of the alimentary bolus from the mouth to the esophagus. [13] After the opening of the glossopalatine seal with the entry of the alimentary bolus into the oropharynx, the soft palate rises, and the posterior wall of the pharynx moves into contact and forms the velopharyngeal seal to prevent nasal regurgitation of the alimentary bolus by closing the nasopharynx. Next and with the progress of the alimentary bolus through the pharynx, a series of adaptations take place that aim to protect the airway such as the adduction of the vocal cords and the arytenoid cartilages sealing the airway, the movement of the arytenoid cartilages contacting the base of the epiglottis and retroflexion of the epiglottis as a result of passive pressure by the base of the tongue and active contraction of the aryepiglottic muscles with closure of the laryngeal vestibule and deviation of the alimentary bolus outside the entrance to the larynx. Regarding the suprahyoid muscles and the longitudinal muscles of the larynx, they generate a movement of the hyoid bone and the larynx upwards and anteriorly that leads to the arrangement of the entrance of the larynx under the base of the tongue, preventing the passage of the alimentary bolus. This movement contributes to the shortening and expansion of the hypopharyngeal space and the opening of the UES, allowing the alimentary bolus to pass into the esophagus. [14] – [18]

-Esophageal phase

In this phase, the bolus is propagated inferiorly by a peristaltic wave once it reaches the esophagus. As in the case of the pharyngeal phase, it is an involuntary process controlled by the enteric nervous system but occurs at a much slower rate than in the case of the pharyngeal phase. [17] This phase begins after the alimentary bolus passes through the UES and ends once the bolus passes through the LES and into the stomach. The UES contracts to prevent reflux from the stomach and relaxes during the swallowing phase. [4], [16]

1.2 Oropharyngeal dysphagia

Oropharyngeal dysphagia (OD) is a symptom of difficulty or inability to safely form or move a bolus from the mouth to the esophagus. [19] OD is a prevalent disorder in the elderly population and in patients with neurological disease. OD is associated with severe nutritional and respiratory complications, increasing the morbidity and mortality of patients who suffer from it. [20] The severity of OD can range from moderate difficulty in swallowing to total disability and can have different causes including neurological, myopathies, structural, metabolic, infectious and iatrogenic causes. [21], [22] Table 1 summarises possible causes of OD in our environment.

CAUSES OF DYSPHAGIA		
NEUROLOGIC	**MYOPATHIC**	**STRUCTURAL**
Stroke Brain tumour Cranial trauma Cerebral palsy Guillain-Barré Huntington's disease Multiple sclerosis Poliomyelitis Tardive dyskinesia Metabolic encephalopathy Amyotrophic lateral sclerosis Parkinson's disease Dementia	Connective tissue disease Dermatomyositis Myasthenia gravis Sarcoidosis Paraneoplastic syndromes	Zenker's diverticulum Oropharyngeal tumour Musculoskeletal abnormalities and osteophytes Structural congenital defects
METABOLIC	**INFECTIOUS**	**IATROGENIC**
Amyloidosis Cushing's syndrome Thyrotoxicosis Wilson's disease	Diphtheria Botulism Neurosyphilis Mucositis	Medication Surgery Radiation or corrosion Prolonged intubation

Table 1. Causes of oropharyngeal dysphagia. Adapted from *Cook IJ* (1999) and *Roden DF* (2013) [21], [22]

The latest editions of the International Classification of Diseases (ICD) and Related Health Problems promoted by the World Health Organization (WHO), ICD-9, ICD-10 and ICD-11 classify OD with specific codes (ICD-9 69.391, ICD-10 R13, ICD-11 MD93). [23], [24] In addition, OD has recently been recognized as a geriatric syndrome by two European scientific societies, the European Society for Swallowing Disorders (ESSD) and the European Geriatric Medicine Society. [25]

1.3 Stroke

Stroke is a vascular neurological disease characterized by the presence of a rapid onset neurological deficit with clinical signs of local (and sometimes global) brain function dysfunction for more than 24 hours which is a consequence of the decrease in vascular blood flow in the affected brain area without another apparent cause of vascular origin. [26] The main characteristic of stroke is the sudden appearance of a reduction in the patient's functional and cognitive abilities that can range from mild to severe (including death) and that can remain long-term in the form of disability. [27], [28] Symptoms of acute stroke include sudden change in language, with difficulty speaking or understanding; sudden loss of strength or sensitivity in one part of the body, affecting half of the body and manifesting itself mainly in the face and/or limbs; sudden vision change; sudden loss of coordination or balance, confusion and severe headache. [29], [30]

Approximately 85% of strokes are ischaemic and 15% haemorrhagic. In addition to atherosclerosis, in the case of strokes, embolism stands out as the aetiological cause of the disease. Embolism usually originates because of a cardiac arrhythmia. [28] Atrial fibrillation is the most frequent arrhythmia and is related to advanced age and the occurrence of stroke. [31] In the case of haemorrhagic strokes, they occur due to the rupture of the vessel wall that produces the bleeding. According to their location, they are classified as cerebral haemorrhage (intraparenchymal or ventricular) or subarachnoid haemorrhage.

Currently, stroke is the first cause of disability, and one of the main causes of dementia in our environment and of death in the world. [32], [33] Moreover, the incidence of stroke is increasing globally in younger people (under 55). [34] Approximately 1.1 million European citizens suffer a stroke each year, with an incidence of around 191.9 cases per 100,000 inhabitants. Of these, it is estimated that between 20% and 35% die, and that approximately one-third of those who survive will suffer a situation of functional dependence. [35] In Spain, nearly 120,000 people suffer a stroke each year and approximately 25,000 die. In addition, it is estimated that by 2025 the number of cases in Europe will reach 1.5 million annually. [35], [36]

1.4 Oropharyngeal dysphagia after stroke

1.4.1 Prevalence of oropharyngeal dysphagia

OD is one of the main complications that patients suffer because of stroke brain injuries. [19], [37] OD has a high prevalence in the acute phases of stroke (40-78% of stroke cases) and, although improvements can be seen during the early phases of recovery after stroke, it can become a condition chronic in up to 41.7% of cases. [38] – [41] Table 2 shows studies that have reported the prevalence of OD in the different phases of stroke (acute, subacute and chronic) and using different assessment methods.

PHENOTYPE	POPULATION	ASSESSMENT METHOD	PREVALENCE (%)	REFERENCE
STROKE	**Acute phase**	Screening (questionnaires)	**37 - 45**	*Martino R* et al. 2005 [40]
		Clinical examination	**51 - 55**	
		Instrumental exploration	**64 - 78**	
		Clinical examination (V-VST)	**39.7**	*Arreola V* et al. 2019 [38]
	Subacute and chronic phases	Clinical examination	**25 - 45**	*Martino R* et al. 2005 [40]
		Clinical/instrumental exploration	**40 - 81**	
		Clinical examination (V-VST)	**41.7**	*Arreola V* et al. 2019 [38]
		Clinical examination (V-VST)	**45.06**	*Rofes L* et al. 2018 [39]

Table 2. Prevalence of oropharyngeal dysphagia in patients with acute, subacute and chronic stroke using different assessment methods. V-VST: volume-viscosity swallow test

OD does not only occur in those patients with neurological vascular disease. It is also a relevant clinical concern in patients affected by various neurodegenerative diseases such as Parkinson's disease, [42] Alzheimer's disease, [43] dementia, [44], [45] multiple sclerosis,[46], [47] or amyotrophic lateral sclerosis.[48], [49] Table 3 shows the prevalence of OD observed in patients with neurodegenerative diseases in different studies.

PHENOTYPE	ASSESSMENT METHOD	PREVALENCE (%)	REFERENCE
Parkinson's disease	Systematic review: reported by patients	**35**	*Kalf JG* et al. 2012 [42]
	Systematic review: Instrumental exploration	**82**	
Alzheimer's disease	Instrumental exploration	**84**	*Horner J* et al. 1994 [43]
Dementia	Reported by caregivers	**19**	*Langmore SE* et al. 2007 [44]
	Instrumental exploration	**57-84**	*Langmore SE* et al. 2007 [44] *Suh MK* et al. 2009 [45]
Multiple sclerosis	Screening (questionnaires)	**24**	*De Pauw A* et al. 2002 [46]
	Instrumental exploration	**34**	*Calcagno P* et al. 2002 [47]
Amyotrophic lateral sclerosis	Clinical and instrumental exploration	**47- 86**	*Chen A* and *Garrett CG* 2005 [48] *Ruoppolo G* et al. 2013 [49]

Table 3. Prevalence of oropharyngeal dysphagia in patients with neurological diseases using different assessment methods.

1.4.2 Pathophysiology and clinical impact

Pathophysiologically, OD after stroke has been associated with impaired sensory and motor oropharyngeal function. Specifically, OD after stroke has been associated with: (a) cortical bihemispheric reduction of excitability of efferent pathways with loss of motor dominance, [50], [51] (b) reduced pharyngeal sensitivity,[52] and with alteration of cortical conduction and integration to pharyngeal sensory stimuli in the area affected by the cerebrovascular accident. [51], [53] The dysfunctions described, together with the decoupling between the sensory and motor pathways of swallowing cause a slow oropharyngeal motor response to swallowing. [51], [54] In this context, the delayed synchronization of the airway protection mechanisms and a weak propulsive force by the tongue cause a worsening of swallowing safety in these patients.[54] Thus, the delay in time until the closure of the laryngeal vestibule compromises the safety of swallowing by causing aspiration that can lead to respiratory infections including pneumonia. [54], [57] OD after stroke can have a significant impact on the health of affected patients presenting two main types of complications: (a) complications related to impairment in swallowing effectiveness, which include oral and pharyngeal residue, impairment of lip seal and inability to form bolus, among others, present in 25%-75% of patients, and which can lead to the development of complications such as dehydration and malnutrition [56] and, (b) impaired swallowing safety, which can lead to tracheobronchial aspiration of oropharyngeal contents with tracheobronchial aspirations that can cause respiratory infections and pneumonia in up to 50% of cases, [20], [57] being aspiration and pneumonia frequent complications after stroke and a relevant cause of mortality. [39], [40], [58] The results of a long study that included 395 patients who suffered an acute stroke and had no previous signs of OD showed that the prevalence of post-stroke OD (PS-OD) was 45.06% during hospital admission and that OD was an independent risk factor for a longer hospital stay and admission to a nursing home or convalescent unit after discharge. In addition, this study showed that OD was independently associated with worse functional capacity and increased mortality at 3 months after stroke. [39] The results of a more recent study conducted in the United States of America (USA) also linked OD with longer hospital stays and higher odds of needing to be referred to a post-acute care facility after hospital discharge and in-hospital mortality. [59] In the same way, other studies have also shown OD as an indicator of poor prognosis presenting a significant effect on the duration of the hospital stay. [60] Finally, a systematic review that evaluated the impact of OD for different aetiologies on hospital stays and costs showed an increase in hospital stays for those patients suffering from OD and an increase in costs. [61]

1.5 Complications of post-stroke oropharyngeal dysphagia

1.5.1 Complications related to the effectiveness of swallowing: malnutrition and dehydration

-Malnutrition

Malnutrition is a major health problem among hospitalised patients. [62], [63] Malnutrition has severe repercussions on the clinical outcomes of patients, worsening their functional status and increasing their hospital stays and mortality.[62] – [64] In the case of stroke patients, malnutrition is a common health problem during hospitalisation that has been associated with worse clinical outcomes in patients hospitalised for acute stroke. [65], [66] Malnutrition affects 8%-28% of patients when they are assessed on admission for stroke and can worsen during hospital admission and in the subsequent phases of recovery. [67], [68] OD in stroke patients plays a critical role in limiting food and liquid intake, causing malnutrition. In the acute phase of stroke, malnutrition may be due to pre-stroke factors, but during the subsequent recovery phases, the presence of OD has an important relevance. In addition, this limitation in intake can also be worsened by other consequences of the stroke, such as a reduction in the level of consciousness and physical exhaustion. [69] OD and its complications can evolve during the phases of recovery after stroke. In this context, the systematic review published by Foley NC et al. in 2009 evaluated the available evidence in 8 studies that included adult patients with stroke. This systematic review showed a higher probability of developing malnutrition after stroke in those patients with OD compared to those who did not present OD (*odds ratio*: 2.425; 95% confidence interval 1.264-4.649, $p<0.008$), and that the probability of malnutrition was significantly increased during the stroke rehabilitation phases (*odds ratio*: 2.445, 95% confidence interval 1.009-5.925, $p<0.048$), not during the first 7 days of hospital admission (*odds ratio*: 2.401, 95% confidence interval 0.981-6.277, $p<0.074$). [70] In addition, the study developed by Arreloa V et al. and published in 2019 shows how younger patients with an optimal functional state tend to improve the efficacy of swallow, even with recoveries of their OD that have a positive effect on their nutritional status. Different from the patients with worse functional states, strokes in the vascular territories other than the posterior circulation or institutionalized after the stroke, tended to a worsening of their swallowing efficacy with a worsening of their nutritional status. [38] Another relevant study is the one published by Carrion S et al. in 2015 in 1662 patients ≥ 70 years hospitalised for acute illnesses with a one-year follow-up. This study showed that 47.4% (95% confidence interval 45%-49.8%) had OD and 30.6% (95% confidence interval 27.9%-33.3%) had malnutrition, assessed with the Mini Nutritional Assessment (MNA) and with the volume-viscosity swallowing test (V-VST), respectively. This study showed that both OD and malnutrition were associated with greater morbidity, multiple geriatric syndromes and worse functional capacity ($p < 0.001$). Patients with OD also presented a higher prevalence of malnutrition defined as an MNA score of less than 17 (45.3% vs. 18%, $p < 0.001$), which was observed independently of their functional status and comorbidities (*odds ratio*: 2.31; 95% confidence interval 1.70-3.14). Moreover, malnourished patients had an increased prevalence of OD (68.4%; 95% confidence interval 63.3%-73.4%). In addition, the presence of malnutrition was significantly associated with mortality and with greater use of health resources, as was the case with the need to be transferred to a nursing home upon discharge (Table 4). [71]

	Malnutrition	Not malnutrition	*p*-value
Nursing home at discharge (%)	52.5	27.6	***< 0.001***
Hospital stays, days (mean ± SD)	11.6 ± 8.1	10.4 ± 7.7	***0.005***
In-hospital mortality (%)	4	1.6	***0.01***
One year mortality (%)	42.4	23.2	***<0.001***

Table 4. In-hospital and one-year mortality, need for nursing home at discharge and hospital stays in hospitalised patients ≥ 70 years of age, with and without malnutrition. Malnutrition was assessed with the Mini Nutritional Assessment. SD: standard deviation. Adapted from Carrion S et al. (2014) [71]

-Dehydration

In the case of dehydration, although there is no standardised method for its evaluation in this phenotype of patients, some studies have shown the presence of hydropenia, reduction of water in the intracellular compartment and reduction in the saliva volume in older patients with OD. [72], [73] These observations could be due to the reduction in water intake because of OD and to the loss of the sensation of thirst. [74], [75] In this context, the results of a recent systematic and scoping review that assessed hydration status in patients with OD due to different aetiologies showed: (a) dehydration is a very prevalent complication in patients with OD secondary to different aetiologies (between 19% and 100% of patients when evaluated using biochemical parameters or bioimpedance), (b) dehydration has a very high prevalence in older patients without OD, but different studies have suggested a higher prevalence of dehydration in those patients with OD and, (c) there is a need to standardize the most appropriate biochemical and bioimpedance markers to assess and monitor hydration status in patients with OD. [57] In addition, the early assessment of the nutritional and hydration status of these patients has been shown to avoid complications such as the development of pressure ulcers during the recovery period after stroke. [76] Moreover, results of a recent observational study on older patients with OD admitted to a general hospital showed a high prevalence of dehydration according to biochemical measurements (75.3%). [77] Tables 5 and 6 show the most important studies that have evaluated the hydration status of patients using bioimpedance (Table 5) and biochemical measurements (Table 6) and OD in patients with neurological diseases, mainly stroke.

POPULATION	ASSESSMENT METHOD	n	RESULTS	REFERENCES
Neurological and geriatric patients	Intracellular, extracellular and total body water	133	Elderly patients with OD with significant reduction of intracellular water	*Carrion S* et al. 2017 [72]
Stroke	Total body water	19	Risk of inadequate hydration status in patients with OD	*Goldberg LR* et al. 2014 [78]
Neurodegenerative and autoimmune disease, stroke, head and neck cancer, infection	Phase angle	79	The major the severity of OD, the smaller the phase angle	*Ramos-Vázquez AG* et al. 2021 [79]

Table 5. Main results of studies evaluating hydration status using bioimpedance and oropharyngeal dysphagia in neurological patients. OD: oropharyngeal dysphagia

POPULATION	ASSESSMENT METHOD	n	RESULTS	REFERENCES
Acute stroke	Urine osmolarity	95	OD not associated with dehydration at discharge	*Buoite SA* et al. 2019 [80]
Stroke	BUN/Cr ratio	100	OD was not a significant predictor	*Murray J* et al. 2018 [81]
Stroke	BUN/Cr ratio, BUN, Sodium	712	Moderate dehydration at hospital discharge	*Goroff H* et al. 2018 [82]
Stroke	Urea	187	Moderate dehydration throughout the sample	*Sala R* et al. 1998 [83]
Brain trauma, stroke	Creatinine, BUN, Sodium	20	BUN, creatinine and natrium levels increased at initial phase	*Howard MM* et al. 2018 [84]
Stroke	BUN/Cr ratio, BUN, Sodium	296	OD dehydration risk marker	*Churchill M* et al. 2004 [85]
Stroke	BUN/Cr ratio	64	Decreased hydration in patients with OD	*Crary MA* et al. 2016 [86]
Older patients	BUN/Cr ratio	235	75.3% of older patients with OD admitted to hospital were dehydrated	*Viñas P* et al. 2023 [77]

Table 6. Main results of studies evaluating hydration status using biochemical methods and oropharyngeal dysphagia in neurological and older patients. BUN: blood urea nitrogen, OD: oropharyngeal dysphagia, BUN/Cr ratio: blood urea nitrogen to creatinine ratio

1.5.2 Complications related to swallowing safety: respiratory infection and aspiration pneumonia

OD after stroke compromises the safety of swallowing. Patients with OD of neurological cause have a high prevalence of videofluoroscopic signs of impaired swallowing safety and efficacy. Specifically, patients with brain damage presented up to 21.6% of fluid aspiration, which is reduced with nectar (8.3%) and pudding (2.9%) viscosity and up to 44% of cases presented residue in the oropharynx. These alterations observed with videofluoroscopy (VFS) carry a high respiratory and neurological complications risk. Specifically, impairment in swallowing safety is associated with slow oropharyngeal reconfiguration and delayed laryngeal vestibule closure, the main mechanism protecting the airway. [87] These altered physiological mechanisms can lead to the aspiration of contents from the oropharynx to the lungs, causing respiratory infections, including pneumonia, with an associated mortality of up to 50% in the long term. [20], [37] OD is also a prevalent clinical finding in older patients with pneumonia (up to 55%) and is an indicator of disease severity in older patients with pneumonia. [20] Moreover, some of the main causes of mortality in the first year after stroke are respiratory infections and aspiration pneumonia, recognised complications of OD after stroke.[56], [88] The presence of respiratory infections, together with dehydration and malnutrition lead to a subsequent deterioration of immunity and the development of frailty. In addition, poor oral hygiene is common among these patients and is associated with oral colonisation by respiratory germs and the development of aspiration pneumonia. [13], [89]

1.6 Management of oropharyngeal dysphagia after stroke

PS-OD has been an underdiagnosed and undertreated condition for a long time. The complete management of PS-OD should involve: (a) early screening of patients and clinical and/or instrumental evaluation during hospital admission, (b) compensation of impaired swallowing mechanisms and (c) the restoration of the swallowing function. This process is necessary to avoid the previously mentioned complications arising from OD and to improve the health status of the patients and their quality of life (QoL). [41], [90] 1.6.1 Diagnosis

-Screening

Regarding patient assessment and diagnosis of OD after stroke, early OD screening is recommended by the American Heart Association/American Stroke Association (AHA/ASA) clinical practice guidelines during the early stroke phases before patients start eating, drinking or taking oral medications. [91] In the same way, it is also recommended by the position statements of the previously mentioned ESSD, [92], [93] and for the recently published guidelines for the diagnosis and treatment of OD after stroke of the European Stroke Organisation (ESO) and the ESSD. These guidelines provided by ESO and ESSD recommend screening for OD in all patients after stroke to prevent episodes of pneumonia and early mortality (moderate quality of evidence) and suggest the evaluation of OD in all those patients identified as being at risk of having OD (low quality of evidence). [93] There are different strategies to perform the screening and assessment of OD after stroke.

The methods used in the screening of OD after stroke aim to detect those patients with a greater risk of affected safety of swallowing, which can compromise the risk of aspiration and respiratory infections. To carry out the screening of OD after stroke requires techniques that are easy and quick to apply, and which are also reliable and minimally or non-invasive. These methods have sensitivities ≥ 70% and specificities ≥ 60%. [94] To carry out this screening, the study of the patient's clinical history, the physical examination and the completion of self-administered validated screening questionnaires such as the Eating Assessment tool-10 (EAT-10) or the Sydney Swallow Questionnaire (SSQ) is necessary. Nowadays, the development of artificial intelligence (AI) methods has led to the development of tools such as Artificial Intelligence Massive Screening for OD (AIMS-OD), which can improve the efficiency of OD screening, saving time and human effort. [95]

<u>Eating Assessment tool-10</u>

It is a tool for easy identification of patients at risk of suffering from OD and who are candidates for subsequent specialised clinical evaluation. It consists of a 10-question questionnaire that assesses the specific symptoms of OD, as well as their severity, and clinical and social impact. This questionnaire has been translated and validated in Spanish. [96] Each question is scored from 0 (no problem) to 4 (it is a serious problem), determining the overall value ≥ 3 to consider the patient at risk of OD. [97] It should be noted that a cutoff point considering a global value ≥ 2 could increase the sensitivity of the questionnaire from 85% to 89% while maintaining the same specificity (82%). [98]

Sydney Swallow Questionnaire

It is a 17-question questionnaire that assesses the severity of OD symptoms. Each of the questions is answered on a visual analogue scale (VAS) of 100 mm in which the evaluated subject indicates with an X the point he considers representing his degree of dysfunction. For each question, a corresponding score is obtained ranging from normal function (0%) to extreme dysfunction (100%). [99]

Artificial Intelligence Massive Screening of Oropharyngeal Dysphagia

AIMS-OD is an expert system based on machine learning that calculates the risk of OD from the electronic clinical records of hospitalised older patients during admission. This expert system aims to provide fast (seconds), early, accurate, systematic and universal detection of OD for older patients during hospital admission to provide them with the most appropriate diagnosis and treatment strategies. In this context, the use of innovative strategies such as the use of AI tools that can assist in the systematic and universal screening and detection of older patients at risk of suffering from OD, can help to improve the efficiency of the OD detection processes. [95]

-Clinical evaluation

If patients at risk of OD are identified with screening methods, more accurate assessments such as clinical or instrumental ones will have to be used. Clinical evaluations aim to perform clinical diagnosis of OD, needed to detect those cases at need further instrumental evaluation or to indicate appropriate treatment (volume, viscosity and texture) for those cases that cannot or should not be subjected to instrumental evaluation.

Volume-viscosity swallowing test

Clinical examination method capable of identifying clinical signs and symptoms of altered swallowing efficacy and safety in patients at risk of OD. The method consists of the administration of boluses of different volumes (5, 10, and 20 mL) and viscosities (<50, 250 and 800 mPa·s) in increasing order of difficulty. The method allows the detection of clinical signs of impaired safety and efficacy of swallowing. Together, the patient's oxygen saturation is measured by a pulse oximeter, which is part of the assessment and at the same time ensures the patient's safety. As can be seen in Figure 1, the exploration begins with the administration of 5 mL boluses of intermediate viscosity (250 mPa·s) and continues with the administration of 10 mL and 20 mL boluses. If there are no safety impairments.

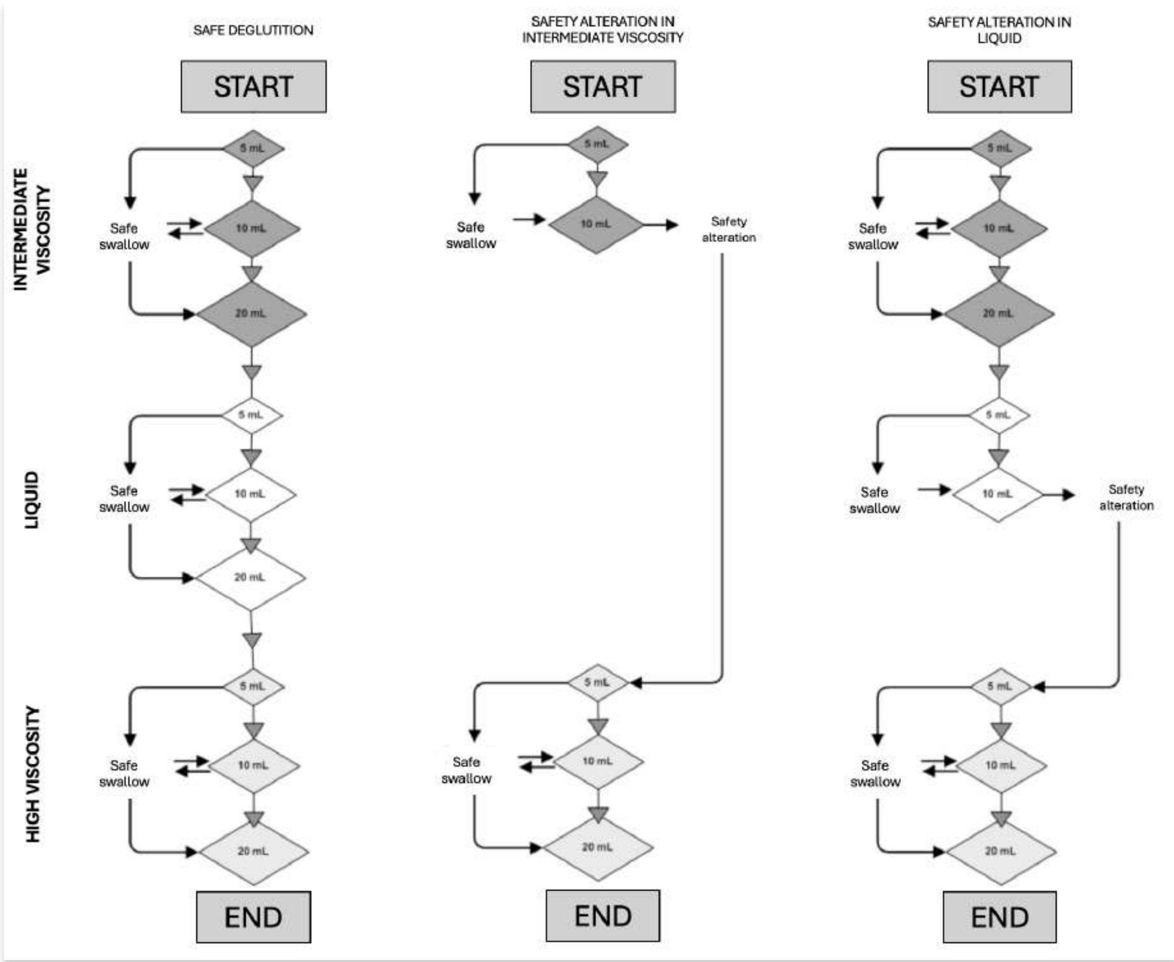

Figure 1. Algorithm of the volume-viscosity swallowing test. Adapted from *Clavé P* (2008) [100]

Then, the same boluses of 5 mL, 10 mL and 20 mL will be administered with liquid viscosities (<50mPa·s), and finally high viscosity (800mPa·s). In the case that the evaluated subject shows any sign of impaired safety of swallowing, it will always be switched to the thicker viscosity and smaller volume, 5 mL in high viscosity (800mPa·s). If with the smaller volume of high viscosity the signs of impaired safety are maintained, the test is ended. The clinical signs of impaired swallowing safety are cough, change of voice or wet voice and reduction in oxygen saturation ≥ 3%. Clinical signs of impaired efficacy of swallowing are impaired lip seal, oral residue, fractional deglutition and pharyngeal residue. [100] A recent systematic and scoping review on the diagnostic properties and clinical utility of the V-VST in the screening and assessment of OD showed a diagnostic sensitivity of 93.17%, specificity of 81.3% and a kappa inter-rater reliability of 0.77. This study concluded that the V-VST has robust diagnostic properties and valid endpoints for OD in different patient phenotypes including those with OD after stroke. [101]

Water swallow test

The water swallow test is a method of clinical evaluation of OD that only evaluates the ability to swallow liquids. The method consists of the ingestion of 90 mL of water without interruption (although there are different adaptations by changing the volume ingested). It is a test that has a high sensitivity for detecting liquid aspiration (94% - 96%) but a low specificity (26% - 46%). [102], [103]

Toronto Bedside Swallowing Screening Test

Clinical bedside swallowing evaluation (CBSE) method for the diagnosis of OD after stroke. The Toronto Bedside Swallowing Screening Test (TOR-BSST) is a simple and accurate tool to identify patients with stroke and OD, regardless of severity and setting. The test includes observation of tongue movement, evaluation of voice quality during phonation, and the ability to swallow teaspoons of water while observing whether the patient has a cough, changes in the quality of the voice or saliva, a positive result is considered when one or more of these signs are observed during the examination. The TOR-BSST has a sensitivity of 91.3% and negative predictive values of 93.3% in patients with acute stroke and 89.5% in the later phases of stroke rehabilitation. [104]

-Instrumental evaluation

The instrumental evaluations make it possible to confirm the diagnosis of OD after the stroke and to evaluate the indication of the optimal treatment for each case. These evaluations allow for examining the swallowing structures and their functionality, as well as assessing the role of volume and viscosity in the pathology of each case. Their complexity is greater than in the previous cases since they may require imaging tests or the use of fibroscopies and evaluation by specialised personnel. Instrumental assessments of OD also allow for examining the contribution of swallowing manoeuvres and postural changes and monitoring patients during their mid- and long-term evolution. Some of the main instrumental tools used for the exploration of OD after stroke are the VFS and the Flexible Endoscopic Evaluation of Swallow (FEES).

Videofluoroscopy

VFS is the *gold standard* for the diagnosis and instrumental evaluation of OD. VFS is a radiological exploration in lateral projection where images are obtained that include the lips, oral cavity, pharynx, larynx, cricoid cartilage spine and esophagus. The VFS allows the systematic evaluation of the physiology of swallowing. It is a dynamic radiological examination in which the patient is evaluated while boluses of variable viscosity are administered with radiological contrast. The subsequent analysis of the images recorded during the VFS allows the evaluation of the swallowing response both qualitatively: signs of impaired safety and/or efficacy of swallowing; and at the quantitative level: the timing of the oropharyngeal motor response, the kinematics of the bolus and the movements of the hyoid and laryngeal structures. The main sign of impaired efficacy of swallowing is oropharyngeal residue and the main signs of impaired safety are penetrations and aspiration. [37], [55]

VFS makes it possible to evaluate the damaged mechanisms in the safety and effectiveness of swallowing. Specifically, the severity of impaired safety of swallow (penetration or aspiration) can be classified according to the penetration-aspiration scale (PAS), [105] and the severity of impaired efficacy according to the Robbins scale. [106] VFS also allows the measurement of the kinematics of the oropharyngeal motor response during swallowing using different measurements, established reference points and formulas. The oropharyngeal reconfiguration is measured through the opening and closing times of the glossopalatine junction, velopharyngeal junction, the closure of the laryngeal vestibule and the opening of the UES. [37] The kinematics of the bolus can also be determined by the mean and final velocity of the bolus (considering the time between the entry of the bolus at the glossopalatine junction and the arrival at the UES and divided by the distance between these two points, and the speed of arrival at the UES, for the average and final speed, respectively) and the propulsion force of the tongue.

Flexible Endoscopic Evaluation of Swallowing

The FEES is utilised to evaluate the swallowing process by observing the anatomical pharyngeal and laryngeal structural forms. The equipment is composed of a flexible fiberscope with light linked to a video equipment that captures the sequence of images during the assessment. It is well tolerated, repeatable and can be performed at the patient's bedside. Signs and mechanisms of impaired swallowing efficacy and safety can be determined while the patient ingests boluses of variable viscosity and volume. However, the oral phase of swallowing cannot be assessed with this technique. [107], [108]

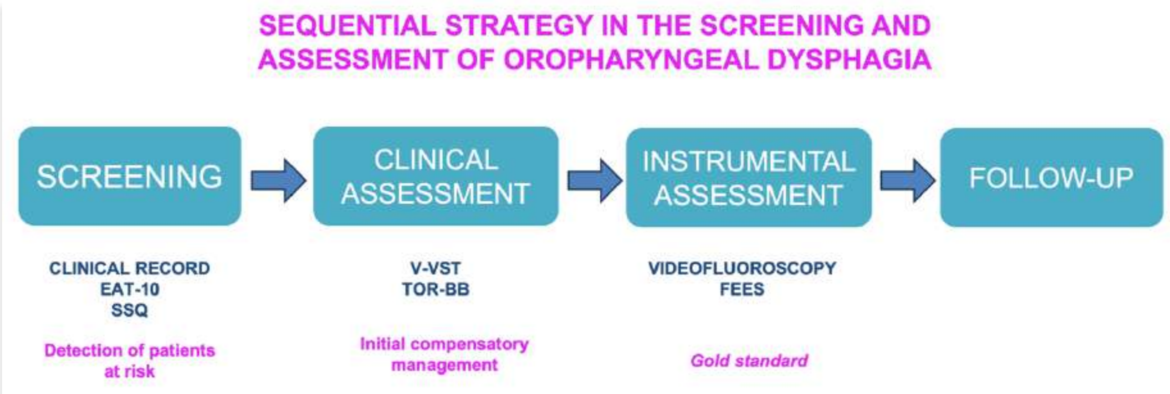

Figure 2. Sequential strategy in the detection of patients at risk, clinical and instrumental evaluation, and follow-up of oropharyngeal dysphagia after stroke. EAT-10: Eating Assessment Tool-10, FEES: Flexible Endoscopic Evaluation of Swallowing, SSQ: Sydney Swallow Questionnaire, TOR-BSST: Toronto Bedside Swallowing Screening Test, V-VST: volume-viscosity swallowing test.

Thus, screening, clinical and instrumental evaluations and follow-up of OD after stroke require a sequential strategy where different types of specialists can participate (Figure 2).

1.6.2 Treatment

Regarding the management of OD after its diagnosis, although the management is generally compensatory and/or rehabilitative, there is currently no standardised management for all patients. The techniques used can range from classic strategies that try to compensate for impaired swallowing mechanisms to rehabilitative strategies that aim to improve the biomechanical mechanisms of impaired swallowing.

-Conventional treatments

The basic recommendations for patients suffering from OD consist of eating 5 or 6 meals a day in a calm and relaxed environment ensuring the patient's state of alertness, supervising meals avoiding foods of greater risk such as those that combine textures and solid and liquid or that can melt, dissolve or fragment and ensure that the patient is in an appropriate position during meals (back straight and head slightly tilted forward). Apart from these basic recommendations, the conventional management of OD can include the adaptation of fluids, postural changes and manoeuvres, neuromuscular exercises, oral hygiene or nutritional supplementation (NS).

<u>Texture-modified diets and adaptation of fluids</u>

The classic management of OD has consisted of the use of compensatory strategies to compensate for the biomechanical deterioration related to the efficacy and safety of swallowing. These compensatory strategies have traditionally been based on the use of thickened fluids and texture-modified diets. [109] Patients with OD suffer impairments in the safety of swallowing with penetration of oropharyngeal contents and bronchopulmonary aspiration. The use of thickened fluids reduces the rate of ingestion of the bolus and its velocity by reducing its bronchial penetration and improving the safety and efficacy of swallowing. [110] In clinical practice, the viscosity obtained will depend on several factors such as the type of thickening agent used (modified starch or gums), the amount of thickening agent used and the characteristics of the fluid to be thickened such as pH, temperature or the macronutrient content. [111] Currently, available evidence shows how modifying viscosity and texture minimizes the risk of aspiration during swallowing. [112] In the case of those patients with stroke and OD, these dietary modifications could reduce the likelihood of pneumonia. [93] In addition, several videofluoroscopic studies performed in patients with PS-OD have shown that the increase in shear viscosity causes an important viscosity-dependent therapeutic effect on the safety of swallowing, reducing penetrations into the laryngeal vestibule and tracheobronchial aspirations and their severity. [109], [113] The increase in viscosity levels therefore reduces the risk of penetration and aspiration into the respiratory tract. Thus, recent studies with gum-based thickeners show the specific ranges of viscosity values that provide the greatest benefit in swallowing safety. [109] Recently published guidelines for the diagnosis and treatment of OD after stroke from the ESO and ESSD suggest the use of texture-modified diets and/or thickened liquids to reduce the risk of pneumonia and recommend their prescription based on in an adequate assessment of swallowing although low quality of evidence is stated. [93] Both fluid and nutritional balance must also be periodically evaluated to ensure adequate nutrient and fluid intake in these patients. [93], [114], [115] On the other hand, thickened liquids could increase the laryngeal residue, so they must be indicated after a specialised evaluation in patients with aspiration of liquids and require adequate follow-up. [116] It should also be considered that the quality of texture-modified diets and fluids can vary significantly due to changes in temperature, preparation and/or the type of thickener used. [110] On the other hand, adherence to these adaptations can be low, so an appropriate adjustment of the viscosity used, as well as the texture and taste used, is required to optimize the therapeutic results. In that sense, the triple adaptation of diet was developed including a) textural and rheological adaptation to avoid impairments in the safety and efficacy of swallow, b) caloric and protein content adaptation to avoid malnutrition and c) organoleptic adaptation to increase patient's adherence. [117], [118]

Rehabilitation exercises, postural changes and manoeuvres

Rehabilitation exercises are probably the most widespread approach for patients with OD for different aetiologies. It is a heterogeneous variety of interventions designed to modify and improve the physiology of swallowing in terms of strength, speed or synchronization and which are thought to produce long-term effects. An example would be the Shaker manoeuvre, intended for patients with difficulty opening the UES. [119]

In contrast, there are compensatory interventions that are used for short-term effects on swallowing. These are voluntary postural changes related to the swallowing process that aim to improve swallowing safety. Chin down or turning the head tends to compensate patients' biomechanical deficits and generate pharyngeal and bolus pressure during the swallowing process and may reduce the incidence of aspiration in specific cases. [120], [121]

Nutritional supplementation and oral hygiene

The consequences of malnutrition in this phenotype of patients have previously been mentioned. Clinical practice guidelines provided by the European Society for Enteral and Parenteral Nutrition (ESPEN) recommend that at-risk or malnourished patients after stroke receive medical nutritional therapy through an individualized nutritional plan (developed and monitored by a nutrition specialist). Thus, in malnourished patients or at risk of malnutrition (RoM), nutritional supplements are recommended. [116] In the same way, the previously mentioned guides provided by the ESO and the ESSD do not recommend systematic nutritional supplements in all cases, but they do consider it in patients at RoM or who are malnourished. [93] It should be considered that the adequate feeding of these patients may involve added complexity due to the need to administer food through feeding tubes or diets of modified consistency in cases at risk of aspiration. [116]

On the other hand, the implementation of interventions to improve the oral health of these patients must be considered. [89] Inadequate oral health in patients affected by OD has been identified as a dominant risk factor for the development of aspiration pneumonia in stroke patients and in cohorts of geriatric patients. [122], [123] In addition, aspiration of oral contents contaminated by bacteria is considered one of the main pathogenic mechanisms involved in pulmonary infections in patients with stroke and severe OD fed through a gastric tube. [124]

Although oral motor exercises, swallowing and positional techniques, and dietary modifications have been studied for decades, [125] studies applying these considerations in the long-term management of subjects with chronic OD after stroke are currently needed. In this context, the application of a minimal massive intervention (MMI) consisting of the use of the adaptation of fluid and food textures, nutritional support and oral hygiene has shown to be useful and effective in older patients with OD. [126]

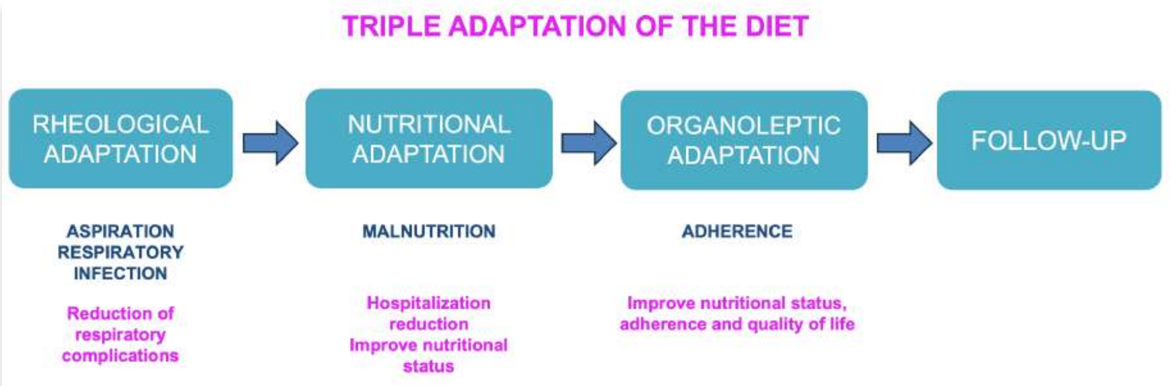

Figure 3. Triple adaptation of the diet. Rheological, nutritional and organoleptic adaptation, along with its main objectives.

-Active treatments

These are treatments in development that aim to restore problems related to swallowing dysfunction related to brain damage. [13], [109] They can be classified into chemical and electrical peripheral stimulation strategies and central stimulation strategies. Peripheral stimulation strategies include ongoing research with active pharmacological agents such as transient receptor potential (TRP) agonists, [127], [128] and transcutaneous electrical stimulation (TES) or intrapharyngeal techniques and aim to improve the oropharyngeal response to swallowing. [129] Other techniques currently in investigation are recovery strategies using non-invasive central stimulation such as transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS) which are currently shown as promising techniques but still limited by variability in responses, lack of data on its safety, uncertainty in patients with certain comorbidities, and difficulty in designing new randomised studies. [130], [131] Recent data have shown that strategies aimed at neurostimulating sensory pathways can cause immediate improvements in the excitability of the motor cortex (pharmacological modulation with capsaicin and intrapharyngeal electrical stimulation) and in sensory pharyngeal conduction (rTMS). [132] These new trends in the treatment of OD could be supported by the results of randomised clinical trials, currently in development, and could induce changes in the management of this pathology in the future.

Transcutaneous electrical stimulation

One of the studies presented in this thesis will focus on the cost and cost-effectiveness of the TES, a non-invasive electrical neurostimulation technique that consists of the application of electrical stimulation through electrodes located in the front of the neck. The guideline published by The National Institute for Health and Care Excellence (NICE) and updated in 2018 assessed the effectiveness of TES and suggested that this technique may have potential clinical benefits without major safety concerns after gathering evidence available in a systematic review and meta-analysis, 7 randomised controlled studies, 1 comparative study and 2 case series. The available evidence was considered limited in quality and quantity. [129]

A recent randomised study at our center compared a control group that received standard compensatory treatment (postural changes, oral hygiene recommendations, thickened fluids, and modified texture diet, when required based on VFS assessment) with two treatment groups who received sensory-level TES (SES), or motor-level TES (NMES) added to the compensatory management that the controls received.

TES showed swallowing parameters significantly improved between baseline and 1-year follow-up both in the sensory (SES) and motor (NMES) stimulation levels groups for prevalence of patients with a safe swallow, mean PAS score, time to laryngeal vestibule closure, and need for thickening agents without significant related adverse events. Patients in the compensatory treatment group showed a weaker improvement of signs of impaired safety of swallow, with no significant variations in time to laryngeal vestibule closure. At the 12-month follow-up, no differences were observed between the groups in terms of 1-year mortality (6.1%), respiratory infections (9.6%), nutritional and functional status, QoL, and hospital readmission rates (27.6%). Moreover, these benefits were sustained in the long term, suggesting that this therapy could be cost-effective by reducing complications associated with PS-OD at a low cost. In this study, both SES and NMES reduced the need for fluid thickening, allowing an improvement in the safety and biomechanics of swallowing and moving the therapeutic management of these patients from the use of classical compensatory strategies to a safe restoration of swallowing. [133]

The results of this study have been accompanied by those of two recent randomised studies also reporting favourable effects of TES, [134], [135] and contributing to the statements of recent clinical practice guidelines suggesting TES as an adjunct to conventional OD treatments to improve swallowing function in OD patients after stroke. [93] However, no studies have been published that have evaluated the cost of treatment and the cost-effectiveness of adding TES to the current management of OD after stroke.

- Minimal massive intervention

Recently in our environment, a MMI has been developed in elderly hospitalised patients with OD consisting of: (a) the early detection of OD, (b) the thickening of liquids and the indication of foods with a modified texture, (c) caloric and protein supplementation and (d) hygiene and oral health recommendations during hospitalisation and discharge. The latest results obtained when applying this MMI in older patients hospitalised with OD suggest improvement in the nutritional status and functionality of the patients and a reduction in hospital readmissions, respiratory infections and mortality. This MMI could become a simple and cost-effective strategy to avoid the complications of OD in the geriatric population admitted with an acute illness in a general hospital, including those patients with OD after a stroke. [126]

1.7 Study of health economics and oropharyngeal dysphagia

Healthcare systems are under significant budgetary pressure due to limitations in available financial resources and an ever-increasing demand for the allocation of costly healthcare programs and interventions together with the ageing of the population. One of the strategies proposed in this context is the allocation of health programs and interventions based on their cost-effectiveness and available budgetary resources. [136], [137] In this context, those chronic clinical conditions, with a high prevalence, and which have associated severe complications are of interest for their study from the side of health economics, especially when potentially cost-effective health interventions must be evaluated for their benefit to the public health system. [138]

OD brings together some of the previously mentioned characteristics. It is a prevalent pathology that tends to become chronic in geriatric populations, in those patients who have suffered cerebrovascular diseases and in those with chronic neurodegenerative diseases. [19], [40], [139], [140] In addition, OD contributes to the development of severe clinical complications that have been previously mentioned such as dehydration, malnutrition and respiratory infections and that could worsen the patient's functional capacity and frailty. [101] These characteristics have a direct impact on the need to use health resources. For example, for those patients who have suffered an acute stroke, OD has been associated with significantly longer hospital stays and a greater likelihood of requiring subsequent stays in post-acute care facilities after acute stroke hospitalisation and with higher in-hospital mortality. [39]

Considering the previously mentioned aspects, the study of the consumption of health resources and costs associated with OD is of interest, especially considering the existence of available methods and tools capable of identifying cases at risk of OD to receive an evaluation and specialised care that could contribute not only by avoiding the important resulting clinical complications but also by assuming significant cost savings. In this context, the study of health costs associated with OD is complex, since not only the costs associated with acute hospital care should be considered, but also other costs such as those arising from its long-term chronic care (costs associated with the institutionalization of patients in residences, social and health care centres or the need for long-term rehabilitation facilities). On the other hand, it would also be necessary to consider the direct non-health costs and indirect costs due to the loss of productivity of these patients. [141] Moreover, the possibility that certain groups of patients are at risk of not having comprehensive OD care, currently a clinical condition insufficiently diagnosed and treated in many settings, could lead to a greater increase in the resources used in the attention to this clinical condition, especially when its long-term complications occur. [142] Table 7 shows the different costs that could be of interest in the study of OD after stroke.

COSTS OF INTEREST IN THE STUDY OF OD			
Direct sanitary costs		**Direct non-sanitary costs**	**Indirect costs**
Hospital stays	Diagnostic tests	Access to health care and treatments	Productivity losses
Sociosanitary care	Adapted diets	Transport	Morbidity
Rehabilitation	Feeding by tube	Social care	Mortality
Primary care	Gastrostomy insertion		Time spent
Specialised care	OD complications	**Intangible costs**	
Access to healthcare professionals: physician, pharmacists, nutritionist, speech therapist	Medication adaptation	Suffering associated with the disease	

Table 7. Costs of interest in the study of costs associated with oropharyngeal dysphagia. OD: oropharyngeal dysphagia

Apart from the costs associated with a certain disease or clinical complication, another important aspect of health economics is economic evaluation. Economic evaluation compares the costs and health consequences of different detection, prevention, management or treatment strategies in a specific clinical condition. This type of study makes it possible to consider both the clinical benefits and the consumption of health resources associated with different alternatives to select the most efficient one. Economic evaluations can provide useful information to policymakers, payers, health professionals, patients, and the public about choices that affect health and resource use. Carrying out economic evaluations should be necessary to increase the efficiency of our clinical practice. Economic evaluation studies can help to prioritise those more efficient health interventions to the detriment of other measures such as restricting access to certain treatments or co-payments. [143], [144]

1.8 Available evidence on the economic impact of oropharyngeal dysphagia

This thesis will be focused on the study of health economics in OD after stroke. For this reason, a previous review of the available literature on economic evaluation studies that have been carried out in OD for stroke and other reasons can be helpful. It should be considered that the experience in the study of the costs associated with OD and its complications is limited. When assessing the economic impact of OD regardless of its aetiology, an observational study conducted in hospitalised patients in the USA showed that OD was significantly associated with higher mean hospital stays and costs. The mean length of hospital stay (LOS) was 3.8 days longer, 43% higher than in cases without OD, and the mean total inpatient costs were 6243 United States Dollars (USD = *US$*) higher. In addition, in those patients with OD, a higher probability of patients being transferred to post-acute care facilities was observed (33.2% higher).[59]

1.8.1 Stroke

The results of a systematic review that evaluated the effect of OD for different aetiologies on hospital stays and costs showed an increase in hospital stays for those patients suffering from OD and an increase in costs of 40.36%. In the case of stroke, an evaluation by subgroups showed longer and more variable hospital stays in those patients with a stroke of 4.73 days, 95% confidence interval 2.7-7.2. [61] In the case of OD after stroke, the studies available before the completion of this doctoral thesis are few, highlighting the retrospective study carried out by Bonilha HS et al. in the USA (2004) which showed an adjusted increase in cost of US$4510 for Medicare at one-year follow-up. [145] Apart from the economic study of OD in stroke patients, we find some other studies in geriatric patient populations, [146], [147] in patients suffering from head and neck neoplasms, [148], [149] and in patients with Parkinson's disease, [150] which are summarised below.

1.8.2 Geriatric patients

OD has a high prevalence in geriatric patients. It can coexist with other comorbidities and at the same time contribute to other clinical complications prevalent in this population such as dehydration, malnutrition, respiratory infections or frailty. [139]

The economic impact of OD has been evaluated in some studies considering geriatric populations. For example, the retrospective study conducted in Denmark by Westmark S et al. evaluated the annual cost of OD after an episode of hospitalisation. The starting point of the study was patients over 60 who were hospitalised in a geriatrics department. The study included 258 patients and reported significantly higher costs for the hospital of €3677 and of €6192 at the municipal level for those patients with OD (results adjusted for age, gender and comorbidities). [146] Another retrospective study to consider is the study conducted in New Zealand by Allen J et al. that evaluated the LOS and the in-hospital cost associated with OD in those patients hospitalised for hip or femur fractures. The study included 165 patients with diagnosis codes of OD together with hip or femur fracture and 2288 patients who only had a hip fracture. A significantly longer LOS was observed (32 versus 14 days, $p<0.05$) and significantly higher mean admission costs for those patients with OD (36,913 versus 22,222 New Zealand dollars $p<0.05$, patients with and without OD, respectively). [147]

Thus, we can observe that despite being a small number of studies, the studies that have evaluated the costs associated with the presence of OD in geriatric populations have found significant data that justify more extensive research in this field in the near future.

1.8.3 Parkinson's disease

In the case of Parkinson's disease, a neurological disease that is a common cause of OD, the available evidence is limited to a single retrospective study conducted in Canada between 2004 and 2014. This study, conducted by Di Luca DG et al. evaluated the healthcare costs associated with OD in hospitalised patients with Parkinson's disease. This study identified 334,395 hospitalisations of patients with Parkinson's disease, 21,288 associated with OD and found a 44% longer LOS and 46% higher admission costs for those patients with OD. [150]

1.8.4 Head and neck cancer

The case of OD in patients affected by head and neck cancer is of particular interest given that in this case we do find some studies available that measured variables such as the LOS or the costs of acute care during the hospitalisation and long-term costs. [151] For instance, the retrospective study conducted in the USA by Semenov YR et al. between 2003 and 2008 evaluated the relationship between pneumonia, short-term outcomes, and costs of care in adult patients who underwent head and neck cancer surgery due to cancer of the oral cavity, larynx, hypopharynx or oropharynx. The study included 93,663 adult patients, with a mean age of 62 years. The study showed a relationship between the presence of OD and the occurrence of aspiration pneumonia (*odds ratio*: 2.0, p <0 .001). In addition, this study showed OD as a significant and independent predictor for an increased LOS of 1.5 days (p <0.001) and higher costs related to hospital care of US$2609 ($p$<0.001). [148] A subsequent retrospective study conducted in the USA by Genther DJ and Gourin CG between 2001 and 2010 evaluated hospital costs in 61,740 patients over 65 years of age who underwent ablative surgery for cancer of the oral cavity, larynx, the hypopharynx and the oropharynx. This study showed that, after adjusting for confounders, OD was a variable significant and independently associated with longer LOS (2.0 days, p<0.001) and hospital costs (US$3976, p<0 .001). [149] These high costs described should not be fixed but could vary depending on the inclusion of certain health interventions, organizational processes or the quality of health care received by patients. The retrospective study conducted in the USA by Gourin CG et al. including 2370 patients aged 66 years or older diagnosed with squamous laryngeal cancer between 2004 and 2007 evaluated the association between quality of care received, treatment-related outcomes in short and long term and costs. This study assessed hospitalisation costs, nonhospital health care costs, and long-term health care costs over a 5-year follow-up and reported lower costs associated with OD for those patients who received higher quality care. In addition, health quality indicators obtained from guideline recommendations and performance measures were used to compute a comprehensive quality assessment, showing an association between higher quality care and a lower risk of death in patients with OD (*hazard ratio* 0.7). Moreover, significantly major costs for patients who developed pneumonia were observed and that average additional costs in patients with OD were lower in those who received higher quality care after controlling for some confounding variables. Furthermore, raw data provided by the investigators in a posterior systematic review showed a mean difference of US$65,766 attributable to OD cost. [61], [152], [153]

POPULATION	ECONOMIC ANALISIS	COUNTRY	RESULTS	REFERENCES
Over 60 years old	Annual hospital and municipal costs after a hospitalisation episode	Denmark	Significantly higher costs for the hospital (€3677) and municipal (€6192)	*Westmark S* et al. 2018 [146]
Hospitalised due to hip or femur fracture	Hospital costs	New Zealand	Significantly higher costs (36,913 versus 22,222 New Zealand dollars)	*Allen J* et al. 2019 [147]
Parkinson's disease	Hospital costs	Canada	46% higher costs	*Di Luca DG* et al. 2021 [150]
Head and neck cancer	Hospital costs	USA	OD significant and independent predictor of higher costs (US$2609)	*Semenov YR* et al. 2012 [148]
Head and neck cancer	Hospital costs	USA	Significant and independent association with higher costs (US$3976)	*Genther DJ* and *Gourin CG* 2015 [149]

Table 8. Studies that evaluated the costs associated with oropharyngeal dysphagia in geriatric patients, patients with head and neck cancer, and patients with Parkinson's disease. USA: United States of America, US$: United States Dollars.

The studies described in the text and summarised in Table 8 provide specific economic data on the expenditure of health resources, such as the LOS or the costs associated with OD in different patient phenotypes. However, to date, there are some important gaps in knowledge in this area such as a lack of systematic reviews of the literature providing pooled data from different studies on the cost of OD in specific aetiologies, lack of data on the costs associated with the complications of OD such as malnutrition and respiratory infections, types of costs that have not been evaluated such as direct non-health costs, indirect costs or intangible costs and lack of economic evaluations aimed at assessing the efficiency and cost savings associated with the comprehensive management of the OD. [152]

2 HYPOTHESIS

2.1 Main hypothesis

OD and its complications (malnutrition and respiratory infections) lead to higher healthcare costs in post-stroke patients, and its management is cost-effective.

2.2 Specific hypothesis

H1. OD and its main complications are related to high costs in post-stroke patients.

H2. PS-OD involves high acute, subacute and long-term costs that can increase with the worsening in nutritional status and the development of respiratory infections in the long term.

H3. Currently, available strategies in the management of PS-OD not only improve the health status of patients but may also lead to cost savings and/or be cost-effective by preventing the development of complications associated with OD.

H4. The cost of adding the TES, a neurostimulation treatment, to compensatory management of chronic PS-OD is reasonable. The possible improvement in swallow physiology and airway protection mechanisms would lead to improved swallowing safety and reduce the need for thickeners.

3 AIMS

3.1 Main aim

The main aim of this doctoral thesis is to assess the healthcare costs associated with PS-OD and its complications, and the efficiency of its management.

3.2 Secondary aims

A1. To assess and synthesise evidence on the economic costs associated with PS-OD and its complications (malnutrition and respiratory infections) available in the literature.

A2. To assess the acute, subacute and long-term costs related to OD in stroke and its complications (malnutrition and respiratory infections).

A3. To assess and synthesise evidence on the cost savings and cost-effectiveness of the management of PS-OD available in the literature.

A4. To assess the resource consumption, cost and cost-utility of adding SES or NMES TES to compensatory PS-OD management from the hospital perspective using data from a prospective randomised controlled study developed at Hospital de Mataró on patients with chronic PS-OD.

4. COMPENDIUM OF PUBLICATIONS

4.1 Article 1: Healthcare-related costs of oropharyngeal dysphagia and its complications pneumonia and malnutrition after stroke: a systematic review

Bibliographic reference: Marin S, Serra-Prat M, Ortega O, Clavé P. Healthcare-related cost of oropharyngeal dysphagia and its complications pneumonia and malnutrition after stroke: a systematic review. BMJ Open. 2020;10(8):e031629. doi: 10.1136/bmjopen-2019-031629.

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BMJ Open

Healthcare-related cost of oropharyngeal dysphagia and its complications pneumonia and malnutrition after stroke: a systematic review

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To cite: Marin S, Serra-Prat M, Ortega O, *et al*. Healthcare-related cost of oropharyngeal dysphagia and its complications pneumonia and malnutrition after stroke: a systematic review. *BMJ Open* 2020;**10**:e031629. doi:10.1136/bmjopen-2019-031629

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-031629).

Received 16 May 2019
Revised 03 March 2020
Accepted 28 May 2020

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ABSTRACT

Objectives To assess the healthcare costs associated with poststroke oropharyngeal dysphagia (OD) and its complications (malnutrition, dehydration, pneumonia and death).

Design Systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.

Data sources MEDLINE, Embase and the National Health Service Economic Evaluation Database were searched up to 31 December 2019.

Participants Patients with poststroke.

Primary outcome measures The costs associated to poststroke OD and its complications.

Data analysis Data were synthetised narratively, quality evaluation was done using an adaptation of Drummond's checklist and Grading of Recommendations Assessment, Development and Evaluation recommendations were used to assess strength of evidence.

Results A total of 166 articles were identified, of which 10 studies were included. The cost of OD during the hospitalisation was assessed in four studies. One prospective study showed an increase of US$6589 for patients requiring tube feeding. Two retrospective studies found higher costs for those patients who developed OD, (US$7329 vs US$5939) among patients with haemorrhagic stroke transferred to inpatient rehabilitation and an increase of €3000 (US$3950) and SFr14 000 (US$15 300) in hospitalisation costs. One study did not found OD as a predictor for total medical costs in the multivariate analysis. One retrospective study showed an increase of US$4510 during the first year after stroke for those patients with OD. For pneumonia, five retrospective studies showed an increase in hospitalisation costs after stroke of between US$1456 and US$27 633. One prospective study showed an increase in hospitalisation costs during 6 months after stroke in patients at high malnutrition risk. Strength of evidence was considered moderate for OD and pneumonia and low for malnutrition.

Conclusions This systematic review shows moderate evidence towards higher costs for those patients who developed OD after stroke. The available literature is heterogeneous, and some important aspects have not been studied yet. Further studies are needed to define the specific cost of poststroke OD.

PROSPERO registration number CRD42018099977.

Strengths and limitations of this study

- ► This systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.
- ► The bibliographic research considers MEDLINE, Embase and the National Health Service Economic Evaluation Database databases.
- ► A quality evaluation using an adaptation of the Drummond's tool was performed.
- ► Strength of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation methodology.
- ► The heterogeneity between the included studies and the variation on costs depending on the context precluded a quantitative data synthesis.

INTRODUCTION

Oropharyngeal dysphagia (OD) is a common condition in patients with poststroke, as a result of the brain injuries suffered.[1] Incidence is high (37%–78%) in the acute phase[2] and, while improvements can be observed in many patients during the first weeks after stroke, OD persists as a chronic condition in nearly 50% and complications arise.[3] The latest editions of the International Classification of Diseases (ICD) and Related Health Problems promoted by WHO ICD-9 and ICD-10 classifies poststroke OD with specific codes I-69.391.[4]

OD can have a high impact on the general health of affected patients and can produce two main types of complications in patients with poststroke: (1) those caused by impaired efficacy of swallow, present in 25%–75% of patients, which leads to malnutrition and dehydration[5] and (2) impaired safety of swallow which leads to tracheobronchial aspiration that may cause pneumonia in 50% of cases.[6–10] Both OD and aspiration are highly prevalent conditions in patients with stroke.[2 6] A recent study on patients with stroke has shown a prevalence of OD of 45.06% on admission, and that OD after stroke was an independent risk factor for prolonged hospital stay and institutionalisation after discharge. Moreover, this study has shown that OD was independently associated with poorer functional capacity and increased mortality 3 months after stroke.[6] A significant increase in length of stay and a poor prognosis has also been observed by other authors in patients with poststroke OD.[11] The impact of all these complications on the costs of poststroke OD is still unknown.

The state-of-the-art of OD management in patients with poststroke aims for early detection, with swallowing being assessed in the first hours after stroke diagnosis[12] in order to prevent the potential complications of OD. Application of specific explorations in the acute setting, therapy development aimed at compensating deficient mechanisms related to this pathology and the recovery of swallowing function in these patients in the long term are key aspects of the management of this condition.[13] Poststroke OD is an underdiagnosed and undertreated condition and the most appropriate care is not available for most patients. Significant reductions in rates of pneumonia (9.0% vs 2.8%) and mortality (7.4% vs 4.2%) have been demonstrated through screening and basic OD treatment application and is reflected in antibiotic expenditure with significant savings of around 50%.[14] The treatment paradigm for poststroke OD is changing from compensatory strategies, which aim to compensate deficient mechanisms related to OD by using fluid adaptation and postural changes, to the recovery of swallowing function with the promotion of brain plasticity with neurorehabilitation techniques such as transcutaneous or intrapharyngeal electrical stimulation, repetitive transcranial magnetic stimulation and transcranial direct current stimulation. These neurorehabilitation strategies are still in the research phase but can already be perceived as an important progress in poststroke OD management.[15]

Costs related to poststroke OD comprise acute in-hospital and long-term sanitary costs, direct non-healthcare costs, indirect costs such as productivity losses and intangible costs. In the recent years, more data on the cost of poststroke OD has become available. However, no systematic literature review has been conducted as yet on this topic. The objective of this systematic review is to assess and summarise all the evidence on the cost related to OD and its complications (malnutrition, dehydration, aspiration pneumonia and death) in patients with poststroke. This study is a first step towards establishing the cost benefits of appropriate management of poststroke OD as an aspect to be taken into consideration by healthcare decision-makers.

METHODS

This systematic review was carried out using methodology Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[16 17 18] In summary, a systematic review of studies related to the cost of OD and its complications (malnutrition, dehydration, aspiration pneumonia and death) in patients with stroke was performed. The main outcome of interest was the additional costs attributable to poststroke OD and its complications during the hospitalisation and follow-up after discharge. Task organisation in this systematic review including those processes performed by two or more authors (selection of studies, data extraction, quality assessment) is explained in the protocol of this systematic review.

Patient and public involvement statement

There was no public or patient involvement in the elaboration of this systematic review.

Search strategy

We searched Medline, Embase and the National Health Service Economic Evaluation Database (NHS EED) up until 31 December 2019. The references of the studies included were further revised to identify possible additional eligible studies. Used search terms are available in the protocol of this systematic review and in the online supplementary appendix.[17 18]

Eligibility criteria

Studies were included if they were cost studies, studies that provide information on costs in adult (>17 years) patients with stroke with OD and/or its complications or economic evaluation studies in which the cost of the disease was estimated. Studies were excluded if they were not related to OD or if they refer to oesophageal dysphagia or OD caused by causes other than stroke. Full-text assessments were done in order to reject those ones not fulfilling all selection criteria. Two independent reviewers participated in this process. In case of disagreement over one or more studies, a third reviewer revised the study and a final consensus was made. A posterior task was carried out to identify possible duplicated information between the articles.

Data presentation and summary measures

Data were reported in its original format using tables and narrative. A narrative method was used to synthesise this evidence. Results are presented according to the following order: (1) costs related to poststroke OD, (2) costs related to OD complications in the following order: (A) aspiration, (B) pneumonia, (C) malnutrition, (D) dehydration and (E) death. A synthesis of studies separating acute and long-term costs was performed. Whenever feasible, data on cost adjusted for the stroke severity (according to National Institutes of Health Stroke (NIHSS) or Canadian scale) or other confounding factors were considered. Information was presented following recommendations of the Centre for Reviews and Dissemination.[19] Results were also discussed as those assessing cost during the hospitalisation compared with cost after discharge and long-term follow-up.

Quality evaluation and strength of the evidence

In this study, we used an adaptation of Drummond's checklist in order to assess the risk of bias and the reporting

Table 1 Main design characteristics

Study ID	Aim	Study population	Design	Time horizon and perspective	Country, year and currency	Quality assessment* (%) (yes (1)+partly (0.5)/total applicable)x100
Wojner[22] AACN Clin Issues 2000	Cost of TF	Ischaemic and haemorrhagic stroke ≥18 years	Prospective	Hospitalisation time Hospital perspective	USA 1995–1996 USD (year not available)	50
Katzan[27] Neurology 2007	Cost of pneumonia	Ischaemic and haemorrhagic stroke	Retrospective	Hospitalisation time Hospital perspective	USA 1991–1997 2000 USD	69
Christensen[28] Acta Neurol Scand 2009	Cost of pneumonia	Ischaemic and haemorrhagic stroke ≥21 years	Retrospective	Hospitalisation time Hospital perspective	Argentina 2004–2006 2005 USD	75
Christensen[29] Neuroepidemiology 2009	Cost of pneumonia	Ischaemic and haemorrhagic stroke ≥21 years	Retrospective	Hospitalisation time Hospital perspective	Brazil 2006–2007 2005 USD	83
Wilson J Stroke Cerebrovasc Dis 2012[30]	Cost of pneumonia	Ischaemic and haemorrhagic stroke ≥18 years	Retrospective	Hospitalisation time Hospital perspective	USA 2005–2006 2009 USD	67
Bonilha[23] Dysphagia 2014	Cost of OD	Ischaemic stroke ≥65 years	Retrospective	One year poststroke Financer perspective	USA 2004 2014 USD	80
Chen[24] J Rehabil Med 2015	Cost of OD	Ischaemic stroke Transferred to a rehabilitation ward during hospitalisation	Retrospective	Hospitalisation time Hospital and patient perspective	Taiwan 2002–2012 2013 USD	67
Chen[25] Top Stroke Rehabil 2016	Cost of OD cost of pneumonia	Haemorrhagic stroke Transferred to a rehabilitation ward during hospitalisation	Retrospective	Hospitalisation time Hospital and patient perspective	Taiwan 2002–2012 USD (year not available)	64
Gomes[31] J Stroke Cerebrovasc Dis 2016	Cost of malnutrition	Ischaemic and haemorrhagic stroke ≥18 years	Prospective	6 months after stroke Hospital perspective	England 2011–2012 GBP (year not available)	69
Muehlemann[26] PLoS One 2019	Cost of OD	Ischaemic stroke	Retrospective	Hospitalisation Hospital perspective	France and Switzerland 2012 2013 Euros and Swiss Francs	80

*Quality assessment: a higher score indicates a lower risk of bias.
OD, oropharyngeal dysphagia; TF, tube feeding.

quality for each study only using the points in the checklist that were applicable to cost studies.[20] Each of these points was rated as: yes, no, partly, not available or not applicable. Two independent reviewers participated in this process. A global score presented as a percentage was calculated for each study dividing the total number of points rated as 'yes' ('partly' counted as 0.5) between the total points applicable for each study. No study was excluded from this review based on risk of bias results. A higher score indicates a lower risk of bias. Quality assessment of the studies in this systematic review is presented in table 1 and expanded in the online supplementary appendix. In addition, we rated the quality of evidence across studies as high, moderate, low or very low using Grading of Recommendations Assessment, Development and Evaluation methodology.[21] The hypothesis of this systematic review is that OD and its main complications are related to high costs in patients with poststroke. If a study demonstrated significantly higher costs for patients with poststroke who developed OD than for those who did not, higher costs

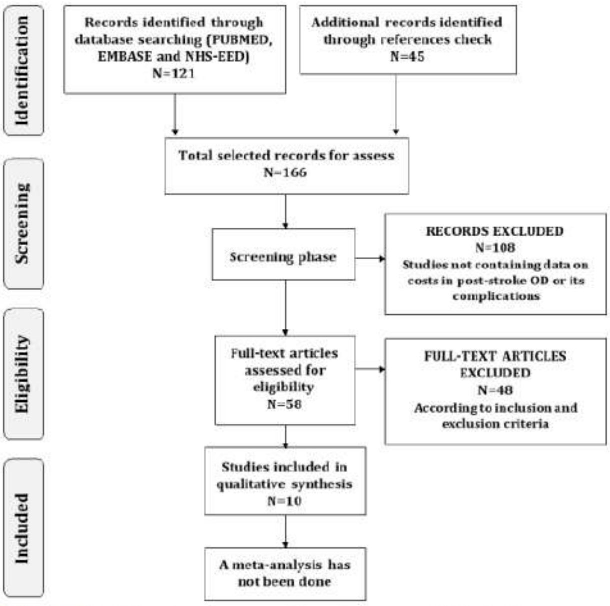

Figure 1 Selection process flow diagram. NHS EED, National Health Service Economic Evaluation Database; OD, oropharyngeal dysphagia.

for those who develop a complication related to OD or an effect of OD or its complications on total costs of stroke, the study was qualified as a 'positive study'.

RESULTS

In the data base search, 121 articles were identified using the search terms (67 through Medline using PubMed, 12 through Embase using Ovid and 42 through NHS EED) and 45 articles were identified through reference check. A total of 166 studies were assessed in the selection phase. After screening both title and abstract of these articles, 108 articles were excluded because they did not provide information on poststroke OD costs or those of its complications or at least minimal relevant information on this aspect. A second evaluation phase was carried out with the 58 remaining studies. After this second evaluation phase, 48 articles were excluded because they did not meet the criteria for inclusion (4 were duplicated articles, 38 did not provide information on costs and 6 did not refer to OD) and 10 articles were included in this systematic review (figure 1). Included study data and features were summed up and presented in both a narrative presentation and evidence (tables 1–4). A great heterogeneity regarding the economic design among studies was found (mainly among study perspective, type of included costs and follow-up time). Results were, therefore, not comparable and studies were evaluated separately.

Costs of OD after stroke

Five studies have assessed the cost of OD in patients with stroke from different perspectives and using different methodologies. These five studies had a longitudinal design. Studies' sample size ranged from 171 to 68334 participants and the mean age of participants ranged from 61.3 to 78.1 years.[22–26] Two studies were performed in the USA,[22 23] two were performed in Taiwan,[24 25] and one was performed in France and Switzerland.[26] The US studies and the study performed in France and Switzerland were cost analysis studies[22 23 26] and the Taiwanese studies were cost prediction studies.[24 25] Incidence of OD ranged from 4.2% to 65.9%. Screening for OD on admission was performed only in the study by Wojner and Alexandrov.[22] One study analysed hospitalisation costs in patients depending on tube feeding (TF) from a hospital perspective.[22] One study analysed hospital care, nursing home, care provider, home health, outpatient and durable medical equipment costs during the first year after ischaemic stroke and from the perspective of Medicare.[23] Two studies analysed hospital costs including diagnoses, ward, laboratory, X-rays, therapeutic and surgical procedures, blood/plasma, anaesthesia, special materials, TF, rehabilitation, drugs, dispensing and injection services, haemodialysis and psychiatric treatment for patients transferred to a rehabilitation ward after ischaemic[24] and haemorrhagic[25] stroke from the hospital and patient perspectives. One study analysed the cost of hospital stay from the hospital perspective.[26]

Wojner and Alexandrov found significantly higher costs during the hospitalisation for those patients who depended on a TF. Mean hospitalisation costs were US$12 538±US$6247 for those patients who depended on a TF and US$5949±US$3428 for those who did not ($p<0.0001$), suggesting a non-adjusted effect of TF of approximately US$6300. The study also showed that those patients depending on a TF were older, with a greater neurological impairment and had longer hospital stays. NIHSS score was found to be an independent risk factor for TF dependency.[22] Bonilha *et al* found an increase of US$4510 ($p<0.0001$) on the total medical costs during the first year after stroke for patients with ischaemic stroke who developed OD, controlling for age, comorbidities, ethnicity and time alive. Nevertheless, stroke severity was not shown as a significant independent predictor for the cost model.[23] Chen *et al* examined the predictors for total medical costs in first ischaemic stroke patients transferred to a rehabilitation ward in Taiwan. In this study, OD was significantly related with total medical costs during hospitalisation in the univariate analysis but not in the multivariate analysis. Significant predictors for total medical costs after multivariate analysis were: impaired consciousness, hypoalbuminaemia, fever, hypokalaemia and hyponatraemia. Mean total costs for dysphagia patients during the hospitalisation were 5134.5±3064.6, and total medical costs for all patients (including those who already had dysphagia) were US$4606.8±US$2926.1.[24] Following the same methodology and perspectives, Chen *et al* examined the predictors for total medical costs in patients with a first haemorrhagic stroke event. This study shows that OD is related to a significant increase in the total medical costs with a beta coefficient of 1025.8 (95% CI

Marin S, *et al*. *BMJ Open* 2020;**10**:e031629. doi:10.1136/bmjopen-2019-031629

Table 2 Specific characteristics of included studies

Study ID	Epidemiological design characteristics: (a) Type of study (b) Epidemiological approach (c) Data gathering (d) Time horizon	Economic design characteristics: (a) Analysis perspective (b) Use of temporary discount rate (c) Sensitivity analysis	Data source	Elements of cost considered: (a) Direct healthcare costs (b) Direct non- healthcare costs (c) Indirect costs
Wojner[22] AACN Clin Issues 2000	a. Cost analysis. b. Longitudinal. c. Prospective. d. Hospitalisation time.	a. Hospital perspective. b. Not available. c. Not available.	Data collected from medical records and the hospital's cost accounting system.	a. Yes. Hospitalisation costs. b. No. c. No.
Katzan[27] Neurology 2007	a. Cost analysis. b. Longitudinal. c. Retrospective. d. Hospitalisation time.	a. Hospital perspective. b. Not available. c. Not available.	Data collected from the Cleveland Health Quality Choice Programme from non-federal hospitals in northeast Ohio. Patient charges were obtained from Medicare files.	a. Yes. Hospitalisation costs. b. No. c. No.
Christensen[28] Acta Neurol Scand 2009	a. Cost analysis. b. Longitudinal. c. Retrospective. d. Hospitalisation time.	a. Hospital perspective. b. Not available. c. Yes.	Medical records. Costs data were obtained from FLENI database.	a. Yes. Hospitalisation costs. b. No. c. No.
Christensen[29] Neuroepidemiology 2009	a. Cost analysis. b. Longitudinal. c. Retrospective. d. Hospitalisation time.	a. Hospital perspective. b. Not available. c. Yes.	Medical records. Costs data were obtained from Sistema Único de Saúde, 2007 values.	a. Yes. Hospitalisation costs. b. No. c. No.
Wilson J Stroke Cerebrovasc Dis 2012[30]	a. Cost analysis. b. Longitudinal. c. Retrospective. d. Hospitalisation time.	a. Hospital perspective. b. Not available. c. Not available.	Data collected from the 2005 and 2006 Nationwide Inpatient Sample from the United States.	a. Yes. Hospitalisation costs. b. No. c. No.
Bonilha[23] Dysphagia 2014	a. Cost analysis. b. Longitudinal. c. Retrospective. d. One year poststroke.	a. Financer perspective. b. Not available. c. Not available.	Data collected from South Carolina Medicare database.	a. Yes, hospital care, nursing home, provider, home health, outpatient and durable medical equipment. b. No. c. No.
Chen[24] J Rehabil Med 2015	a. Predictors of cost study. b. Longitudinal. c. Retrospective. d. Hospitalisation time.	a. Hospital and patient perspective. b. Not available. c. Not available.	Medical records and the hospital's management information system.	a. Yes, hospital costs including diagnoses, ward, laboratory, X-rays, therapeutic and surgical procedures, blood/plasma, anaesthesia, special materials, tube feeding, rehabilitation, drugs, dispensing and injection services, haemodialysis and psychiatric treatment. b. No. c. No.

Continued

Table 2 Continued

Study ID	**Epidemiological design characteristics:** (a) Type of study (b) Epidemiological approach (c) Data gathering (d) Time horizon	**Economic design characteristics:** (a) Analysis perspective (b) Use of temporary discount rate (c) Sensitivity analysis	**Data source**	**Elements of cost considered:** (a) Direct healthcare costs (b) Direct non- healthcare costs (c) Indirect costs
Chen[25] Top Stroke Rehabil 2016	a. Predictors of cost study. b. Longitudinal. c. Retrospective. d. Hospitalisation time.	a. Hospital and patient perspective. b. Not available. c. Not available.	Medical records and the hospital's management information system.	a. Yes, hospital costs including diagnoses, ward, laboratory, X-rays, therapeutic and surgical procedures, blood/plasma, anaesthesia, special materials, tube feeding, rehabilitation, drugs, dispensing and injection services, haemodialysis and psychiatric treatment. b. No. c. No.
Gomes[31] J Stroke Cerebrovasc Dis 2016	a. Cost predictors. b. Longitudinal. c. Prospective. d. 6 months after stroke.	a. Hospital perspective. b. Not available. c. Yes.	Medical records. Cost data was obtained from the Department of Health Payment by Results Tariff Information Spreadsheet.	a. Yes. Hospitalisation costs. b. No. c. No.
Muehlemann[26] PLoS One 2019	a. Cost analysis. b. Longitudinal. c. Retrospective. d. Hospitalisation time.	a. Hospital perspective. b. Not available. c. Not available.	Data collected from the French Medical Information System Programme and the Swiss OFS Database 'Office federal de la statistique: Statistique des couts par cas 2012'.	a. Yes. Hospitalisation costs. b. No. c. No.

Table 3 Specific characteristics of study populations

Study ID	Age and gender	Patient inclusion or exclusion criteria	Method of OD diagnostic	OD and/or complication incidence	Previous OD or stroke in patients
Wojner[22] AACN Clin Issues 2000	Age: Overall 67.2 (14.3)* TF dependency 72.7 (13.9)* No TF: 64.8 (13.4)* Gender (male): Overall 80 (46.78%)†	Inclusion criteria: ► ≥18 years. ► Haemorrhagic or ischaemic stroke Exclusion criteria: ► Subarachnoid haemorrhage. ► Aneurism or intravenous deformation. ► Craniotomy management.	Dysphagia screening on admission and during hospitalisation .The assessment method was not described.	TF dependence prevalence during hospitalisation: 30 (17.54).†	Not available.
Katzan[27] Neurology 2007	Age: Total: 76.8 (8.14)* Pneumonia: 77.6 (8.24)* No pneumonia: 76.7 (8.13)* Gender (female): Total: 6.405 (56.7)† Pneumonia: 266 (41.9)† No pneumonia: 6.139 (57.6)†	Inclusion criteria: ► Haemorrhagic or ischaemic stroke Exclusion criteria: ► Patients with a code of 'occlusion/ stenosis of precerebral artery' (ICD-9 433). ► Died within 3 days of admission. ► Those in which medical records of 3 days of admission could not be recovered.	Not available.	Dysphagia: Not available. Pneumonia (%): Hospitalisation: 5.6	Not available.
Christensen[28] Acta Neurol Scand 2009	Age: Ischaemic stroke: 64.8 (15.5)* Haemorrhagic stroke: 61.8 (15.5)* Gender (male, %): Ischaemic stroke: 66.7 Haemorrhagic stroke: 58.6	Inclusion criteria: ► ≥21 years. ► First-ever ischaemic or haemorrhagic stroke according to brain image. Exclusion criteria: ► Previous stroke.	Not available.	Dysphagia: Not available Pneumonia : Not available	Only first haemorrhagic or ischaemic stroke patients. Presence of previous dysphagia was not recorded.
Christensen[29] Neuroepidemiology 2009	Age: Ischaemic stroke: 61(14)* Haemorrhagic stroke: 64(13).* Gender (male): Ischaemic stroke: 145(54)† Haemorrhagic stroke: 26(60).†	Inclusion criteria: ► ≥21 years. ► First-ever ischaemic or haemorrhagic stroke according to brain image. Exclusion criteria: ► Previous stroke.	Not available.	Dysphagia: Not available Pneumonia (%): Hospitalisation: 6	Only first haemorrhagic or ischaemic stroke patients. Presence of previous dysphagia was not recorded.
Wilson J Stroke Cerebrovasc Dis 2012[30]	Age (mean): Pneumonia: 73.3 No pneumonia: 70.6 Gender (female, %): Pneumonia: 49.4 No pneumonia: 54.6	Inclusion criteria: ► Stroke Exclusion criteria: ► Died within 3 days of admission. ► <18 years. ► Patients who had missing values. ► Hospitalisation in Texas on 2005.	Not available.	Dysphagia: Hospitalisation: Pneumonia: 0.43 No pneumonia: 0.115 Pneumonia (%): Hospitalisation: 8.1 (95% CI. 7.8 to 8.3)	Not available.
Bonilha[23] Dysphagia 2014	Age: Overall: 78.1 (6.9)* OD: 79.4 (6.7)* No OD: 78.0 (6.9).* Gender (male): Overall: 1228 (38.4)† OD: 118 (37,2)† No OD: 1110 (38.5)†	Inclusion criteria: Primary diagnosis of ischaemic stroke. Exclusion criteria: ► <65 years. ► A complication associated to a previous stroke. ► Ethnicity data missed. ► Cost data not available.	Not available.	Dysphagia: Hospitalisation: 317 (9.9%) patients.†	Not available.

Continued

Table 3 Continued

Study ID	Age and gender	Patient inclusion or exclusion criteria	Method of OD diagnostic	OD and/or complication incidence	Previous OD or stroke in patients
Chen[24] J Rehabil Med 2015	Age: Overall: 68.9 (12.2)* Gender (male): Overall: 137 (44.1)†	Inclusion criteria: ▶ First-time ischaemic stroke according to WHO criteria. ▶ Transferred to a rehabilitation ward from acute ward during hospitalisation. ▶ Discharged from the rehabilitation ward.	Examination or bedside test performed by a physiatrist.	Dysphagia: Admission: 205 (65.9)†	Only first ischaemic stroke patients. Presence of previous dysphagia was not recorded.
Chen[25] Top Stroke Rehabil 2016	Age: Overall: 61.3 (13.5)* Gender (male): Overall: 137 (57.8%)†	Inclusion criteria: ▶ First-time haemorrhagic stroke. ▶ Transferred to a rehabilitation ward . ▶ Discharged from the rehabilitation ward.	Examination or bedside test performed by a clinician.	Dysphagia: Hospitalisation: 118 (49.8)†	Only first haemorrhagic stroke patients. Presence of previous dysphagia was not recorded.
Gomes[31] J Stroke Cerebrovasc Dis 2016	Age (mean): Overall: 74.5 Gender (male, %): Overall: 51	Inclusion criteria: ▶ ≥18 years. ▶ Not pregnant. ▶ Stroke diagnosis. ▶ National Health Service No.	Screening test (not specified) by nurses on admission.	Dysphagia (%): Low RoM: 19 Medium RoM: 26 High RoM: 61 RoM: 156/537(29)† were at high RoM	Presence of previous dysphagia was not recorded. 22% of the patients had a previous stroke.
Muehlemann[26] PLoS One 2019	Age (mean): Not available. Gender (male, %): OD: 47% No OD:52% (France) OD: 51% No OD: 55% (Switzerland)	Inclusion criteria: -Cerebral infarction or sequelae of cerebral infarction. Exclusion criteria: ▶ Subarachnoid haemorrhage, intracerebral haemorrhage, non-traumatic intracerebral haemorrhage, transient ischaemic attack and related symptoms as secondary diagnoses. ▶ Head and neck cancer, dementia, Parkinson's disease, multiple sclerosis or other acute brain injury.	Not available.	Dysphagia (%): Hospitalisation: 4.2 (France), 8.4 (Switzerland).	Not available.

*Values are mean (SD).
†Values are n (%).
ICD, International Classification of Diseases ; OD, oropharyngeal dysphagia; RoM, risk of malnutrition; TF, stands for tube feeding.

Table 4 Results of individual studies

Study ID	Aim	Sample size	Crude incremental costs	P value	Adjusted incremental costs	P value
Wojner[22] AACN Clin Issues 2000	Cost of TF	171	Mean cost for TF patients: US$12 538±US$6247. Mean cost for non-TF patients: US$5949±US$3428=.	<0.0001	–	–
Katzan[27] Neurology 2007	Cost of pneumonia	11 286	US$14 901 (95% CI US$14 279 to US$15 524)	–	US$14 836 (95% CI US$14 436 to US$15 236	–
Christense[28] Acta Neurol Scand 2009	Cost of pneumonia	167	Ischaemic stroke: US$36 149 Haemorrhagic stroke: US$16 893	=0.003 =0.003	– –	–
Christensen[29] Neuroepidemiology 2009	Cost of pneumonia	316	Ischaemic stroke: Mean cost for non-pneumonia patients: US$1776. Mean cost for patients who developed pneumonia: US$4251. Haemorrhagic stroke: Mean cost for non-pneumonia patients: US$3553. Mean cost for patients who developed pneumonia: US$8485.	<0.001 =0.015	US$1456 –	<0.001
Wilson J Stroke Cerebrovasc Dis 2012[30]	Cost of pneumonia	183 976	US$23 102	–	US$27 633 (95% CI US$27 078 to US$27 988)	–
Bonilha[23] Dysphagia 2014	Cost of OD	3200	Mean total payments for OD patients: US$22 379±US$14 250 Mean total payments for non-OD patients: US$18 560±US$14 429 Crude incremental costs: US$3819	<0.0001	Mean adjusted total payments for OD patients: US$22 266 (95% CI US$20 839 to US$23 787) Mean adjusted total payments for non-OD patients: US$17 756 (95% CI US$17 372 to US$18 150) Adjusted incremental costs: US$4510	<0.0001
Chen[24] J Rehabil Med 2015	Cost of OD	311	Mean cost for OD patients: US$5134.5±US$3064.6 Mean patients cost: US$4606.80±US$2926.1.	<0.001	–	–
Chen[25] Top Stroke Rehabil 2016	Cost of OD Cost of pneumonia	237	Mean cost for OD patients: US$7329.2±US$3977.2. Mean cost for patients who developed pneumonia: US$9053.7±US$5142.0. Mean patients cost: US$5939.5±US$3578.5D	<0.001 <0.001	–	–

Continued

Table 4 Continued

Study ID	Aim	Sample size	Crude incremental costs	P value	Adjusted incremental costs	P value
Gomes[31] J Stroke Cerebrovasc Dis 2016	Cost of malnutrition	543	Median costs low-risk patients: 4920 (£ 437–£38 200) Median costs medium-risk patients: 6490 (£1050–£19 600) Median costs high-risk patients: 8720 (£552–£31 900)	<0.001	–	–
Muehlemann[26] PLoS One 2019	Cost of OD	62 297 (F) 6037 (S)	2926 euros (F) 13 959 Swiss Francs (S)	–	–	–

F, France; OD, oropharyngeal dysphagia; R, range minimum-maximum; S, Switzerland; TF, tube feeding.

193.9 to 1857.8; p<0.001). Total cost for OD patients was US$7329.2±US$3977.2 while total medical cost for all patients (including those who already had OD or pneumonia) was US$5935.5±US$3578.5.[25] Muehlemann *et al* found an incremental cost for patients who had OD of €3000 (approx. US$4300, 2019 USD) in France and SFr14 000 (approx. US$16 900, 2019 USD) in Switzerland. OD was associated with a significant increase in hospital costs during admission after adjusting for the presence of motor or/and sensory stroke complications (p<0.0001).[26]

Cost of poststroke safety of swallow complications: pneumonia

We found five studies that evaluated the cost of pneumonia in patients with stroke,[25 27–30] one of which has been previously mentioned for providing information on the cost of OD after stroke.[25] These five studies had a longitudinal, retrospective cost analysis design with sample sizes between 167 and 183 976 participants with a mean age of 61.3–76.8 years.[25 27–30] Two studies were performed in the USA,[27 30] one in Taiwan,[25] one in Argentina[28] and one in Brazil.[29] Presence of OD among analysed patients was reported in two studies.[25 30] Chem *et al* found that 49.8% of the assessed patients suffered OD during hospitalisation[25] and Wilson *et al* found that OD was present in 42.9% of patients who developed pneumonia and in 11.5% of those who did not (p<0.0001).[30] Pneumonia incidence ranged from 5.6% to 8.1%[25 27–30] The studies, except for the one performed by Chen and Ke,[25] analysed hospitalisation costs after stroke from the hospital perspective.[27–30]

Chen and Ke showed that pneumonia was related to a significant increase in the total medical costs with a beta coefficient of 2330.1 (95% CI 1339.5 to 3320.7; p<0.001). Total cost for patients who developed pneumonia was US$9053.7±US$5142.0 while total medical cost for all patients (including those who already had pneumonia) was US$5939.5±US$3578.5.[25] Katzan *et al* showed an incremental cost for patients who developed pneumonia during the hospitalisation of US$14 863 (95% CI 14 436 to 15 236) adjusting for stroke severity, stroke patients' propensity for pneumonia and other factors associated with higher hospitalisation costs. Pneumonia was more commonly identified in those patients with a more severe stroke (p<0.001).[27] Wilson found an additional adjusted cost of US$27 633 (95% CI 27 078 to 27 988) for a pneumonia episode during hospitalisation after stroke. Costs were adjusted for age, gender, hospital factors (teaching, rural, urban), admission from emergency department, illness severity, propensity for pneumonia and comorbidities.[30] Christensen *et al* estimated that patients who developed pneumonia incurred significantly higher costs in both ischaemic (US$36 149; p=0.003), and haemorrhagic stroke (US$16 893; p=0.003) in Argentina.[28] Finally, in the Christensen *et al* study performed in Sao Paulo, Brazil, an increase in hospitalisation cost for patients who developed pneumonia was observed for haemorrhagic stroke (US$8485 vs US$3553; p=0.015) and for ischaemic stroke (US$4251 vs US$1776; p<0.001). Development of pneumonia during admission was found to be a significant independent predictor of acute treatment costs in the multivariate analysis. An adjusted cost of pneumonia of US$1456 was found when adjusting for all patient and treatment characteristics (p<0.001).[29]

Cost of poststroke efficacy of swallow complications: malnutrition

Gomes *et al* aimed to assess the validity of a nutrition-screening tool (Malnutrition Universal Screening Tool) to predict poor outcomes and hospitalisation costs in patients after a stroke episode. A total of 543 patients were enrolled in a longitudinal, prospective study. Costs were measured during 6 months after stroke from a hospital perspective. Mean age of participants was 74.5 years. The study was performed in London in two hyperacute stroke units and compared the hospitalisation costs according to risk of malnutrition. The study showed that an increase in malnutrition risk involved an increase in hospitalisation costs, from £4920 sterling (GBP) 2011 (approx. US$8780, 2019 USD) in low risk patients to £8720 (approx. US$15 560, 2019 USD) in high-risk patients (p<0.001). Risk of malnutrition was identified as an independent predictor for hospitalisation costs. Moreover, the study showed an association between high risk of malnutrition and inadequate swallow on hospital admission.[31]

Synthesis of the study's findings

Short-term cost of OD and its complications during hospital admission

In the case of patients admitted to a rehabilitation ward due to haemorrhagic stroke, the median cost for those who developed OD was US$7329.2 while for the entire sample it was US$5939.5.[25] In the case of ischaemic stroke patients admitted to a rehabilitation ward, OD was not identified as a predictor for the total medial costs in the multivariate analysis. An additional cost for those patients may be US$528 per case.[24] For patients who needed TF, an approximate increase of US$6300 was observed.[22] For patients hospitalised in France and Switzerland after stroke an increase of €3000 and SFr14 000 was observed.[26] In the five studies reporting data on the cost of pneumonia after stroke, an adjusted effect of pneumonia on costs during hospitalisation after stroke was found to be between US$1456 and US$27 633 depending on the setting and the design of the study.[25–30]

Long-term cost of OD and it's complications including post hospital discharge costs

We found only two studies assessing cost related to OD or it's complications beyond the first hospital stay due to acute stroke. The study performed by Bonilha *et al* found an increase of US$4510 for those patients who developed OD during the first year after acute stroke.[23] In malnutrition, Gomes *et al* showed an increase in all hospitalisation costs during the first 6 months after stroke. These costs increased from £4920 (approx.US$8780, 2019 USD) in low risk of malnutrition patients to £8720 (approx. US$15 560, 2019 USD) in high-risk patients.[31]

Quality assessment

Risk of bias was assessed for each study. Total scores for each study are available in table 1 and specific results for each study are available in the online supplementary appendix. Productivity losses secondary to the pathology were not assessed in any of the studies and quantities of consumed resources were only reported by Christensen *et al* and Muehlemann *et al* and separately from their unit costs[26 28] Methods for the estimation of quantities and units costs were barely described in the studies, the studies by Katzan *et al* and Christensen *et al* were the only ones to completely include them.[27–29] A sensitivity analysis was only offered in the studies by Christensen *et al* and Gomes *et al*.[28 29 31] The majority of data for these studies was retrospectively obtained from databases based on diagnosis codes. This can cause major information loss when calculating a disease cost as some conditions are underdiagnosed. We suspect that OD and/or pneumonia underdiagnosis could occur in some studies due to the absence of screenings for OD and low codification of these events in the databases.

Confidence in cumulative evidence

In the case of OD, one prospective and four retrospective studies were assessed. The risk of bias ranged from 50 to 80. High consistency with a large and direct effect was found among the results of four studies. In the study performed by Chen *et al*, OD was significantly correlated with the total medical costs in univariate analysis but not in multivariate analysis so we have not qualified this study as a positive study.[24] We consider the level of evidence regarding higher costs related to poststroke OD to be moderate. In the case of pneumonia, we also consider the level of evidence in favour of higher costs related to this complication to be moderate based on the five retrospective positive studies. The risk of bias punctuation ranged from 64 to 83. Despite the fact that the longitudinal design of the considered studies indicates moderate strength of scientific evidence, a high consistency with a large and direct effect was found among the results of the different studies. In the case of malnutrition, we only found one prospective study and the level of evidence was low.

DISCUSSION

This systematic review shows moderate quality evidence towards higher costs for those patients who developed OD or pneumonia after stroke. Acute in-hospital costs related to OD were analysed in five studies. Despite this, design and results were very different across studies and it is difficult to show definitive conclusions as a quantitative synthesis of the results cannot be made. The results of these economic studies do not match recent clinical studies that clearly show OD after stroke is an independent risk factor for prolonged hospital stay and institutionalisation after discharge; OD has been shown to be an independent risk factor for poorer functional capacity and increased mortality 3 months after stroke.[6] A recent study performed in the USA also related OD to longer length of stay, higher inpatient costs and likelihood of being transferred to postacute care facility and inpatient mortality during hospitalisation.[32] Monetisation of these poor clinical outcomes specifically caused by OD is urgent and would probably indicate specific incremental costs for OD. Regarding the costs of pneumonia, Christensen *et al* showed, in Brazil and Argentina, an increase in hospitalisation costs for stroke patients who developed pneumonia of between US$1456 and US$36 149 depending on the type of the stroke and the country.[28 29] These higher health costs more closely approximate what we estimate could be the increment in costs from OD and pneumonia from the clinical trials we are performing: US$27 633 to US$36 149 seem reasonable and can be translated to a 2019 USD value of US$32 500 to US$48 000. In the study performed by Gomes *et al*, an association between OD and malnutrition is observed on admission. However, this study did not directly assess OD costs or deglutition alterations and it cannot be directly extrapolated that malnutrition costs were a consequence of OD although we can assume that malnutrition in OD patients can also lead to higher costs[31] It should be noted that the cost associated with complications related to OD accounted for a large part of the total costs of hospitalisation in the included studies and that it is possible that hospitalisation costs do not include all the costs attributable to these complications. Health economic studies on the cost of other complications of stroke are scarce. No article measuring aspiration, dehydration or mortality costs was found.

We believe that from our data we can estimate the cost of OD in the acute phase might be up to €15 000 (approx. US$16900) and the cost of an episode of aspiration pneumonia up to €24 000 (approx. US$27600). Our systematic review differs from a previously published systematic review because it focused on poststroke OD and explored the costs related to OD complications. This previous systematic review aimed to assess the influence of OD secondary to all aetiologies on length of stay and costs showed an increase of 40.36% in costs of patients with OD. A subgroup evaluation showed a higher and more variable length of stay of 4.73 days (95% CI 2.7 to 7.2) for patients with stroke.[33]

Two important aspects in this field must be highlighted. First, poststroke OD is a condition for which effective interventions are available that may reduce long-term cost and related complications. Costs related to caring for poststroke OD patients have been little reported. Further research should be done to assess the poststroke OD economic and social burden to better understand and raise awareness about minimal care for this common and severe complication in patients with poststroke. It is becoming increasingly difficult to ignore the need for early screening and basic treatment in poststroke OD patients to reduce their mortality rate and improve their outcomes. Second, in most of the included studies, patients with poststroke were not screened for OD so only the most severe patients may have been diagnosed with OD. This fact could affect the prevalence of OD in these studies and the results of this systematic review and explain the underdiagnosis of OD in some of these studies compared with the literature.[2] Furthermore, the high presence of false negatives could have led to a dilution of the effect. A future prospective study on costs related to poststroke OD in a sample of patients screened early for dysphagia could provide more accurate results.

We found only one study providing information on OD cost beyond the first admission due to acute stroke. However, we could not find any economic evaluation regarding other relevant complications of poststroke OD such as: (1) the need for institutionalisation after discharge, (2) loss of functional capacity, (3) costs related to home care of these patients, (4) and the related short-term and long-term mortality and impaired quality of life.[6] Furthermore, costs of patient care outside the acute hospital setting, social costs and non-sanitary costs have been barely studied. This systematic review shows the need for future high-quality studies to quantify the acute and chronic cost of poststroke OD and its specific complications.

CONCLUSIONS

This systematic review only partially fulfils the proposed objectives. The studies found were conducted in very different contexts and following very different approaches, limiting the analysis to a narrative explanation of what has been investigated to date. In addition, for those studies related to complications associated with OD, the relationship between OD and the complication was not clearly established. Despite this, this systematic review shows increased economic costs during hospitalisation and long-term follow-up in patients who developed poststroke OD or its complications. Future studies on OD after stroke on patients screened and detected early for OD will enable the long-term costs of OD and the true cost of its severe complications to be calculated. Taking into account the chronic nature of this condition, it is necessary to discover the real health and social costs associated with this pathology. In addition, due to the severe complications that patients with poststroke with OD present and their increased associated cost, it would be interesting to assess the cost-effectiveness of the current available treatments for these patients.

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Acknowledgements The authors thank Agustí Viladot, member of Mataró Hospital Library Service, for his assistance with literature search development and realization, Jane Lewis for reviewing the English and Maurice Driessen for reviewing the final version of this manuscript and advice on healthcare economics. This work has been conducted within the framework of a doctoral thesis in medicine from the Medicine Department of the Autonomous University of Barcelona.

Contributors SM is the guarantor. He drafted the first version of this manuscript. He provided expertise on health economics. He contributed to the realisation of the introduction and the conclusions. He reviewed and extracted data of selected studies and contributed with Drummond's and GRADE application. He contributed with data synthesis. MS-P provided expertise on investigation methodology and health economics. He collaborated in writing the manuscript. He provided important references for the development of the methodology of this work. He reviewed and made contributions on the methodology of all the sections of this protocol. He reviewed the correct use of all the economic terms included in this manuscript. He reviewed and extracted data of selected studies and contributed with Drummond's and GRADE application. He contributed with data synthesis. He read and approval the final revision of this systematic review. OO provided expertise on poststroke OD treatments and interventions. He collaborated in writing the manuscript. He contributed on the development of the data collection, quality assessment and data synthesis sections. He provided a critical revision of all the sections of this systematic review. He reviewed and extracted data of selected studies and contributed with Drummond's and GRADE application. He contributed with data synthesis. PC provided expertise on poststroke OD and the design of the study.

He reviewed the correct use of all the medical terms included in this manuscript. He contributed on the study design, and the development and writing of the introduction, the methodology and the conclusions of the manuscript. He provided a critical revision of all the sections of this protocol. He contributed to the correct following of the recommendations proposed by PRISMA. He provided a critical revision of all the sections of this systematic review. He reviewed and extracted data of selected studies and contributed with Drummond's and GRADE application. He contributed with data synthesis. All authors provided a critical revision and read and approved the final revision of this systematic review. All authors contributed with the realisation of the protocol for this systematic review.

Funding This study is funded by an educational grant from Nutricia Advanced Medical Nutrition. This study is supported by Fundació Salut del Consorci Sanitari del Maresme, Ciberehd (in turn supported by the Instituto de Salud Carlos III, Barcelona, Spain) and Fundació de Recerca en Gastroenterologia (FUREGA).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This systematic review is the first part of a research project. The full extent of this project includes (1) a systematic review on the cost of OD and its complications after stroke; (2) a systematic review on economic evaluations of interventions related to screening, diagnosis, management and treatment of OD after stroke; (3) a cost of illness study with one year follow up in patients with poststroke to assess the acute and chronic cost of OD and its complications; and (4) a cost-effectiveness study of compensatory versus active interventions aimed at recovering swallowing function in patients with poststroke.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No additional data is available.

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4.2 Article 2: Healthcare costs of post-stroke oropharyngeal dysphagia and its complications: malnutrition and respiratory infections

Bibliographic reference: Marin S, Serra-Prat M, Ortega O, Audouard Fericgla M, Valls J, Palomera E, Cunillera R, Palomeras E, Ibàñez JM, Clavé P. Healthcare costs of post-stroke oropharyngeal dysphagia and its complications: malnutrition and respiratory infections. Eur J Neurol. 2021;28(11):3670-3681. doi: 10.1111/ene.14998. Epub 2021 Jul 27.

Received: 28 March 2021 | Accepted: 7 June 2021
DOI: 10.1111/ene.14998

ORIGINAL ARTICLE

european journal of neurology

Healthcare costs of post-stroke oropharyngeal dysphagia and its complications: malnutrition and respiratory infections

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Funding information
Financial support received from research grants from Nutricia Danone Advanced Medical Nutrition (HESDY Grant); Fundació Salut del CSdM, Strategic Action Grant in Oropharyngeal Dysphagia provided by the Centro de Investigación Biomédica en Red en el Área de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, DJO Global, and la Fundació la Marató de TV3 (11/2310).

Abstract

Background and purpose: The healthcare economic costs of post-stroke oropharyngeal dysphagia (OD) are not fully understood. The purpose of this study was to assess the acute, subacute and long-term costs related to post-stroke OD and its main complications (malnutrition and respiratory infections).

Methods: A cost of illness study of patients admitted to Mataró Hospital (Catalonia, Spain) from May 2010 to September 2014 with a stroke diagnosis was performed. OD, malnutrition and respiratory infections were assessed during hospitalization and follow-up (3 and 12 months). Hospitalization and long-term costs were measured from hospital and healthcare system perspectives. Multivariate linear regression analysis was performed to assess the independent effect of OD, malnutrition and respiratory infections on healthcare costs during hospitalization, and at 3 and 12 months' follow-up.

Results: In all, 395 patients were included of whom 178 had OD at admission. Patients with OD incurred major total in-hospital costs (€5357.67 ± €3391.62 vs. €3976.30 ± €1992.58, $p < 0.0001$), 3-month costs (€8242.0 ± €5376.0 vs. €5320.0 ± €4053.0, $p < 0.0001$) and 12-month costs (€11,617.58 ± €12,033.58 vs. €7242.78 ± €7402.55, $p < 0.0001$). OD was independently associated with a cost increase of €789.68 ($p = 0.011$) during hospitalization and of €873.5 ($p = 0.084$) at 3 months but not at 12 months. However, patients with OD who were at risk of malnutrition or malnourished and suffered respiratory infections incurred major mean costs compared with those patients without OD (€19,817.58 ± €13,724.83 vs. €7242.8 ± €7402.6, $p < 0.0004$) at 12 months' follow-up.

Conclusion: Oropharyngeal dysphagia causes significant high economic costs during hospitalization that strongly and significantly increase with the development of malnutrition and respiratory infections at long-term follow-up.

KEYWORDS
deglutition disorders, economics, malnutrition, respiratory tract infections, stroke

BACKGROUND

Oropharyngeal dysphagia (OD) is a common complication after stroke [1]. In the acute stroke phase, the incidence of OD is very high (37%–78%) [2] but improves after hospital discharge, remaining as a chronic condition in over 50% of patients [3]. OD impairs the efficacy and the safety of deglutition in acute and long-term stroke patients [4]. This can lead to dehydration, malnutrition and tracheobronchial aspiration that may cause respiratory infections and pneumonia with an associated mortality of up to 50% [1, 4–6]. The main causes of mortality for stroke survivors at 1-year follow-up are respiratory infections and aspiration pneumonia, two well recognized complications of post-stroke OD (PS-OD) [7, 8].

Key aspects of PS-OD management are early evaluation of patient deglutition in the acute phase, compensation of the deficient mechanisms related to the efficacy and safety of deglutition and restoration of the swallowing function [9]. American Heart Association/American Stroke Association guidelines recommend early screening of OD before patients begin eating, drinking or taking oral drugs after acute stroke [10]. Moreover, position statements of the European Society for Swallowing Disorders also recommend screening for OD with a validated tool in the first hours after acute stroke followed by expert assessment if required (videofluoroscopy or fibre optic endoscopic evaluation of swallowing) [11, 12].

A 45.06% prevalence of new-onset dysphagia after stroke was found recently. Moreover, it was found that presenting PS-OD was associated with high mortality rates during hospital stay and was an independent risk factor for prolonged hospital stay and to be institutionalized after hospital discharge; OD was also an independent risk factor for poorer functional capacity and increased risk of mortality 3 months after stroke [13]. OD has also been associated with increased length of stay and mortality during hospitalization, inpatient costs and probability of transfer to a post-acute care facility independent of its aetiology in other studies [14]. Recently, health economic data on the cost of PS-OD have become available [15]. A recent systematic review by our group estimates up to €15,000 (approximately US$16,900) as the cost of PS-OD in the acute phase and €24,000 (approximately US$27,600) as the cost of an episode of pneumonia in patients with PS-OD based on studies performed in France, Switzerland, Argentina, Brazil, Taiwan and the USA. The review revealed few studies describing health economic and social costs of PS-OD after acute hospitalization (subacute and long-term costs) or related to PS-OD complications [16].

The objective of this study was to assess the costs related to OD, malnutrition and respiratory infections after stroke, during hospitalization, and at 3 months' (subacute phase) and 12 months' follow-up (chronic phase) from the hospital and the healthcare system perspectives, respectively. It aims to establish the basis for cost-effectiveness of appropriate PS-OD management to influence healthcare policies.

METHODS

Design and study population

This is an observational, longitudinal, cost-of-illness study in two phases: (a) an acute phase that includes a cost analysis of OD after an acute stroke episode during hospitalization from the hospital perspective and (b) a subacute and a chronic phase that includes a cost analysis of OD, malnutrition and the presence of respiratory infections at 3 months' and 12 months' follow-up from the healthcare system perspective.

The study sample included all patients admitted to the Mataró Hospital, Catalonia, Spain, from May 2010 to September 2014 with a confirmed diagnosis of stroke and who gave their written informed consent to participate. Patients were excluded if they had a previous diagnosis of OD, if the final diagnosis on admission was transient ischaemic attack or if they were transferred to another hospital before admission to Mataró Hospital. Recruited patients were classified into two groups according to the presence or absence of OD. The presence of OD was assessed during the first 24–48 h of admission by specially trained nursing staff using the volume–viscosity swallow test previously described by our group [17, 18].

Cost elements considered (health resource consumption)

Phase 1

Acute hospitalization costs included (a) fixed costs (stay in neurology department, stay in intensive care unit and transfers to a tertiary care centre—Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona—for medical attention, revascularization, nursing, imaging and laboratory tests) and (b) variable costs (medication, enteral feeding [EF] and nutritional supplementation [NS]). Medication included fibrinolysis, anticoagulation, antiplatelet inhibitors, acute in-hospital drugs and chronic medication reconciliation during hospital stay.

Phase 2

Cost in phase 2 comprised subacute (from discharge to 3 months' follow-up) and chronic (from 3 months' to 12 months' follow-up) costs. Subacute and long-term costs included visits to the emergency department, re-hospitalization, stays in a socio-sanitary institution (Hospital de Sant Jaume, Mataró, Barcelona) or in long-term rehabilitation/convalescence facilities (Casal de Curació, Vilassar de Mar, Barcelona) or in a nursing home, and chronic medication. Costs related to institutionalization were based on length of stay at each institution. Costs related to chronic medication were assessed according to electronic prescriptions of the Catalan Health Service and drug consumption during re-hospitalization and socio-sanitary care stay.

Translation into monetary units (€)

The cost of 1 day in the neurology ward or in the intensive care unit was estimated from price data on diagnosis related groups (brain ischaemia and intracerebral haemorrhage) in the hospital discharge records of the Spanish National Health Services and were considered as €626.38 and €569.78 (brain ischaemia, 201–500 and 501–1000 bed tertiary care hospital, respectively) and €681.88 and €591.96 (intracerebral haemorrhage, 201–500 and 501–1000 bed tertiary care hospital), respectively [19]. Costs related to 1 day in medium-term socio-sanitary centres, long-term rehabilitation/convalescence facilities and nursing homes were estimated from the published public price health agreements of the Catalan Health Service, the Catalan Institute for Social Assistance and Services, the Consorci Sanitari del Maresme (CSdM) and the Fundació Casal de la Salut and were estimated as €92.91, €91.58 and €62.9 respectively [20]. Cost of acute in-hospital medication, EF and NS for each patient was obtained from the billing data of the CSdM Pharmacy Department. Cost attributable to each drug of chronic medication was obtained from the published public prices of reference of the Spanish National Health Services and the Ministerio de Sanidad, Servicios Sociales e Igualdad [21]. All resource use was translated into costs using 2019 unitary values. Cost updates were performed using the corresponding annual Consumer Price Index of Spain provided by the Instituto Nacional de Estadística [22].

Other study variables

Age and gender, as well as the Charlson Comorbidity Index and the number of comorbidities, the modified Rankin Scale, the Barthel index and the Mini Nutritional Assessment Short Form were assessed and recorded on admission. Stroke type (ischaemic or haemorrhagic) and neurological status using the National Institutes of Health Stroke Scale were assessed. The risk and presence of malnutrition were assessed using the Mini Nutritional Assessment Short Form at 3 months' follow-up. Respiratory infections and/or pneumonia diagnosis at 3 months' and 12 months' follow-up were also collected. Costs for those patients with and without OD who were at risk of or had malnutrition and who developed respiratory infections were also calculated.

Statistical analysis

The main outcome of interest was the independently associated cost increase for OD, malnutrition and respiratory infections in post-stroke patients. Statistical analysis was performed using GraphPad Prism 6.01 (San Diego, CA, USA). Comparisons of qualitative variables between groups were made using Fisher's exact test or the chi-squared test. Continuous data were presented as mean ± SD and compared between groups with the non-parametric Mann–Whitney *U* test or the Kruskal–Wallis test for multiple comparisons (with Dunn's post-test). To assess normality the D'Agostino and Pearson omnibus normality test was used.

First, a bivariate analysis of the association of OD, malnutrition and risk of malnutrition and the presence of respiratory infections with acute, subacute and chronic healthcare costs was assessed using a simple linear regression analysis. Secondly, a multivariate linear regression analysis was used in three different multivariate models to adjust for the effect of OD, malnutrition or respiratory infections on costs by age, comorbidities, baseline functionality and stroke severity. Statistical significance was set at $p < 0.05$.

Legal and ethical issues

This research was performed and reported following the recommendations stated in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies [23].

The protocol of this study was evaluated and approved by the Ethical Committee for Clinical Investigation of the Hospital de Mataró (protocol code 35/14), 'La Marató' de TV3 register code 11/2310. All procedures contributing to this investigation were conducted according to the principles stated in the Helsinki Declaration of 1975 and its subsequent amendments. The General Data Protection Regulation of the European Union 2016/679 was followed. All patients included in this study or their legal representative signed an informed consent.

RESULTS

Recruitment and main sample characteristics

A total of 608 patients were recruited and 395 were included in the study following eligibility criteria, of whom 178 had OD on admission (45.0%). Figure S1 (Appendix S1) shows the number of individuals at each phase of the study. Descriptive sociodemographic and clinical characteristics of patients included in this study were previously published in a study on the prevalence, risk factors and complications of PS-OD [13, 24]. Table 1 shows a summary of the main sociodemographic, clinical characteristics and nutritional status of patients on admission. A total of 21 patients died during hospitalization and early follow-up (5.31% hospital mortality) and 41 during long-term follow-up (10.38% mortality at long term).

Health resource consumption in the acute phase

Mean hospitalization days were 7.16 ± 4.30. Patients with OD had longer stays (mean stay, OD 8.33 ± 5.21 days vs. non-OD 6.20 ± 3.05 days; $p < 0.0001$). Also, more patients with OD used EF and NS (patients treated with EF and/or NS, OD 23 (12.92), non-OD 5 (1.26); $p < 0.0001$). A total of seven patients were referred to a tertiary care centre (mean stay, OD 0.08 ± 0.64 days vs. non-OD 0.07 ± 0.50 days; $p < 0.926$). Table S1 shows a summary of patient stays and resource consumption including EF and NS.

Costs in the acute phase

Mean costs during hospitalization were €4598.79 ± €2799.51 but patients with OD cost significantly more during hospitalization for both fixed and variable costs: hospital stay, €5265.11 ± €3319.62 versus €3902.55 ± €1925.78, $p < 0.0001$; in-hospital medication, €87.86 ± €264.16 versus €73.57 ± €216.25, $p < 0.0001$; EF and/or NS, €4.69 ± €23.28 versus €0.18 ± €1.33, $p < 0.0001$; and total in-hospital costs, €5357.67 ± €3391.62 versus €3976.30 ± €1992.58, $p < 0.0001$, patients with OD being reported first. Table 2 summarizes these findings.

Health resource consumption in the subacute and chronic phases

In the subacute phase, mean patient visits to the emergency department were 0.16 ± 0.36, and mean stays in re-hospitalizations 0.61 ± 2.3; in a socio-sanitary institution, 6.9 ± 17.5; in a long-term

TABLE 1 Main sociodemographic and clinical characteristics of the 395 patients included in this study

OD using V-VST	All patients (*n* = 395)	OD admission (*n* = 178)	Non-OD admission (*n* = 217)	*p* value
Sociodemographic data				
Age, years (mean ± SD)	73.2 ± 13.3	77.9 ± 11.1	69.4 ± 13.7	**<0.0001**
Male, *n* (%)	211 (53.42)	85 (47.75)	126 (58.06)	**0.043**
Patient status on admission				
Comorbidity, *n* (%)				
No comorbidity, 0	35 (8.86)	9 (5.01)	26 (11.98)	**0.0008**
Moderate comorbidity, 1–2	172 (43.54)	67 (37.64)	105 (48.39)	
Severe comorbidity, ≥3	188 (47.59)	102 (57.30)	86 (39.63)	
CCI, *n* (%)				
0–1	111 (28.10)	34 (19.10)	77 (35.48)	**0.002**
2	108 (27.34)	55 (30.89)	53 (24.42)	
≥3	176 (44.55)	89 (50.00)	87 (40.09)	
Barthel index (mean ± SD)	91.00 ± 18.41	85.28 ± 23.59	95.69 ± 10.64	**<0.0001**
Barthel ≤ 90, *n* (%)	105 (26.58)	68 (38.2)	37 (17.05)	**<0.0001**
mRS (mean ± SD)	0.78 ± 1.38	1.16 ± 1.57	0.47 ± 1.10	**<0.0001**
mRS > 1, *n* (%)	93 (23.54)	62 (34.83)	31 (14.29)	**<0.0001**
NIHSS admission (mean ± SD)	5.06 ± 6.04	8.10 ± 7.60	2.56 ± 2.30	**<0.0001**
NIHSS admission >6, *n* (%)	42 (10.63)	27 (15.17)	15 (6.91)	**0.009**
	All patients (*n* = 266)	OD admission (*n* = 114)	Non-OD admission (*n* = 152)	
Nutritional status on admission				
MNA-sf (mean ± SD)	12.18 ± 2.04	11.87 ± 1.97	12.41 ± 1.76	0.023
Well-nourished (12–14), *n* (%)	174 (65.41)	68 (59.65)	106 (69.74)	0.190
At risk (8–11), *n* (%)	80 (30.08)	39 (34.21)	41 (26.97)	
Malnourished (0–7), *n* (%)	12 (4.51)	7 (6.14)	5 (3.29)	

Bold indicates statistical significance value ($p < 0.05$).

Abbreviations: CCI, Charlson Comorbidity Index; MNA-sf, Mini Nutritional Assessment Short Form; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OD, oropharyngeal dysphagia; V-VST, volume–viscosity swallow test.

TABLE 2 Total mean direct healthcare related and non direct healthcare related costs during acute in-hospital admission, and at 12 months' follow-up (euros, 2019)

OD using V-VST	All patients ($n = 395$)	OD ($n = 178$)	Non-OD ($n = 217$)	p value
Acute in-hospital costs				
Hospitalization (ICU + neurology ward + tertiary hospital)	4516.57 ± 2731.84	5265.11 ± 3319.62	3902.55 ± 1925.78	**<0.0001**
Medication	80.01 ± 254.57	87.86 ± 264.16	73.57 ± 216.25	**<0.0001**
Enteral feeding and nutritional supplementation	2.21 ± 15.82	4.69 ± 23.28	0.18 ± 1.33	**<0.0001**
Total	4598.79 ± 2799.51	5357.67 ± 3391.62	3976.30 ± 1992.58	**<0.0001**
OD using V-VST	**All patients ($n = 374$)**	**OD ($n = 158$)**	**Non-OD ($n = 216$)**	
Subacute costs (3 months' follow-up)				
Direct healthcare and direct non-healthcare costs				
Chronic medication	232.3 ± 270.3	265.7 ± 296.8	207.9 ± 247.0	**0.036**
Re-hospitalization	388.6 ± 2055.4	416.3 ± 1651.0	368.3 ± 2310.0	0.163
In-hospital medication cost	4.7 ± 50.4	3.8 ± 19.9	5.4 ± 64.1	0.226
In-hospital enteral feeding and nutritional supplementation	0.02 ± 0.35	0.04 ± 0.50	0.01 ± 0.2	0.824
Emergency department	14.4 ± 33.2	11.0 ± 29.7	16.9 ± 35.4	0.090
Socio-sanitary care	641.7 ± 1628.6	992.6 ± 1946.0	385.0 ± 1296.0	**0.0002**
Long-term rehabilitation facilities	221.1 ± 1270.8	266.0 ± 1401.0	188.2 ± 1169.0	0.582
Nursing home	458.6 ± 1402.9	843.6 ± 1798.0	177.1 ± 930.3	**<0.0001**
Total	1961.4 ± 3284.5	2799.0 ± 3395.0	1349.0 ± 3067.0	**<0.0001**
Total (admission + subacute)	6554.3 ± 4870.7	8242.0 ± 5376.0	5320.0 ± 4053.0	**<0.0001**
Long-term costs (12 months' follow-up)				
Direct healthcare and direct non-healthcare costs				
Chronic medication	881.75 ± 961.48	936.94 ± 893.07	841.38 ± 1.006.67	0.169
Re-hospitalization	930.84 ± 4.423.50	1083.76 ± 5.985.29	818.98 ± 2765.23	0.970
In-hospital medication cost	10.73 ± 84.88	14.98 ± 104.50	7.64 ± 66.98	0.875
In-hospital enteral feeding and nutritional supplementation	0.09 ± 1.48	0.21 ± 2.21	0.01 ± 0.18	0.389
Emergency department	64.49 ± 120.49	64.52 ± 125.98	64.48 ± 116.30	0.162
Socio-sanitary care	716.69 ± 2.146.19	1156.67 ± 2.834.90	394.86 ± 1360.72	**0.0002**
Long-term rehabilitation facilities	428.76 ± 2.820.82	395.30 ± 2.243.84	453.24 ± 3176.97	0.597
Nursing home	1464.53 ± 5.002.62	2522.37 ± 6392.77	690.73 ± 3467.16	**<0.0001**
Total	4497.89 ± 8839.78	6174.68 ± 10,957.68	3271.34 ± 6626.48	**<0.0001**
Acute and long-term direct healthcare and non-healthcare costs				
1-year total costs	9090.88 ± 9873.82	11,617.58 ± 12,033.58	7242.78 ± 7402.55	**<0.0001**

Bold indicates statistical significance value ($p < 0.05$).

Abbreviations: ICU, intensive care unit; OD, oropharyngeal dysphagia; V-VST, volume-viscosity swallow test.

rehabilitation/convalescence facility, 2.4 ± 13.9; and in nursing homes, 7.3 ± 22.3. Significantly higher patient stays in socio-sanitary institutions (10.7 ± 20.9 days vs. 4.1 ± 14.00 days, $p = 0.0002$) and nursing homes (13.4 ± 28.6 days vs. 2.8 ± 17.8 days, $p < 0.0001$) were observed for patients with OD.

At 12 months' follow-up, mean patient visits to the emergency department were 0.71 ± 1.32, and mean stays in re-hospitalizations 1.47 ± 7.02; in a socio-sanitary institution, 7.71 ± 23.09; in a long-term rehabilitation/convalescence facility, 4.69 ± 30.84; and in nursing homes, 23.28 ± 79.53. Significantly higher patient stays in socio-sanitary institutions (12.45 ± 30.51 days vs. 4.25 ± 14.64 days, $p = 0.0002$) and nursing homes (40.10 ± 101.63 days vs. 10.98 ± 55.12 days, $p < 0.0001$) were observed for patients with PS-OD. Table S1 summarizes long-term resource consumption of the variables measured in this study.

Costs in the subacute and chronic phases

At 3 months' follow-up, mean costs were €6554.3 ± €4870.7 per patient. The only significant differences found between patients with and without PS-OD were related to socio-sanitary care (€992.6 ± €1946.0 vs. €385.0 ± €1296.0, $p = 0.0002$) and nursing homes (€843.6 ± €1798.0 vs. €177.1 ± €930.3, $p < 0.0001$), higher for patients with PS-OD. At 3 months' follow-up, total costs (acute plus subacute direct healthcare and non-healthcare costs) were higher for those patients with PS-OD (€8242.0 ± €5376.0 vs. €5320.0 ± €4053.0, $p < 0.0001$).

At 12 months' follow-up, mean costs were €9090.88 ± €9873.82 per patient. Although there was a constant trend towards higher costs related to chronic medication, re-hospitalizations, in-hospital EF and NS and visits to the emergency department, no significant differences were found between those patients with PS-OD and those without. Costs related to socio-sanitary care (€1156.67 ± €2834.90 vs. €394.86 ± €1360.72, $p = 0.0002$) and nursing homes (€2522.37 ± €6392.77 vs. €690.73 ± €3467.16, $p < 0.0001$) were higher for patients with PS-OD. At 12 months of follow-up, total costs (acute plus long-term direct healthcare and non-healthcare costs) were higher for those patients with PS-OD (€11,617.58 ± €12,033.58 vs. €7242.78 ± €7402.55, $p < 0.0001$). Table 2 summarizes these findings.

Resource consumption and costs associated with nutritional risk or malnutrition on admission and at 3 months' follow-up

Patients at risk of malnutrition or malnourished on admission had significantly higher hospital stays (8.4 ± 4.8 days vs. 6.9 ± 4.2 days, $p = 0.004$) and EF and NS consumption (9.8% vs. 2.3%, $p = 0.013$) and incurred major costs (€5370.0 ± €3052.0 vs. €4445.0 ± €2759.0, $p = 0.004$) during acute hospitalization and at 3 months' follow-up (€8145.0 ± €5868.0 vs. €5830.0 ± €4204.0, $p = 0.001$). Table 3 shows a summary of the main sociodemographic and clinical characteristics and nutritional status of patients on admission. At 3 months' follow-up, 69 out of 231 patients (29.8%) that could be evaluated were at risk of malnutrition or malnourished, with more visits to the emergency department (1.0 ± 1.4 vs. 0.67 ± 1.2, $p = 0.029$) and stays in nursing homes (47.1 ± 118.1 days vs. 4.3 ± 38.8 days, $p < 0.0001$) at 1-year follow-up without significant differences on stays related to re-hospitalizations, socio-sanitary institution and long-term rehabilitation/convalescence facilities. Table S2 summarizes acute and long-term resource consumption and its

TABLE 3 Main sociodemographic and clinical characteristics of the patients included in the study with and without malnutrition or risk of malnutrition

Risk MN/MN using MNA-sf	All patients ($n = 395$)	Risk MN/MN ($n = 92$)	No risk MN/MN ($n = 174$)	p value
Sociodemographic data				
Age, years (mean ± SD)	73.2 ± 13.3	75.0 ± 12.5	70.9 ± 12.7	**0.008**
Male, n (%)	211 (53.42)	(41)	(112)	**0.003**
Patient status before admission				
Comorbidity, n (%)				
No comorbidity, 0	35 (8.86)	12 (13.0)	8 (4.6)	**0.037**
Moderate comorbidity, 1–2	172 (43.54)	37 (40.2)	84 (48.3)	
Severe comorbidity, ≥3	188 (47.59)	43 (46.7)	82 (47.1)	
CCI, n (%)				
0–1	111 (28.10)	21 (22.8)	54 (31.0)	0.346
2	108 (27.34)	29 (31.5)	46 (26.4)	
≥3	176 (44.55)	42 (45.7)	74 (42.5)	
Barthel index (mean ± SD)	91.00 ± 18.41	86.9 ± 21.6	95.7 ± 10.2	**<0.0001**
Barthel ≤ 90, n (%)	105 (26.58)	33 (35.9)	29 (16.7)	**0.0007**
mRS (mean ± SD)	0.78 ± 1.38	0.9 ± 1.5	0.4 ± 1.0	**0.002**
mRS > 1, n (%)	93 (23.54)	25 (27.2)	24 (13.8)	**0.012**
NIHSS admission (mean ± SD)	5.06 ± 6.04	5.3 ± 5.6	3.6 ± 3.9	**0.012**
NIHSS admission >6, n (%)	42 (10.63)	22 (23.9)	25 (14.4)	0.063

Bold indicates statistical significance value ($p < 0.05$).

Abbreviations: CCI, Charlson Comorbidity Index; MN, malnutrition; MNA-sf, Mini Nutritional Assessment Short Form; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

relation with nutritional status. Long-term costs were significantly higher for those patients at risk of malnutrition or malnourished compared with well-nourished patients (€10,678.0 ± €10,466.9 vs. €6230 ± €4326.0, $p = 0.01$). Table 4 summarizes these findings. Table 5 summarizes differences in costs between those patients with and without OD and with and without risk of malnutrition or malnutrition.

Respiratory infections at 1-year follow-up and their influence on costs

Sixty-two out of 374 patients (16.6%) who underwent the 1-year follow-up suffered at least one episode of respiratory infection (78 episodes in total, mean 1.26/affected patient) and incurred significantly higher long-term costs (€13,806.0 ± €11,834.0 vs. €8154.0 ± €9190.0, $p < 0.0001$). Table 5 summarizes differences in costs between patients with and without PS-OD and with or without respiratory infections.

Total acute and long-term costs on those patients who suffered from OD and its complications

Those patients with PS-OD and at risk of malnutrition or malnourished at 3 months' follow-up incurred higher costs at 12 months' follow-up than patients without PS-OD (€14,295.6 ± €11,334.5 vs. €7242.8 ± €7402.6, $p < 0.001$). Patients with PS-OD and respiratory infection incurred higher costs than patients without PS-OD (€16,487.0 ± €11,603.9 vs. €7242.8 ± €7402.6, $p < 0.0001$) at 12 months' follow-up. Patients with PS-OD at risk of or malnourished who had a respiratory infection incurred greater mean costs than patients without PS-OD (€19,817.58 ± €13,724.83 vs. €7242.8 ± €7402.6, $p < 0.0004$) at 12 months' follow-up. Table 6 shows a comparison of mean costs between patients with and without PS-OD, risk of or malnutrition, and respiratory infections.

Multivariate analysis

After adjusting for possible confounding factors, OD was independently associated with an increased cost of €789.68 ($p = 0.011$) during hospitalization in the acute phase and €873.5 ($p = 0.084$) in the subacute phase but no significant effect was observed in the chronic phase. For nutritional status, moving from one category (well-nourished, at risk of malnutrition and malnourished) to the next, worse one, was independently associated with a cost increase of €1277.39 ($p = 0.004$) at subacute phase and of €2303.38 ($p = 0.001$) at chronic phase. The presence of at least one respiratory infection was independently associated with a cost increase of €3792.62 ($p < 0.001$) in the subacute phase and of €3034.08 ($p < 0.011$) in the chronic phase. Results of the multivariate analysis are described in Table S3.

Costs from the hospital and the healthcare system perspectives

In the case of patients with PS-OD, mean hospitalization costs (hospital perspective) were lower than costs outside acute hospitalization (health care system perspective) (€5357.67 ± €3391.62 vs. €6174.68 ± €10,957.68, respectively), whilst in those patients without OD mean hospitalization costs were higher than subacute and chronic costs (€3976.30 ± €1992.58 vs. €3271.34 ± €6626.48, respectively). In the case of patients affected or not by risk of malnutrition or malnutrition, chronic costs were higher in both cases compared to hospitalization costs (€2945.00 ± €4593.00 vs. €6029.00 ± €9018.00 and €1384.00 ± €2397.00 vs. €2120.00 ± €3494.00, respectively).

DISCUSSION

This study shows a significant and independent increase in health economic costs of €789.68 during hospitalization for patients with PS-OD, and €873.5 at 3 months' follow-up. Patients with poor nutritional status at 3 months showed a significant and independent cost increase of €2303.38 at 12 months' follow-up, and for patients with at least one respiratory infection at 3 and 12 months' follow-up the costs were increased by €3792.62 and €3034.08, respectively. This shows an independent increase in costs associated with PS-OD during hospitalization that can increase exponentially with the development of its main complications (malnutrition and respiratory infections) during long-term follow-up. The 1-year cost of a patient with PS-OD, malnutrition and at least one episode of respiratory infection is €19,817.58 ± €13,724.83 versus €7242.8 ± €7402.6 for post-stroke patients without OD, a clear indication of the economic burden of PS-OD from both the hospital and the healthcare system perspective.

In this study, about half the costs incurred by our post-stroke patients were attributed to acute hospitalization. Significant mean cost increases were observed for patients with PS-OD (€5357.67 ± €3391.62 vs. €3976.30 ± €1992.58) and patients at risk of malnutrition or malnourished on stroke admission (€5370.0 ± €3052.0 vs. €4445.0 ± €2759.0), mainly due to longer hospital stays (8.33 ± 5.21 vs. 6.20 ± 3.05 days and 8.40 ± 4.80 vs. 6.90 ± 4.20 days respectively). These data coincide with a previously published systematic review that assessed the influence of OD secondary to all aetiologies on length of stay and costs finding that PS-OD patients had a longer and more variable length of stay of 4.73 days (95% confidence interval 2.7–7.2) and an increase of 40.36% in costs [25]. Moreover, previous studies showed an increase of €3000 on hospitalization costs for patients with ischaemic PS-OD in France and of 14,000 Swiss Francs in Switzerland [26], and an increase of approximately US$6589 on patients needing tube feeding after ischaemic or haemorrhagic stroke in the USA [27]. In patients transferred to a rehabilitation ward after haemorrhagic stroke, OD has been identified as a significant predictor of the total medical costs using a stepwise multivariate analysis with a

TABLE 4 Total mean direct healthcare related and non direct healthcare related costs during acute in-hospital admission and at 12 months' follow-up

Risk of MN/MN at admission	All patients ($n = 395$)	Risk MN/MN ($n = 92$)	No risk MN/MN ($n = 174$)	*p* value
Acute in-hospital costs				
Hospitalization (ICU + neurology ward + tertiary hospital)	4516.57 ± 2731.84	5321.0 ± 3038.0	4350.0 ± 2655.0	**0.004**
Medication	80.01 ± 254.57	46.6 ± 149.0	93.3 ± 294.8	**0.007**
Enteral feeding and nutritional supplementation	2.21 ± 15.82	3.2 ± 14.3	2.4 ± 21.1	**0.013**
Total	4598.79 ± 2799.51	5370.0 ± 3052.0	4445.0 ± 2759.0	**0.004**
Risk of MN/MN at admission	**All patients ($n = 374$)**	**Risk MN/MN ($n = 88$)**	**No risk MN/MN ($n = 174$)**	
Subacute costs (3 months' follow-up)				
Direct healthcare and direct non-healthcare costs				
Chronic medication	232.3 ± 270.3	260.9 ± 295.6	236.4 ± 275.8	0.344
Re-hospitalization	388.6 ± 2055.4	797.2 ± 3534.0	237.6 ± 1250.0	0.177
In-hospital medication cost	4.7 ± 50.4	12.7 ± 100.1	2.1 ± 15.4	0.188
In-hospital enteral feeding and nutritional supplementation	0.02 ± 0.35	0.03 ± 0.3	0.04 ± 0.5	1.000
Emergency department	14.4 ± 33.2	13.5 ± 32.5	13.6 ± 32.6	1.000
Socio-sanitary care	641.7 ± 1628.6	821.4 ± 1998.0	575.1 ± 1310.0	0.963
Long-term rehabilitation facilities	221.1 ± 1270.8	368.4 ± 1596.0	142.1 ± 1076.0	0.123
Nursing home	458.6 ± 1402.9	671.2 ± 1654.0	177.5 ± 932.2	**0.0002**
Total	1961.4 ± 3284.5	2945.0 ± 4593.0	1384.0 ± 2397.0	**0.022**
Total (admission + subacute)	6554.3 ± 4870.7	8145.0 ± 5868.0	5830.0 ± 4204.0	**0.001**
Risk of MN/MN assessed at 3 months' follow-up	**All patients ($n = 374$)**	**Risk MN/MN ($n = 69$)**	**No risk MN/MN ($n = 162$)**	
Long-term costs (12 months' follow-up)				
Direct healthcare and direct non-healthcare costs				
Chronic medication	881.75 ± 961.48	993.4 ± 746.1	884.4 ± 1060.0	**0.048**
Re-hospitalization	930.84 ± 4.423.50	930.6 ± 2837.0	478.0 ± 1664.0	0.358
In-hospital medication cost	10.73 ± 84.88	17.51 ± 113.4	3.2 ± 24.5	0.363
In-hospital enteral feeding and nutritional supplementation	0.09 ± 1.48	0.0 ± 0.0	0.0 ± 0.0	1.000
Emergency department	64.49 ± 120.49	93.7 ± 126.8	61.3 ± 111.5	**0.029**
Socio-sanitary care	716.69 ± 2.146.19	681.3 ± 1719.0	421.0 ± 1357.0	0.068
Long-term rehabilitation facilities	428.76 ± 2.820.82	526.9 ± 3089.0	0.0 ± 0.0	0.088
Nursing home	1464.53 ± 5002.62	2965.0 ± 7431.0	271.8 ± 2441.0	**<0.0001**
Total	4497.89 ± 8839.78	6029.0 ± 9018.0	2120.0 ± 3494.0	**0.0008**
Acute and long-term direct healthcare and non-healthcare costs				
1-year total costs according to risk or malnutrition at 3-month follow-up	9090.88 ± 9873.82	10,678.0 ± 10,446.0	6230.0 ± 4326.0	**0.010**

Bold indicates statistical significance value ($p < 0.05$).

Abbreviations: ICU, intensive care unit; MN, malnutrition.

beta coefficient of 1025.8 (95% confidence interval 193.9–1857.8, $p < 0.001$) in Taiwan [28].

To our knowledge, the only study that has previously reported data on the long-term adjusted effect of PS-OD on sanitary costs was performed by Bonilha et al. in the USA. This study reported an adjusted incremental cost at 1-year follow-up of US$4510 for Medicare for patients with ischaemic PS-OD [29]. In the case of respiratory infections, five previous retrospective studies reported

TABLE 5 Chronic, 12 months' follow-up mean total cost of patients with PS-OD, patients at risk of malnutrition/malnutrition at 3 months' follow-up and patients with respiratory tract infections

Acute and long-term direct healthcare and non-healthcare costs

	All patients ($n = 374$)	Risk MN/MN ($n = 69$)	Well-nourished ($n = 162$)	Non-OD ($n = 216$)	OD ($n = 158$)
Comparison between OD and risk of MN/MN					
1-year total costs	9090.88 ± 9873.82	10,678.0 ± 10,446.0	6230.0 ± 4326.0	7242.8 ± 7402.6	11,617.6 ± 12,033.6
p value	Risk MN/MN		**	*	ns
	Well-nourished			ns	****
	Non-OD				****
	OD				

	All patients ($n = 374$)	RTI ($n = 62$)	Non-RTI ($n = 312$)	Non-OD ($n = 216$)	OD ($n = 158$)
Comparison between OD and RTI					
1-year total costs	9090.88 ± 9873.82	13,806.0 ± 11,834.0	8154.0 ± 9190.0	7242.8 ± 7402.6	11,617.6 ± 12,033.6
p value	RTI		***	****	ns
	Non-RTI			ns	****
	Non-OD				****
	OD				

Abbreviations: MN, malnutrition; OD, oropharyngeal dysphagia; RTI, respiratory tract infection.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

**** $p < 0.0001$.

cost increases between US$1456 and US$27,633 during hospitalization after stroke on patients who developed pneumonia, but did not study beyond acute hospitalization [28, 30–33]. Regarding malnutrition, the prospective study performed by Gomes et al. reported an increase in costs during hospitalization at 6 months after stroke for patients at high risk of malnutrition in the UK (£8720 vs. £4920, $p < 0.001$) [34].

In our patients with PS-OD, total mean hospitalization costs (acute phase) were lower than subacute and long-term chronic costs (subacute and chronic phases) whilst in patients without PS-OD most costs occurred during hospitalization. The multivariate analysis showed that the long-term costs of OD could be more related to its complications (malnutrition and respiratory infections) and the costs during hospitalization due to its effect on resource consumption. This would explain why the chronification of OD together with the appearance of its long-term complications is the main explanation for the exponential increase of costs in these patients.

The early and appropriate management of PS-OD patients is essential in the acute phase of hospitalization and the subacute and chronic phases of patient rehabilitation. These data agree with a previously published systematic review on PS-OD but add insights into the costs of OD beyond acute admission, and the impact of malnutrition and respiratory infections, which are direct consequences of OD [15, 16]. The data provided in this study could be a first step to study the cost-effectiveness of appropriate management of these complications. Considering that OD, malnutrition and respiratory infections are associated with higher costs after stroke, massive screening and specialized management of patients with PS-OD and malnutrition could significantly improve patient outcome and cost-effectiveness. A recent Cochrane review on the treatment of PS-OD concluded that, whilst new treatment strategies improved swallowing parameters, they seemed not enough to reduce clinical outcomes such as mortality or respiratory infections [35]. Early screening after admission, accurate clinical and instrumental assessment and appropriate compensatory and rehabilitation strategies would reduce dysphagia costs and complications in post-stroke patients.

Costs of PS-OD comprise acute in-hospital and long-term sanitary and social costs related to nutritional and respiratory complications, but also direct non-healthcare costs and indirect costs associated with loss of patient productivity and other unknown intangible costs. In addition, the healthcare expenses related to instrumental diagnosis and treatment of PS-OD should also be considered. In centres with protocols using instrumental explorations (videofluoroscopy or fibre optic endoscopic evaluation of swallowing), the costs of these explorations during the acute phase must be added. In centres using behavioural intervention provided by speech and language therapists or neurorehabilitation strategies (electrical or pharmacological), the cost of these treatments must also be considered for patients with PS-OD. Costs related to patient stays were estimated from public prices. Costs related to patient mortality

TABLE 6 Mean total cost of PS-OD including respiratory tract infections and risk of malnutrition/malnutrition (3 months)

OD V-VST	All patients ($n = 374$)	Non-OD admission ($n = 216$)	Non-OD+RTI ($n = 28$)	Non-OD+risk MN/MN ($n = 40$)	Non-OD non-RTI ($n = 188$)	Non-OD non-risk MN/MN ($n = 103$)	OD ($n = 158$)	OD + RTI ($n = 34$)	OD + risk MN/MN 3m ($n = 29$)	OD non-RTI ($n = 124$)	OD + non-risk MN/MN ($n = 59$)
Acute and long-term direct healthcare and non-healthcare costs											
1-year total costs	9090.9 ± 9873.8	7242.8 ± 7402.6	10,550.0 ± 11,260.0	8055.0 ± 8829.0	6750.0 ± 6566.0	5726.0 ± 4070.0	11,617.6 ± 12,033.6	16,487.0 ± 11,603.9	14,295.6 ± 11,334.5	10,282.0 ± 11,851.0	7111.0 ± 4645.0
p value	Non-OD		ns	ns	ns	ns	****	****	***	**	ns
	Non-OD + RTI			ns	ns	ns	ns	ns	ns	ns	ns
	Non-OD + MN				ns	ns	ns	**	*	ns	ns
	Non-OD − RTI					ns	****	****	***	***	ns
	Non-OD − MN						****	****	***	***	ns
	OD							ns	ns	ns	ns
	OD + RTI								ns	ns	**
	OD + MN									ns	ns
	OD − RTI										ns
	OD − MN										

Abbreviations: MN, malnutrition; OD, oropharyngeal dysphagia; PS-OD, post-stroke oropharyngeal dysphagia; RTI, respiratory tract infection; V-VST, volume–viscosity swallow test.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

**** $p < 0.0001$.

were not measured which could lead to an artificial reduction of the real cost of the dysphagia group, as they had a significantly higher mortality. This study was performed at Mataró Hospital, a 300-bed community hospital near Barcelona that serves more than 275,000 inhabitants. Management of all types of strokes is performed at the emergency room and neurology ward by specialized nursing and medical teams and at the intensive care unit if required. Strokes can be treated with thrombolysis and transferred to our referral centre if thrombectomy is required. The results of a prospective stroke registry of patients admitted to Mataró Hospital during the last 10 years describing the main clinical characteristics and the outcomes of treatment have been published [36].

In summary, this study shows increased costs—direct and resource consumption—during hospitalization and long-term follow-up in patients with PS-OD and/or its main complications, malnutrition and respiratory infections. Future studies are needed to assess cost savings related to the correct management of PS-OD, malnutrition and the risk of aspiration which can cause pneumonia. This increase in the economic costs of OD is also a reflection of the severe clinical consequences for stroke patients with these complications.

ACKNOWLEDGEMENTS

This work has been conducted within the framework of a doctoral thesis in medicine from the Medicine Department of the Autonomous University of Barcelona. The authors thank Dr Desiree Muriana, MD, PhD, from the Neurology Department of Mataró Hospital for her assistance with the performance of this study; David López Faixó, BPharm, from the Pharmacy Department of Mataró Hospital for his assistance with the recompilation of in-hospital and socio-sanitary care institution medication and nutrition data; and Laura Chercoles and Jane Lewis for editing the English.

CONFLICT OF INTEREST

The authors affirm that there are no conflicts of interest. The sponsors had no role in the design or development of this study.

AUTHOR CONTRIBUTIONS

Sergio Marin: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); software (lead); supervision (lead); validation (lead); visualization (lead); writing—original draft (lead); writing—review and editing (lead). Mateu Serra-Prat: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); resources (supporting); software (supporting); supervision (lead); validation (lead); visualization (lead); writing—original draft (supporting); writing—review and editing (supporting). Omar Ortega Fernández: Conceptualization (lead); data curation (lead); formal analysis (lead); investigation (lead); methodology (lead); software (lead); supervision (lead); validation (lead); visualization (lead); writing—original draft (supporting); writing—review and editing (supporting). Monica Audouard Fericgla: Data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); software (supporting); validation (supporting); writing—review and editing (supporting). Jordi Valls: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (lead); resources (supporting); supervision (supporting); validation (supporting). Elisabet Palomera: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); software (supporting); supervision (supporting); validation (supporting). Ramon Cunillera: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (lead); resources (supporting); supervision (supporting); validation (supporting). Ernest Palomeras: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (lead); resources (supporting); supervision (supporting); validation (supporting). Josep Maria Ibáñez: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (lead); resources (supporting); supervision (supporting); validation (supporting). Pere Clave: Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); software (lead); supervision (lead); validation (lead); visualization (lead); writing—original draft (lead); writing—review and editing (lead).

DATA AVAILABILITY STATEMENT

Due to the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to CSdM at Professor Pere Clavé, Director of Research and Innovation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Marin S, Serra-Prat M, Ortega O, et al. Healthcare costs of post-stroke oropharyngeal dysphagia and its complications: malnutrition and respiratory infections. *Eur J Neurol*. 2021;28:3670–3681. https://doi.org/10.1111/ene.14998

DOI: 10.1111/ene.15223

european journal
of neurology
the official journal of the european academy of neurology

CORRIGENDUM

In the article by Marin et al. [1], one of the funder details was previously missing on page 3670. The complete funding information should read:

Funding information

Financial support received from research grants from Nutricia Danone Advanced Medical Nutrition (HESDY Grant); Fundació Salut del CSdM, Strategic Action Grant in Oropharyngeal Dysphagia provided by the Centro de Investigación Biomédica en Red en el Área de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, DJO Global, la Fundació la Marató de TV3 (11/2310) and Proyectos de Investigación Clínica Independiente, Instituto de Salud Carlos III (ICI20/00117).

The authors apologise for the error.

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1. Marin S, Serra-Prat M, Ortega O, et al. Healthcare costs of post-stroke oropharyngeal dysphagia and its complications: malnutrition and respiratory infections. *Eur J Neurol*. 2021;28:3670–3681. doi:10.1111/ene.14998

4.3 Article 3: Economic evaluation of clinical, nutritional and rehabilitation interventions on oropharyngeal dysphagia after stroke: a systematic review

Bibliographic reference: Marin S, Ortega O, Serra-Prat M, Valls E, Pérez-Cordón L, Clavé P. Economic Evaluation of Clinical, Nutritional and Rehabilitation Interventions on Oropharyngeal Dysphagia after Stroke: A Systematic Review. Nutrients. 2023;15(7):1714. doi: 10.3390/nu15071714.

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Systematic Review

Economic Evaluation of Clinical, Nutritional and Rehabilitation Interventions on Oropharyngeal Dysphagia after Stroke: A Systematic Review

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Abstract: Background: Post-stroke oropharyngeal dysphagia (PS-OD) and its complications increase healthcare costs, suggesting that its appropriate management is cost-effective. We aimed to assess the efficiency of healthcare interventions in PS-OD management. Methods: A systematic review was conducted following PRISMA recommendations. Four databases were searched from inception through 30 June 2021. Outcome measures were cost-effectiveness and cost-savings of healthcare interventions. English and Spanish literature were included. Narrative and tables were used to present and synthesise evidence. Quality was evaluated using the CHEERS Statement. Results: A total of 244 studies were identified, and 10 were included. Screening and diagnosis of PS-OD studies found: (1) adjusted reduction in hospitalisation costs when assessed during the first admission day; (2) non-significant reduction in hospitalisation costs with OD management after thrombolysis; and (3) videofluoroscopy as the most cost-effective screening method (compared to bedside evaluation and a combination of both). Two studies showed cost-effective rehabilitation programmes, including OD management. Pelczarska et al. showed an incremental cost–utility ratio of texture-modified diets using a gum-based thickener of 20,977 PLN (4660€) following a dynamic model, and Kotecki et al. commercially prepared thickened fluids that were 44% to 59% less expensive than in situ prepared fluids. Elia et al. showed home enteral nutrition was cost-effective (£12,817/QALY), and Beavan et al. showed higher nutrient intake and low increase in hospitalisation costs using looped-nasogastric tubes (£5.20 for every 1% increase). Heterogeneity between studies precluded a quantitative synthesis. Conclusions: Included studies suggest that healthcare interventions aiming to prevent OD complications are cost-effective. However, studies assessing novel strategies are needed.

Keywords: deglutition disorders; nutrition therapy; stroke; brain ischemia/complications; cerebral haemorrhage; economics; health resources; systematic review

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Citation: Marin, S.; Ortega, O.; Serra-Prat, M.; Valls, E.; Pérez-Cordón, L.; Clavé, P. Economic Evaluation of Clinical, Nutritional and Rehabilitation Interventions on Oropharyngeal Dysphagia after Stroke: A Systematic Review. *Nutrients* **2023**, *15*, 1714. https://doi.org/10.3390/nu15071714

Academic Editor: Susanna C. Larsson

Received: 26 February 2023
Revised: 25 March 2023
Accepted: 27 March 2023
Published: 31 March 2023

1. Introduction

Oropharyngeal dysphagia (OD) is one of the main complications suffered by post-stroke patients [1,2]. OD is highly prevalent in the acute stroke phase (40–78%), and although improvements can be observed during post-stroke recovery, it becomes a chronic condition in up to half of cases [1,3–5]. Post-stroke OD (PS-OD) impairs the efficacy and safety of swallowing, which causes severe complications such as dehydration, malnutrition, respiratory infection, aspiration pneumonia, hospital readmission and death [6–9]. PS-OD leads to a deterioration in the health status of patients, and it is an independent risk factor for longer hospital stay, institutionalisation after hospital discharge, poorer functional capacity and increased mortality 3 months after stroke [3]. Patients with PS-OD had longer hospital stays [10] and increased healthcare-related costs of around 15,000€ (approx. 16,900 USD), which could reach 24,000€ (approx. 27,600 USD) in patients with a pneumonia episode [11,12]. A recent study aiming to assess the independent cost of PS-OD and its main complications (malnutrition and respiratory infections) found that OD produced a significant and independent increase in healthcare costs of 789.68€ during hospitalisation and 873.50€ in the subacute stroke phase. Additionally, significant and independent costs were attributed to malnutrition and respiratory infections, two well-recognized complications of PS-OD [13]. In this study, the presence of poorer nutritional status (at risk of malnutrition or malnourished) led to a significant and independent increase of 1277.39€ during the sub-acute stroke phase (3-months follow up) and 2303.38€ in the chronic phase (12-months follow up); the presence of at least one episode of respiratory infection was associated with a significant and independent increase of 3792.62€ in the sub-acute stroke phase and 3034.08€ in the chronic phase; and a greater significant increase in healthcare-related costs at 12-months follow up was observed in those patients who had OD, were at risk of malnutrition or malnourished and had an episode of respiratory infection vs. those patients who did not develop PS-OD (19,817.58 $\pm$ 13,724.83 vs. 7242.80 $\pm$ 7402.60€, $p < 0.0004$) [13].

Appropriate management of PS-OD involves early screening and diagnosis of patients, compensation of the deglutition-impaired mechanisms and restoration of the swallowing function. This process is needed in order to avoid PS-OD-related complications and to improve patients' health and quality of life [4,14]. The screening of OD is recommended by the AHA/ASA guidelines in the early stroke phases before the patients begin eating, drinking or taking oral medication [15] and is also recommended by the position statements of the European Society for Swallowing Disorders (ESSD) and by the recent European Guideline on diagnosis and treatment of PS-OD developed by the European Stroke Organisation (ESO) and the ESSD [16,17].

Current management of PS-OD is not standardised and can go from classical compensatory strategies to more innovative restorative strategies. Classical treatment for OD is mainly based on compensatory strategies to avoid biomechanical impairment related to the efficacy and safety of deglutition, such as the use of thickened fluids, texture-modified foods and postural changes [18]. There is evidence showing that viscosity and texture modification minimises the risk for aspiration during swallowing [19]. Several studies in PS-OD patients using thickened fluids during videofluoroscopy have shown that increasing shear-viscosity causes a strong viscosity-dependent therapeutic effect on the safety of swallowing, reducing laryngeal vestibule penetrations and tracheobronchial aspirations and their severity [18,20]. Changes in posture, such as chin down or head turn, usually change the biomechanics and pharyngeal and intrabolus pressure generation during swallowing and may reduce the incidence of aspiration in the specific cases [21,22].

On the other hand, innovative strategies that aim to restore the swallowing function are divided into peripheral sensory and central stimulation [23]. Peripheral stimulation includes the use of pharmacological agents such as transient receptor potential (TRP) channel agonists as well as intrapharyngeal or transcutaneous electrical stimulation (TES) strategies to increase the sensory input to improve the oropharyngeal swallow response. A recent systematic review on pharmacological agents for neurogenic dysphagia concluded that TRP channel agonists may be beneficial for neurogenic dysphagic patients [24]. Regarding TES, the National Institute for Health and Care Excellence (NICE) declared it as a safe and potentially beneficial therapy for PS-OD patients, although the actual evidence is limited in quality/quantity [25,26]. We previously found that TES greatly improved the safety of swallow and reduced the need for fluid thickening in PS-OD patients and that the effects were maintained in the long term [27].

Central stimulation strategies, including transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS), are currently being developed [28]. A recent review on non-invasive brain stimulation concluded that evidence suggests that rTMS and tDCS show promise as a treatment for PS-OD [29]. A systematic review and meta-analysis on the efficacy of noninvasive neurostimulation therapies for PS-OD patients found that rTMS, tDCS and electrical stimulation were effective for treating these patients; furthermore, rTMS was the most effective therapy [30]. Finally, a review on the current evidence on treatment for OD concluded that the quality of evidence that supports the use of innovative treatments is comparable if not better than classical treatments, as their clinical efficacy is evaluated by randomised controlled trials mainly in patients with PS-OD. However, there is still a high heterogeneity in treatment regimens, long-term effects, underlying mechanisms, and the effects of these strategies in other phenotypes of OD patients [31].

Although some important data on the healthcare-related costs associated with PS-OD and its main complications have emerged recently, the potential cost-savings and the cost-effectiveness of the mentioned strategies is not well known [12,13]. We hypothesise that these strategies not only can improve patients' health status and quality of life, but can also provide important cost savings by avoiding the development of PS-OD complications. These interventions are safe, simple and based on the best scientific evidence collected over decades [30]. The purpose of this study is to collect all the available literature on the efficiency or cost-effectiveness of clinical, rehabilitation, and nutritional interventions such as early PS-OD screening and assessment as well as on the compensatory and neurorehabilitation strategies for the management of PS-OD.

2. Materials and Methods

A systematic review on the economic evaluations of clinical, rehabilitation and nutritional interventions on the appropriate management of PS-OD in patients who suffered a stroke was performed. This systematic review was performed following the recommendations stated by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [32]. The protocol for this systematic review was registered in the international prospective register of systematic reviews of the Center for Reviews and Dissemination (PROSPERO) (registration number: CRD42020136245) and published in a peer-reviewed journal [33]. The main outcome of interest was cost together with the health benefits (such as cost-effectiveness) associated with the healthcare interventions aimed to assess, treat and care for PS-OD. The processes to carry out this systematic review (literature selection process and extraction and quality assessment of included articles) together with task organisation and the resource and data management software used are also explained in the protocol of this study [33].

2.1. Literature Search

We searched MEDLINE using PubMed, Embase using Ovid, the National Health Service Economic Evaluation Database (NHS-EED) using the Center for Reviews and Dissemination Database of the University of York and the Cost-Effectiveness Analysis (CEA) Registry database of the Center for the Evaluation of Value and Risk in Health. English and Spanish literature was searched from inception through 30 June 2021. The systematic review did not include posters, abstracts, book chapters or unpublished literature. The search strategy (combined MeSH and search terms used) is available in the previously published protocol of this study and reported in the Supplementary Material [33].

2.2. Selection Process

Studies identified through literature search were selected using a double-phase process. In the first phase, a screening of the title and abstract of the identified articles was performed to avoid studies not reporting at least minimal relevant information in this field. A second phase to exclude articles according to eligibility criteria was performed. Studies were included if they (i) had economic evaluations in which the intervention effect was quantified by effectiveness results or other measures of effect on healthcare (cost minimization, cost-utility, cost-effectiveness and cost–benefit analysis) or (ii) studies in which cost-savings-applying healthcare interventions in OD management were assessed (studies in which potential savings were reported by applying interventions on OD assessment and management) and provided information on post-stroke adult patients (≥18 years) with PS-OD. Studies were excluded if they were (i) partial economic evaluation studies such as cost-of-illness studies, (ii) studies on oesophageal dysphagia management, or (iii) studies in which OD was related to an aetiology different than stroke or (iv) duplicate publications of the same study.

2.3. *Data Presentation and Summary Measures*

Data were reported in their original format using tables and narrative. A meta-narrative method and tables were used to synthesise evidence. Results are presented in the following order: (i) studies reporting economic evaluations of the screening and/or assessment of OD, (ii) studies reporting economic evaluations of rehabilitation programs that included interventions on PS-OD, (iii) economic evaluation studies of OD interventions related to compensatory treatment strategies such as food consistency modification and, (iv) studies reporting economic evaluations of enteral tube feeding nutrition and provision in patients with PS-OD. Information was presented according to the Centre for Reviews and Dissemination recommendations [34]. Finally, a meta-narrative synthesis of the extracted information was performed in which we described both the assessed evidence on the efficiency of different interventions together with some of the key aspects of quality assessment evaluation. We reported whether studies identified, measured, and assessed the complete form of all the important costs for each assessed alternative, whether the study structure (study approach, data source) was performed in the most appropriate way to answer the study question and whether the most important factors to understand these economic evaluations were properly reported.

2.4. *Quality Assessment*

A specific tool to assess the internal validity and the reporting of key factors of economic evaluation studies was used. We applied the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement [35]. A set of items that apply to a critical appraisal of economic evaluation studies is provided in this checklist. Each item represents a study aspect that we rated as "Yes, partly, no, or not applicable". For each study, the total amounts of items rated as "yes (1 point)" and "partly (0.5 points)" were divided between the total applicable items. This was expressed as a percentage; a higher score represents a lower risk of bias. We consider a score of 100% as a study with very low risk of bias. Of note, this specific tool does not provide an overall score of the internal validity of the assessed studies (including outcomes and aims different from economic evaluations), only of the economic-related outcomes and aims. As we wanted to assess the current state of the literature on this topic, and the heterogeneity across included studies precluded a final quantitative synthesis of the evidence, we did not exclude any study from this review based on its quality assessment score nor the directness in relation to this review question.

3. Results

A total of 235 articles were identified in the bibliographic database search (134 through MEDLINE using PubMed, 53 through Embase using Ovid, 42 through NHS-EED and 6 through the CEA Registry database), and 9 additional articles were identified through a bibliographic reference check. A total of 244 studies were assessed in the selection phases. After screening both the title and abstract of these articles, 167 articles were excluded in the first selection phase because they did not provide at least minimal relevant information on the topic. A second evaluation phase was carried out with full text review of the 77 remaining studies. After this second evaluation phase, 67 articles were excluded because they did not meet the criteria for inclusion (44 were not economic evaluation studies, 10 were partial economic evaluation studies, 6 did not refer to OD, in 1 study OD was not related to stroke, 5 were duplicated articles, and 1 did not fulfil the publication criteria as it was an abstract); finally, 10 articles were included in this systematic review (Figure 1) [36–45].

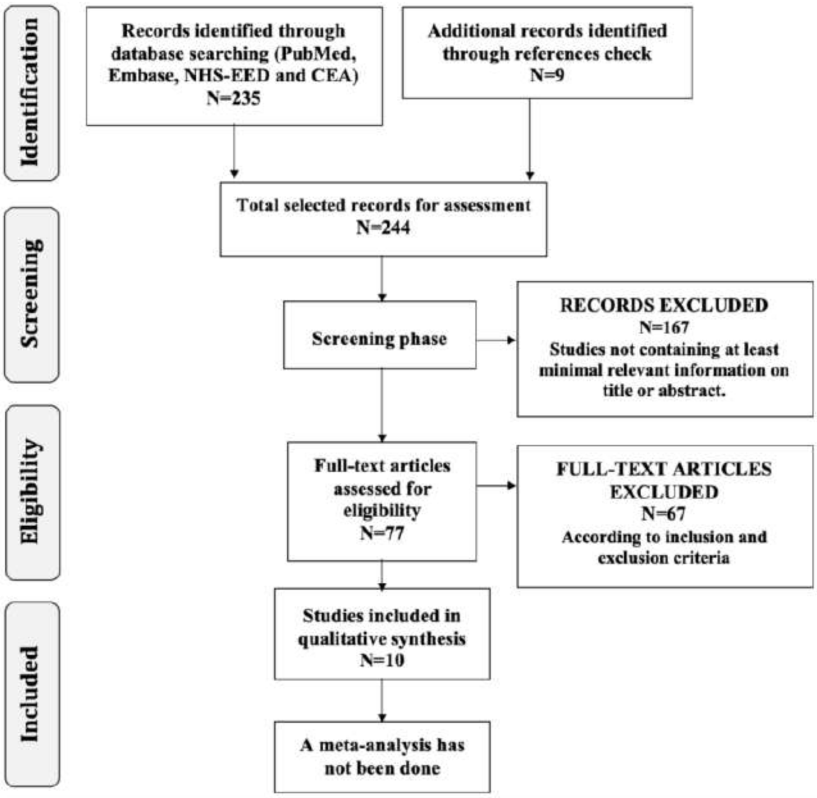

Figure 1. Selection process flow diagram.

The data and features of the included studies were summed up and presented both in a narrative presentation and evidence tables. Table 1 summarises the main design characteristics of the studies. Table 2 summarises specific economic characteristics of the included studies, such as the elements of cost considered and the used currency. Table 3 summarises characteristics of study populations. Table 4 summarises the results of individual studies along with quality evaluation scores. Study designs, economic evaluation methods and techniques, study interventions, outcome measurements, cost elements considered, settings, and perspective were heterogeneous across the studies, which precluded a quantitative synthesis.

Table 1. Main design characteristics.

Study ID	Aim	Evaluated Intervention	Study Population	Design/Data Gathering	Time Horizon and Perspective
Assessment of OD after Stroke					
Wilson, R,D.; 2012 [38]	Cost-effectiveness of dysphagia screening methods	- VFS - CBSE - CBSE followed by VFS if swallow abnormal	Hospitalised acute stroke (model-based)	Cost-effectiveness Decision-analysis model NA	Hospitalisation Societal perspective
Svendsen, M.L.; 2014 [37]	Association between processes of early stroke care and hospital costs	Early assessment of the swallowing function and 10 other processes related to acute stroke care	Ischemic and haemorrhagic stroke patients ≥18 years	Cost-saving Prospective	Hospitalisation Hospital perspective
Schwarz, M.; 2017 [39]	Impact of an OD screening protocol for thrombolysed stroke patients on operational outcomes (cost, length of stay, service compliance)	Protocol for the early screening of OD in thrombolysed patients	Ischemic stroke ≥18 years	Cost-saving Retrospective	Hospitalisation Hospital perspective
Liu, Z.Y.; 2020 [36]	Differences in total hospitalisation costs assessing OD with the WST test vs. the WST test and the V-VST if the first failed	Early assessment of PS-OD with two different screening tests: - WST - WST followed by V-VST if the first failed	Ischemic stroke >18 years	Cost-saving Retrospective	Hospitalisation Hospital perspective
Rehabilitation Services Including OD Management					
Khiaocharoen, O.; 2012 [40]	Cost-utility of rehabilitation programme, including swallow training	- Rehabilitation services (including swallow training) at subacute and non-acute phases - Comparator group that did not receive rehabilitation or just once	Hospitalised acute stroke (subacute and non-acute phases) and discharged >17 years	Cost-utility Prospective	4 months Societal perspective (also provided data on governmental)
Suksathien, R.; 2015 [41]	Efficiency and cost of short-course rehabilitation program	Short-course rehabilitation program (including speech-language therapy)	Inpatient rehabilitation after stroke >18 years	Cost-effectiveness Prospective	Inpatient rehabilitation Hospital perspective
Nutrition by Enteral Tube Feeding					
Elia, M.; 2008 [44]	Cost-utility of long-term enteral tube feeding	Enteral tube feeding	Cerebrovascular disease, nourished by enteral tube at home or nursing home	Cost-utility Retrospective	3 years after starting tube feeding NA
Beavan, J.; 2010 [45]	Cost-effectiveness of nasal loop	Looped vs. non-looped nasogastric tube feeding	Hospitalised acute stroke	Cost-effectiveness Prospective (randomised controlled trial)	2 weeks Cost associated to feeding perspective
Compensatory Strategies: Food Consistency Modification and Thickened Fluids					
Kotecki, S.; 2010 [42]	Differences in time and costs between nursing-staff-prepared and commercially prepared thickened liquids	Nursing-staff-prepared thickened liquids using Resource ThickenUp® and commercially prepared thickened liquids	NA	Cost-saving NA	Hospitalisation Hospital Perspective
Pelczarska, A.; 2020 [43]	Cost-utility of xanthan gum-based consistency modification therapy (Nutilis Clear®)	Routine clinical practice: behavioural compensations, manoeuvres, and rehabilitation exercises Xanthan gum–based consistency modification therapy (Nutilis Clear®)	Adult post-stroke (model-based)	Model-based cost-utility analysis (static and dynamic model) NA	Time horizon: -Static model: 8 weeks -Dynamic model: 1 year Public payer perspective

Abbreviations: CBSE: clinical bedside swallowing evaluation; ID: identification; OD: oropharyngeal dysphagia; NA: not available/not applicable; PLN: polish zloty; VFS: videofluoroscopy; V-VST: volume-viscosity swallow test; WST: water swallowing test.

Table 2. Specific characteristics of included studies: data source and elements of cost considered.

Study ID	Data Source	Elements of Cost Considered: (a) Direct Healthcare Costs (b) Direct Non-Healthcare Costs (c) Indirect Costs	Country, Year and Currency
		Assessment of OD after Stroke	
Wilson, R.D.; **2012 [38]**	Available literature Estimations	(a) Yes, direct medical costs of VFS, non-oral feeding and pneumonia (b) No (c) No	United States NA USD (2010)
Svendsen, M.L.; **2014 [37]**	Medical registries, national population-based, including the Danish Stroke Registry, the Danish National Registry of Patients, and the Danish Civil Registration System	(a) Yes, hospitalisation costs (b) No (c) No	Denmark 2005–2010 USD (2010)
Schwarz, M.; **2017 [39]**	Clinical records	(a) Yes, hospitalisation costs (b) No (c) No	Australia 2011–2014 Australian dollars (year not available)
Liu, Z.Y.; **2020 [36]**	Questionnaire Clinical records	(a) Yes, hospitalisation costs (b) No (c) No	China 2017 USD (year not available)
		Rehabilitation Services Including OD Management	
Khiaocharoen, O.; **2012 [40]**	Data collection process by health professionals and cost diary recorded by patients and relatives both checked and confirmed by investigators	(a) Yes, including rehabilitation and medical costs (b) Yes, cost of living during the stroke episode (e.g., transport, food) (c) Yes, loss of income of patients and relatives	Thailand 2008–2009 Baht (year NA)
Suksathien, R.; **2015 [41]**	Data collection process by investigators	(a) Yes, medicine, laboratory, rehabilitation training, nursing, bed, and others (not defined) (b) No (c) No	Thailand 2014 Baht (year NA)
		Nutrition by Enteral Tube Feeding	
Elia, M.; **2008 [44]**	Database of the British Artificial Nutrition Survey	(a) Yes, in hospital cost of gastrostomy insertion and patient training, cost of home visits by general practitioners, dietitians, nurses, speech and language therapists, physiotherapists, chiropodists, community occupational therapists, the cost of feeding, ancillaries and delivery, hospital readmissions and nursing home (b) No (c) No	United Kingdom 1995–2005 Pounds Sterling (2005)
Beavan, J.; **2010 [45]**	Data collected during randomised controlled trial, local purchase costs and the cost for a single loop set	(a) Yes, direct medical costs of feeding (b) No (c) No	United Kingdom 2006–2007 Pounds Sterling (year NA)

Table 2. *Cont.*

Study ID	Data Source	Elements of Cost Considered: (a) Direct Healthcare Costs (b) Direct Non-Healthcare Costs (c) Indirect Costs	Country, Year and Currency
		Compensatory Strategies: Food Consistency Modification and Thickened Fluids	
Kotecki, S.; 2010 [42]	Data collected during study performance from a neuroscience hospitalisation unit	(a) Yes, direct medical costs of liquid products, thickeners, nurses and technicians, and viscometer (b) No (c) No	United States NA USD (year not available)
Pelczarska, A.; 2020 [43]	Literature review Clinical expert consultations	(a) Yes, OD treatment costs, aspiration pneumonia treatment costs and monitoring costs (monitoring costs only for the dynamic model) (b) No (c) No	Poland NA PLN (year NA)

Abbreviations: ID: identification; NA: not available/not applicable; OD: oropharyngeal dysphagia; PLN: polish zloty; USD: United States dollars; VFS: videofluoroscopy.

Table 3. Specific characteristics of study populations.

Study ID	Age (Years) and Gender (Male)	Patient Inclusion or Exclusion Criteria	Method of OD Diagnostic
		Assessment of OD after Stroke	
Wilson, R.D.; 2012 [38]	NA (model-based)	NA (model-based, typical hospitalised stroke patient without previous OD nor contraindication to OD screening)	VFS CBSE CBSE followed by VFS if abnormal swallow
Svendsen, M.L.; 2014 [37]	Mean age (SD): Processes received 0–24%: 72.2 (14.3) Processes received 25–49%: 73.6 (12.7) Processes received 50–74%: 72.6 (12.9) Processes received 75–100%: 69.9 (13.3) Gender *n* (%): Processes received 0–24%: 212 (47.9) Processes received 25–49%: 344 (49.9) Processes received 50–74%: 798 (54.1) Processes received 75–100%: 1875 (56.8)	Inclusion criteria: - Hospitalised with acute stroke - First-time registered in the Danish Stroke Registry - Discharged from a stroke unit during the study period Exclusion criteria: - Patients hospitalised for more than one year	GUS
Schwarz, M.; 2017 [39]	Mean age (range): Overall: 69.9 (31–92) Gender *n* (%): Overall: 37 (44.6)	Inclusion criteria: - >18 years - Ischemic stroke Exclusion criteria: - Haemorrhagic stroke - Transient ischemic attack - Transferred to another facility or considered for palliative care during emergency department admission	Speech-language pathologist assessment Trained nursing staff using the Royal Brisbane and Women's Hospital Dysphagia Screening Tool

Table 3. *Cont.*

Study ID	Age (Years) and Gender (Male)	Patient Inclusion or Exclusion Criteria	Method of OD Diagnostic
Liu, Z.Y.; 2020 [36]	Mean age (range): Pre-V-VST: 69.73 (80.92–80.54) V-VST period: 67.36 (56.48–78.24) Gender *n* (%): Pre-V-VST: 93 (63.3) V-VST period: 55 (57.9)	Inclusion criteria: - ≥18 years - Ischemic stroke Exclusion criteria: - Tracheal intubation - Glasgow Coma Scale score of < 10 - More than 14 days after stroke onset passed	WST or WST followed by V-VST if the first failed
		Rehabilitation Services Including OD Management	
Khiaocharoen, O.; 2012 [40]	Mean age (SD): Control group: 60.8 (12.9) Rehabilitation group: 61.1 (12.5) Gender *n* (%): Control group: 53 (58.9) Rehabilitation group: 67 (57.3)	Inclusion criteria: - First stroke episode within 2 weeks after the onset - No other acute medical conditions requiring treatment - Without previous disability Exclusion criteria: - Bilateral hemiplegia or brain stem pathology - Depression - Barthel index score > 19 out of 20 - Surgery for stroke - Death - Critically ill at subacute and non-acute phases	NA
Suksathien, R.; 2015 [41]	Mean age (SD): 57 (19–86) Gender *n* (%): 28 (56)	Inclusion criteria: - <18 years - Able to follow one-step command - Need rehabilitation - Had stable vital signs - Started the program not later than six months after stroke Exclusion criteria: - Patients who had serious complications - Cognitive impairments - Other causes that prevented patients from cooperating with rehabilitation program	NA
		Nutrition by Enteral Tube Feeding	
Elia, M.; 2008 [44]	Mean age (SD): Own home: 73 (13) Nursing home: 78 (10) Gender: NA	Inclusion criteria: - After cerebrovascular accident - Receiving long-term ETF in own homes or nursing homes	NA

Table 3. *Cont.*

Study ID	Age (Years) and Gender (Male)	Patient Inclusion or Exclusion Criteria	Method of OD Diagnostic
Beavan, J.; 2010 [45]	Mean age (SD): Loop group: 79 (10) Control group: 81 (10) Gender *n* (%): Loop group: 20 (39) Control group: 23 (43)	Inclusion criteria: - Acute stroke - NGT feeding required - Dysphagia identified Exclusion criteria: - Contraindications to NGT feeding - NGT feeding had been established for more than 7 days elsewhere	Standardised WST
Compensatory Strategies: Food Consistency Modification and Thickened Fluids			
Kotecki, S.; 2010 [42]	NA	NA	NA
Pelczarska, A.; 2020 [43]	NA (model-based)	NA (model-based, adult stroke patient with OD, analysis restricted to patients with an aspiration level of 10–14 on GUS)	GUS (model-based)

Abbreviations: CBSE: clinical bedside swallowing evaluation; EFT: enteral tube feeding; GUS: Gugging Swallowing Screen; ID: identification; NA: not available/not applicable; NGT: nasogastric tube; OD: oropharyngeal dysphagia; VFS: videofluoroscopy; V-VST: volume-viscosity swallow test; WST: water swallowing test.

Table 4. Results of individual studies and quality assessment.

Study ID	Aim	Sample Size	Specific Data Depending on the Type of Economic Evaluation	Result of Study: Cost Difference (+ Increase and – Reduction)/Incremental Cost-Effectiveness/Utility Ratio	Main Findings of Studies	Quality Assessment [c] (%)
Assessment of OD after Stroke						
Wilson, R.D.; 2012 [38]	Cost-effectiveness of dysphagia screening methods	NA	Cost: VFS: 1853 USD CBSE: 1968 USD CBSE plus VFS: 1943 USD QALY: VFS: 1.791 QALYs CBSE: 1.789 QALYs CBSE plus VFS: 1.790 QALYs	Incremental effectiveness: VFS: NA CBSE plus VFS (vs. VFS): −0.001 CBSE (vs. CBSE plus VFS): −0.001 Incremental costs: VFS: NA CBSE plus VFS (vs. VFS): + 90 USD CBSE (vs. CBSE plus VFS): + 25 USD Cost/QALY of VFS: 1034 USD	VFS was the most cost-effective screening method compared to CBSE and a combination of both	82.1
Svendsen, M.L.; 2014 [37]	Association between processes of early stroke care and hospital costs	5909	Mean crude costs: Early swallowing assessment (first 24 h): 20,232 (25,459) [a] USD Delayed swallowing assessment: 29,222 (30,177) USD Mean adjusted costs: Early swallowing assessment (first 24 h): 19,487 (10,662) [a] USD Delayed swallowing assessment: 32,043 (15,097) USD	Adjusted cost difference: −12,556 (95% CI 9751–15,361) USD	Reduction in hospitalisation costs of 12,556 USD when swallow was assessed during the first admission day	78.8
Schwarz, M.; 2017 [39]	Impact of an OD screening protocol for thrombolysed stroke patients on operational outcomes (cost, length of stay, service compliance)	83	Costs: Screening protocol: 16,548 Australian dollars Non screening protocol: 18,053 Australian dollars	Crude costs difference: −1505 Australian dollars (p = 0.722; F = 0.129)	Non-significant reduction of 1505 Australian dollars in hospitalisation costs using a protocol to manage OD after thrombolysis	61.5

Table 4. *Cont.*

Study ID	Aim	Sample Size	Specific Data Depending on the Type of Economic Evaluation	Result of Study: Cost Difference (+ Increase and − Reduction)/Incremental Cost-Effectiveness/Utility Ratio	Main Findings of Studies	Quality Assessment [c] (%)
Liu, Z.Y.; 2020 [36]	Differences in total hospitalisation costs assessing OD with the WST test vs. the WST test and the V-VST if the first failed	242	No differences in median total hospitalisation costs: -WST group: 2807.8 (1951.4–4461.5) [b] -WST followed by V-VST: 2899.4 (2012.9–5074.7) [b] $p = 0.0846$	NA	No differences in hospitalisation costs when PS-OD was assessed with the WST vs. V-VST if the WST failed	57.6
Rehabilitation Services Including OD Management						
Khiaocharoen, O.; 2012 [40]	Cost-utility of rehabilitation programme including swallow training	207	Incremental program costs: - Hospital perspective: 5592 bahts - Societal perspective: 6880 bahts QALY: Rehabilitation group: 0.632 Control group: 0.352	ICUR (Cost/QALY): - Governmental perspective: 19,971 bahts - Societal perspective: 24,571 bahts	ICUR of rehabilitation programme including swallow training (starting at the subacute and non-acute stroke phases) of 24,571 bahts from societal perspective	79.6
Suksathien, R.; 2015 [41]	Efficiency and cost of short-course rehabilitation program	50	Change in BI score between admission and discharge: 5.00 (2.25) [a] Total cost of rehabilitation admission: 7729 (4330) [a] 95% CI 1828–22,450 bahts	Change score of the BI/LOS: 0.56 (0.33) Cost/change score of the BI: 1545.8 bahts	Positive mean change in the BI score of 5 points between discharge and admission with mean total costs of 7729 bahts	54.1
Nutrition by Enteral Tube Feeding						
Elia, M.; 2008 [44]	Cost-utility of long-term enteral tube feeding	9895 QoL assessment (n = 25)	QoL (EuroQol): Home: 0.47 (0.28) [a] Nursing home: 0.47 (0.25) [a] QoL (both groups): 0.47 (95% CI 0.358–0.582) Mortality at 2 years: Home: 43% Nursing home: 56%	ICUR (Cost/QALY): - Patients at home: £12,817 (95% CI for quality of life £10,351–£16,826) - Nursing home: £10,303–£68,064	ICUR of home enteral nutrition of £12,817 ICUR of nursing home enteral nutrition of £10,303–£68,064	81.4
Beavan, J.; 2010 [45]	Cost-effectiveness of nasal loop	104	Percentage of received nutrition of total prescribed: - Looped nasogastric tube: 75% (95% CI 67–83%) - Control group: 57% (95% CI 49–65%) Incremental percentage: 17% (95% CI 5–28%) Mean feeding costs: - - Looped nasogastric tube: £426 - - Control group: £338	Incremental cost for an 1% additional total nutrition received: + £5.20	Higher nutrient intake and low increase in hospitalisation costs using looped-nasogastric tube (£5.20 for every 1% increase)	70.3
Compensatory Strategies: Food Consistency Modification and Thickened Fluids						
Kotecki, S.; 2010 [42]	Differences in time and costs between nursing-staff-prepared and commercially prepared thickened liquids	NA	Cost of preparing thickened liquids: Nectar texture: Water: 0.54 USD Milk: 1.34 USD Orange Juice: 0.86 USD Honey texture: Water: 0.75 USD Milk: 1.41 USD Orange Juice: 0.83 USD Commercially prepared products: Nectar texture: Water (4 ounces): 0.30 USD Milk (8 ounces): 0.61 USD Orange Juice (4 ounces): 0.36 USD Honey texture: Water (4 ounces): 0.31 USD Milk (8 ounces): 0.66 USD Orange Juice (4 ounces): 0.36 USD	Cost savings using commercially prepared thickened liquids: Nectar texture: Water: 44% Milk: 54% Orange Juice: 58% Honey texture: Water: 59% Milk: 53% Orange Juice: 57%	Commercially prepared thickened fluids 44% to 59% cheaper than in situ prepared	71.7

Table 4. *Cont.*

Study ID	Aim	Sample Size	Specific Data Depending on the Type of Economic Evaluation	Result of Study: Cost Difference (+ Increase and − Reduction)/Incremental Cost-Effectiveness/Utility Ratio	Main Findings of Studies	Quality Assessment [c] (%)
Pelczarska, A.; 2020 [43]	Cost-utility of xanthan gum-based consistency modification therapy (Nutilis Clear®)	NA	QALY and total costs: Static model: - Nutilis Clear ®: 0.057 QALYs, total cost of 970 PLN - RCP: 0.022 QALYs, total cost of 235 PLN Dynamic model: - Nutilis Clear ®: 0.351 QALYs, total cost of 994 PLN - RCP: 0.331 QALYs, total cost of 570 PLN	ICUR (Cost/QALY): Static model: 21,387 PLN Dynamic model: 20,977 PLN	ICUR of texture-modified diets using a gum-based thickener of 20,977 PLN following a dynamic model and of 21,387 PLN following a static model	83.9

Abbreviations: BI: Barthel index; ICUR: incremental cost–utility ratio; ID: identification; LOS: length of hospital stays; PLN: polish zloty; QALY: quality-adjusted life-year; QoL: quality of life; RCP: routine clinical practice; USD: United States dollars. [a] values are mean (SD); [b] values are median (interquartile range); [c] Quality assessment: a higher score indicates a lower risk of bias. Score calculation: [Yes (1) + Partly (0.5)/Total applicable] × 100.

3.1. Data Presentation and Results of Individual Studies

3.1.1. Screening and Assessment of PS-OD

Four studies assessed different strategies to assess PS-OD in hospitalised patients with acute stroke, from different perspectives and using different methodologies. Three of these studies had a longitudinal design, and one was a model-based study. Study sample size ranged from 83 to 5909 adult (≥18 year) participants [36–39]. Each study was performed in a different country: China [36], Denmark [37], the United States [38], and Australia [39]. The Chinese, Australian and Danish studies evaluated cost-savings [36,37,39], and the study performed in the United States was a cost-effectiveness study [38].

Liu, Z.Y. et al. analysed the differences in total hospitalisation costs, comparing a period when the water-swallowing test (WST) was systematically performed on acute ischemic stroke patients and a posterior period when all patients underwent the WST, and the volume-viscosity swallow test (V-VST) was performed on those who failed the WST. This study did not find differences in the total hospitalisation costs nor in length of hospitalisation between patients assessed with the WST and those assessed with the WST and the V-VST if required. Median total hospitalisation costs were 2907.80 USD for patients assessed with the WST and 2899.40 USD for those patients who were assessed with the WST and then the V-VST if required. However, this study found a significant and relevant reduction in the occurrence of pneumonia (21.8% vs. 10.5%, $p = 0.024$) and in the rate of nasogastric tube feeding (25.9% vs. 14.7%, $p = 0.040$) when the V-VST was systematically applied [36].

Schwarz, M. et al. assessed the impact of an OD screening protocol in which OD was assessed by a speech-language pathologist in thrombolysed ischemic stroke patients on the operational outcomes (hospitalisation cost, length of stay, and sanitary service compliance) from the hospital perspective. This study found a non-significant reduction in hospital costs of 1505 Australian dollars (18,053 vs. 16,548 Australian dollars) when a clinical protocol aimed at managing dysphagia in post-stroke thrombolysed patients was utilized [39].

Svendsen, M.L. et al. evaluated the adjusted reduction in hospitalisation costs when a set of healthcare processes, such as swallow assessment through Gugging Swallow Screen (GUS), were performed early after acute stroke admission. To do this, this study compared total direct sanitary costs of hospitalisation based on stays in different hospital units, comparing patients in whom the swallowing function was assessed early after hospital admission and those who were not. This study found an adjusted reduction in hospitalisation costs in patients in whom the swallowing function was assessed during the first day of hospitalisation after acute stroke of 12,556 USD (95% CI 9751–15 361) after adjusting for a set of confounders such as age or modified Rankin Scale and Charlson comorbidity scale scores [37].

Wilson, R.D. and Howe, E.C. compared the cost-effectiveness of different screening methods for the detection of OD in hospitalised stroke patients (videofluoroscopic swallow assessment vs. clinical bedside swallow assessment vs. a combined approach in which videofluoroscopy was performed on patients with abnormal swallows at bedside assessment). This study was performed by using a decision-analysis model created with data from multiple sources. Direct medical costs of videofluoroscopy, non-oral feeding and pneumonia were considered. Quality-adjusted life-years (QALY) were measured, and an incremental cost-effectiveness analysis was made. The time horizon was hospitalisation, and analysis was performed from the societal perspective. This study found that videofluoroscopy was a more effective and cheaper screening method for OD in patients with acute stroke when compared with clinical bedside swallow assessment alone or a combination of both (QALY/costs: videofluoroscopy: 1.791 QALYs/1853 USD; clinical bedside swallow evaluation: 1.789 QALYs/1968 USD; and combined approach: 1.790 QALYs/1943 USD) [38].

3.1.2. Rehabilitation Services including PS-OD Management

Two studies assessed different rehabilitation programmes that included hospitalised patients with stroke, from different perspectives and using different methodologies [40,41].

These two studies were longitudinally designed with prospective data gathering [40,41]. Study sample sizes were 207 [40] and 50 [41]. Both studies were performed in Thailand [40,41]. One was a cost-utility analysis [28], and the other a cost-effectiveness analysis [41].

Khiaocharoen, O. et al. analysed the cost-utility of a rehabilitation programme that included swallow training (together with physical therapies such as exercise, trunk and walking training and occupational therapies such as self-care, cognitive and communication training) in subacute and non-acute hospitalised post-stroke patients and after discharge in two regional hospitals in Thailand. Swallow training consisted of orofacial motor skills training and swallowing and eating therapy included in a set of occupational therapy activities. To achieve this, the study measured patients' functional status according to a modified Barthel index and quality of life following the EuroQol five-dimensional questionnaire (and converted to a utility score). This study analysed direct healthcare costs such as rehabilitation and medical costs, direct non-healthcare costs such as the costs of living during the stroke episode (e.g., transport or food) and indirect costs such as patients' and relatives' loss of income during hospitalisation and up to 4-months' follow-up from the societal perspective. This study found a significantly higher average gained utility score for the group of patients that received those rehabilitation services more than once compared with those who did not receive them or just once (0.632 vs. 0.352). Moreover, the incremental cost per QALY for those patients who received rehabilitation services was 24,571 bahts (incremental cost-effectiveness ratio) when costs were assessed from a societal perspective (and 19,971 bahts when assessed from a governmental one) and that this ratio was robust in terms of program costs and outcome uncertainty estimations [40].

Suksathien, R. et al. analysed the outcomes and cost-effectiveness of a short-course inpatient rehabilitation program that included speech-language therapy (together with physical and occupational therapy) in a tertiary hospital in Thailand. This study measured mean patient functional status differences between admission and discharge according to the Barthel index, as well as mean total costs by assessing direct healthcare costs such as the costs of medicine, laboratory time, rehabilitation training and nursing from the hospital perspective. This study found a mean change in the Barthel index score between discharge and admission of 5 ± 2.25 (95% CI 2–10) and mean total costs of 7729 ± 4330 (95% CI 1828–22,450) baht (incremental cost per each one-point change in the Barthel index score of 1545.8 bahts). Of note, only 10% of included participants suffered OD, and a specific assessment of OD evolution across rehabilitation programme performance was not reported [41].

3.1.3. Compensatory Strategies: Food Consistency Modification and Thickened Fluids

Two studies assessed interventions on food consistency modification therapies [42,43]. One study was a cost-savings analysis [42], and the other a model-based cost-utility analysis [43]. One study was performed in the United States [42], and the other in Poland [43].

Kotecki, S. and Schmidt, R. compared the cost of thickened liquids prepared by nursing staff using Resource ThickenUp® with the cost of using commercially prepared thickened liquids. To do this, the study analysed how experienced hospital nurses and technicians prepared nectar- and honey-consistency thickened water, milk, and orange juice. This study was performed in a neuroscience acute care unit of a large urban community hospital. This study analysed the time spent and the cost of the compared interventions: the use of thickened liquids to the consistency of nectar and honey from water, milk and orange juice prepared by nurses using Resource ThickenUp® vs. the use of commercially prepared thickened liquids. Costs were measured from the hospital perspective, and the time horizon was hospitalisation. This study found commercially prepared thickened liquids were 44% to 59% less expensive than those manually prepared by nurses and technicians [42].

Following a different methodology, Pelckzarska, A. et al. assessed the cost-utility of texture modified foods with xanthan-gum-based Nutilis Clear® compared with routine clinical practice (behavioural compensations, manoeuvres, and rehabilitation exercises). To do this, the study followed two different models: (i) an 8-week fixed simple-equation static model in which the duration of OD was fixed and (ii) a 1-year Markov dynamic model in which the duration of OD was modelled. This study was limited to persons who tolerate semisolid intake but not fluids (score 10 to 14 according to GUS) and analysed the costs, the health state utilities, and clinical events such as aspiration, aspiration pneumonia and death. Analysed costs were direct OD treatment costs, aspiration pneumonia treatment costs and monitoring costs (only in the dynamic model) and were assessed from the public payer perspective. This study found cost-effective food consistency modification therapy with xanthan-gum-based Nutilis Clear® (incremental cost-utility ratio of 21,387 PLN and 20,977 PLN following a static and dynamic model, respectively). Moreover, these findings were confirmed following one-way, multi-way and probabilistic sensitivity analysis. This study also found the cost of xanthan-gum-based products as the major contributor to costs, the reduction of aspiration pneumonia prevalence as the major contributor to costs-savings and the utility increment of aspiration avoidance and the risk of aspiration pneumonia occurrence as the factors with a major impact on study results, according to sensitivity analyses [43].

3.1.4. Nutrition by Enteral Tube Feeding in Patients with PS-OD

Two studies reported costs associated with health interventions related to the use of tube feeding in patients affected by cerebrovascular diseases [44,45]. One of these studies had an observational, longitudinal design with a sample size of 9895 patients (25 patients for the quality-of-life assessment) [44], and the other was a randomised clinical trial with a sample size of 104 patients [45]. Both were performed in the United Kingdom [44,45]. One study reported costs savings associated with looped nasogastric tube feeding use [45], and the other was a cost-utility study [44].

Beavan, J. et al. analysed the cost-effectiveness of nourishing acute stroke patients using a looped nasogastric tube compared to the use of a nasogastric tube secured by an adhesive nasal sticker. This study analysed the additional cost associated with any 1% of additional nutrition received of the total nutrition prescribed using the strategy of the looped nasogastric tube. Feeding costs were assessed over 2 weeks in acute stroke patients. This randomised clinical trial found that patients assigned to the looped nasogastric tube received a higher mean volume of feed and fluids (17% more, 95% CI 5% to 28%) and estimated that the incremental cost per any 1% additional total nutrition prescribed was 5.20 sterling (GBP) (loop group, mean costs: 426 GBP vs. control group, mean costs: 338 GBP) [45].

Elia, M. and Stratton, R.J. analysed the cost-utility of the application of enteral tube feeding in patients who had suffered a cerebrovascular accident. This study assessed in-hospital costs such as costs of gastrostomy insertion, patient training and readmissions, the cost of nursing homes and costs beyond acute hospitalisation such as home visits by general practitioners, dietitians, nurses, speech and language therapists, physiotherapists, chiropodists, community occupational therapists and the cost of feeding, including ancillaries and delivery, in 9895 patients who initiated enteral tube feeding beyond hospitalisation from 1995 to 2005. QALYs were assessed on a sub-sample of 25 participants for 3 years, and the cost per each gained QALY was calculated and quality of life measured following the EuroQol visual analogue scale. This study found that the cost per QALY for those patients who received enteral tube feeding at home was £12,817 (95% CI for quality of life £10,351–£16,826) and that this ratio was insensitive to the frequency of received home visits, the outcome of patients who reversed to full oral feeding, and the computed outcome of a "control" group not given enteral tube feeding. In the case of patients who received enteral tube feeding nutrition in nursing homes, the cost per QALY varied from £10,303 to £68,064. The value of cost per QALY in this wide range on the incremental cost-utility ratio of enteral tube feeding nutrition in those patients in nursing home depended on the state contribution to non-medical costs [44].

3.2. Synthesis of the Studies Findings

3.2.1. Screening and Assessment of PS-OD

For acute stroke patients who were assessed with the WST vs. the WST and the V-VST if the first failed, Liu, Z.Y. et al. did not find significant differences in total hospitalisation costs in China though significant and relevant reductions in pneumonia occurrence and in the rate of nasogastric tube feeding when the V-VST was systematically used [36]. A non-significant reduction of 1505 Australian dollars in hospital costs during admission was found when assessing the implementation of a protocol aimed to manage OD in post-stroke thrombolysed hospitalised patients [39]. However, an independent reduction in hospitalisation costs in Denmark was observed in patients in whom swallowing function was assessed early after acute stroke (first 24 h) compared to those in whom it was delayed [37]. In the case of screening methods for OD after acute stroke admission, one study showed videofluoroscopy as the most cost-effective approach when compared with clinical bedside swallow evaluation or a combined approach (1034 USD/QALY) in the United States [38].

3.2.2. Rehabilitation Services including PS-OD Management

Rehabilitation services that included post-stroke inpatient swallow training (starting at the subacute and non-acute stroke phases) was found to be cost-effective from the societal perspective in Thailand (incremental cost-effectiveness ratio of 24,571 bahts per QALY gained, below the established threshold of 100,000 bahts per QALY, or about 2780 euros) [40]. Moreover, a short-course in-hospital rehabilitation program that included speech-language therapy saw a favourable mean change in the Barthel index score of 5 points between discharge and admission, with a mean total cost of 7729 bahts [41].

3.2.3. Compensatory Strategies: Food Consistency Modification and Thickened Fluids

The use of texture-modified diets using a gum-based thickener was found to be cost-effective from the public payer perspective in Poland (incremental cost-utility ratios from 21,387 PLN to 20,977 PLN per QALY gained, or about 4750–4660 euros, below the established threshold of 147,024 PLN per QALY in Poland) following a two-model-based approach and confirmed through comprehensive sensitivity analyses [43]. Moreover, the only study that assessed this point found commercially prepared thickened liquids more consistent regarding low viscosity variability and less expensive compared with those prepared in situ (44% to 59%) from the hospital perspective in the United States [42].

3.2.4. Nutrition by Enteral Tube Feeding in Patients with PS-OD

The use of enteral tube feeding nutrition at home was found to be cost-effective in the United Kingdom (£12,817 per QALY gained and from £10,351 to £16,826 using the 95% CI of quality-of-life measurements, below the established threshold of £30,000 per QALY). However, in the case of patients attended to in nursing homes, the incremental cost-effectiveness ratio depended on the state contribution to non-medical costs and varied from £10,303 to £68,064, with the lower value of this range corresponding to when the state did not contribute to overall costs and the higher when the state contributed 100% of overall costs (e.g., less than £30,000 per QALY gained with a state contribution less than 34%) [44]. Moreover, a study performed in the United Kingdom reported that those patients receiving feeding through looped nasogastric tubes received a 17% higher mean volume of feed and fluids and estimated £5.20 as the cost of receiving the 1% additional total nutrition prescribed using this strategy [45].

3.3. Quality Assessment

Risk of bias was assessed for each study. Total calculated scores for each study are presented in Table 4 along with the main results of presented studies, and specific evaluations for each item are available in Table S1 of the Supplementary Materials. Scores ranged from 54.1% to 83.9%. The mean quality studies score was 72.1%. Only one study assessed costs other than direct healthcare costs, such as direct non-healthcare costs or indirect costs [40].

Only two studies offered analysis performed from the societal perspective [38,40]. Only one study described the use of a discount rate to obtain an estimation of the present value of costs [44]. Sensitivity analyses to assess the robustness of the performed investigations were performed in three studies [40,43,44]. Target population and subgroups, comparators, health outcome measurements and cost and resource estimations were generally widely described in the included studies.

4. Discussion

This systematic review provides a comprehensive description of the available literature on the efficiency of some healthcare interventions to detect and manage PS-OD. Economic evaluation and cost-savings studies on healthcare interventions in the detection of PS-OD, rehabilitation programmes in which OD was considered, and the use of food-consistency modification strategies and tube-feeding nutrition were presented and summarized [36–45].

Regarding the efficiency of screening and diagnosis of PS-OD, Liu, Z.Y. et al. did not find differences in hospitalisation costs when PS-OD was assessed with the WST vs. V-VST if the WST failed, although this study did find a significant and relevant reduction in pneumonia incidence and also in the rate of nasogastric tube feeding in those patients assessed with the V-VST, providing new data on the clinical utility of the V-VST, which has been recently confirmed by comprehensive studies [36,46]. A recent systematic and scoping review on the psychometrics and clinical utility of the V-VST in the clinical screening and assessment of OD also developed by our group found V-VST had a diagnostic sensitivity for OD of 93.17%, a specificity of 81.39%, and an inter-rater reliability Kappa of 0.77 and concluded that V-VST has strong psychometric properties and valid endpoints for OD in several phenotypes of patients, including PS-OD. Our results support its utility in the screening and clinical diagnosis and management of OD [46]. On the other hand, Schwartz, M. et al. found a non-significant reduction of 1505 Australian dollars in hospitalisation costs using a protocol to manage OD after thrombolysis [39]. Of note, the prospective study performed by Svendsen, M.L. et al. in Denmark found an adjusted reduction in hospitalisation costs of more than 12,500 USD when swallow function was assessed during the first 24 h after acute stroke admission, emphasising the importance of early swallow assessment not only from a clinical perspective but also from an economic one [37]. Finally, Wilson, R.D. and Howe, E.C. found a videofluoroscopic swallowing study more cost-effective than clinical bedside swallow evaluation or a combined approach through model-based decision-analysis [38]. We believe that programs including systematic early screening and assessment of PS-OD are clinically profitable, as they reduce the nutritional and respiratory complications of PS-OD and improve the clinical outcomes of PS-OD patients and also reduce costs. Moreover, the use of innovative strategies such as artificial intelligence, which can provide accurate and systematic universal screening for OD to hospitalised patients, could improve the cost-effectiveness of OD assessment and further reduce complications and hospitalisation costs [47].

Only two economic evaluation studies are available in the literature regarding OD compensatory-treatment strategies. The study performed by Pelczarska, A. et al. is the first economic evaluation study addressing the cost-effectiveness of food-consistency modification compared with routine clinical practice. This study showed the cost-effectiveness of food consistency modification with xanthan gum-based Nutilis Clear® in the treatment of PS-OD in Poland from the public payer perspective [43]. The model-based cost-savings analysis performed by Kotecki, S. and Schmidt, R. found that the use of commercially pre-thickened fluids was less expensive than in situ preparation. Although both studies were promoted by the medical nutrition industry, they clearly show the cost-effectiveness of this compensatory therapeutic strategy. However, patients affected by severe and chronic PS-OD may require tube-feeding nutrition to avoid aspiration pneumonia and malnutrition [42]. Elia, M. and Stratton, R.J. analysed the cost-utility of enteral tube feeding beyond acute hospitalisation after cerebrovascular disease in the United Kingdom. This study showed the cost-effectiveness of enteral tube feeding at home and in nursing homes in which non-medical costs were paid privately. However, when the totality of the non-medical costs was paid by the state, the incremental cost-effectiveness ratio went up to £68,064/QALY, well above the established threshold of £30,000/QALY [44]. The measurement of QALYs and the assessment of the paid cost per incremental QALY (incremental cost-utility ratio) in studies assessing compensatory or enteral tube feeding strategies is necessary due to the nature of OD, which can affect not only patient mortality but also quality of life. Future economic studies assessing other interventions such as restorative ones need to be designed and carried out [26]. We recently developed a minimal-massive intervention (MMI) in hospitalised older patients with OD. This MMI consists of early screening of OD and of: (i) fluid thickening and texture-modified foods, (ii) caloric and protein supplementation; and (iii) oral health and hygiene recommendations during hospitalisation and following discharge. This intervention was recently improved by adding oral nutritional supplements in patients at risk of malnutrition. Our results suggest that MMI in hospitalised older patients with OD improves nutritional status and functionality and reduces hospital readmissions, respiratory infections and mortality. MMI might become a simple and cost-effective strategy to avoid OD complications in the geriatric population admitted with an acute disease to a general hospital, including those with PS-OD [48].

In recent years, the aim of post-stroke management of OD has been to restore the swallowing function using different strategies. In the present review, two studies assessed costs associated with rehabilitation services that included swallow training [40,41]. Khiaocharoen, O. et al. assessed the cost-utility of a rehabilitation programme including swallow training starting at the subacute and non-acute phases of stroke in Thailand and found the program cost-effective from the societal perspective in Thailand at a cost of 24,571 bahts per QALY gained (well below the 100,000 bahts/QALY established threshold in Thailand in the period which the study was carried out, 2008–2009) [40,49]. A subsequent study performed by Suksathien, R. et al. to assess outcomes of a short-course inpatient rehabilitation program that included speech-language therapy in Thailand reported a functional ability improvement on discharge with low costs. Of note, only 10% of participants included in this study suffered PS-OD, and non-specific OD-related outcome measures were used, which should be considered when interpreting the contributions of this last study for the specific aim of this systematic review [41].

The recently published ESO and ESSD guideline for the diagnosis and treatment of PS-OD found low to moderate quality of evidence for a variety of treatment options to improve swallowing physiology and swallowing safety. These options include dietary interventions, behavioural swallowing treatment including acupuncture, nutritional interventions, oral health care, different pharmacological agents and different types of neurostimulation treatment. Some of the studied interventions also had an impact on other clinical endpoints, such as feeding status or pneumonia [16]. This systematic review only partially fulfils the initially proposed objectives. The studies found assessed different health interventions and were conducted with very different methodologies regarding clinical and economic assessment. This limits the robustness of findings and reduces the synthesis to a narrative explanation of what has been reported to date. Heterogeneity between economic techniques used, assessed interventions, and cost elements considered precluded a quantitative synthesis and a meta-analysis. Moreover, no literature was found assessing the cost-effectiveness of restorative strategies, and data on the cost-effectiveness of OD management beyond acute stroke hospital admission is scarce. Despite this, this systematic review shows that some healthcare interventions on the detection and management of PS-OD have proven to be cost-effective or save costs in different settings.

PS-OD is a dynamic condition and, although improvements can be observed during the first weeks of rehabilitation, it remains as a chronic condition in up to half of patients, and new signs and symptoms can arise in long-term follow up of patients with poorer functionality [5,50]. Early and comprehensive management of PS-OD is imperative during acute stroke hospitalization and subsequent rehabilitation phases to prevent severe clinical complications such as respiratory infections and malnutrition and to avoid the high healthcare costs of these complications [13]. In this context, the systematic detection and specialised management of PS-OD and the prevention of its complications could provide a cost-effective improvement of patient outcomes. A systematic summary of the literature on the efficiency and cost savings associated with comprehensive PS-OD management could help decision making in terms of the appropriate management and treatment of this condition and also bolster future research in this field to create an economic model that considers the full management of this disease.

Future studies must be performed on the evaluation of the cost-effectiveness of health interventions on the management of OD beyond acute hospitalisation and on the efficiency of restorative strategies. Future studies are needed to establish the cost-effectiveness of the appropriate management of PS-OD and its complications (malnutrition, dehydration and respiratory infections) not only during hospitalisation but also at the sub-acute and long-term phases of OD due its chronic impact. These studies could be a first step to create an economic model of the disease that could help healthcare providers with decision making.

5. Conclusions

This study has three main conclusions: (i) interventions in the early detection or management of OD that have a positive effect preventing the main complications of OD (malnutrition and respiratory infections) tend to be cost-effective by reducing hospitalisation costs and improving clinical outcomes; (ii) the cost-effectiveness of interventions beyond acute hospital admission has been little explored, and future studies are needed to assess the cost-effectiveness of appropriate management of OD after acute stroke hospitalisation; and (iii) in contrast to compensatory strategies, we found little evidence assessing the cost-effectiveness of strategies aimed at restoring the swallowing function after stroke. Studies assessing the cost-effectiveness of novel screening, assessment, compensatory and restorative strategies are needed.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu15071714/s1, Table S1: Quality assessment adapted from the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement Checklist and Literature search section, describing full search terms used in the bibliographic search of the four databases.

Author Contributions: Conceptualization, S.M., O.O., M.S.-P. and P.C.; methodology, S.M., O.O., M.S.-P. and P.C.; software, S.M., O.O., M.S.-P. and P.C.; validation, S.M., O.O., M.S.-P., E.V., L.P.-C. and P.C.; formal analysis, S.M., O.O., M.S.-P., E.V., L.P.-C. and P.C.; investigation, S.M., O.O., M.S.-P., E.V., L.P.-C. and P.C.; resources, S.M., O.O., M.S.-P. and P.C.; data curation, S.M., O.O., M.S.-P., E.V., L.P.-C. and P.C.; writing—original draft preparation, S.M., O.O., M.S.-P., E.V., L.P.-C. and P.C.; writing—review and editing, S.M., O.O., M.S.-P., E.V., L.P.-C. and P.C.; visualization, S.M., O.O., M.S.-P. and P.C.; supervision, S.M., O.O., M.S.-P. and P.C.; project administration, O.O., M.S.-P. and P.C.; funding acquisition, O.O. and P.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by research grants from Nutricia Danone Advanced Medical Nutrition (grant number: HESDY Grant); Fundació Salut Del Csdm, Strategic Action Grant in Oropharyngeal Dysphagia provided by the Centro de Investigación Biomédica en Red en El Área de Enfermedades Hepáticas Y Digestivas (CIBERehd), Instituto de Salud Carlos III; Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III (grant number: PI22/01101); and Proyectos de Investigación Clínica Independiente, Instituto de Salud Carlos III (grant number: ICI20/00117).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No additional data is available.

Acknowledgments: This work was conducted within the framework of a doctoral thesis in medicine from the Medicine Department of the Autonomous University of Barcelona. We thank Jane Lewis for reviewing the English.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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4.4 Additional information

Cost and cost-utility of adding a neurostimulation treatment using TES to compensatory treatment in patients with chronic PS-OD

Study design and population

Additionally, an economic evaluation was conducted to evaluate the cost and cost-utility of adding TES to compensatory treatment in patients with chronic PS-OD to entirely meet this doctoral thesis's objectives. Data for this economic evaluation were obtained from a previously published randomised, prospective, controlled, three-arm, open-label, blinded-analysis clinical trial. [133] This study assessed the effect of SES and NMES stimulation levels using VitalStim™ (Chattanooga, DJO Global, Lewisville, TX, United States). This randomised study was performed at Mataró Hospital, from 01 October 2014 to 16 June 2016. The sample included adult post-stroke patients (≥ 18 years old, ≥3 months after stroke) assessed for OD using the V-VST and a VFS, with PAS score ≥2 and/or pharyngeal residue, capable of complying with the study protocol, without previous diagnosis of OD before stroke, score 0 or 1 on NIHSS question 1a, and who gave their written informed consent to participate. Recruited patients were randomised into three groups (a) a control group in which OD was managed using standard compensatory strategies at our center (postural changes, oral hygiene recommendations, and fluid thickening and texture-modified foods, when required, following VFS evaluation); and two active groups in which TES was added to standard compensatory management (b) SES and, (c) NMES. SES and NMES were applied in up to two treatment cycles consisting of 15 sessions over two weeks each. The second treatment cycle was conducted six months later, only for patients who still exhibited clinical and videofluoroscopic signs of impaired swallowing safety. Patients were monitored for one year. The methodologies involved in this investigation, including patient screening and inclusion processes, as well as specific operational details of TES and videofluoroscopic and V-VST swallowing assessments, are explained in the original publication of this study. Additionally, flow diagrams delineating treatment cycles, patient follow-up, and management software for randomization are provided in the original publication. [133] A total of ninety patients were recruited, and finally, 89 participated in this study (1 loss before randomisation). Twenty-nine patients were randomised to the control group and 30 to the SES and NMES groups. No patients were removed from the analysis due to data loss or reasons other than death or study withdrawal (data from those cases were treated as explained above and considered for follow-up calculations). A total of 5 patients died, and 3 abandoned the study during the first six months of follow-up (prior 6-month follow-up visits and/or second cycles of SES and NMES). Five of these losses occurred before 6-months EQ-5D measurements (one case in the control group, one in the SES group and three in the NMES group). Four other patients abandoned during the last six follow-up months. Descriptive sociodemographic and clinical characteristics of patients enrolled in this clinical trial were previously published in the original article reporting data on the clinical efficacy of TES. No significant baseline differences were observed between study groups when comparing baseline age, gender, comorbidities (CCI), functional status (Barthel Index [BI] and modified Rankin scale), QoL, stroke severity (NIHSS [National Institutes of Health Stroke Scale]) and time from stroke onset.[133]

Cost and cost-utility analysis

-Perspective and time horizon

The one-year direct healthcare costs of TES treatment were analysed from the hospital perspective.

-Cost elements considered

Only additional costs and effects of TES treatment were considered. For patients receiving TES treatment, information on the total number of TES sessions received and any instances of early treatment discontinuation for any reason were collected. The costs of a TES session included fixed costs (the costs of the TES device, the cost of the speech therapist that attended patients at study visits, and structural hospital costs) and variable costs for fungible use during each TES session (electrodes).

-Translation into monetary units (€)

The information to calculate the cost of VitalStim™ device per TES session was obtained from Enovis™ and considered to be 0.63€ for this study (calculated considering the device price of €3312.14, assuming 10% annual amortisation and divided into 1446 total sessions performed during the 2 years and 9 months that the study lasted). The cost for the speech therapist to attend to patients during study visits was €29.70 per hour at our hospital. Hospital structural costs per TES session were considered to be €4.35 and were calculated based on the taxed price of a 16 square meter outpatient care room (calculated considering a one-year room price of €2289.59 divided into 1446 total sessions performed during the 2 years and 9 months that the study lasted). The fungible cost for each TES session was €10.83 considering the price of a 100-electrodes pack of €1083.43 including taxes. Then, the calculated total cost per TES session was €45.51. All resource use was considered using 2023 unitary values (since the outcome data were collected over three years, and participants were enrolled in the clinical trial at different times, with some finishing before others started).

-Effectiveness estimation

Patient-level resource use and health outcome data were collected over the study period. The number of TES sessions, the patient's follow-up and the QoL were collected at baseline and 6- and 12-month follow-ups for each participant. Intervention effectiveness was evaluated by assessing QoL, and QALYs. QoL was determined based on the European Quality of Life-5 Dimensions (EQ-5D) scores, which were obtained from patients' responses to VAS (the scale range from 0, the worst possible QoL, to 100, which represents the best possible QoL). The QoL gained was computed at 6- and 12-month follow-ups for each patient, in relation to baseline scores. In cases where patients died or were lost to follow-up between study periods, we assumed an unchanged course of the latest QoL measurement. Similarly, if a patient could not complete the questionnaire, we also assumed no change in QoL from the last measurement (two cases occurred, one in the SES group and the other in the NMES group).

QALYs were determined based on QoL collected at baseline and 2 points follow-up (6- and 12-months follow-up). We determined patient-specific change in QALYs by calculating the area under the curve (AUC) based on the area defined by the change from baseline utility and 6-month follow-up utility and 6- and 12-month values as described by Manca A et al. [154] Linear changes in utility values over follow-up points were assumed for AUC calculations. For patients who discontinued before the 6-month follow-up or between 6 and 12 months, 0.25 and 0.75 years followed were considered, respectively. Subsequently, the difference in the mean change in QALYs in the three assessed arms of the trial was calculated.

<u>Fluid thickeners and resource consumption</u>

As the original clinical trial showed improvement in the safety and biomechanics of swallowing, allowing a reduction in the need for fluid thickeners, we performed a theoretical complementary calculation of the thickener consumption during the study period. [133] We calculated the amount of fluid thickening agents used at our institution during the study period. The amount of fluid thickener used for each patient was calculated assuming a fluid intake of 1.750 litres per patient and day and a fluid thickener consumption of 78.75 grams per day for these patients at the need for “nectar” consistency and of 157.5 grams per day for those needing “pudding” consistency (each thickener unit contains 227 grams and supposed a mean cost of 3.56€ translated to 2023 values). 100% adherence to fluid thickener therapy was assumed. [155]

<u>Statistical analysis</u>

Analysis was performed by intention-to-treat and participant-level data approach. Patients were followed up from study inception and up to die, abandoned or one-year follow-up. The main outcomes of interest were the cost per QoL and QALY gained for each treatment group. Categorical variables were compared with the chi-square test and continuous variables with the ANOVA test for nonparametric samples (Kruskal–Wallis) with a post hoc analysis (Dunn’s multiple comparison test).

Baseline mean QoL values were imbalanced between study groups. To control for imbalance baseline QoL and avoid misleading incremental cost-utility ratio estimation, the areas between the curves were adjusted to calculate incremental QALYs. Multiple linear regression analyses were performed to account for imbalanced baseline utilities to estimate differential mean QALYs and their associated measures of sampling variability. Moreover, stepwise multivariate linear regression analysis was used in different multivariate models to adjust for the effect of treatment group (assessing SES and NMES separately, and both TES levels together) on incremental QALYs by gender, age, comorbidities, baseline functionality, the degree of disability and time from stroke onset. Discount rate was not applied since follow-up time was restricted to one year. Statistical significance was set at $p < 0.05$.

<u>Legal and ethical issues</u>

The protocol for this trial, including economic analysis performance, was assessed, and approved by the Ethical Committee for Clinical Investigation of the Hospital de Mataró (protocol code CEIC:36/14). This study was performed following the principles stated in the Helsinki Declaration 1975 and its subsequent amendments. The General Data Protection Regulation of the European Union 2016/679 was followed. All patients included in this study, or their legal representative signed an informed consent.

5 OVERALL SUMMARY OF THE RESULTS

This doctoral thesis assessed the costs associated with PS-OD and its complications, and the cost-effectiveness of current management strategies.

Systematic review of the costs of OD and its complications after stroke

A systematic review of the costs of OD and its complications after stroke was performed. The main findings were: (a) higher hospitalisation costs of US$6589 in patients requiring tube feeding (TF) in the USA, in patients with ischaemic stroke in France (€3000 or about US$3950) and in Switzerland (SFr14,000 or about US$15,300) and in patients with OD and haemorrhagic stroke transferred to a rehabilitation centre in Taiwan (US$7329 vs. US$5939), (b) independent cost increase for Medicare in patients with OD during the first year after stroke in the USA (US$4510), (c) increase in hospitalisation costs associated with pneumonia (between US$1456 and US$27,633, assessed in different countries), and with a higher RoM in England. This systematic review shows moderate evidence of major costs associated with OD (considering a high consistency and a large and direct effect through the data provided by four longitudinal studies). It estimates that the cost of caring for a patient with a stroke who develops OD could end up reaching €15,000 and €24,000 in cases in which the patient suffers an episode of pneumonia, including data from studies carried out in France, Switzerland, Argentina, Brazil, Taiwan and the USA.

The costs of PS-OD and its complications: malnutrition and respiratory infections

An observational study of 395 patients with acute stroke consecutively admitted to the Hospital de Mataró without prior OD was performed. Prevalence of PS-OD was 45.06%. The main findings were: (a) OD supposed a significant and independent increase in costs during hospitalisation (€789.68, p=0.011) and significantly higher costs at 3 and 12 months after stroke compared with patients without OD (3 months: €8242.0 ± €5376.0 vs. €5320.0 ± €4053.0, $p < 0.0001$; 12 months: €11,617.58 ± €12,033.58 vs. €7242.78 ± €7402.55, $p < 0.0001$), (b) these costs independently and significantly increased with the worsening of the nutritional status at 3-months follow-up (12 months costs: €2303.38, $p = 0.001$) and in those patients that suffered at least one episode of respiratory infection during the one-year follow-up (12 months costs: €3034.08, $p < 0.011$), (c) higher mean costs where observed at 12 months follow-up for those patients who developed PS-OD, were at RoM or malnourished and had at least one episode of respiratory infection compared with those who did not develop PS-OD (€19,817.58 ± €13,724.83 vs. €7242.78 ± €7402.55, $p < 0.0004$).

Systematic review of economic evaluations of OD management after stroke

A systematic review of economic evaluations of OD management after stroke was performed. The main findings were: (a) reduction in hospitalisation costs with early assessment of OD in Denmark (adjusted cost reduction of more than US$12,500), protocolising its management after thrombolysis in Australia (non-significant reduction of hospitalisation costs of 1505 Australian dollars), and using commercially prepared thickened fluids in the USA (compared to thickened fluids prepared by nursing staff), (b) cost-effectiveness of VFS as a screening method through model-based analysis (compared to CBSE and a combination of the two), of rehabilitation programs that included the management of PS-OD in Thailand, and of home enteral nutrition in the United Kingdom (£12,817 per QALY), (c) favourable ICUR of texture-modified diets using a gum-based thickener in Poland (ICUR of 20,977 Polish zloty [PLN] or about €4660 following a dynamic model), and (d) major nutrient intake and low higher hospitalisation costs using looped nasogastric tube (NGT) of £5.20 for every 1% increase in nutrient intake. Results of this systematic review showed that some healthcare interventions in the detection and management of OD after stroke are cost-effective or cost-saving.

The cost and cost-utility of adding TES to the compensatory management of chronic PS-OD

As additional information to the findings of this systematic review, we conducted an economic evaluation of the cost and the cost-utility of adding TES (SES or NMES) to the compensatory management of chronic PS-OD from the hospital perspective.

-Resource consumption, treatment costs and treatment efficacy:

The mean number of treatment sessions and cost per patient at 6- and 12-month follow-up are described in Table 9.

-Incremental QoL and QALYs

Significant higher incremental QoL was observed when comparing SES and control groups at 12 months, SES group: 12.17±35.57, and control group: -2.07±23.77, p=0.027; Non observed with other comparisons: NMES: 4.63±20.73, p=0.243 vs. control; p=0.123 SES vs. NMES; p =0.057 comparing the three groups. Although mean incremental QALYs were higher for both SES and NMES groups compared to the control group, no significant differences were observed between study groups, NMES group: 0.0416±0.1274, SES group: 0.0321±0.1608, and control group: 0.0047±0.1681, *p*=0.274; *p*=0.192 control vs. SES; *p*=0.138 control vs. NMES; *p*=0.959 SES vs. NMES.

	Controls (mean±SD) N=29	**SES (mean±SD) N=30**	**NMES (mean±SD) N=30**	***p*-value[c]**	**TES (mean±SD) N=60**	***p*-value[d]**
TES sessions (6 months)	0	14.53±1.46	14.60±1.65	-	14.57±1.54	-
TES sessions (12 months)[a]	0	25.67±6.98	22.53±8.02	-	24.10±7.62	-
Treatment costs, (6 months, €[a])	0	661.26±66.26 ****	664.45±75.21 ****	***<0.0001***	662.93±70.29	***<0.0001***
Treatment costs, (12 months, €[a])	0	1168.09±317.90 ****	1025.49±365.00 ****	***<0.0001***	1096.79±346.87	***<0.0001***
Follow-up time (years)	0.95±0.16	0.91±0.22	0.91±0.24	*0.777*	0.91±0.23	*0.550*
Incremental QoL (12 months, EQ-5D[b])	-2.07±23.77	12.17±35.57	4.63±20.73	*0.057*	8.40±28.15	-
Incremental QALYs (12 months)	0.0047±0.1681	0.0321±0.1608	0.0416±0.1274	*0.274*	0.0368±0.1439	*0.107*

**** *p*-value <0.0001 vs. control. [a] The monetary value for each TES session was set at €45.51. Cost expressed as 2023€. [b] EQ-5D health status: unchanged course of the latest utility measurement was considered for those patients who were not able to answer, died or abandoned between follow-up study periods. [c] *p-value* column shows a comparison between controls, SES and NMES groups. [d] *p-value* column shows a comparison between controls and TES groups.

Table 9. Treatment costs and effectiveness of TES vs. controls at 6- and 12-month follow-up [a,b] EQ-5D: European Quality of Life-5 Dimensions, NMES: motor-level transcutaneous electrical stimulation, QALYs: Quality-adjusted life-years, QoL: quality of life, SD: standard deviation, SES: sensory-level transcutaneous electrical stimulation, TES: transcutaneous electrical stimulation

-Fluid thickeners consumption

A non-significant reduction in fluid thickeners consumption was observed comparing SES, NMES, and control groups (mean number of thickener units consumed at 12-month follow-up: 123.50±95.55, 96.35±78.35 and 80.06±83.67; control, SES and NMES, respectively, *p*=0.169).

-Multivariate analyses

Multiple regression analyses did not find an independent and significant group effect on incremental QoL or QALYs after adjusting for basal QoL (Table 10). Moreover, we did not find an independent and significant group effect on incremental QALYs after adjusting for multiple confounders (Table 11). Thus, ICUR calculation controlling incremental QALYs by imbalance baseline utility was not calculated.

	SES vs. control				**NMES vs. control**			
	QoL		**QALYs**		**QoL**		**QALYs**	
	β	***p***	**β**	***p***	**β**	***p***	**β**	***p***
Treatment group	0.063	*0.306*	-0.012	*0.740*	0.024	*0.326*	0.012	*0.461*
Basal QoL	-0.955	***<0.001***	-0.473	***<0.001***	-0.577	***<0.001***	-0.449	***<0.001***

Table 10. Multivariate analysis, treatment group effect on quality of life and quality-adjusted life-years adjusted by basal quality of life. NMES: motor-level transcutaneous electrical stimulation, QALYs: quality-adjusted life-years, QoL: quality of life, SES: sensory-level transcutaneous electrical stimulation

QALYs	**SES vs. control**		**NMES vs. control**		**TES vs. control**	
	β	***p***	**β**	***p***	**β**	***p***
Treatment group	0.011	*0.755*	0.008	*0.615*	0.010	*0.717*
Basal QoL	-0.480	***<0.001***	-0.460	***<0.001***	-0.444	***<0.001***
Age	-0.005	***0.007***	-0.002	*0.086*	-0.003	*0.019*
Gender	0.031	*0.399*	0.018	*0.622*	0.008	*0.787*

Table 11. Multivariate analysis, treatment group effect on quality-adjusted life-years adjusted by basal quality of life, age and gender. NMES: motor-level transcutaneous electrical stimulation, QoL: quality of life, SES: sensory-level transcutaneous electrical stimulation, TES: transcutaneous electrical stimulation

6 OVERALL SUMMARY OF THE DISCUSSION OF THE RESULTS OBTAINED

This doctoral thesis has comprehensively assessed the healthcare costs associated with PS-OD and with nutritional status worsening and respiratory infections, two well-recognized PS-OD complications, and the available literature on the cost-effectiveness of their management and of adding TES to PS-OD compensatory management.

The first study **evaluated and synthesised the available evidence on the health costs associated with OD and its complications** through a systematic review of the literature following the recommendations proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[156] The protocol of this systematic review has been published in an indexed scientific journal and registered in The International Prospective Register of Systematic Reviews of the Center for Reviews and Dissemination (PROSPERO) (register number: CRD420180999779). [142], [157] This systematic review has been published in an indexed journal. [158] This systematic review shows moderate evidence of major costs associated with OD (considering a high consistency and a large and direct effect through the data provided by four longitudinal studies), for major costs associated with pneumonia, and low evidence for major costs associated with a higher nutritional risk in post-stroke patients, including data from studies carried out in France, Switzerland, England, Argentina, Brazil, Taiwan and the USA. This systematic review differs from another previously published one in that it focused on the study of OD after stroke and explored the costs related to the complications of this disease. The previous systematic review aimed to evaluate the influence of OD secondary to all aetiologies on length of stay and costs, showing a 40.36% increase in costs for patients with OD. A subgroup assessment showed a higher and more variable length of stay of 4.73 days (95% confidence interval 2.7-7.2) for stroke patients. [61] However, this systematic review revealed some knowledge gaps that need to be explored in a subsequent study. For instance, we found only one study reporting data on the costs of OD after stroke beyond acute hospitalisation. On the other hand, the design and results of the studies were methodologically very heterogeneous, which makes it difficult to draw definitive conclusions since it was not possible to make a quantitative synthesis of the results. In addition, there is a lack of data on the non-health and social costs associated with OD. On the other hand, it must be considered that the relationship between the complications studied with OD and OD was not established in the included studies. Moreover, we could not find any economic evaluation regarding the costs associated with other relevant complications of OD after stroke, such as (a) the need for institutionalisation after discharge, (b) the loss of functional capacity, (c) the costs related to the home care of these patients, (d) and the related mortality in the short and long term and the impaired QoL. [39]

The second study of this doctoral thesis provides additional relevant data in this field. It assessed the **acute, subacute (3 months) and long-term (12 months) costs related to OD and its main complications (malnutrition and respiratory infections).** This study has been published in an indexed journal. [141] OD supposed a significant and independent increase in healthcare costs during hospitalisation and significantly higher mean costs at 3- and 12-month follow-up comparing those patients with OD at admission and those without, that strongly and independently increased with the worsening of the nutritional status at three months and for cases that suffered at least one episode of respiratory infection at 12-months. [141] Results from this analysis showed that patients presenting with OD at acute stroke admission concurred 60% greater costs at 12 months than those without. This cost increase is higher than that mentioned in the available evidence presented in the introduction of this doctoral thesis. For example, the study by Patel DA et al. reported a 42% increase for patients with oropharyngeal or oesophageal dysphagia in the USA, and the systematic review and meta-analysis provided by Attrill S et al. showed that dysphagia secondary to different aetiologies could increase costs by 40.36%. [59], [61] Our study showed a greater increase in costs for those patients with OD, this could be due to the broader range of costs considered in this study, including long-term care needs such as nursing home care facilities.

This study shows how in patients with PS-OD the mean total costs of hospitalisation were lower than the chronic subacute and long-term costs, while in patients without OD after stroke, most costs occurred during hospitalisation. Multivariate analysis showed that long-term costs could be more related to complications such as malnutrition or respiratory infections and costs during hospitalisation, more related to their effect on the consumption of healthcare resources. This would explain that the chronification of OD, together with the appearance of long-term complications, is the main explanation for the exponential increase in costs in these patients. Costs related to patient stays are an estimation made from public prices, not from actual costs provided by the hospital. These two aspects should be considered for future research studies. [141]

These high costs could not be fixed, but variable, since they could vary depending on the integration of health interventions, the early and comprehensive management of this clinical condition, the operational processes involved in each environment, or the quality-of-care patients receive. In this context, the aim of the third study of this doctoral thesis was to **assess and synthesise the available evidence on the cost-effectiveness and health cost savings associated with the clinical, nutritional and rehabilitative management of OD after stroke.** For this aim, we performed a systematic review of the literature following the recommendations proposed by PRISMA.[156] The protocol of this systematic review has been published in an indexed scientific journal and registered in PROSPERO (register number: CRD42020136245). [159], [160] This systematic review has been published in an indexed journal. [161] The main findings were (a) reduction in hospitalisation costs: with early assessment of OD in Denmark, protocolising its management after thrombolysis in Australia, and using commercially prepared thickened fluids in the USA, (b) cost-effectiveness of: VFS as a screening method through model-based analysis (compared to clinical bedside evaluation and a combination of the two), of rehabilitation programs that included the management of OD in Thailand, and home enteral nutrition in the United Kingdom (£12,817 per QALY) and, (c) favourable ICUR of texture-modified diets using a gum-based thickener in Poland (ICUR of €4660 following a dynamic model).

The studies shown in this systematic review evaluated different health interventions and were conducted using very diverse methodologies in clinical and economic evaluation. In this context, the synthesis of the evidence was limited to a narrative explanation of everything that has been reported so far. In addition, no literature was found that assessed the cost-effectiveness of most interventions currently used in the care of OD, and data on the cost-effectiveness or cost savings associated with management interventions of OD beyond hospital admission for acute stroke were scarce. In addition, no intervention was evaluated in our setting. Despite this, this systematic review shows that some healthcare interventions in the detection and management of OD after stroke are cost-effective or cost-saving and could assist in decision-making regarding the appropriate management and treatment of OD. Moreover, this study serves as a framework for future research in this field and for the creation of an economic model of the disease that considers its comprehensive management. In addition, this systematic review showed the need for studies evaluating the cost-effectiveness of healthcare interventions in the management of OD beyond acute hospitalisation (including the cost-effectiveness of those interventions aimed at preventing

PS-OD nutritional and respiratory complications) and the efficiency of innovative strategies in the detection, compensation and rehabilitation of OD. [161]

As additional information to the findings of this systematic review, we conducted an economic evaluation that assessed the **cost and cost-utility of adding TES to compensatory management in patients with chronic OD after stroke.** For this purpose, we evaluated 90 patients who were included in a clinical trial that compared the compensatory management of OD (control group: postural changes, oral hygiene recommendations, thickened fluids and modified texture diet, when required according to VFS evaluation), with the addition of SES or NMES. Data were obtained from a previously published randomised, prospective, controlled, three-arm, open-label, analysis-blinded clinical trial. [133] This clinical trial showed SES and NMES-treated groups significantly improved swallowing parameters at one year of follow-up for the prevalence of patients with safe swallowing, mean PAS score, time to closure of the laryngeal vestibule and the need for thickening agents, with no significant related adverse events reported. Patients in the compensatory treatment group showed a weaker improvement in signs of impaired swallowing safety, with no significant changes in laryngeal vestibule closure time. In addition, no differences were observed between the groups in terms of mortality (6.1%), respiratory infections (9.6%), nutritional and functional status, QoL and hospital readmission rates (27.6%) in the follow-up year. These benefits were maintained in the long term, suggesting that this therapy could be cost-effective by improving swallowing function at a low cost. On the other hand, both SES and NMES reduced the need to thicken fluids, allowing an improvement in the safety and biomechanics of swallowing, moving the therapeutic management of these patients from the use of classic compensatory strategies to the safe restoration of swallowing. [133] This thesis presents a study showing the added hospital resource consumption, cost and cost-utility of adding TES to compensatory management in patients with chronic OD after stroke. The mean treatment cost of TES at 12 months was €1096.79 ± €346.87, mainly attributed to healthcare facilities and specialised personnel requirements. Bivariate analysis showed a significantly higher incremental QoL for those patients in the SES group compared to the control group at 12 months (SES: 12.17 ± 35.57, and control: -2.07 ± 23.77, p=0.027), but non-significant differences for incremental QALYs (SES: 0.0321 ± 0.1608, control: 0.0047 ± 0.1681, p=0.192 vs. control, and NMES: 0.0416 ± 0.1274, p=0.138 vs. control), nor when adjusted for additional confounders. Additionally, we observed a non-significant reduction in thickener units resource consumption for those patients in the SES and NMES groups compared to controls (mean number of thickener units consumed at 12-month follow-up: 123.50±95.55, 96.35±78.35 and 80.06±83.67; control, SES and NMES, respectively, p=0.169). This study shows how the cost of incorporating TES in the compensatory management of chronic OD after stroke was mainly attributable to the structural and specialised personnel requirements and could represent favourable cost-benefit due to the reduction in the need to use thickeners. When calculating mean differential QALYs, we used multiple regression analysis to control for imbalance baseline QoL and avoid misleading ICUR estimation. In this study, SES was significantly related to a greater improvement in patients' QoL and to an increase in incremental QALY, which was not observed when adjusting for basal QoL or also considering other confounders in multivariate analyses. QALYs are the most widely used measure of health gain in economic evaluation studies. However, some explanations could contribute to the limited findings of this analysis. For instance, the effect of treatment on QALY was only measured during the first year of follow-up after the start of treatment, which could limit the findings of this study, especially in the case of using QALYs for calculations. On the other hand, the small size of the studied sample could contribute to limiting the results of multivariate analysis considering multiple variables. In addition, the fact that all patients in this study received comprehensive OD care, including appropriate diagnosis, follow-up and compensatory management in both the control and the study group, which could reduce the clinical and QoL differences between the two groups, must be considered. Thus, further analyses considering the cost-effectiveness of TES improvement in signs of impaired swallowing safety could be appropriate.

According to the results observed in this doctoral thesis and the evidence accumulated in other previous investigations, we can affirm that the economic burden of PS-OD is high. PS-OD is associated with significantly longer lengths of hospital stay, higher costs associated with hospital stays, greater likelihood of patients being discharged to post-acute care facilities after hospitalisation, and poorer prognosis. [59] Apart from the costs associated with the acute hospital care of OD and its complications, other costs must also be considered, such as those arising from its long-term chronic care. Some of these costs would be associated with the institutionalisation of patients in nursing homes and sociosanitary care institutions or long-term rehabilitation facilities. On the other hand, it would also be necessary to consider the direct non-health costs and indirect costs due to the loss of productivity of these patients. [141] However, the fact that many cases are at risk of not benefiting from the comprehensive care of OD, currently an underdiagnosed and undertreated clinical condition in many settings, could lead to a greater increase in the costs associated with its complications. [142] Currently, stroke is the first cause of disability and one of the main causes of dementia in our environment and the second cause of death in the world, with an incidence that is increasing globally in young people. [32] - [34] Approximately 1.1 million European citizens suffer a stroke each year, with an incidence of around 191.9 cases per 100,000 inhabitants. Of these, it is estimated that between 20% and 35% die, and that approximately one-third of those who survive will suffer a situation of functional dependence. [35] In Spain, nearly 120,000 people suffer a stroke each year and approximately 25,000 die. In addition, it is estimated that by 2025 the number of cases in Europe will reach 1.5 million annually. [35], [36] This progressive increase in the prevalence of patients who will survive an acute episode of stroke will, at the same time, lead to an increased prevalence of PS-OD in our environment. As previously mentioned, OD affects between 40% and 78% of patients with acute stroke and remains chronic in up to half of the cases. [38] - [41] These data could compromise a significant increase in the number of patients affected by PS-OD in the coming years. In addition, these patients will be at greater risk of developing complications related to malnutrition or respiratory infections, one of the main causes of poorer prognosis and an increase in the need for health resources in this population. [20], [37]

7 CONCLUSIONS

C1. OD and its complications are associated with a significant increase in the need for health resources during hospitalisation for acute stroke and also during later recovery phases and long-term follow up.

C2. OD involves significantly higher healthcare costs during the acute stroke phases that increase substantially and significantly with the development of its main complications, malnutrition and respiratory infections in the subsequent phases of stroke recovery and long-term follow up.

C3. Interventions aimed at the early detection and comprehensive management of OD after stroke which have a positive clinical effect by preventing OD complications tend to be cost-effective and/or save economic costs.

C4. The cost of adding the TES to the rehabilitative and compensatory management of chronic PS-OD is mainly attributable to healthcare facilities and specialised personnel requirements. Prior analyses showed TES improved the biomechanics and the safety of swallowing, leading to a reduction in the need for fluid thickening for safe swallowing in these patients at 1-year follow up. More studies are required to assess the resource and cost reduction associated with the need for thickener use and the cost-effectiveness of OD improvement.

8 FUTURE PERSPECTIVES

This doctoral thesis has increased the available evidence on the costs associated with OD after stroke and on the cost-effectiveness of its therapeutic management.

The main future perspectives that can be derived from these studies are:

-The comprehensive interest in the costs associated with PS-OD is broad and includes: (a) the costs associated with the increase in healthcare resources as a result of the presence of OD, obtained from health economic analysis studies and considering the prevalence and evolution of PS-OD and the long-term development of its nutritional and respiratory complications, (b) the impact of OD on the consumption of health resources beyond acute healthcare contexts such as institutionalization costs, direct non-health costs, indirect costs and intangible costs, and also those costs measured from perspectives other than healthcare but which also have an effect on society such as costs considered from the patient perspective or from the societal perspective, (c) the cost-effectiveness relationship associated with the comprehensive management of the OD, obtained from economic evaluation studies in health, an analytical methodology aimed at comparing the costs and consequences for health of applying different alternatives, and (d) the cost-effectiveness of innovative PS-OD management strategies that should be assessed through economic analysis studies and randomised clinical trials in the near future. [152]

-These different perspectives in cost analysis would condition both the type of analysis to be carried out and the costs to be considered. Therefore, different types of costs would be of interest in the case of PS-OD: (a) direct costs of healthcare (related to the consumption of health resources such as hospitalisation, need for care at institutions such as nursing homes, socio-sanitary centers or rehabilitation facilities, visits to primary care or outpatient hospital care, costs associated with attention from healthcare professionals such as physicians, pharmacists, dietitians, physiotherapists or speech therapists, and the costs associated with the consumption of medicines, diagnostic tests, adapted diets, the need for NS and endoscopic insertions of percutaneous gastrostomies, in addition to the specific costs related to the care of complications associated with OD, (b) direct non-healthcare costs (related to the provision of or access to medical services and treatments such as transport or social care), (c) indirect costs (costs due to lost productivity, and costs associated with the morbidity and mortality of OD and the time spent) and, (d) intangible costs which would be the costs related to the suffering and pain associated with a disease or its management. These mentioned costs are high and comparable to those of other chronic diseases such as metabolic, cardiovascular, neurodegenerative or infectious ones. [152]

-The health impact and costs of PS-OD should be considered not only from the hospital perspective but also during the subsequent subacute and chronic phases of stroke and considering the development of OD complications in the long term. This increase in the economic costs of OD is also a reflection of the serious clinical consequences of OD and its complications in stroke patients.

-OD is associated with significantly longer lengths of hospital stay and a greater likelihood of patients being discharged to post-acute care facilities after hospitalisation, and poorer functional status and prognosis. Moreover, it is related to higher economic costs during acute stroke hospitalisation and subsequent recovery phases. In addition, the increasing number of stroke cases in Europe will compromise an even greater economic burden of OD both for the health system and for society. However, the fact that in many cases these patients cannot benefit from the comprehensive care of OD, currently a clinical condition insufficiently detected and addressed in many settings, could lead to a greater increase in the costs associated with its complications. Some of these costs would be related to institutionalising patients in nursing homes or social health care centres or the need for long-term rehabilitation facilities. These high costs could not be fixed, but variable, since they could vary depending on the integration of health interventions, the early and comprehensive management of this clinical condition, the operational processes involved in each environment, or the quality-of-care patients receive. In this context, the application of programs for the screening and systematic care of OD in patients after stroke would be justified and could lead to cost savings in addition to the clinical benefits for patients. Economic evaluation studies assessing these programs will have a relevant importance, providing data on the potential cost savings and the cost-effectiveness of the comprehensive management of OD after stroke.

-There is still little data in some points related to the economic impact of PS-OD, future PS-OD cost studies should consider the costs of the patient's care outside the acute hospital stay, social costs and non-healthcare costs, and the cost-effectiveness of therapeutic management. Moreover, some aspects remained unstudied and must be considered as future research areas. For instance, it would also be necessary to consider the health costs related to the instrumental evaluation and treatment of OD after stroke, which have not been comprehensively considered yet in the available literature. For instance, it could be the hospital costs associated with instrumental assessments such as VFS or FEES, that should be considered during the acute and subsequent stroke recovery phases. Moreover, healthcare costs associated with behavioural interventions provided by speech therapists or rehabilitation programmes should also be considered. Finally, costs related to patient mortality have not been yet considered in any study, and this could lead to an artificial reduction of the mean cost for those patients in OD groups, as they have higher mortality rates.

-Beyond the importance of knowing the consumption of health resources and costs associated with pathology, the study of the cost-effectiveness of health interventions that can be used in its management provides relevant information to be used by health managers in the allocation of resources for the management of this pathology. To date, the cost-effectiveness of healthcare interventions aimed at detecting, providing an assessment and specialied management and treating OD, avoiding its complications, has been little studied. Studies in this area have recently appeared and have focused on the population with OD after stroke. However, the findings of these studies could be very dependent on the study context and difficult to extrapolate to other realities, so the performance of economic evaluations in this field could be a relevant work framework in the coming years. [160], [161]

According to these perspectives, the main advances in this area of knowledge in the coming years will be obtaining more data on the costs associated with OD, especially beyond the acute management of patients, and considering acute health and social costs in-hospital and long-term related to nutritional and respiratory complications, as well as direct non-healthcare and indirect costs, and on the cost and cost-effectiveness of those interventions intended to improve post-stroke swallow physiology and prevent the clinical complications of OD.

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10 ANNEXES

10.1 Funding

The studies that form part of this doctoral thesis have been financed by the following grants, projects and entities:

- Nutricia Danone Advanced Medical Nutrition: HESDY Grant. Cost of illness of oropharyngeal dysphagia after stroke from a hospital perspective for the Spanish setting.
- Proyectos de Investigación Clínica Independiente, Instituto de Salud Carlos III: ICI20/00117; and co-funded by the European Union (FEDER funds).
- Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III: PI18/00241 i PI22/01101; and co-funded by the European Union (FEDER funds).
- Fundació la Marató de TV3: 11/2310.
- DJO Global, Enovis.
- Fundació de Recerca en Gastroenterologia (FUREGA).
- Fundació Salut del Consorci Sanitari del Maresme.
- Centro de Investigación Biomédica en Red en El Área de Enfermedades Hepáticas y Digestivas (CIBERehd) (CB06/04/1087), Instituto de Salud Carlos III: Strategic Action Grant in Oropharyngeal Dysphagia (EHDPI01).

The PhD student would like to thank the financial support that these studies have received from the different entities.