



The sequel of age and frailty on the pathophysiology and treatment of surgical esophageal diseases

Marcel L. Andrade[^], Fernando A. M. Herbella[^]

Department of Surgery, Escola Paulista de Medicina, Federal University of São Paulo, Sao Paulo, Brazil

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Correspondence to: Fernando A. M. Herbella, MD. Department of Surgery, Escola Paulista de Medicina, Rua Diogo de Faria 1087 cj 301 Sao Paulo, SP 04037-003, Brazil. Email: herbella.dcir@epm.br.

Abstract: The impact of natural aging and frailty on various physiological systems also extends to the process of swallowing. This article provides a comprehensive review of how frailty and age influence surgical esophageal disorders. During healthy aging, alterations in esophageal motility and sensitivity occur due to reductions in neurons and myenteric cells, leading to atypical manifestations in this age group. Frail and sarcopenic patients face an elevated risk of oropharyngeal dysphagia, which subsequently increases the likelihood of malnutrition and aspiration, irrespective of the underlying cause of frailty. Furthermore, frailty is closely associated with unfavorable prognoses for esophageal disorders, emphasizing the critical need for early intervention in patients. Elderly individuals with frailty exhibit a higher incidence of gastroesophageal reflux disease (GERD). Additionally, frailty contributes to adverse clinical and surgical outcomes in esophageal oncologic surgeries, resulting in prolonged hospitalization, increased costs, and elevated mortality rates. In the context of patients with achalasia and GERD, the choice of the most suitable surgical technique should not solely rely on their age; instead, consideration of comorbidities and overall clinical condition is imperative. Integrating frailty screening in the perioperative evaluation of elderly patients becomes essential to determine their eligibility for surgeries, improve nutritional status, address sarcopenia, and facilitate oral rehabilitation, thereby mitigating adverse outcomes.

Keywords: Frailty; esophagus; dysphagia; gastroesophageal reflux disease (GERD)

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Introduction

The natural aging process can lead to changes in the gastrointestinal tract, including the esophagus. Alterations in the contractility and relaxation of the esophageal musculature can be found in older individuals, even if asymptomatic (1).

In addition, with increasing age, there is a higher occurrence of frailty in the elderly. Frailty is characterized as a decline in functioning in various physiological systems, accompanied by an increased vulnerability to stressors (2).

In 2001, Fried *et al.* (2) described the clinical presentation of frailty as a physical phenotype, a definable biological syndrome. This phenotype of frailty considers three or more positive symptoms or signs in five criteria: weakness, slow walking speed, low physical activity, exhaustion, and unintentional weight loss (2). This process does not only occur as an extreme process of aging, but can also be related to systemic diseases, including malnutrition, inflammatory diseases, and other chronic conditions (3).

[^] ORCID: Marcel L. Andrade, 0000-0002-9424-1598; Fernando A. M. Herbella, 0000-0003-3594-5744.

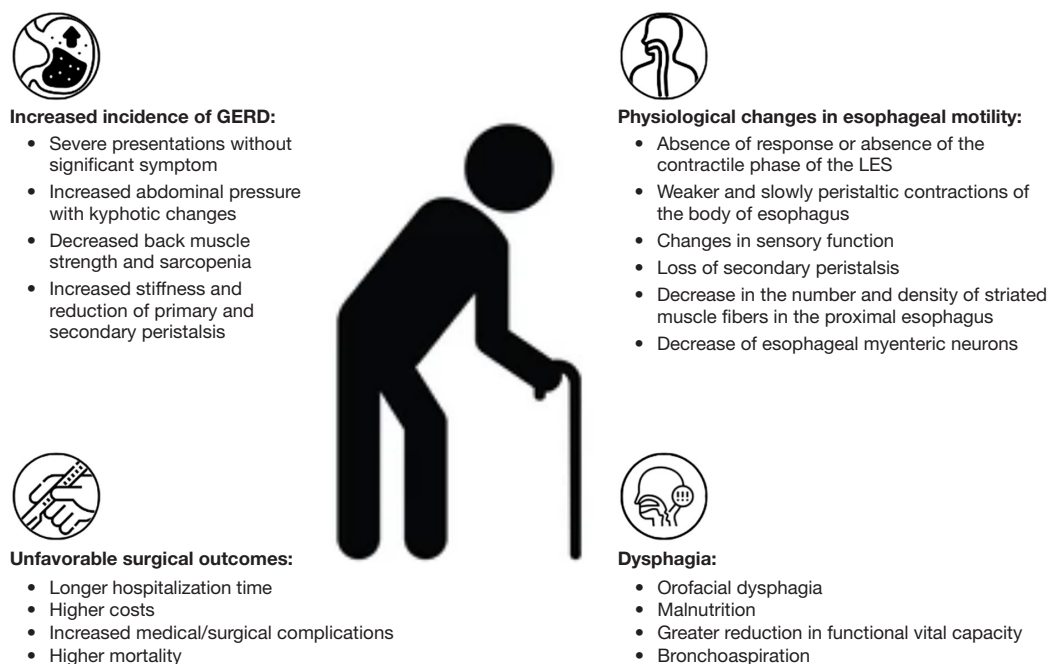


Figure 1 The sequel of frailty on the pathophysiology and treatment of esophageal diseases. GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter.

There are different scales and indices that can be used to assess frailty, including handgrip strength, gait speed, anthropometric assessment, presence of comorbidities, and functionality. However, a multidimensional approach that evaluates various parameters may be more effective in identifying frail older adults, allowing for early interventions, and reducing the risks of adverse health events (4,5).

It is important to highlight that frailty is a predictive factor of poor prognosis in older adults, increasing rates of mortality, hospitalization, falls, and admission to long-term care institutions (2,6).

This article seeks to comprehensively review the existing literature on the influence and impact of frailty on esophageal disorders, with the goal of enhancing our understanding of the interplay between these two factors in the health of older adults. Specifically, we will conduct a detailed examination of the age and frailty-related changes observed in patients with esophageal diseases, while placing a particular emphasis on their relevance to the field of esophageal surgery.

Motility changes associated with frailty

Healthy aging, also known as senescence, is responsible for several changes throughout the body. As we can see in

Figure 1, various studies have sought to correlate esophageal motility changes with the aging process (7,8).

Esophageal manometry studies have shown alterations in the contraction and relaxation of the esophagus in healthy elderly individuals. Djinbachian *et al.* (9) evaluated manometric parameters considered normal by the Chicago 4.0 classification and observed a positive correlation between age and the integral of the relaxation pressure (IRP) and the integral of the distal contractile integral (DCI), and a negative correlation, to a lesser degree, with distal latency, in symptomatic patients. Jung *et al.* (10) evaluated asymptomatic healthy individuals to assess the effect of age and sex on manometric profiles and found a positive correlation between age and the IRP and DCI. Possible reasons for altered relaxation of lower esophageal sphincter (LES) are increase in the stiffness of the smooth muscle, reduction of primary and secondary peristalsis and impaired coordination of the upper esophageal sphincter (UES) and pharynx (11). Distal contractile amplitude and duration increased significantly with age, with also may justify the increase of DCI (12).

In older individuals, even if asymptomatic, an inadequate response of the LES can be found, characterized by a partial or complete absence of relaxation phase initiated by deglutition, an absence of the contractile phase after relaxation of LES or both of them. In addition, in the

body of the esophagus, peristaltic contractions are weaker and progress more slowly, leading to a higher incidence of disordered contractions (13,14).

The aging process is responsible for several physiological changes in the gastrointestinal system. Among these changes, the sensory function of the esophagus may deteriorate over time, which contributes to the atypical presentation of many esophageal disorders in this age group. In 1964, the concept of presbyesophagus was proposed to explain the changes in peristaltic pressures and esophageal contractility secondary to the natural aging process (7). However, with the advent of esophageal manometry, modern manometric techniques, and classification systems, this concept has been questioned. The majority of elderly patients with abnormal peristalsis are now classified into one of the described motility disorders (8). In spite of motor disorders are more frequent in the old, it does not mean that motility inexorably degrades with time (15). Therefore, many cases of esophageal dysmotility previously labeled as presbyesophagus may be related to damage caused by untreated long-term gastroesophageal reflux disease (GERD), for example (8).

Changes manifest in the physiology of the esophagus and in the symptoms presented in older patients (8). Among the possible causes, the loss of peristaltic function in these patients may be explained by the decrease in the number of esophageal myenteric neurons (16).

The decrease in esophageal innervation is possibly causative of the loss of secondary peristalsis (17). This peristalsis depends on the sensory and motor function of the esophagus, both of which can be affected by aging. Although the thickness of the wall does not change with age, a study by Leese *et al.* (18) suggests a decrease in the number and density of striated muscle fibers in the proximal esophagus, which was not observed in the smooth muscle portion. Hollis and Castell (19) evaluated the response of esophageal pressures to edrophonium chloride, a cholinergic agonist that stimulates the contraction of the smooth muscle fibers in the body of the esophagus, and noted that in older individuals, pressures do not increase as promptly as in younger individuals, indicating muscle weakening without alteration in neurological function.

Effect of frailty on esophageal diseases

GERD

The changes of sensory function of the esophagus with

age contribute to a more severe presentation of GERD without significant symptoms in this population (8). The increase in stiffness and reduction of primary and secondary peristalsis found in the human esophagus with deterioration of esophageal function over the years may contribute to a higher prevalence of GERD in older adults (20).

Frailty may be one of the risk factors for the increased incidence of GERD in the elderly population. In a prospective cohort, Imagama *et al.* (21) demonstrated that kyphotic changes, vertebral column inclination, decreased back muscle strength, and sarcopenia are significant risk factors for the development of GERD. The study suggests that an increase in intra-abdominal pressure caused by kyphosis can induce a decrease in the LES pressure and hiatal hernia, leading to gastroesophageal reflux. Although not significant, the prevalence of frailty was higher in individuals with GERD when compared to those without the pathology both at the beginning of the study (10.5% *vs.* 5.7%) and 5 years later, among those who did not have GERD and developed it during those years (10.5% *vs.* 6.4%) (21).

In a retrospective cross-sectional study involving consecutive outpatients aged 65 years or older, Asaoka *et al.* (22) examined medical records from a geriatric center. The study assessed various aspects, including patient profiles, osteoporosis evaluation, sarcopenia evaluation, frailty assessment, nutritional status, findings from upper gastrointestinal endoscopy, and questionnaire responses regarding abdominal symptoms. The subjects were then categorized into frailty and non-frailty groups, and the researchers investigated the risk factors for frailty. The results revealed that frailty was significantly associated with a higher prevalence of symptoms related to GERD and constipation. Constipation is a significant risk factor for malnutrition, that is a significant cause of frailty (23). In a logistic regression model for the prevalence of prefrailty, Matsushita *et al.* showed that chronic constipation was a significant and independent determinant, and they suggested that autonomic failure is associated with prefrailty among older individuals (24). Other factors such as age and sarcopenia were also associated with frailty and contribute to GERD occurrence.

Dysphagia

The process of swallowing is complex and involves different structures, organs, and systems. Difficulty in swallowing, defined as dysphagia, can be broadly categorized into two regions. Oropharyngeal dysphagia involves the oral

cavity, striated muscles of the tongue and pharynx and is primarily associated with central neurological disorders and esophageal or conductive dysphagia, is intrinsically related to the smooth muscles of the esophagus and its motility.

A fragility in older individuals is related to a worsening of nutritional status, which has an impact on patients' lives and increases the risk of morbidity, such as aspiration pneumonia. An institutionalized Japanese elderly population study showed that the occurrence of dysphagia was independently associated with worse nutritional status and frailty (25).

Frail patients have a higher risk of dysphagia, which is associated with adverse outcomes in hospitalizations or surgery, such as longer hospital stays, increased costs, and more complications (26). The main components of frailty that lead to increased dysphagia are sarcopenia, functional impairment, and drugs that affect swallowing (27).

Sarcopenia is the loss of muscle mass that leads to a loss of function (28). There are indirect ways to assess this muscle loss, such as grip strength and walking speed (29). Regarding swallowing function, most studies have evaluated the consequences of a reduction in generalized skeletal muscle in the proximal portion of the esophagus, also composed of striated muscle. It is observed that older patients with sarcopenia have weaker pharyngeal contractility and dysfunction of the UES (30).

Dysphagia tends to be more severe in the elderly and can be caused by health conditions unrelated to swallowing. The increase in inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) in response to physiological and environmental stressors associated with a reduction in immune system activity in diseases that course with chronic inflammation has a role in the development of age-related diseases, including frailty (31,32). Diabetes, cardiovascular diseases, obesity, alterations in gut microbiota, and depression are some examples of comorbidities associated with this pathophysiological process (32-34).

Therefore, despite age being a factor for higher prevalence, the presence of dysphagia can result from other factors or comorbidities. Regardless of age, malnutrition and frailty are positively correlated with the severity of dysphagia (35).

Frailty-related dysphagia is also associated with a more pronounced decline in functional vital capacity. In a comparative study between individuals experiencing dysphagia caused by frailty and those with dysphagia resulting from brain injury, multivariate logistic regression analysis demonstrated a significant correlation between

forced vital capacity (FVC) and severity scores assessed through videolaryngofluoroscopy in frailty-induced dysphagia ($P < 0.05$). However, no such significance was observed in dysphagia induced by brain injury ($P \geq 0.05$) (36). This discrepancy between the two groups can be attributed to the presence of systemic sarcopenia in the first group.

Different forms of assessment can be used to evaluate frailty and estimate the risk of dysphagia (29,37). Despite the differences between assessment models, they all focus on function and physical activity. Changes in oral and swallowing functions are evident in older individuals, which can affect functional domains such as nutrition and sarcopenia in frail elderly, but their evaluation is not included in many frailty assessment models and tools (38). Hathaway *et al.* (39) showed that while age and hospitalization were associated with lower grip strength as a form of frailty assessment, hospitalized patients also had an association with dysphagia and bronchoaspiration.

Dysphagia is a multifactorial condition that is not only related to swallowing disorders but also to other components of frailty, such as physical, cognitive, and psychological aspects (40). In addition to ensuring adequate nutritional intake, it is important to perform appropriate oral rehabilitation to treat problems related to dentition and xerostomia, as well as to perform resistance training for the tongue and oropharyngeal muscles (41). Early detection of dysphagia and treatment based on nutritional rehabilitation and resistance physical exercises can modify poor prognostic factors for clinical and surgical outcomes associated with frailty (42).

Effect of frailty on the outcomes of esophageal surgery

The occurrence of unfavorable surgical outcomes in older patients is multifactorial and depends on factors such as comorbidities, functional status, and cognition (43-45). Among the factors of poor prognosis, dysphagia appears to be an independent risk factor for the occurrence of unfavorable outcomes in surgical patients. Longer hospitalization time, higher costs, and increased medical/surgical complications were observed among frail and non-frail patients. In turn, the prevalence of dysphagia is higher in populations with frailty (46).

Esophagectomy

The elderly patient undergoing esophagectomy for

cancer usually has a coexistence of other diseases that can adversely affect their postoperative course. These comorbidities seem to play a more important role than age alone. Madhavan *et al.* (47) found that a population over 70 years of age would be more prone to greater perioperative morbidity and mortality in esophagectomy for cancer. Pultrum *et al.* (48) found in their study that, after multivariate analysis, age alone (above 70 years) was not a prognostic indicator for survival, but the presence of comorbidities was a significant factor.

Considering that frailty affects postoperative outcomes (49), Lee *et al.* (50) evaluated the effects of frailty in a retrospective cohort of patients undergoing surgical resection for esophageal cancer. Populations between 18 and 65 years and over 65 years were observed. In both groups, frail patients had higher mortality and postoperative respiratory failure, showing that frailty is an important factor independent of age.

Sarcopenia as a component of frailty evaluation also has an important role as a predictor of favorable outcome. A lower muscle mass in patients undergoing esophagectomy for cancer is an independent predictor of mortality and disease-free survival time (45).

Heller's myotomy

Laparoscopic Heller's myotomy (LHM), per-oral endoscopic myotomy (POEM), and pneumatic dilatation (PD) are well-established methods for treating achalasia. In older patients, less invasive procedures are preferred to reduce the risk of complications. However, in specialized centers, treatment of the oldest-old patients should be based solely on their physiological and mental health, not their age (51). In a multicenter study, Zotti *et al.* (51) reviewed outcomes and changes in routine clinical therapeutic options in achalasia patients over 80 years of age and found that LHM can be safely performed in patients with achalasia aged 80 years or older and should be considered as the first choice for treatment since it is associated with a low rate of complications and a satisfactory improvement in symptoms.

Laparoscopic antireflux surgery

The studies for the evaluation and definition of better surgical techniques often exclude older populations, leading to uncertainty regarding the best therapeutic strategy for this population. Retrospective studies with octogenarian populations for laparoscopic anti-reflux surgery show,

on the other hand, that despite higher rates of morbidity and mortality compared to individuals under 80 years of age, elective repair of paraesophageal hiatal hernia can be performed in octogenarians, especially in patients without comorbidity (52), with symptomatic improvement and minimal morbidity and mortality (52,53). It is evident that age *per se* is not a complicating factor, and it is mainly linked to the presence of comorbidities and the patient's clinical condition. However, studies with this specific population are more necessary for better evaluation and therapeutic definition.

Management of frailty and esophageal diseases

A comprehensive care plan for frailty should address various aspects, including polypharmacy (whether rational or nonrational), management of sarcopenia, treatable causes of weight loss, and the underlying causes of exhaustion, such as depression, anemia, hypotension, hypothyroidism, and B12 deficiency (54).

To prevent malnutrition and complications related to dysphagia, such as aspiration pneumonia, effective interventions have been studied (55). Sire conducted a review of different approaches to managing sarcopenic dysphagia, malnutrition, and oral frailty in the elderly (55).

Oral rehabilitation interventions include functional training, compensatory maneuvers, postural adjustments, swallowing maneuvers, and dietary modifications (55). In the case of sarcopenic dysphagic patients, adopting an upright seated position with head/neck flexed is recommended as it optimizes swallowing performance (56,57). Postural adjustments have also been shown to significantly improve self-perceived difficulties in swallowing maneuvers (57,58). Specifically, maintaining an upright 90° seated position for at least 30 minutes after eating reduces the risk of food inhalation (58,59).

Tongue-pressure resistance training, a strengthening exercise, has been found to improve hyoid bone movements, tongue pressure, and the width of the UES (60). Additionally, modifying the consistency of solid and/or liquid foods can enhance the safety and effectiveness of oral feeding and intake for dysphagic patients (61).

Given the increased risk of complications and higher mortality associated with frailty, a frailty screen should be included in the perioperative evaluation of elderly patients undergoing elective major surgery (62). A detailed assessment of frail patients is necessary to identify the underlying causes of their frailty. Implementing multimodal

prehabilitation programs may improve the perioperative prognosis for frail patients (63). Diagnosing frailty enables the determination of patients' eligibility for surgeries, as well as prehabilitation and rehabilitation programs, which can help reduce postoperative complications, hospital length-of-stay, and improve outcomes (64).

Conclusions

The natural aging process is responsible for physiological changes in esophageal motility, but these changes alone cannot be blamed for the pathological alterations found in the elderly population. On the other hand, frailty is an isolated risk factor for the occurrence of severe gastroesophageal reflux, unfavorable surgical outcomes, and dysphagia.

Different instruments can be used to assess frailty and sarcopenia, which hinders result comparisons and the establishment of protocols for studies. The physiopathology involved in this process is complex and further studies are necessary for better understanding. The exact mechanisms underlying the impact of frailty on esophageal disorders remain uncertain and appear to be multifactorial. However, the impact on clinical features is significant. The management of this disorder encompasses various strategies, including improving nutritional status, addressing sarcopenia, and implementing oral rehabilitation. Whenever possible, these interventions should be instituted before considering invasive procedures.

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