AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–
Head and Neck Surgery
2023, Vol. 168(5) 935–943

DOI: 10.1002/ohn.168
http://otojournal.org
WILEY

Is Postextubation Dysphagia Underestimated in the Era of COVID-19? A Systematic Review and Meta-analysis

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Abstract

Objective. To investigate the incidence rate of postextubation dysphagia (PED) in patients with COVID-19, as well as relative factors potentially influencing the clinical course of dysphagia.

Data Sources. Six databases including PubMed, MEDLINE, Embase, ScienceDirect, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science were searched with no restriction on the language.

Review Methods. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Data were extracted and cross-examined among 3 of the authors. The random-effects model was adopted for the statistical synthesis. The percentage and 95% confidence interval (CI) were adopted as the effect measurements of the PED incidence rate. Subgroup analyses, sensitivity analyses, and metaregression were also performed to identify the heterogeneity among the studies.

Results. A total of 594 patients were enrolled and analyzed from the 10 eligible studies. The weighted incidence of PED in patients with COVID-19 was 66.5% (95% CI: 49.7%-79.9%). Age was the potential factor influencing the incidence rate after heterogeneity was adjusted by the metaregression analysis.

Conclusion. Compared to the current evidence reporting only 41% of the non-COVID patients experienced PED, our study further disclosed that a higher 66.5% of COVID-19 patients suffered from PED, which deserves global physicians' attention. With the association between COVID-19 and dysphagia having been more clearly understood, future clinicians are suggested to identify intubated patients' risk factors earlier to strengthen PED care programs in the era of COVID-19.

Keywords

coronavirus, deglutition disorders, incidence, intubation, ventilation

Received July 21, 2022; accepted September 4, 2022.

Since the end of 2019, the world has been profoundly influenced by the coronavirus disease of the 2019 (COVID-19) pandemic. Although still a proportion of patients infected with COVID-19 were asymptomatic,[1] more patients experienced symptoms with varying severity.[2] Furthermore, the persistent post-COVID sequelae after recovery have been widely reported to pose an impact on systemic organs and systems.[3] Hence, it remains a global issue to quickly cope with the disease to minimize the negative health influence on patients.

For patients infected with COVID-19, treatments for disease progression and symptom relief were essentially required. In those with critical respiratory symptoms, a series of oxygen supply management were necessary based on the suggestions of the World Health Organization (WHO).[4] Moreover, at emergent stages, mechanical ventilation is usually the first-line therapy to temporarily maintain adequate oxygen supply by invasively establishing an airway passage; early intubation was also proved to decrease hospital mortality and was related to fewer pulmonary sequelae.[5] Given that 4% to 12% of patients with COVID-19 require invasive respiratory support,[6,7] the care and administration for endotracheal

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tube ventilation are definitely essential. However, in patients requiring prolonged intubation, there are accompanying complications, which include dysphagia, dysphonia, and throat pain.[8] This may even lead to a decrease in quality of life after extubation, which deserves our close attention.

Dysphagia after endotracheal intubation, or postextubation dysphagia (PED), is an important adverse effect in patients receiving invasive mechanical ventilation.[9] It has been well known that dysphagia is associated with delayed oral feeding, malnutrition, and decreased quality of life[9]; PED, moreover, has been reported to be linked to increased hospitalized duration,[10] rates of aspiration pneumonia,[11] and even mortality.[12] The estimated rates of PED ranged from 3% to 62%,[13] and a recent meta-analysis by McIntyre et al[14] further reported an overall 41% PED incidence in non-COVID patients. Nonetheless, to take COVID-19 into consideration, it is unclear how the incidence of PED alters compared to the previous non-COVID population due to the uncertainty of the viral mechanisms. Recently, studies have proposed probable pathways that COVID-19 may lead to non-intubated dysphagia,[15-17] and PED may thus be underestimated in COVID-19 populations. Therefore, our study aims to identify the real-world incidence rate of PED in patients with COVID-19, as well as factors potentially contributing to a higher occurrence of PED.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[18] guidelines and was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (Registration number: CRD42022329015). The PRISMA checklist was shown from page 3 to page 6 in the Supplement, available online.

Literature Search and Selection

Two authors (T.-Y.C. and Y.-C.S.) systematically searched PubMed, MEDLINE, Embase, ScienceDirect, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science for relevant kinds of literature until July 13, 2022. The major keywords for searching were (COVID-19 OR SARS-COV-2) AND (intubation OR extubation) AND (dysphagia OR swallowing dysfunction); a detailed searching strategy was presented in eTable 1 (Supplemental Materials). The references of the recruited articles were also viewed for the literature enrollment if necessary. After removing duplicates, the 2 authors (T.-Y.C. and Y.-C.S.) independently screened the articles for eligibility and enrolled the final eligible literature. The inclusion criteria were (i) articles of prospective and retrospective cohort studies, case-control studies, and clinical trials; (ii) articles with abstract and full-text for further appraisals; (iii) studies on postextubation patients which could be distinctly extracted; (iv) studies regarding dysphagia following extubation with a clear definition or diagnosis; and (v) studies able to provide sufficient information of the incidence rate of PED. The exclusion criteria were (i) article types of systematic review, narrative review, case series, case reports, editorials, letters, comments, and expert opinions; and (ii) studies not investigating and demonstrating the incidence of PED. Studies that were published between November 2019 and July 2022 were collected, and there was no restriction on the language for a more comprehensive analysis. Any inconsistency during the process was discussed with a third author (C.-W.L.).

Data Extraction

One author (C.-W.L.) extracted the required data, which was cross-examined by the other 2 authors (T.-Y.C. and Y.-C.S.). The data included (i) the name of the first author and the publication year; (ii) the country of the study; (iii) the study type; (iv) the sample size; (v) the mean age of the subjects; (vi) the population setting; (vii) the percentage of pre-existing dysphagia of the subjects; (viii) the mean intubation duration; (ix) the percentage of tracheostomy of the subjects; (x) the methods used for dysphagia assessment; (xi) the mean duration from extubation to dysphagia assessment; and (xii) the incidence of PED. If data from the same population were presented in more than 1 article, the most recent and complete study was selected.

Risk of Bias Assessment and Quality of Evidence

Two authors (T.-Y.C. and Y.-C.S.) independently assessed the risk of bias and the quality of evidence of the studies. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was followed to evaluate the risk of bias.[19] The quality of evidence was assessed based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guidelines.[20] Any discrepancy was discussed with a third author (C.-W.L.).

Data Processing

The percentage and 95% confidence interval (CI) were adopted as the effect measurements of the PED incidence rate. Since there was expected heterogeneity across the studies due to the real-world divergence of the study setting, the random-effects model was more suitable and was adopted for analyzing the pooled incidence of PED and 95% CI. The proportion of variation among the studies was calculated with the I^2 statistic. Further subgroup analyses of "mean age (≦*65 years old* versus >*65 years old*)," based on the definition of the elderly who were potentially at higher risks promoted by the WHO,[21] and "major dysphagia assessment method (*non-instrumental tools* versus *instrumental tools*)," due to the difference regarding the accuracy in diagnosis,[22] were conducted to identify the heterogeneity.

The one-study-removal method was used for the sensitivity analysis to detect potential outliers. Additionally, the metaregression was performed to quantify the effects of the potential covariates related to PED, including mean age, major dysphagia assessment method, mean intubation duration, mean duration from extubation to dysphagia assessment, and tracheostomy.

In the major dysphagia assessment method, the definitions for instrumental tools were using fiberoptic endoscopic examination of swallowing (FEES) and videofluroscopic swallowing study (VFSS); and noninstrumental tools were using means of either history taking, questionnaire, or subjective judgments (eg, viscosity volume swallowing test). Since there were higher risks of generating extra aerosol during the FEES examinations and VFSS was not applicable in all units, noninstrumental tools appeared to be relatively suitable as a mainstream diagnosis under the current pandemic. Therefore, in the metaregression, instrumental tools were set as the reference group to see if any potential deviation was led by the more commonly used noninstrumental tools.

To evaluate possible publication bias, the funnel plot and Egger's test were applied, and the Duval and Tweedie' trim-and-fill method was used for adjusting the existing bias. A 2-tailed $p < .05$ was considered as of significance. The analyses were conducted using the Comprehensive Meta-Analysis software, version 3 (Biostat Inc).

Results

Literature Selection

A total of 533 articles were collected after searching the databases. Among these identified articles, 418 of them were screened following the removal of duplicates, yielding 67 studies for eligibility evaluation. Eventually, a total of 10 studies[23-32] were included in the meta-analysis after the exclusion of ineligible articles (**Figure 1**).

Characteristics of the Studies

Among the 10 recruited studies, 594 patients in total were included. Descriptive data were presented in eTable 2 (Supplemental Materials). The incidence of PED varied from 26.9% to 93.0%, and 7[25-29,31,32] out of the 10 studies reported more than half of patients (>50%) experienced dysphagia after the removal of the endotracheal tube. The reported mean age in percentage of the studies[27,29-32] ranged from 54 to 67 years, with 3[27,29,30] of them under 65 and 2[31,32] of them above 65; and the mean intubation duration recorded in 5 of the studies[23,27,28,30,31] ranged from 14.1 to 20.0 days. The percentage of pre-existing dysphagia (reported in 5 articles[23-25,29,32]) and tracheostomy (reported in 9 articles[23-31]) varied from 0% to 4% and 15% to 80%, respectively. As to the dysphagia assessment method, 2 studies[29,31] majorly adopted instrumental tools assisted with noninstrumental tools for diagnosis; 2 studies[25,26] used noninstrumental tools for primary evaluations in combination with instrumental tools; and 5 studies[24,27,28,30,32] only took nontools as the only mean for dysphagia assessment. The mean duration from extubation to dysphagia assessment ranged from 1 to 4 days.[24,26,27,30,32]

Risk of Bias Assessment and Quality of Evidence

The general risks of bias in the enrolled studies were not high (eTable 3 in the Supplemental Materials). The quality of evidence based on outcomes was either low or very low since the enrolled articles were all observational studies, bringing about low baseline ratings among the studies and in turn generating the results (eTable 4 in the Supplemental Materials).

Results of Meta-analysis

PED incidence in patients with COVID-19

Among the 594 patients, 356 of them experienced PED. The weighted incidence of PED in patients with COVID-19 was 66.5% (95% CI: 49.7%-79.9%) (**Figure 2**). The heterogeneity analysis ($I^2 = 91.967\%$, $p < .001$) revealed a high variation across the studies.

Subgroup analysis, sensitivity test, and metaregression

The subgroup analyses (**Figure 3**) revealed that substantial intragroup heterogeneity remained when categorizing the studies based on the age of 65 (*≦65 years old*: 59.0%, 95% CI: 38.8%-76.5%, $I^2 = 87.763\%$, $p < .001$; *>65 years old*: 71.5%, 95% CI: 45.8%-88.1%, $I^2 = 75.412\%$, $p = .044$); the overall heterogeneity among the above studies did not significantly decrease (63.7%, 95% CI: 48.4%-76.7%, $I^2 = 83.733\%$, $p < .001$), and thus could not explain well the variation across the studies based on an age of 65. However, when grouping the studies based on major dysphagia assessment methods, the heterogeneity decreased in those using instrumental tools (73.1%, 95% CI: 54.5%-86.0%, $I^2 = 66.493\%$, $p = .084$), but was still high in those adopting noninstrumental means (69.4%, 95% CI: 47.0%-85.3%, $I^2 = 93.430\%$, $p < .001$); the overall heterogeneity among the above studies remained high as well (70.2%, 95% CI: 53.2%-83.1%, $I^2 = 92.222\%$, $p < .001$), and thus could not explain well the variation across the studies based on this classification. The one-study-removal method for sensitivity analysis was performed with no changes to the outcome (eFigure 1 in the Supplemental Materials). The further metaregression (**Table 1**) demonstrated that age alone (coefficients: 0.095, 95% CI: 0.007-0.183, $p = .035$), although not exactly based on being 65 years old (coefficients: 0.555, 95% CI: −0.794-1.903, $p = .420$), was the only measured variable presented with statistical significance in the analysis of the heterogeneity; instead, the rest of the variables did not show significance in the metaregression analysis and thus were not capable of explaining the variation.

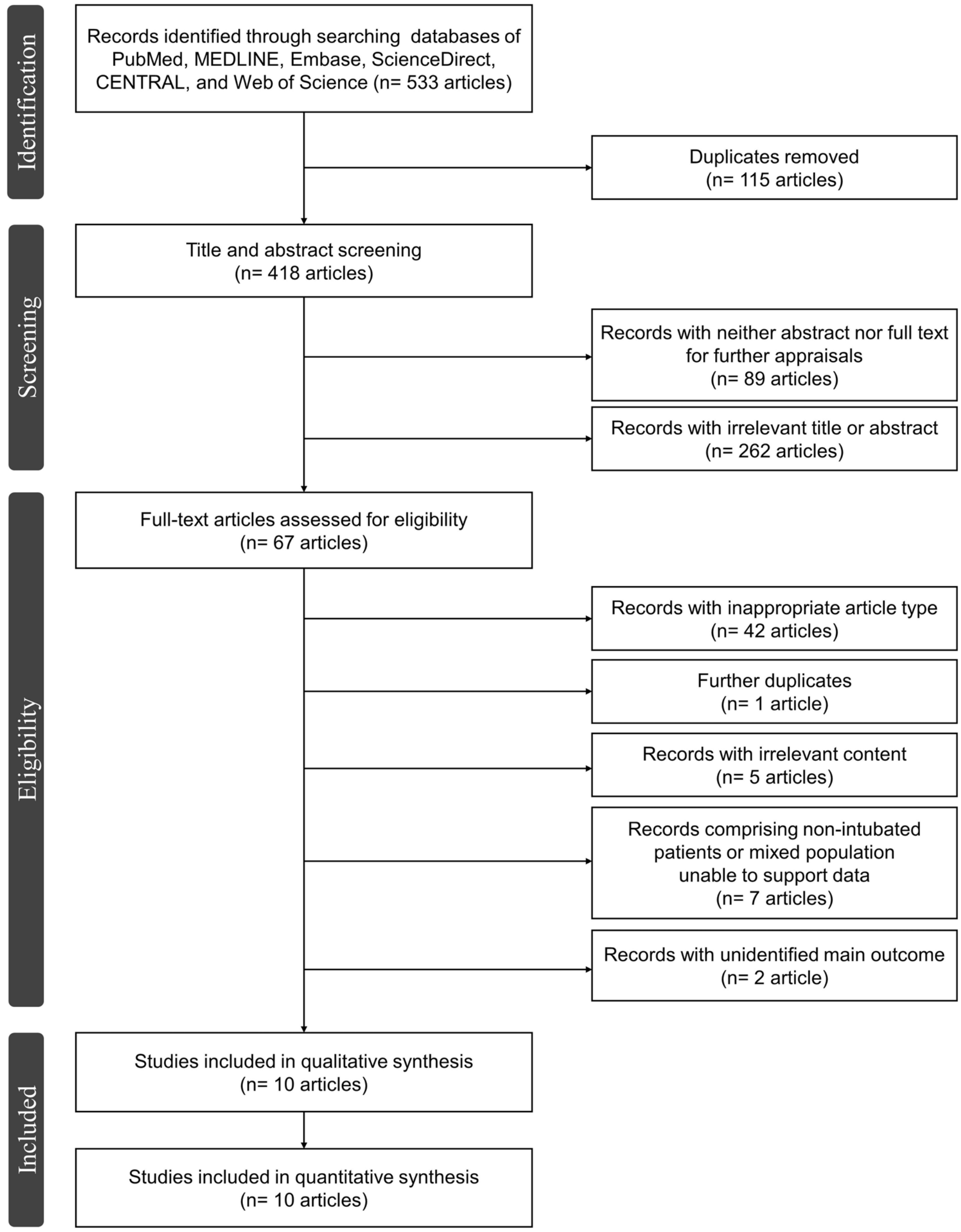

Figure 1. The PRISMA flowchart of the literature selection process. The database search yielded 533 articles meeting the requirements. After removing the ineligible studies, 10 were enrolled for the meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Publication bias

The asymmetrical funnel plot (eFigure 2 in the Supplemental Materials) implied probable publication bias. However, the results of the further Egger's test indicated no existing bias ($p = .112$). Further, the trim-and-fill method did not alter the main results as well.

Discussion

To the best of our knowledge, this is the first meta-analysis exploring the PED incidence in patients with COVID-19. Compared to the recent meta-analysis[14] reporting only 41% of the non-COVID patients experienced PED, our analysis further disclosed that a higher 66.5% of COVID-19 patients suffered from PED, which deserves global physicians' attention. With the findings of our study, it is also expected that patients with COVID-19 who experienced PED are in a higher demand for dysphagia care following extubation. Therapies such as diet modification, postural adjustment, and a series of targeted rehabilitation from the speech and language therapy team may be beneficial in the care of this vulnerable population.[26]

Some previous studies did not exclude the substantial impact of endotracheal intubation when discussing dysphagia in patients with COVID-19[33-35]; Grilli et al[15]

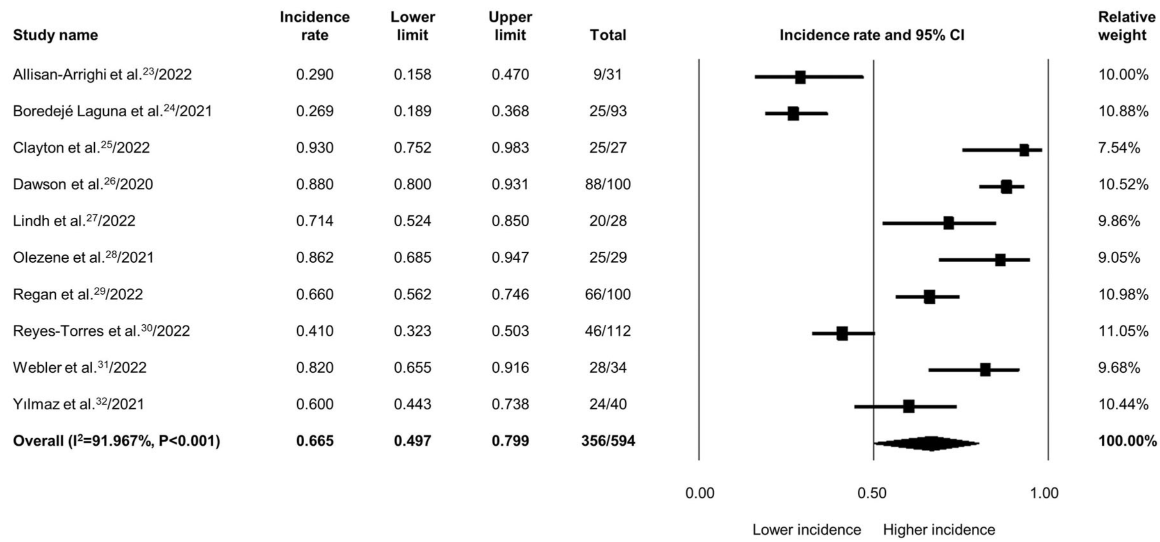

Figure 2. Forest plot of the overall pooled incidence of PED in patients with COVID-19. Among the 594 enrolled COVID-19 patients, the weighted incidence of PED was 66.5% (95% CI: 49.7%-79.9%, $I^2 = 91.967\%$, $p < .001$). CI, confidence interval; PED, postextubation dysphagia.

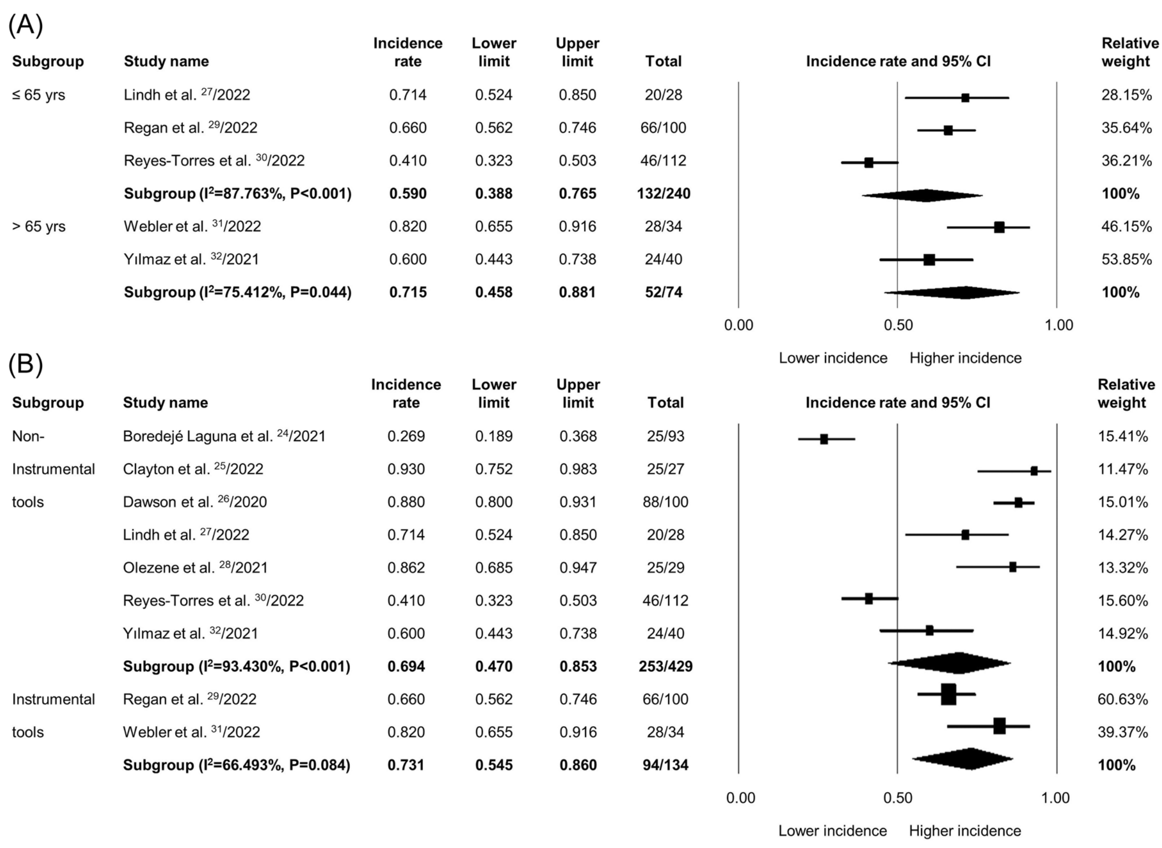

Figure 3. Results of the subgroup analysis. (A) The weighted incidence of PED in age subgroups of "≦65" and ">65." (B) The weighted incidence of PED in subgroups using "non-instrumental tools" and "instrumental tools." CI, confidence interval; PED, postextubation dysphagia.

nonetheless investigated dysphagia solely in nonintubated COVID-19 patients and proved 20% of the patients also suffered from dysphagia, which could be a reference to the previous statements. After being infected with COVID-19, the inflammation response secondary to the infection may interfere with normal oral and pharyngolaryngeal motility[15]; a multilevel swallowing impairment is thus generated. Additional probable pathways may be linked to the angiotensin-converting enzyme 2 receptors and transmembrane serine protease 2 enzymes, by which

Table 1. Results of the Metaregression Analysis of Potential Clinical Covariates

Variables	Coefficient (95% CI)	Standard error	p value
Mean age (years)[27,29-32]	0.095 (0.007, 0.183)	0.045	.035
>65 years[31,32] (Reference group: ≦65 years[27,29,30])	0.555 (−0.794, 1.903)	0.688	.420
Major dysphagia assessment method			
Noninstrumental tool[24-28,30,32] (Reference group: Instrumental tool[29,31])	−0.255 (−2.130, 1.621)	0.957	.790
Mean intubation duration (days)[23,27,28,30,31]	−0.101 (−0.659, 0.457)	0.285	.723
Mean duration from extubation to dysphagia assessment (days)[24,26,27,30,32]	0.632 (−0.355, 1.619)	0.504	.210
Tracheostomy (%)[23-31]	1.288 (−2.529, 5.104)	1.947	.509

Abbreviation: CI, confidence interval.

the virus gains entry into human cells and interferes with normal immune response.[16,17] The high expression of these receptors in the oral cavity and oropharyngeal epithelium might result in virus penetration into cranial nerves by a trans-neuronal retrograde pathway,[16,17] making it easier to generate neurogenic dysphagia. As to PED, common mechanisms include neuromuscular weakness, oropharyngeal and laryngeal trauma, reduced laryngeal sensitivity, impaired synchronization of breathing and swallowing, delirium, and cognitive impairment.[36] This study further focuses on the clinical factors in intubation practice and their impacts on the following postextubated swallowing impairment during the COVID-19 pandemic.

The Impact of Age

Age could be considered a contributor to dysphagia,[37] and the prevalence of dysphagia in persons over fifty ranged from 15% to 22%.[38] Considering the recent pandemic, age could pose an impact on innate immunity by attenuating interferon responses to viral infection.[39,40] Furthermore, costimulatory signals of the antigen-presenting cells, crucial for activating T cells to prevent infection, were reduced.[39] These made the elderly with COVID-19 more vulnerable and at a higher risk to develop dysphagia following extubation.[41] Based on our results, the metaregression did support that age alone positively correlates with PED incidence, which may be an important factor in PED development. However, both subgroup analysis and metaregression turned out that the traditionally defined "age of 65" could not fully explain the heterogeneity of the PED incidence. Therefore, the exact age for generating the difference should be further studied with future research and data.

The Impact of Intubation Duration

The intubation duration is an important clinical factor related to PED.[10,13,14,42] However, the meta-analysis of PED in non-COVID patients reported no differences in incidence between prolonged (>48 h) and shorter (≦48 h) durations of intubation.[14] Similar results were also seen in a previous systematic review, claiming that though a higher dysphagia frequency was observed following prolonged intubation, this condition occurred mostly when patients were intubated for less than 2 weeks.[13] Moreover, a multicenter prospective study proposed that intubation duration over 6 days was not associated with a further increase in the odds of dysphagia.[43] In this COVID-19 study, the intubation duration was proved to not be the factor potentially correlating to PED incidence. Given that the participants were intubated longer, the proportion of patients with PED could be thus less affected by this clinical variable.

The Impact of the Major Dysphagia Assessment Method

The subgroup analysis revealed that the diagnoses made by noninstrumental tools were highly heterogeneous compared to those using instrumental tools, and further metaregression discovered that the use of noninstrumental tools was indeed not the factor influencing the PED incidence. Both methods served as effective methods for evaluating PED in patients with COVID-19. As emphasized by Bordeje Laguna et al,[24] noninstrumental tools were convenient and played crucial roles in the risky and challenging intensive care unit; a similar statement was also promoted by Dawson et al[26] using noninstrumental tools as major substitutions. Considering both efficacy and safety, noninstrumental tools may also be suitable options for clinicians in the COVID-19 era.

The Impact of Duration From Extubation to Dysphagia Assessment

The duration from extubation to dysphagia assessment was not the factor associated with the PED incidence in patients with COVID-19 after the metaregression. In previous non-COVID research studies, most of them took "evaluating dysphagia at least 24 hours following extubation" as the indicator of better outcomes,[14,44,45] and Leder et al[45] further claimed that most of the postextubated patients passed the swallow screening within an even merely 1 h following extubation. To prevent early aspiration, none of the enrolled studies assessed the patients within 24 h after extubation. Therefore, this may in turn generate insignificant results in patients with COVID-19.

The Impact of Tracheostomy

Tracheostomy was necessary for those with severe respiratory problems needing prolonged mechanical ventilation[46] and was recommended to be performed within 7 days of intubation.[47] However, the PED incidence may be argued when considering the co-effect of tracheostomy, which was hard to be distinguished. Therefore, we performed the metaregression, and figured out that tracheostomy was not the factor affecting the PED incidence during COVID-19. Interestingly, this insignificant result was also similar to that in the intubation duration as these 2 factors correlated to each other during the clinical course,[46,47] which could be the explanation for this issue. Still, a COVID-19 study of 100% tracheostomized patients claimed that 19% had remarkable pathological findings on the following laryngeal examination, and 30% experienced dysphagia[48]; this may provide hints for future studies on the effects of dysphagia in patients with COVID-19 with a tracheostomy.

Quality of Evidence

All of the included studies were cohort studies, and the overall ratings for qualities of evidence did not reach the highest level. However, this meta-analysis could still provide insights into evaluating PED in patients with COVID-19. Since PED was still mainly affected by the intubation and extubation procedure and is less influenced by other clinical interventions, eligible data could be reasonably pooled for analysis in this study. Moreover, despite the high heterogeneity generated in the data pooling of PED incidence, we have examined common and possible leading causes during the period between intubation and dysphagia development using subgroup analysis and metaregression. Although the subgroup analysis only turned out to decreased heterogeneity to a less extent, which could not fully explain the variation across the studies, further metaregression indicated that age, although not exactly based on groups of 65 years old, might be able to explain the heterogeneity with significant results. Therefore, the findings could be expected to help tailor the evaluation of PED during the COVID-19 pandemic.

Limitations and Future Directions

There are some limitations in the study. First, pre-existing dysphagia was not analyzed since only a very low percentage of patients suffered from the disease, and its effect on PED may be misleading after pooling. Being an equally valuable factor,[41] future studies are suggested to investigate the increase in PED in those with pre-existing dysphagia to better understand this topic. Second, the impact of tracheostomy on PED incidence. Nevertheless, the insignificant result of the metaregression has provided probable answers to this issue. Last, the studies included for analyses only provided outcomes observed in a short period after extubation. Given that the recent predominant omicron variant tends to attenuate the severity of symptoms,[49,50] whether the long-term impact on PED incidence may alter remains unclear and should be further discovered in the postpandemic era.

Conclusion

Up to 66.5% of the intubated COVID-19 patients experience PED, which deserves our close attention. Although the deviation among the kinds of literature still cannot be fully explained, this study has explored the impact of potential clinical causes on this issue. More future studies are warranted to elucidate the relationship between the various possible factors and PED in the COVID-19 era.

Acknowledgments

The authors would like to thank the authors and the patients of the enrolled studies for sharing their experience and reports during the pandemic. The authors also thank the research grant from the Ministry of Science and Technology Research Project (MOST 110-2314-B-182A-124-MY3), Taiwan, and Dr Pei-Wen Lin from the Division of Glaucoma, Department of Ophthalmology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan for the assistance of entire manuscript review.

Author Contributions

Chung-Wei Lin, conceptualized the idea, designed the study scheme, curated the data, performed the analysis, and drafted the manuscript; **Ting-Yi Chiang**, searched and appraised the literature, curated the data, and drafted the manuscript; **Wen-Ching Chen**, created and modified the tables and figures, and justified all the analyzed results; **Li-Wen Chiu**, curated the data, and drafted the manuscript; **Yung-Chung Su**, searched and appraised the literature, curated the data, and drafted the manuscript; **Hsin-Ching Lin**, conceptualized the idea, data interpretation, critical revision of the manuscript and final approval; **Chun-Tuan Chang**, justified all the analyzed results and final approval.

Disclosures

Competing interests: Dr. Hsin-Ching Lin received 2 research grants from Intuitive Surgical Inc (Sunnyvale, CA). However, Intuitive Surgical Inc had no role in the design or conduct of this study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. Drs Chung-Wei Lin, Ting-Yi Chiang, Wen-Ching Chen, Li-Wen Chiu, Yung-Chung Su, and Professor Chun-Tuan Chang declare no potential conflict of interest.

Funding source: This study was partially sponsored by the grant from the Ministry of Science and Technology Research Project (MOST 110-2314-B-182A-124-MY3), Taiwan.

Supplemental Material

Additional supporting information is available in the online version of the article.

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