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Postoperative dysphagia as a predictor of functional decline and prognosis after undergoing cardiovascular surgery

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Running title: Impact of postoperative dysphagia in cardiovascular surgery patients

Keywords: Dysphagia, cardiac surgery, cardiac events, hospital-associated disability

Abstract

Aims: Post-extubation dysphagia (PED), an often-overlooked problem, is a common and serious complication associated with mortality and major morbidity after cardiovascular surgery. Dysphagia is considered an age-related disease, and evaluating its long-term effects is a pressing issue with rapidly progressing ageing worldwide. Therefore, we examined the effect of PED on functional status and long-term cardiovascular events in patients undergoing cardiovascular surgery.

Methods and Results*:* This single-centre, retrospective cohort study included 712 patients who underwent elective cardiovascular surgery and met the inclusion criteria. Patients were divided into the PED and non-PED groups based on their postoperative swallowing status. Swallowing status was assessed using the Food Intake Level Scale. Functional status was evaluated as hospital-associated disability (HAD), defined as a decrease in activities of daily living after hospital discharge compared to preoperative values. Patients were subsequently followed up to detect major adverse cardiac and cerebrovascular events (MACCE). PED was present in 23% of the 712 patients and was independently associated with HAD (adjusted odds ratio, 2.70). Over a 3.5-year median follow-up period, MACCE occurred in 14.1% of patients. Multivariate Cox proportional hazard analysis revealed HAD to be independently associated with an increased risk of

MACCE (adjusted hazard ratio, 1.85), although PED was not significantly associated with MACCE.

***Conclusions**:* PED was an independent HAD predictor, with the odds of HAD occurrence being increased by 2.7-fold due to PED. HAD accompanied by PED is a powerful predictor of poor prognosis. Perioperative evaluation and management of swallowing status, and appropriate therapeutic interventions, are warranted.

Introduction

Post-extubation dysphagia (PED) is a common and serious complication closely associated with mortality and major morbidity after cardiovascular surgery.[1] Previous studies have shown that PED incidence varies from 10% to 80% in patients, depending on their diagnostic criteria.[2,3] The PED mechanisms are multifactorial and still not fully understood; however, mechanical causes, cognitive dysfunction, and residual narcotics and anxiolytic medications effects are thought to be key factors in PED development.[4] On the other hand, most patients experience rapid spontaneous PED recovery[5]; therefore, PED is often overlooked and disregarded as an important symptom in clinical practice.

Notably, a previous study demonstrated that patients at high risk of PED were physically frail preoperatively.[6] If such vulnerable patients develop PED, even temporarily, they may be at risk of further functional status decline and rehabilitation retardation. The functional decline in acute hospital care has recently been called hospital-associated disability (HAD). It has attracted attention for its importance in long-term prognosis and patients' poor quality of life.[7,8] HAD prevalence is as high as 20% in older patients and increases with population ageing.[7] Therefore, HAD prevention is an extremely important agenda in a super-ageing society undergoing highly invasive interventions such as cardiovascular surgery. However, to the best of our knowledge, no

study has assessed the relationship between PED and HAD yet.

Moreover, there are very few reports on the relationship between PED and cardiovascular disease, although two recent studies have reported that PED causes frailty and poor nutritional status due to reduced dietary intake.[9,10] Given that frailty and malnutrition are independent predictors of the development of cardiovascular disease,[11,12] PED may be a significant contributor to long-term cardiovascular events. Previous studies on PED have focused on short-term complications. However, the impact of PED on HAD and its long-term prognosis are unclear.

We examined the effect of PED on functional status and long-term cardiovascular events in patients undergoing cardiovascular surgery to address these limitations. We hypothesized that PED is related to HAD and that the presence of both PED and HAD would result in MACCE development. Clarifying the relationships between PED and HAD or prognosis will pave the way for new risk stratification of preoperative assessment, perioperative management, and effective intervention.

Methods

Study Population

This retrospective cohort study was conducted between May 2014 and April

2021 at a single university hospital in Japan. We enrolled 800 consecutive in-patients who had undergone elective cardiovascular surgery. All patients undergoing cardiovascular surgery were by a recruited multidisciplinary cardiac rehabilitation team, including a surgeon, physician, physiotherapist, and trained nurse, to determine swallowing function. The exclusion criteria included patients whose functional status was not measured and those with severe dementia, preoperative dysphagia, postoperative complications such as new-onset stroke, tracheostomy without postoperative extubation, making it impossible to assess patients for dysphagia, and hospital death. The present study complied with the principles of the Declaration of Helsinki regarding investigations on human participants and was approved by the local ethics committee (approval no. B200339). Owing to the retrospective study design, we used the opt-out method in the present study. All participants were notified of their participation in the study, and it was explained that they were free to opt-out of participation at any time.

Clinical Characteristics of Study Participants

Baseline characteristics evaluated included age, sex, body mass index (BMI), left ventricular ejection fraction, brain natriuretic peptide (BNP) level, haemoglobin, comorbidities such as diabetes, chronic obstructive pulmonary disease, hypertension,

haemodialysis, dyslipidaemia, history of cardiac surgery, chronic kidney disease (CKD), medications, New York Heart Association (NYHA) functional class, and nutritional status, assessed using the Mini Nutritional Assessment Short Form (MNA-SF).[13] The reliability and validity of the MNA-SF have already been well established for the detection of malnutrition. The MNA-SF score ranges from 0 to 14, with a higher score indicating a well-nourished status.[14]

Laboratory data were evaluated within 1 week of cardiac surgery. Perioperative clinical variables recorded included the cardiac surgery type, surgery and ventilation durations, postoperative surgery-related complications, length of intensive care unit stay, length of hospital stay, and discharge location.

Frailty was assessed using the Japanese version of the Cardiovascular Health Study frailty index.[15] Patients with at least three of the following factors were considered physically frail: weakness (handgrip), slow gait speed, weight loss, exhaustion, and low physical activity. Physical performance was assessed using the Short Physical Performance Battery (SPPB),[16] including gait speed from the timed 5-meter walk test, 5-chair stands, and a hierarchal standing balance test. The SPPB is strongly recommended owing to its reliability, validity, feasibility, and predictive value following cardiac surgery.[17]

Dysphagia Assessment

The swallowing status was assessed using the Food Intake Level Scale (FILS).[18] Based on the FILS score, dysphagia was categorized as no oral intake (score: 1–3), oral intake and alternative nutrition (score: 4–6), or oral intake alone (score: 7–10). The FILS assessment was performed three times: 1) within 1 week before surgery; 2) when postoperative oral intake was permitted after the attending cardiologists had confirmed that the patient's circulatory status was stable; and 3) immediately before hospital discharge. Following postoperative extubation, bedside swallowing evaluation of the consciousness level, mouth or tongue function, vocal function, oral hygiene, and cough reflex was performed by a well-trained ICU nurse. A water-swallowing test was then performed in patients with sufficient swallowing ability. The eating patterns were determined based on the test results. As described previously, this study defined dysphagia as an FILS score of ≤7.[19] We excluded patients with a preoperative FILS score of ≤7 from the analysis.

Functional Status and HAD Assessments

Functional status was assessed using the Barthel index (BI) score. The BI consists of 10 items (feeding, transfer, grooming, toilet use, bathing, ambulation, stair

climbing, dressing, urination, and defaecation management) to evaluate activities of daily living (ADL) on a scale of 0–100, with lower scores indicating greater dependency.[20] In this study, HAD was defined as a ≥5-point decrease in the BI score from before to after surgery, as described elsewhere.[21] All patients began postoperative rehabilitation the day after surgery, in line with the Japanese Circulation Society guidelines for rehabilitation in cardiovascular disease patients.[22]

Follow-up Assessment

The primary endpoint of this study was major adverse cardiac and cerebrovascular events (MACCE) after discharge, which included a composite of death, myocardial infarction, hospital readmission for worsening heart failure or angina, and stroke. All events were based on the clinical diagnoses assigned by the treating physician. The patients were followed up as outpatients, and the date and cause of any reported event identified during regularly scheduled outpatient visits were confirmed based on hospital medical record review. Patients who could not be followed up in the outpatient setting were surveyed via telephone interview.

Statistical Analysis

Statistical analyses were conducted after confirming the normal data distribution using the Shapiro–Wilk test. Patients were stratified into two groups according to the presence or absence of PED. Intergroup differences in baseline clinical characteristics were determined using an independent *t*-test and chi-square test. The results are reported as mean (standard deviation) for parametric data and as median and interquartile range (IQR) for nonparametric data. We conducted logistic regression analysis to investigate risk factors for HAD; HAD incidence was the dependent variable in this analysis and clinical characteristics and PED were the independent variables. Confounding factors were selected using prior evidence regarding their effect on both exposure variables and outcome, in addition to demographics (age, sex, BMI) and clinical characteristics (frailty, MNA-SF, NYHA class, surgery type).[23, 24] Further, to analyse the factors affecting MACCE, univariate and multivariate analyses were performed using a Cox proportional hazard regression model. In this analysis, the incidence of MACCE was used as the dependent variable, and the independent variables included patient clinical characteristics, HAD, and PED. Factors theoretically related to MACCE, such as age, sex, BMI, HAD, nutritional status, NYHA class, surgery type, and CKD, were included as confounding factors. Mediation analysis was performed to assess HAD as mediators of the relationship between PED and MACCE. The mediation model indicated through estimation of indirect

effects whether HAD was a mediator between PED and MACCE. Kaplan–Meier survival statistics were used to examine the time to the first event. Log-rank analysis was performed to compare MACCE with or without PED and with or without HAD. The sample size was calculated with reference to a previous study[25] and our unpublished data (power = 0.8, significance level = 0.05, mean difference = 14.0%; n = 680 patients). Statistical significance was set at a p-value of <0.05. Statistical analyses were performed using R (The R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism version 9.0 (GraphPad Software, La Jolla, CA, USA).

Results

Baseline Characteristics

Of the 800 consecutive patients, 712 met the inclusion criteria and 88 were excluded. Of the 88 excluded patients, 12 had preoperative dysphagia, 20 did not have their functional status measured, 16 had undergone tracheostomy without extubation, 32 developed new-onset stroke, 2 had severe dementia before surgery, and 6 had hospital death. The overall mean age was 67.7 ± 13.7 years, and 42.5% were female. The median follow-up period was 3.45 years (IQR 1.62–5.00 days). The prevalence of PED was 14.6%. The patients were divided into PED (n = 104) and non-PED (n = 608) groups.

Clinical characteristics and between-group differences are shown in **Table 1**. Compared with the patients in the non-PED group, those in the PED group were significantly older and had lower haemoglobin levels, higher BNP levels and NYHA functional class, higher malnutrition rates, CKD, cardiac surgery history, and frailty ($p < 0.05$). **Table 2** shows a comparison of the postoperative courses. Surgery and postoperative ventilation durations were longer in the PED group than in the non-PED ($p < 0.001$). Postoperative complications such as pneumonia and renal failure were more common in the PED group than in the non-PED ($p < 0.05$). Regarding surgery type, there were significantly higher rates of aortic surgery in the PED group than in the non-PED group ($p < 0.001$). PED was associated with a reduced discharge rate ($p < 0.001$).

HAD and Its Predictors

The prevalence of HAD in the PED group was 57.8%, which was more than double that in the non-PED group (24.4%; $p < 0.001$). The findings of univariate and multivariate logistic analyses for HAD are shown in **Table 3**. In the multivariate analysis, age (adjusted odds ratio [OR] = 1.05; 95% confidence interval [CI]: 1.03–1.08), female sex (adjusted OR = 1.84; 95% CI: 1.22–2.78), PED (adjusted OR = 2.70; 95% CI: 1.54–4.76), NYHA functional class (adjusted OR = 1.57; 95% CI: 1.09–2.28), and aortic

surgery (adjusted OR = 2.17; 95% CI: 1.02–4.54) were independently associated with HAD development after adjusting for potential confounders.

MACCE

During the follow-up period (median 3.45 years), 21.4% of the patients developed MACCE. **Table 4** summarizes the results of univariate and multivariate analyses using the Cox proportional hazard regression model to predict MACCE. The multivariate Cox proportional hazard regression analysis showed that age (hazard ratio [HR], 1.02; 95% CI: 1.00–1.04; p = 0.019), HAD (HR = 1.85; 95% CI: 1.27–2.68; p = 0.001), and NYHA functional class (HR = 1.65; 95% CI: 1.23–2.20; p = 0.0009) were significantly associated with MACCE after covariate adjustment. However, PED was not a significant MACCE predictor (p = 0.23). The Kaplan–Meier analyses results are shown in **Figure 1**. **Figure 1** (A) shows a comparison based on the presence or absence of PED. The cumulative MACCE incidence in the PED group was significantly higher than that in the non-PED group (log-rank test, p < 0.001). **Figure 1 (B)** shows a comparison of the three groups: control, PED without HAD, and PED with HAD. PED concurrent with HAD had the worst prognosis; however, PED without HAD did not reveal a significant difference in prognosis (**Figure 1**). In mediation analysis, PED showed a positive

relationship with HAD (β = 0.474: p = 0.02), and HAD was also significantly associated with MACCE (β = 0.788: p = 0.001). Indirect effects, which indicate that the effect of PED on MACCE is transmitted through mediators, showed that HAD (β = 0.257; p = 0.016) was a significant mediator of the detrimental effect of PED on MACCE. Furthermore, the total and direct effects for PED and MACCE were also significant (β = 0.410; p = 0.01 and β = 0.374; p = 0.04, respectively; **Figure S1**).

Discussion

A significant finding of the present study was that PED after cardiovascular surgery was an independent HAD predictor. Furthermore, HAD overlapping with PED led to a worse clinical prognosis after adjusting for confounding variables, and PED caused HAD-mediated MACCE. We are the first to report on the long-term effects of PED, although some studies have investigated the causes or frequency of short-term PED.[3,4] In this study, PED prevalence was 14.4%, consistent with that in previous studies.[2,3] HAD developed in 57.8% of PED patients, and MACCE occurred in 21.4% of all participants.

In this study, we found that PED leads to MACCE mediated by HAD. Prolonged dysphagia or pneumonia complications affect prognosis.[25] Nevertheless, PED, which was thought to be transient and underestimated postoperatively, continued to impact MACCE

via HAD for a long time. This indicates the importance of detailed and multidisciplinary perioperative evaluation in clinical practice. In a Japanese multicentre registry, HAD patients did not recover mobility or nutritional status and had increased depression symptoms compared with non-HAD patients after 1 year.[7] Prolonged functional recovery, poor nutritional status, and depression may lead to a poor prognosis.

In this study, HAD developed in more than half of PED patients. There are several possible explanations for this observation. First, several previous studies have shown that the swallowing function is associated with muscle mass, muscle strength, ADL, and nutritional status.[26,27] Furthermore, postoperative dietary intake during the first week after surgery is crucial and independently associated with functional recovery.[28] PED development could delay return to oral intake and lead to loss of muscle mass and poor functional status and subsequent frailty.[9] Frailty, sarcopenia, nutritional risk, and dysphagia are all common in older people, and the presence and management of each influence others directly or indirectly. Smithard et al. demonstrated that frailty, sarcopenia, nutritional risk, and dysphagia comprise an "Older Adult Quartet".[27] PED likely triggers these vicious cycles as a consequence of HAD. Second, PED patients were already frail before surgery.[6] A large cohort study demonstrated that preoperative functional status in the elderly was the most influential factor in predicting HAD.[29] Frail patients cannot

increase their physical activity and reacquiring ADL could be delayed in them, making them more likely to develop HAD. Basically, vulnerabilities inherent in frailty manifest in PED.

Other than PED, age, female, NYHA class, and aortic surgery were independent predictors of HAD, consistent with the findings of previous studies.[9,23] Regarding aortic surgery, a catabolic response commonly occurs after major surgery. It is well known that hypothermic circulatory arrest attenuates postoperative proteolysis.[30] Moreover, cardiopulmonary bypass time was indirectly associated with surgery-induced muscle proteolysis.[30] Cardiopulmonary bypass has also been reported to facilitate immune responses during cardiac surgery. Differences in surgical techniques and invasiveness with postoperative systemic inflammation of skeletal muscles likely affected HAD.

Furthermore, it was wells known that frailty is an independent MACCE predictor.[11] Recently, HAD after cardiac surgery was shown to be an independent cardiac event predictor.[7] Our results agree with those of previous studies. A possible explanation for these observations is that HAD decreases the ability to mobilize and ambulate, and diminishes the physiological reserve capacity to maintain homeostasis. Other than HAD, age and NYHA class were independent predictors of MACCE, consistent with the findings of previous studies.[11,31] Surprisingly, PED without HAD was not significantly

associated with MACCE. It is conceivable that PED is often transient, and that early postoperative improvement could have prevented nutritional status and physical function deterioration to a minimum.

HAD prevention is important for patients with PED or with a high risk of PED development, given that HAD-accompanied PED leads to poor prognosis. A possible strategy for PED and HAD prevention is preoperative exercise-based rehabilitation. “Prehabilitation” in older patients awaiting cardiac surgery effectively improves functional capacity and quality of life.[32] Preoperative intervention effectively improves postoperative cardiac rehabilitation functional capacity results. Nagano et al. showed that physical rehabilitation and nutritional management for older in-patients with sarcopenia could effectively improve swallowing function.[33] Specifically, a daily intake of at least 30 kcal/kg was recommended to improve swallowing function.[34] The combination of aggressive intervention with nutritional management and high-energy intake could prevent PED and HAD in cardiovascular surgery patients.

Furthermore, multidisciplinary oral care interventions by nurses, dental hygienists, and speech-language pathologists can improve impaired oral function and dysphagia outcomes.[35] Evaluation of oral health status and adequate intervention had favourable effects on PED and HAD, as oral health status was independently associated with

functional recovery.[36] Further studies are needed to clarify the causal relationship between physical and swallowing functions and the multidisciplinary intervention effects on PED. This overwhelming evidence suggests that PED evaluation improves patient management and that its omission from routine clinical practice is no longer acceptable for most patients.

The limitations of this study include its single-centre retrospective design, which may have affected the external validity of our observations. However, to minimize its limitations, we calculated the necessary sample size in a prior study and, therefore, the present study had sufficient statistical power. Furthermore, we did not investigate longitudinal psychometric cognitive measures in the present study. Moreover, the swallowing function was only assessed during hospitalization; therefore, the long-term swallowing status was not evaluated. Future studies are needed to assess the long-term recovery of swallowing function. Moreover, we used the FILS score to assess PED as an indirect assessment of the swallowing function from food substances. Subsequently, there remain unanswered questions concerning mechanical injuries, such as vocal cord immobility. Videofluoroscopic swallow evaluation or fiberoptic endoscopic evaluation is the gold standard for diagnosing swallowing disability. However, these assessments are unsuitable for routine use in the clinical setting because of their complexity and

invasiveness. Despite these limitations, this is the largest study to demonstrate the effects of PED on HAD and its long-term prognosis.

Conclusion

We demonstrated that PED development is associated with functional decline in patients undergoing cardiovascular surgery. Notably, functional decline accompanied by PED was a powerful predictor of poor prognosis over 3 years postoperatively. Perioperative evaluation and management of the swallowing status and increased physical function in postoperative care are warranted.

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Conflicts of interest: The Authors declare that there is no conflict of interest.

Data availability statement: The derived data generated in this research will be shared on reasonable request to the corresponding author, SSK.

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Figure legends

Figure 1. Time to the major adverse cardiac and cerebrovascular events.

Kaplan–Meier curves show major adverse cardiac and cerebrovascular event rates between the PED group (red line) and non-PED group (black line) (Panel A, log-rank test: $p = 0.009$), and among the three groups: normal (black line), PED without HAD (red line), and PED with HAD (blue line) (Panel B, log-rank test: $p = 0.022$). Overlapping HAD with PED was associated with a worse prognosis.

PED: Post-extubation dysphagia, HAD: hospital-associated disability

Figure S1. Relationship between PED and MACCE through HAD.

PED: post-extubation dysphagia, MACCE: major adverse cerebrocardiovascular events, HAD: hospital-associated disability

Legends

Table 1. Baseline characteristics of patients and between-group comparison according to the presence of postoperative dysphagia

Data are expressed as mean ± standard deviation, median (IQR), or number (percentage). SMD, standardized mean difference; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate.

Table 2. Comparison of the perioperative data of patients according to the presence of postoperative dysphagia

Abbreviations as in Table 1.

Table 3. Univariate and multivariable analyses of the predictive factors for the development of hospital-associated disability

Abbreviations as in Table 1.

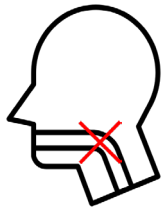
Table 4. Cox proportional hazard regression analysis of the predictive factors for the development of MACCE

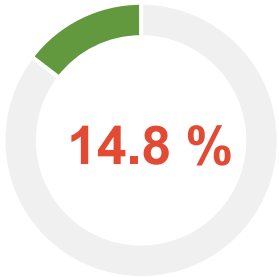
Abbreviations as in Table 1.

PED as a predictor of functional decline and prognosis after undergoing CV surgery

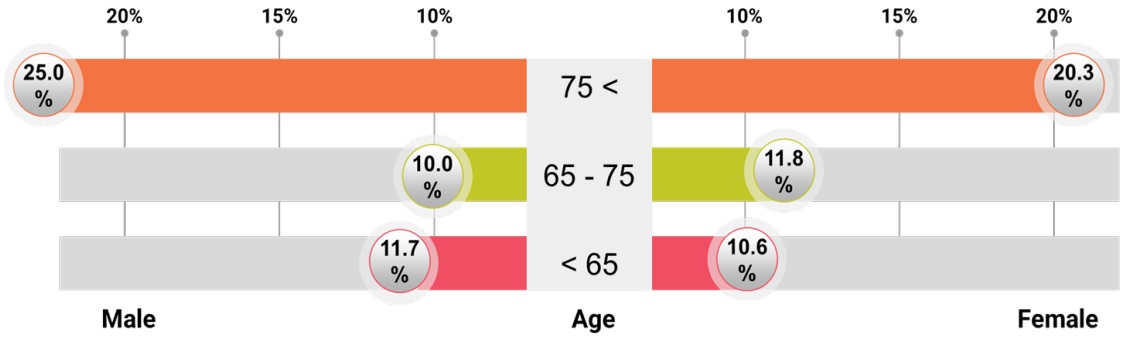
Clarifying the impact of PED on HAD and long-term cardiovascular events in patients with CV surgery.

The prevalence of PED





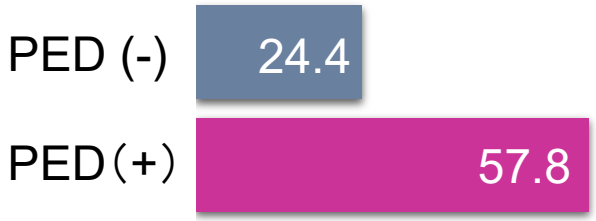
PED: postoperative dysphagia
HAD: hospital associated disability



PED led to a worse clinical prognosis mediated by hospital associated disability

The relationship between PED and HAD

Rate of HAD(%)



Adjusted odds ratio of PED for HAD

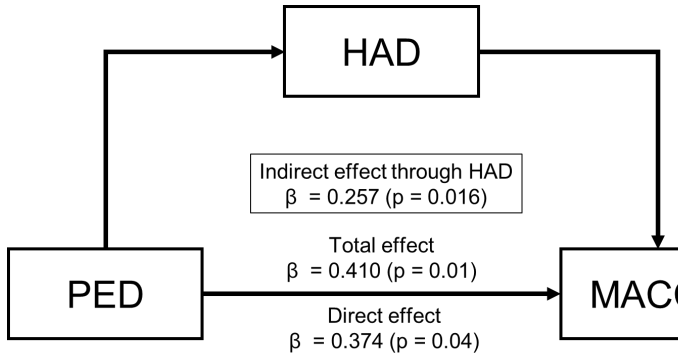
▶ 2.70 (1.54 - 4.76)

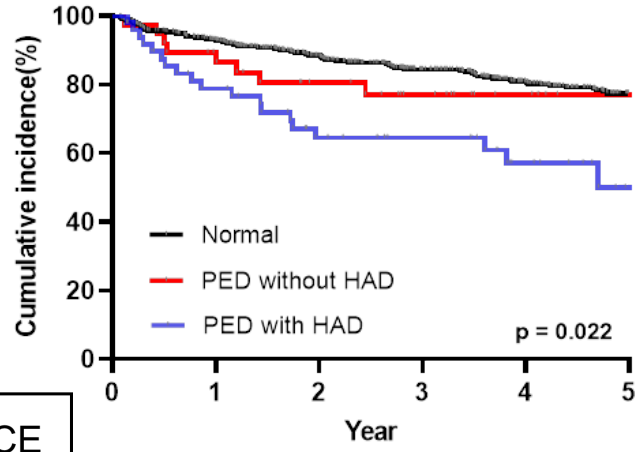
PED was an independent predictor of HAD.

The relationship between PED and cardiac events through HAD

HAD overlapping with PED led to MACCE

PEDs caused cardiac events mediated by HAD.





MACCE: major adverse cardiac and cerebrovascular events

Table 1. Baseline characteristics of patients and between-group comparison according to the presence of postoperative dysphagia

Variables	PED group (n =104)	Non-PED group (n=608)	p-value
Age, years	73.5 ± 9.8	66.8 ± 14.0	<0.001
Sex, female, n (%)	49 (47.1)	255 (41.9)	0.10
BMI, kg/m^2	22.3 ± 3.6	22.9 ± 3.8	0.15
Laboratory data			
BNP, pg/mL	219.7 ± 293.9	167.2 ± 210.7	0.05
Haemoglobin, g/dL	11.4 ± 2.8	12.7 ± 2.4	<0.001
Comorbidity, n (%)			
Diabetes	13 (12.5)	124 (20.4)	0.06
COPD	14 (13.5)	84 (13.8)	1.0
Hypertension	69 (66.3)	361 (59.4)	0.19
Hemodialysis	7 (6.7)	17 (2.8)	0.07
Dyslipidemia	43 (41.3)	232 (38.2)	0.59
Previous cardiac surgery	22 (21.2)	77 (12.7)	0.03
CKD	64(67.4)	286(42.8)	0.001
LVEF, %	57.5 ± 17.8	59.3 ± 13.1	0.21
NYHA class, I/ II/ III, %	26.0 / 49.0 / 25.0	29.4 / 58.8/ 11.8	0.004
MNA-SF, Good/ At risk/ Malnutrition, %	48.5 / 33.3 / 18.2	73.0 / 20.6/ 6.3	<0.001
Medications, n (%)			
β-blocker	40 (38.5)	311 (51.2)	0.019
ACE-I	9 (8.7)	77 (12.7)	0.328
ARB	41 (39.4)	200 (32.9)	0.217
Statin	27 (26.0)	183 (30.1)	0.418
Diuretic	39 (37.5)	215 (35.4)	0.74
Frailty, n (%)	43 (48.9)	104 (19.4)	< 0.001
SPPB, points	9.7 ± 2.7	11.1 ± 1.8	< 0.001

Data are expressed as the mean ± standard deviation, median (IQR), or number (percentage). SMD, standardized mean difference; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate.**Table 1.** Baseline characteristics of patients and between-group comparison according to the presence of postoperative dysphagia

Table 2. Comparison of the perioperative data of patients according to the presence of postoperative dysphagia

Variables	PED group (n =98)	Non-PED group (n=566)	p-*value*
Operative time, hours	409.4 ± 151.9	354.1 ± 117.6	<0.001
Ventilation time, hours	31.4 ± 37.1	10.6 ± 13.7	<0.001
Procedure type, n (%)			<0.001
Aortic	27 (26.0)	61 (10.8)	
CABG	11 (10.6)	84 (13.8)	
Valve	55 (52.9)	411 (67.6)	
Combination	11 (10.6)	52 (8.6)	
Pneumonia, n (%)	20 (19.2)	5 (0.8)	<0.001
Infection-related complications, n (%)	4 (3.8)	18 (3.0)	0.55
Renal failure, n (%)	12 (11.5)	13 (2.1)	<0.001
ICU stay, days	5.9 ± 4.4	2.8 ± 1.4	<0.001
Hospital stay, days	30.2 ± 13.02	20.0 ± 9.1	<0.001
Discharge location, home	46 (44.2)	550 (90.5)	<0.001
Hospital-associated disability, n(%)	52 (57.8)	144 (24.4)	< 0.001

Abbreviations as in Table 1.

Table 3. Univariate and multivariable analysis of the predictive factors for the development of hospital-associated disability

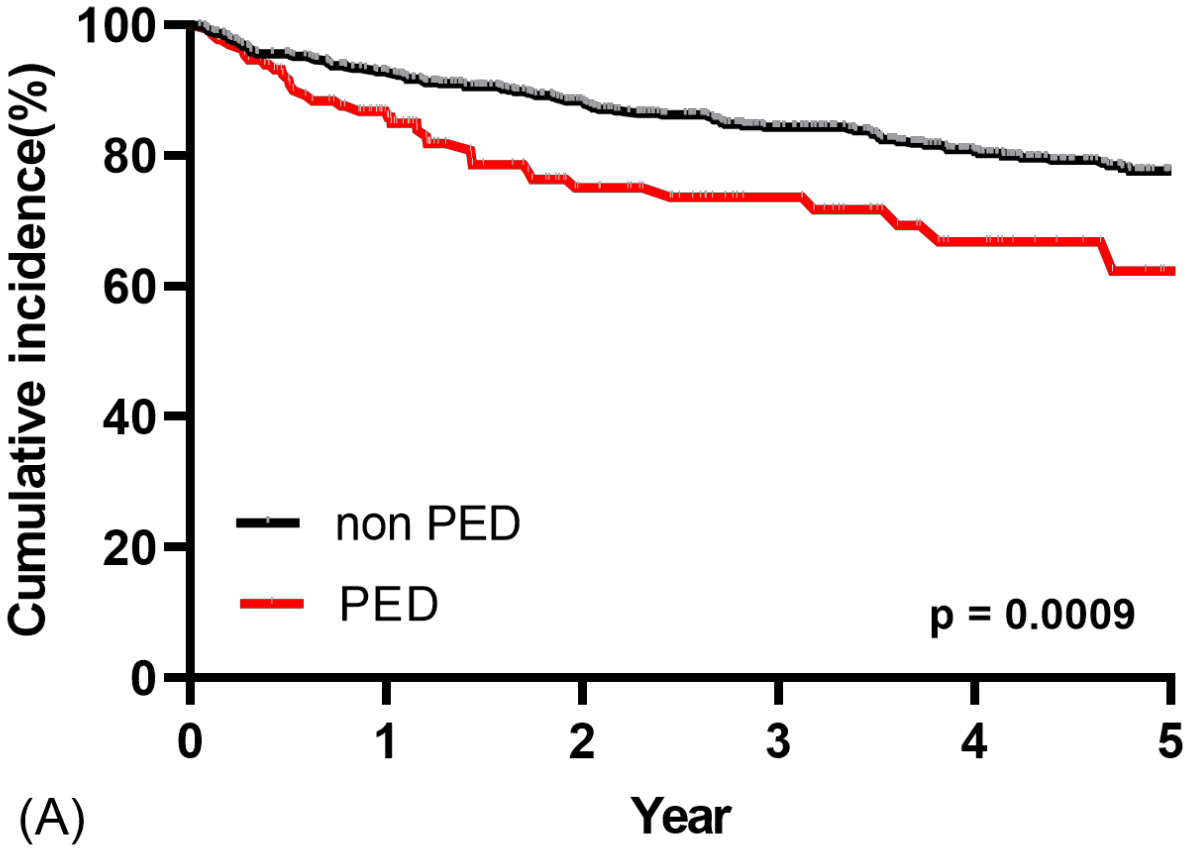
	Univariate model		Multivariable model	
Variables	OR (95% CI)	*p*-value	OR (95% CI)	p-value
Age	1.06 (1.04-1.08)	<0.0001	1.05 (1.03-1.08)	<0.0001
Sex, female	1.70 (1.22-2.38)	0.001	1.84 (1.22-2.78)	0.004
BMI	0.99 (0.95-1.04)	0.76	1.03 (0.97-1.09)	0.34
PED	4.24 (2.64-6.76)	<0.0001	2.70 (1.54-4.76)	0.0005
Frailty	2.88 (1.93-4.29)	<0.0001	1.41 (0.86-2.28)	0.16
MNA-SF, At risk/Malnutrition	2.00 (1.12-3.54)	0.017	1.05 (0.49-2.27)	0.91
NYHA class	1.51 (1.15-1.99)	0.003	1.57 (1.09-2.28)	0.01
Type, Aortic	1.98 (1.23-3.17)	0.05	2.17 (1.02-4.54)	0.04

Abbreviations as in Table 1.

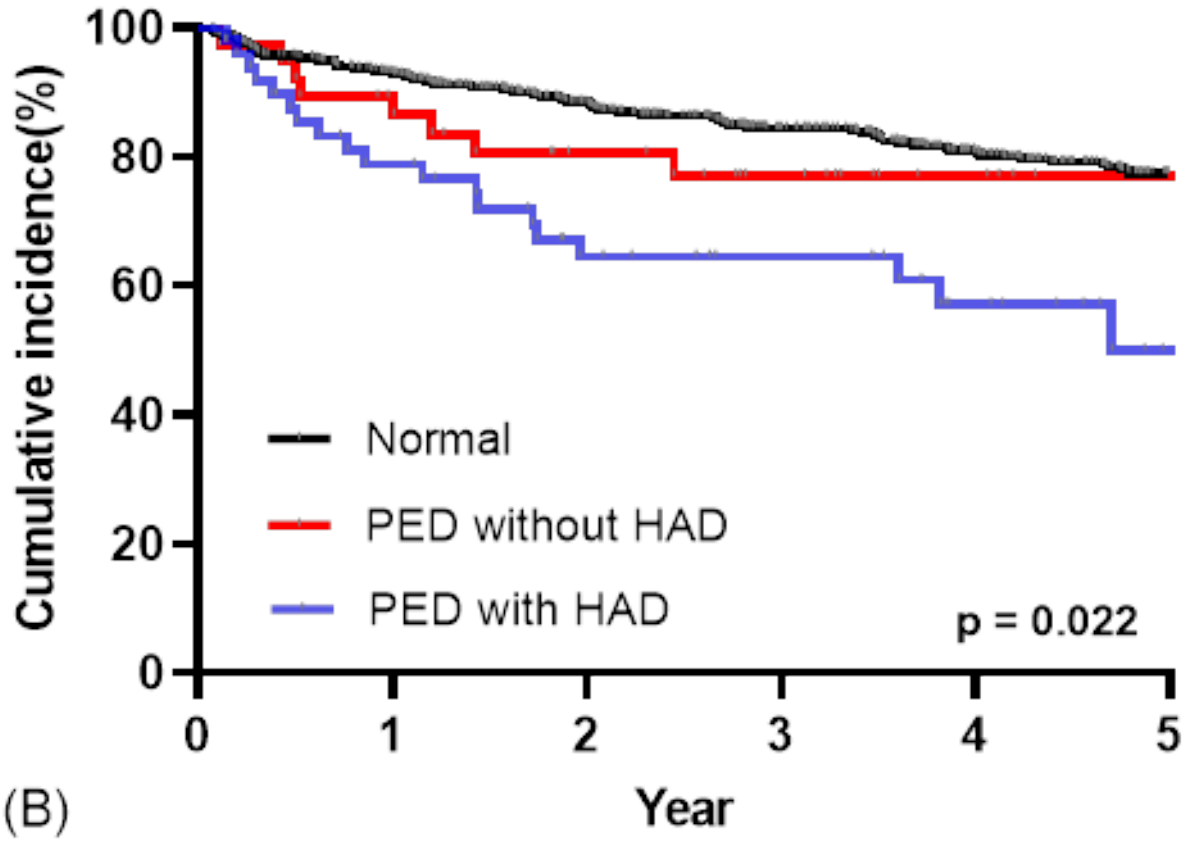
Table 4. Cox-proportional hazard regression analysis of the predictive factors for the development of MACCE

	Univariate model		Multivariable model	
Variables	HR (95% CI)	*p*-value	HR (95% CI)	p-value
Age	1.03 (1.02-1.05)	<0.0001	1.02 (1.00-1.04)	0.02
Sex, female	1.22 (0.88-1.69)	0.22	0.98 (0.69-1.39)	0.91
BMI	0.98 (0.94-1.02)	0.33	0.98 (0.93-1.03)	0.49
PED	2.18 (1.44-3.21)	0.0004	1.36 (0.82-2.16)	0.22
HAD	2.28 (1.62-3.19)	<0.0001	1.85 (1.27-2.68)	0.002
MNA-SF, At risk/Malnutrition	1.89 (1.12-3.02)	0.02	1.19 (0.49-1.49)	0.53
NYHA class	2.00 (1.54-2.59)	<0.0001	1.65 (1.23-2.20)	0.0009
Type, Aortic	0.71 (0.39-1.19)	0.19	0.61 (0.29-1.16)	0.14
CKD	1.56 (1.12-2.20)	0.009	1.03 (0.69-1.52)	0.88

Abbreviations as in Table 1.


Cumulative incidence(%)
100
80
60
40
20
0
non PED
PED
p = 0.0009
0
1
2
3
4
5
Year

(A)


Cumulative incidence(%)
100
80
60
40
20
0
Normal
PED without HAD
PED with HAD
p = 0.022
0
1
2
3
4
5
Year

(B)

Figure.1

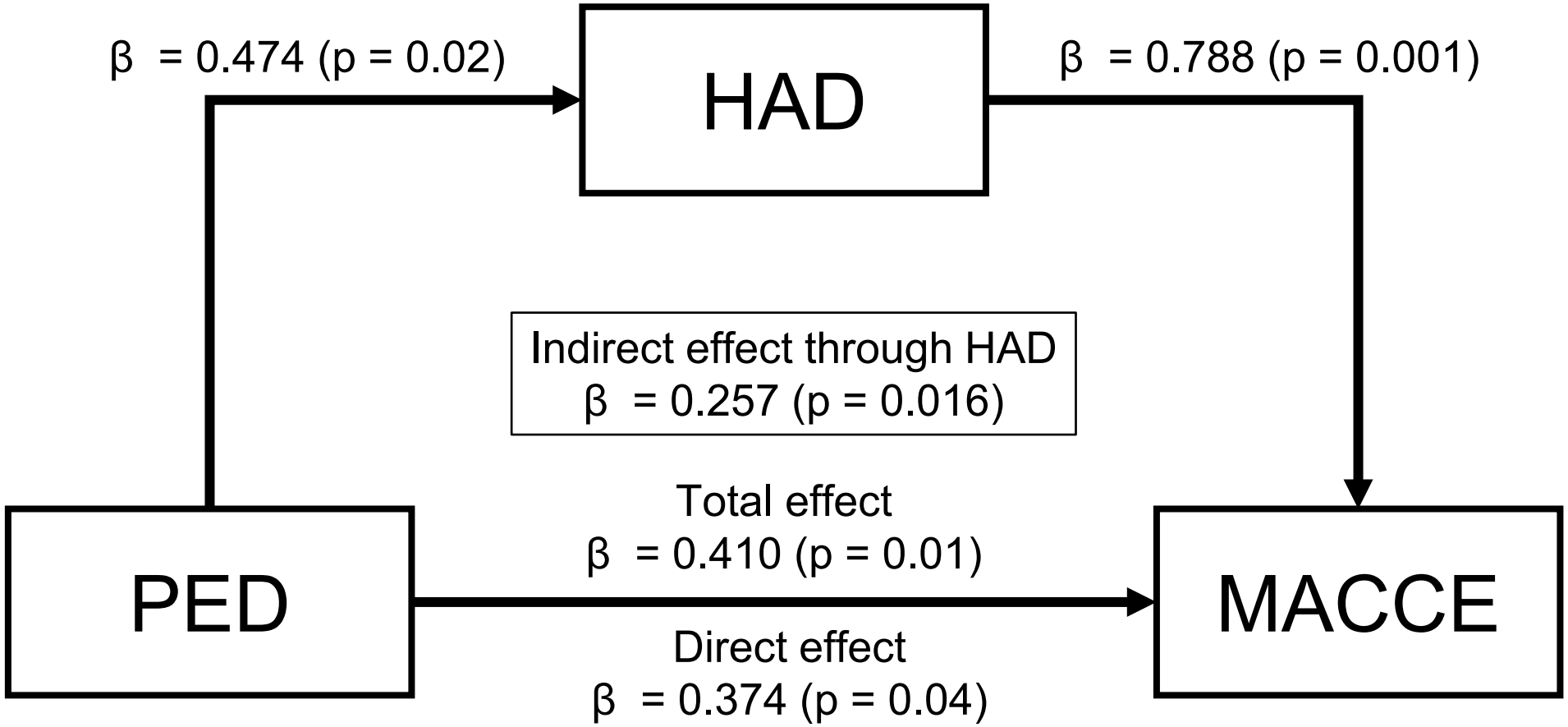

β = 0.474 (p = 0.02)
HAD
β = 0.788 (p = 0.001)
Indirect effect through HAD
β = 0.257 (p = 0.016)
Total effect
β = 0.410 (p = 0.01)
PED
MACCE
Direct effect
β = 0.374 (p = 0.04)

Figure. S1