Peer Review File

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Reviewer A

Dear Authors,

Thank you for submitting your manuscript entitled 'THE SEQUEL OF FRAILTY ON THE PATHOPHYSIOLOGY AND TREATMENT OF ESOPHAGEAL DISEASES'. It provided a good summary of the topic and highlights the impact of frailty. I have a few comments:

1. Throughout the manuscript but particularly in Section 4, the impact of age rather than frailty is discussed. I wonder whether the manuscript title should include 'age and frailty'? Although distinct there is overlap and it would be good to cover the impact of both.

Reply 1: We changed the tittle adding "age and frailty". (see page 1, line 1)
Changes in the text: THE SEQUEL OF AGE AND FRAILTY ON THE PATHOPHYSIOLOGY AND TREATMENT OF SURGICAL ESOPHAGEAL DISEASES

2. I feel the manuscript would benefit from a section on the impact of age/frailty on the Oncological management of Oesophageal Cancer however you may feel this falls outwith the intended scope. If so, please state in introduction.

Reply 2: We feel that discuss about Oncological management of Oesophageal Cancer would fall outwith the intended scope of this manuscript, so we changed the title of the paper, emphasizing that the review focuses on surgical management, and added a paragraph at the end of the introduction, reinforcing that we will review age and frailty changes in patients with esophageal diseases, with a specific focus on the interest of the esophageal surgeon. (see page 3, line 41)
Changes in the text: 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.

3. Line 100 - explain mechanism of action of edrophonium chloride

Reply 3: We added the explanation of mechanism of action of edrophonium chloride. (see page 6, line 107)
Changes in the text: Hollis and Castell 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.

4. I think the first sentences of section 3 (GERD) would be better placed in section 2 - discussion on physiology and innervation.
Reply 4: We placed the first sentences of section 3 to section 2. (see page 4, line 85)
Changes in the text: 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.

5. Lines 125-127 would benefit from being expanded with greater discussion on referenced studies.
Reply 5: We expanded with greater discussion on referenced studies. (see page 7, line 131)
Changes in the text: In a retrospective cross-sectional study involving consecutive outpatients aged 65 years or older, Asaoka et al. 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 gastroesophageal reflux disease (GERD) and constipation.
Constipation is a significant risk factor for malnutrition, which is a significant cause of frailty, 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. Other factors such as age and sarcopenia were also associated with frailty and contribute to GERD occurrence. Constipation is a significant risk factor for malnutrition, wich is a significant cause of frailty, 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.

6. Section on Dysphagia could benefit from an introductory paragraph to

summarise section content and improve flow.
Reply 6: We included an introductory paragraph in section dysphagia. (see page 7, line 147)
Changes in the text: 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.

7. Line 156 - which cytokines in particular?
Reply 7: We included that cytokines like Il-6 and TNF-a are involved. (see page 8, line 169)
Changes in the text: The increase in inflammatory cytokines such as tumor necrosis factor-alpha (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.

8. Line 165-171 - discussion on potential reason for observed difference should be added. ?due to systemic sarcopenia.
Reply 8: We added that the potential reason for observed difference is due to systemic sarcopenia. (see page 9, 179)
Changes in the text: 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 ($p \geq 0.05$). This discrepancy between the two groups can be attributed to the presence of systemic sarcopenia in the first group.

9. When discussing studies throughout, how frailty is defined should be stated.
Reply 9: We included the definition of frailty in introduction and a statement about the differences between definitions and evaluation of frailty In conclusion. (see page 3, line 41 and page 14, line 388)
Changes in the text: In 2001, Fried et al. 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.

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.

Reviewer B

Marcel L. Andrade. et al. clearly stated that frailty is an isolated risk factor for the occurrence of severe gastroesophageal reflux, unfavorable surgical outcomes, and dysphagia, and the physiopathology involved in this process is complex and further studies are necessary for better understanding.

This review includes plenty of information regarding the association of frailty and esophagus disorders.

However, there is a lacking statement regarding the hypothesis of mechanisms behind the impact of frailty on esophagus disorders and the clinical importance of the impact.

This review is academically interesting, but the reader may not be able to apply the information to clinical practice or future trials because of the lacking information.

So, I recommend adding statements regarding the hypothesis of mechanisms behind the impact of frailty on esophagus disorder and how to use the information in clinical practice.

Reply 1: We added statements regarding the hypothesis of mechanisms behind the impact of frailty on esophagus disorder and how to use the information in clinical practice in a new topic and at conclusions.

Changes in the text: (see page 12, line 252 and page 14, line 388)

Management of frailty among esophagus 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.

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

Oral rehabilitation interventions include functional training, compensatory maneuvers, postural adjustments, swallowing maneuvers, and dietary

modifications. In the case of sarcopenic dysphagic patients, adopting an upright seated position with head/neck flexed is recommended as it optimizes swallowing performance. Postural adjustments have also been shown to significantly improve self-perceived difficulties in swallowing maneuvers. Specifically, maintaining an upright 90° seated position for at least 30 minutes after eating reduces the risk of food inhalation.
Tongue-pressure resistance training, a strengthening exercise, has been found to improve hyoid bone movements, tongue pressure, and the width of the upper esophageal sphincter. Additionally, modifying the consistency of solid and/or liquid foods can enhance the safety and effectiveness of oral feeding and intake for dysphagic patients.
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. 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. 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.
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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. Early identification of frailty and intervention are essential to change the natural history of this condition.

Reviewer C

General comments

The authors described the influence of frailty on esophageal disorders.

This is a well-organized review.

Please provide answers to the following comments.

Major comments

1. Lines 66-72.

Why was the age positive correlated with IRP and DCI? What were the reasons? It seems like IRP or DCI would decrease with age.

Reply 1: We explained the reasons of these findings. (see page 4, line 73)
Changes in the text: Possible reasons for altered relaxation of 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].

2. Line 106-.
With regard to GERD and its risk factors, why were sarcopenia and frailty associated with GERD? What were the mechanisms (including pathological perspectives)?
Reply 2: We discussed the mechanisms why were sarcopenia and frailty associated with GERD. (see page 6, line 117)
Changes in the text: 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.

3. Line 129-.
The discussion of dysphagia in the pharyngeal and esophageal phases was mixed. This review article focuses on dysphagia in the esophageal phase. If you are going to write a description of dysphagia in the pharyngeal phase, you may want to add the relationship to dysphagia in the esophageal phase and why the pharyngeal phase is important.
Reply 3: As the primary focus of this article is on the esophageal phase, we have chosen to exclude the paragraphs related to the pharyngeal phase.

4. Overall, I think that the authors described a good summary of esophageal issues in the elderly, but could you add some additional information about care and treatment? The title also mentions treatment as well as diseases, I think it would be an even better review if you added the information.
For example, regarding GERD, the head should be elevated when supine (Ness-Jensen E, et al: Lifestyle Intervention in Gastroesophageal Reflux Disease. Clin Gastroenterol Hepatol 14:175-182, 2016).
There were also previous studies that esophageal peristalsis changes with posture, and esophageal function might be trained in the bridge swallowing in the elderly (Aoyama K, et al: Bridge swallowing exercise for gastroesophageal reflux disease symptoms: a pilot study. Prog Rehabil Med 7, 2022).
In addition, prior studies have suggested that chewing gum increases saliva and swallowing frequency, which increases esophageal and pharyngeal pH and may help prevent reflux. (Moazzez R, et al: The Effect of Chewing Sugar-free Gum on Gastro-esophageal Reflux. J Dent Res 84:1062–1065, 2005.)
Reply 4: We added information about care and treatment.
Changes in the text: (see page 12, line 252)

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Minor comments

1. If there were more Figures, such as esophageal residuals, manometry, etc., it might be easier for the reader to understand.

Unfortunately, there is no typical figure that represents the swallowing of a patient with frailty that could guide the readers. For this reason, we chose not to include it in our review.