Respiratory Rehabilitation Does not Prevent Post-Operative Pulmonary Complications, Morbidity and Mortality After Esophagectomy.- A Systematic Review and Meta-Analysis.

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Abstract

Aim: The analysis aimed to study the effect of preoperative pulmonary rehabilitation on post-operative pulmonary complications, overall morbidity, and mortality after esophagectomy.

Methods: The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (2020) and MOOSE guidelines. The meta-analysis was done using Review Manager 5.4. We compared postoperative pneumonia, postoperative pulmonary complications, morbidity, and mortality between the preoperative respiratory group vs. no prehabilitation group. Heterogeneity was evaluated using the I² test. The random-effect model was used with I² was more than 25% otherwise fixed-effect model was used. I² less than 25%, 25-50%, and more than 50% were taken as low, moderate, or high heterogeneity.

Results: Seven studies consisting of 606 patients were included in the analysis. 322 patients in the respiratory prehabilitation group and 284 in the control group. There was no statistically significant difference in postoperative pneumonia ($p=0.11$), post-operative pulmonary complications ($p=0.09$), All cause morbidity and mortality. ($p=0.98$, and 0.30 respectively). However, heterogeneity was moderate to high in most analyses.

Conclusion: There is no conclusive evidence as of now regarding the benefits of preoperative pulmonary rehabilitation in esophagectomy. However, further studies are needed to confirm it.

Introduction:

Esophagectomy through various approaches remains the only curative treatment option for esophageal cancer with neoadjuvant and adjuvant chemoradiotherapy. Esophagectomy is also required in some benign esophageal diseases. Esophagectomy is still associated with very high perioperative mortality and morbidity rates, particularly pulmonary complications including postoperative pneumonia. [1, 2, 3].

Cancer prehabilitation has been defined as a 'process on the cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes physical and psychological assessments that establish a baseline functional level, identify impairments, and provide interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments' [4, 5]. This definition can be extended to any disease process and should not be limited to only cancer.

Poor preoperative physical performance has been shown to increase the number of postoperative complications and the risk of mortality. [6, 7, 8].

Prehabilitation is a preoperative exercise program aimed at increasing the perioperative functional reserve of an individual to enable him or her to withstand the upcoming surgical

stress and to accelerate the postoperative functional recovery. [9]. Some studies have shown the benefit of prehabilitation in thoracic and upper abdominal surgeries. [10,11].

The aim of this systematic and review and meta-analysis was to analyze the effect of respiratory prehabilitation on postoperative pulmonary complications, pneumonia, morbidity, and mortality following oesophagectomy.

Methods:

The study was conducted according to the PRISMA statement and MOOSE guidelines. [12, 13].

Study selection

We conducted a literature search as described by Gossen et al. [14]. Pubmed, Cochrane Library, Embase, Google Scholar, Web of Science with keywords like “esophagectomy” AND/OR “prehabilitation” AND/OR esophageal cancer”. Two independent authors extracted the data

(B.V. and H.P.).

Statistical analysis:

The meta-analysis was conducted using Review Manager 5.4. Heterogeneity was measured using Q tests and I², and P < .10 was determined as significant. I² < 25%, I² 25-50% and I² > 50% were defined as low, moderate and high heterogeneity respectively. the random-effects model was used when I² is more than 50% otherwise fixed-effect model was used. The odds ratio (OR) was calculated for dichotomous data. A risk of bias summary was prepared in Revman 5.4 software. Publication bias was assessed using funnel plots.

Inclusion criteria:

- Studies that included any type of respiratory prehabilitation pre-operatively on post esophagectomy outcomes.
- Full-text articles
- English language articles.

Exclusion criteria:

- Studies that did not evaluate esophagectomies
- Studies that evaluated only post-operative respiratory physiotherapy
- Non-English language studies
- Studies where full text could not be retrieved.

Results:

Seven studies including 606 patients were included in the analysis. [15–21]. The search strategy is mentioned in the PRISMA flow chart. [Figure 1]. The characteristics of included studies are shown in Table 1. 322 patients were in the prehabilitation group and 284 were in the control group. The summary of bias is shown in Figure 2.

Table 1
Study characteristics.

STUDY	TYPE OF STUDY	TOTAL PATIENTS (N)	PREHABILITATION GROUP (N)	CONTROL GROUP (N)
AKIYAMA 2017	COHORT	52	31	21
AKIYAMA 2021	COHORT	48	23	25
ALLEN 2021	RCT	54	26	28
DETTLING 2021	COHORT	78	39	39
DEWBERRY 2018	COHORT	22	11	11
HALLIDAY 2020	COHORT	111	72	39
VELKENET 2018	COHORT	241	120	121

Postoperative Pulmonary complications: [Figure 3]

5 studies including 527 patients evaluated postoperative pulmonary complications, 100 patients out of 283 patients developed pulmonary complications in prehabilitation group, and 108 out of 244 patients developed pulmonary complications in the control group. There was no significant difference between both the groups. [$p=0.09$, Odds ratio 0.51, 95% C.I. 0.23-1.11]. The Forest plot is shown in Figure 3 (a). Publication bias is analyzed with a funnel plot. (Figure

3b). Heterogeneity was high and significant. (I^2 72%, $p=0.007$)

5 studies including 530 patients evaluated postoperative pneumonia, 87 patients out of 285 patients developed pneumonia in the prehabilitation group and 87 out of 245 patients developed pneumonia in the control group. There was no significant difference between both the groups. [$p=0.11$, Odds ratio 0.55, 95% C.I. 0.26-1.16]. The Forest plot is shown in Figure 3 (c). Publication bias is analyzed with a funnel plot. (Figure 3d). Heterogeneity was high and significant. (I^2 61%, $p=0.04$)

Postoperative morbidity and mortality: [Figure 4,5]

Total 426 patients out of 606 patients developed complications. We defined any complications mentioned in the study as morbidity. 225 out of 322 patients developed various complications in prehabilitation group. 201 out of 284 patients developed any complications in the control group. There was no statistically significant difference between the two groups. [$p=0.98$, Odds ratio 0.99, 95% C.I 0.68-1.45] [Figure 4 (a) Forest plot, Figure 4 (b) Funnel plot for publication bias]. Heterogeneity was moderate and nonsignificant. ($I^2= 29\%$, $p =0.021$).

Total 14 patients died in postoperative period out of 499 patients (6 studies), 7 out of 255 died in prehabilitation group, 5 out of 244 died in the control group. There was no significant difference in mortality between the two groups. [$p=0.30$, Odds ratio 1.76, 95% c.i. 0.60-5.11] [Figure 5 (a) Forest plot, Figure 5(b) Funnel plot for publication bias]. Heterogeneity was low and nonsignificant. ($I^2= 0\%$, $p =0.84$)

Discussion:

Esophagectomy though most of the time only curative treatment is usually associated with very high morbidity and mortality. Pulmonary complications are the most common complications post-operatively. Post-operative pneumonia and not anastomotic leak were independently associated with mortality. [22]

There has been an ongoing debate regarding the benefits of prehabilitation in abdominal cancer surgeries and still, there is no conclusive evidence for the same. [23]. LIPPSMAck-POP [24] trial showed the potential benefit of preoperative respiratory physiotherapy. Minnella et al [25] showed improvement of functional capacity due to prehabilitation but they did not mention effects of pulmonary complication and morbidity. There are many small number cohort studies that evaluated the effect of respiratory prehabilitation on pulmonary complication, morbidity, and mortality but very few larger sample size studies.

We aimed to do a systematic review and meta-analysis to evaluate the literature available to study the effect of any form of respiratory prehabilitation on post-operative pneumonia, pulmonary complications, morbidity, and mortality.

We defined any type of pre-operative respiratory physiotherapy as prehabilitation and compared postoperative pneumonia, overall pulmonary complication, morbidity, and mortality between study and the control group in this meta-analysis.

In our metaanalysis prehabilitation failed to show any benefit concerning post-operative pneumonia, overall pulmonary complications, morbidity, and mortality. There was a trend toward reduced risk in overall postoperative pulmonary complications, however, it failed to achieve statistical significance with an odds ratio of 0.51 [0.23-1.11] with $p=0.09$. [Figure 3]

There were several limitations of the study with very limited studies were available to evaluate and each study with a very limited sample size. Heterogeneity was moderate to high, Funnel plots showed that we

cannot completely rule out publication bias also. As shown in the summary of bias, there were chances of various biases in included studies. {Figure 2}.

The strength of this meta-analysis is that it is one of the first meta-analyses studying the effect of pre-operative prehabilitation on postoperative outcomes. As meta-analysis did not show any benefit of prehabilitation on postoperative outcomes it shows that we need to focus on analysis with a larger sample size to understand more about the effect of prehabilitation before formulating prehabilitation protocols.

In conclusion, respiratory prehabilitation was not beneficial in reducing postoperative pulmonary complications, post-operative pneumonia, morbidity, and mortality. However, a larger sample size and randomized control trials are needed to confirm the findings.

Declarations:

Conflict of interests: nothing to declare.

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Figures

Figure 1

PRISMA FLOW CHART

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
aklyama 2017	-	+		-	+	+	
aklyama 2021	-	+		+	+	+	
allen 2021	+	+		+	+	+	+
dettling 2012	-	+	+	+	-	-	
dewberry 2018	-			+	+	-	
Halliday 2020	-	+		+	-	-	
velkenet 2018	-	+	-	+	+	-	

Figure 2

SUMMARY OF BIAS

(a)

(b)

(c)

(d)

Figure 3

(a) Forest plot for pulmonary complications. (b) Funnel plot for pulmonary complications. (c) Forest plot for postoperative pneumonia (d) Funnel plot for postoperative pneumonia

(a)

(b)

Figure 4

(a) Forest plot of morbidity (b) Funnel plot of morbidity

(a)

(b)

Figure 5

(a) Forest plot of mortality (b) Funnel plot of morbidity