Postoperative Respiratory Complications and Clinical Outcome among Patients Undergoing Upper Gastrointestinal Tumor Surgery: A Systematic Review and Meta-analysis

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Background: Cancer's incidence has been increasing world-wide and has become the leading cause of death in many countries. Upper Gastrointestinal cancer is highly prevalent and associated with a high mortality rate. For Upper GIT carcinomas, the mainstay of therapy is always surgery as it usually promises higher rates of survival than other treatment options. Although surgery is considered the mainstay of therapy but it may be associated with some complications and adverse events.

Objective: To evaluate the post-operative respiratory complications following upper gastrointestinal tumour surgery according to timing, severity, type, incidence and possible measures for prophylaxis and management.

Patients and Methods: Fifteen trials included postoperative respiratory complications and clinical outcomes among patients undergoing upper gastrointestinal tumor surgery. Outcomes of this study included pneumonia, ARDS, atelectasis, ventilator dependency, hospital mortality and chylothorax.

Results: Regarding pneumonia was assessed in fifteen included studies there was no significant heterogeneity among trials (P 0.001, I2 = 97.86%), OR 0.206, 95% CI (0.157, 0.256). While ARDS was assessed in 8 included studies there was no significant heterogeneity among trials (P 0.001, I2 = 91.87%), OR 0.042, 95% CI (0.024, 0.061). Regarding Atelectasis was assessed in 4 included studies. There was no significant heterogeneity among trials (P 0.001, I2 = 99.59%), OR 0.236, 95% CI (0.018, 0.454). Regarding ventilator dependency, it was evaluated in 6 included studies there was no significant heterogeneity among trials (P 0.001, I2 = 96.17%), OR 0.099, 95% CI (0.064, 0.133). Regarding Hospital mortality due to respiratory complications it was assessed in five included studies, there was no significant heterogeneity among trials (P 0.001, I2 = 88.88%), OR 0.045, 95% CI (0.015, 0.075). Regarding chylothorax was assessed in 4 included studies, there was no significant heterogeneity among trials (P 0.004, I2 = 77.44%), OR 0.039, 95% CI (0.019, 0.059).

Data Sources: Medline databases (PubMed, Medscape, and Science Direct. EMF-Portal) and all materials available in the internet till 2021.

Conclusion: Our meta-analysis is done on 15 studies including 18,817 patients. Pneumonia, ARDS, ventilator dependency, atelectasis and chylothorax are statistically significant post-operative complications and are significant causes that lead to hospital mortality. Those complications are found more in patients with increase in tumor size, T4 staging, bad general condition and patients with co-morbidities. In addition, prevention of those complications by early intervention, early ambulation and well preparation of the patients pre-operatively are significant cause in decreasing the pulmonary complications post-operative.

Key words: Chest complications, respiratory complications, gastrectomy, esophagectomy.

Introduction

Cancer's incidence has been increasing world-wide and has become the leading cause of death in many countries. Upper gastrointestinal cancer is highly prevalent and associated with a high mortality rate. For Upper GIT carcinomas, the mainstay of therapy is always surgery because it usually promises higher rates of survival than other treatment options but it may be associated with some complications and adverse events.[1]

Diagnosing GIT malignancies is usually challenging as the signs and symptoms aren't specific and similar to many conditions. They are diagnosed by endoscopy and tissue biopsy. Treatment and prognosis depends on the location of the tumor, its stage and the type of cancer cell.[2]

Postoperative respiratory complications are frequent events that occur in high-risk patients.

These include pneumonia, macroscopic atelectasis, pneumothorax, and acute respiratory distress syndrome, these complications range from short-term to long-term events leading to compromise the quality of life and increasing mortality risk.[3]

Identification of the causes of post-operative respiratory complications leads to better clinical judgment as well as a better perspective pre-operative to optimize the surgical operation. Although there are a number of studies assessing post-operative complications, the available knowledge on post-operative respiratory complications and its prophylactic measures is limited thus; this study is intended to evaluate the post-operative respiratory complications in patients undergoing upper gastrointestinal tumor surgery and its prophylactic measures.[4]

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Aim Of The Work

To evaluate the post-operative respiratory complications following upper gastrointestinal tumour surgery according to timing, severity, type, incidence and possible measures for prophylaxis and management.

Methods

Search strategy

The PubMed, web of science and Scopus were searched on November 15, 2021. The keywords were chest complications, respiratory complications, gastrectomy and esophagectomy.

The details of the search process and study selection are shown in **(Fig. 1).** Relevant articles referenced in these primary studies were also searched to enroll additional cases, some articles were searched from the references to reach other relevant studies and one article we have contacted their authors to send it on email.

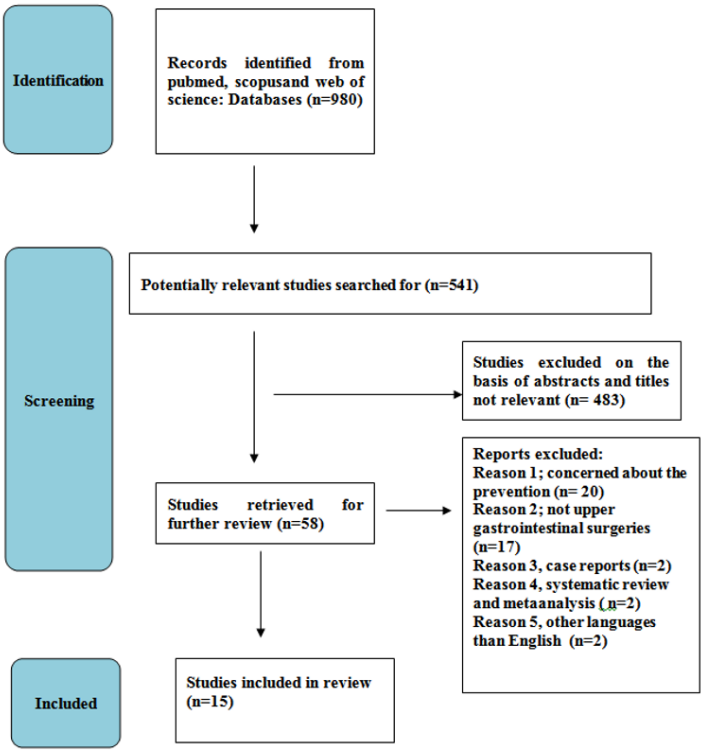


Fig 1: Shows PRISMA Flowchart.

Eligibility criteria

All trials including adults from 18 to 65 years who underwent surgery for upper GI malignancies and suffered from postoperative respiratory disorders were included.

Patients with chronic/Acute respiratory diseases as: Asthma, chronic obstructive pulmonary disease, cystic fibrosis, tuberculosis, bronchitis, pneumonia and emphysema. Patients taking medications that impact the respiratory system and who underwent surgery for local recurrence were excluded. In addition, papers written in a language other than English, reviews, case reports and studies regarding animals were excluded.

Outcomes

Outcomes of this study included pneumonia, ARDS, atelectasis, ventilator dependency, hospital mortality and chylothorax.

Quality assessment

Each article was assessed by two independent researchers based on the Cochrane Handbook 5.0.2 and data were extracted separately by the two researchers. The included trials were evaluated with the following criteria: adequate sequence generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, free of selecting, reporting and other bias. Each type of bias was defined by an answer (Yes/No/Unclear). "Yes" indicated low risk of bias, "No" represented high risk and "Unclear" represented unclear risk. In addition, the quality of evidence for each outcome was assessed by the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system5.

Characteristics and quality assessment of enrolled studies are listed in **(Tables 1,2)**.

Statistical analysis

Statistical analysis was performed by Review Manager Version 5.3 software (Cochrane). The odds ratio (OR) with 95% confidence interval (95% CI) for dichotomous variables and the mean difference (MD) with 95% CI for continuous variables were computed in fixed-effect or random-effect model. Heterogeneity among trials was justified using Chi-squared test with P < 0.1 demonstrating statistical significance. The quantity of heterogeneity was measured by I2 and I2 > 50% indicated significant heterogeneity. If no significant heterogeneity was confirmed, we did the meta-analysis in fixed effect model.

Results

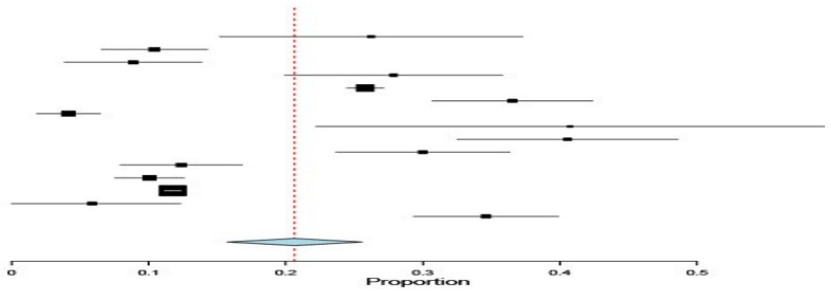
Fifteen trials included postoperative respiratory complications and clinical outcome among patients undergoing upper gastrointestinal tumor surgery, the search process is shown in **Fig. 1**.

(Table 3): Outcome parameters:

1. Pneumonia.
2. Acute respiratory distress syndrome.
3. Atelectasis.
4. Ventilator dependency.
5. Hospital mortality.
6. Chylothorax.

Pneumonia

Pneumonia was stated in fifteen trials Aramesh et al. stated 16 patients diagnosed with pneumonia from 61 patients, Wan et al. 25 patients diagnosed with pneumonia from 240 patients, Takesue et al. 11 patients diagnosed with pneumonia from 124 patients, Tamagawa et al. 34 patients diagnosed with pneumonia from 122 patients, Goense et al. 1057 patients diagnosed with pneumonia from 4096 patients, Vrba et al. 95 patients diagnosed with pneumonia from 260 patients, Norero et al. 12 patients diagnosed with pneumonia from 289 patients, Tsujimoto et al. 11 patients diagnosed with pneumonia from 27 patients, Reichert et al. 58 patients diagnosed with pneumonia from 143 patients, Shirinzadeh et al. 60 patients diagnosed with pneumonia from 200 patients, Nozaki et al. 26 patients diagnosed with pneumonia from 210 patients, Uchihara et al. 55 patients diagnosed with pneumonia from 546 patients, Linden et al. 1405 patients diagnosed with pneumonia from 11943 patients, Amari et al. 3 patients diagnosed with pneumonia from 51 patients and Tanaka et al. 108 patients diagnosed with pneumonia from 312 patients there was no significant heterogeneity among trials (P 0.001, I2 = 97.86%), OR 0.206, 95% CI (0.157, 0.256).**(Fig. 2).**

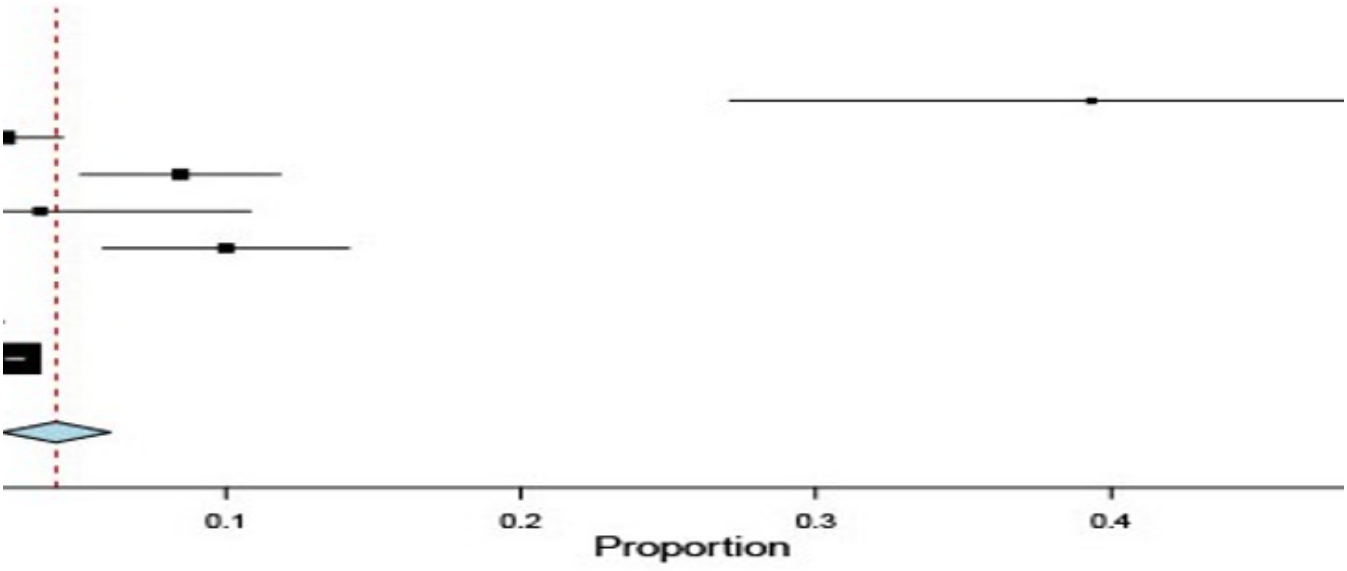


Studies	Estimate	(95% C.I.)	Ev/Trt
Aramesh et al. 2018	0.262	(0.152, 0.373)	16/61
Wan et al. 2016	0.104	(0.066, 0.143)	25/240
Takesue et al. 2019	0.089	(0.039, 0.139)	11/124
Tamagawa et al. 2019	0.279	(0.199, 0.358)	34/122
Goense et al. 2018	0.258	(0.245, 0.271)	1057/4096
Vrba et al. 2019	0.365	(0.307, 0.424)	95/260
Norero et al. 2019	0.042	(0.019, 0.065)	12/289
Tsujimoto et al. 2012	0.407	(0.222, 0.593)	11/27
Reichert et al. 2020	0.406	(0.325, 0.486)	58/143
Shirinzadeh et al. 2011	0.300	(0.236, 0.364)	60/200
Nozaki et al. 2017	0.124	(0.079, 0.168)	26/210
Uchihara et al. 2017	0.101	(0.075, 0.126)	55/546
Linden et al. 2019	0.118	(0.112, 0.123)	1405/11943
Amari et al. 2021	0.059	(0.000, 0.123)	3/51
Tanaka et al. 2021	0.346	(0.293, 0.399)	108/312
Overall (I^2=97.86 % , P< 0.001)	0.206	(0.157, 0.256)	2976/18624

Fig 2: Forest plot of postoperative pneumonia.

Acute Respiratory Distress Syndrome

ARDS was found in eight trials Aramesh et al. stated 24 patients diagnosed with ARDS from 61 patients, Wan et al. 6 patients diagnosed with ARDS from 240 patients, Vrba et al. 22 patients diagnosed with ARDS from 260 patients, Tsujimoto et al. 1 patients diagnosed with ARDS from 27 patients,,Shirinzadeh et al. 20 patients diagnosed with ARDS from 200 patients, Nozaki et al. 1 patients diagnosed with ARDS from 210 patients, Uchihara et al. 8 patients diagnosed with ARDS from 546 patients and Linden et al. 342 patients diagnosed with ARDS from 11943 patients there was no significant heterogeneity among trials (P 0.001, I2 = 91.87%), OR 0.042, 95% CI (0.024, 0.061).**(Fig. 3)**

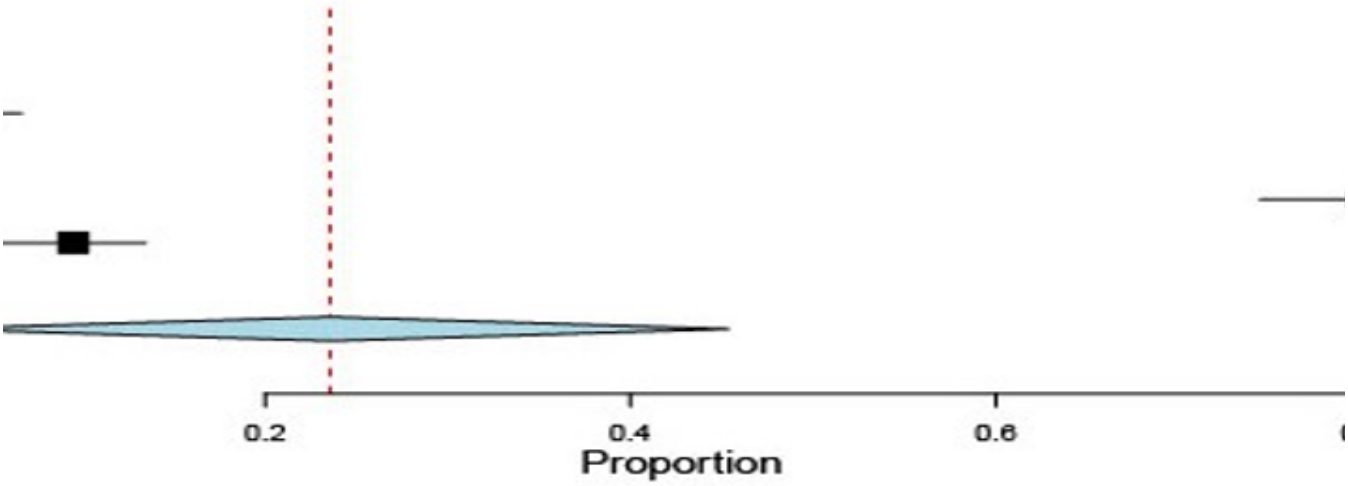


Studies	Estimate	(95% C.I.)	Ev/Trt
Aramesh et al. 2018	0.393	(0.271, 0.516)	24/61
Wan et al. 2016	0.025	(0.005, 0.045)	6/240
Vrba et al. 2019	0.085	(0.051, 0.118)	22/260
Tsujimoto et al. 2012	0.037	(0.000, 0.108)	1/27
Shirinzadeh et al. 2011	0.100	(0.058, 0.142)	20/200
Nozaki et al. 2017	0.005	(0.000, 0.014)	1/210
Uchihara et al. 2017	0.015	(0.005, 0.025)	8/546
Linden et al. 2019	0.029	(0.026, 0.032)	342/11943
Overall (I^2=91.87 % , P< 0.001)	0.042	(0.024, 0.061)	424/13487

Fig 3: Forest plot of postoperative ARDS.

Atelectasis

Atelectasis was assessed in four trials , Wan et al. 10 patients diagnosed with Atelectasis from 240 patients, Norero et al. 4 patients diagnosed with Atelectasis from 289 patients, Shirinzadeh et al. 160 patients diagnosed with Atelectasis from 200 patients and Nozaki et al. 20 patients diagnosed with Atelectasis from 210 patients. There was no significant heterogeneity among trials (P 0.001, I2 = 99.59%), OR 0.236, 95% CI (0.018, 0.454). **(Fig. 4)**

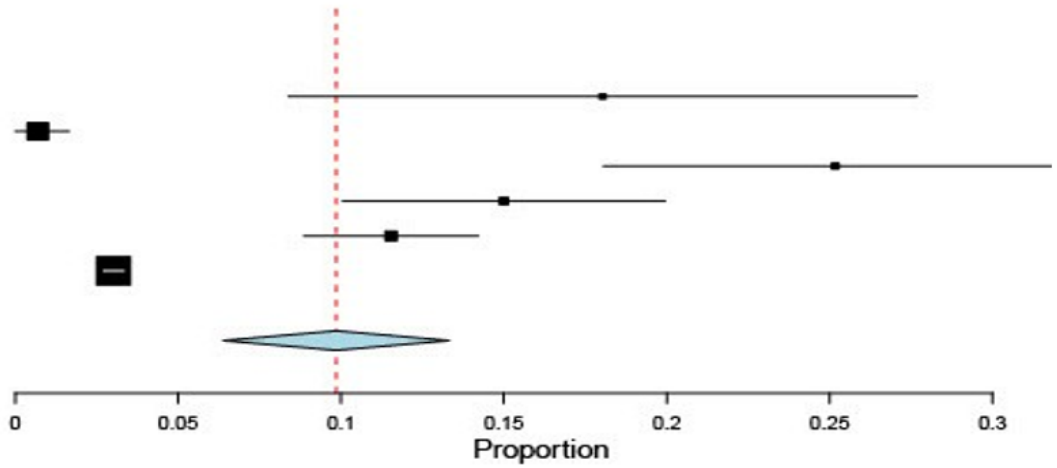


Studies	Estimate	(95% C.I.)	Ev/T
Wan et al. 2016	0.042	(0.016, 0.067)	10/2
Norero et al. 2019	0.014	(0.000, 0.027)	4/28
Shirinzadeh et al. 2011	0.800	(0.745, 0.855)	160/2
Nozaki et al. 2017	0.095	(0.056, 0.135)	20/2
Overall (I^2=99.59 % , P< 0.001)	0.236	(0.018, 0.454)	194/9

Fig 4: Forest plot of postoperative atelectasis.

Ventilator dependency

Ventilator dependency was assessed in six trials Aramesh et al. stated 11 patients diagnosed with ventilator dependency from 61 patients, Norero et al. 2 patients diagnosed with ventilator dependency from 289 patients, Reichert et al. 36 patients diagnosed with ventilator dependency from 143 patients, Shirinzadeh et al. 30 patients diagnosed with ventilator dependency from 200 patients, Uchihara et al. 63 patients diagnosed with ventilator dependency from 546 patients and Linden et al. 361 patients diagnosed with ventilator dependency from 11943 patients, there was no significant heterogeneity among trials (P 0.001, I2 = 96.17%), OR 0.099, 95% CI (0.064, 0.133). **(Fig. 5)**

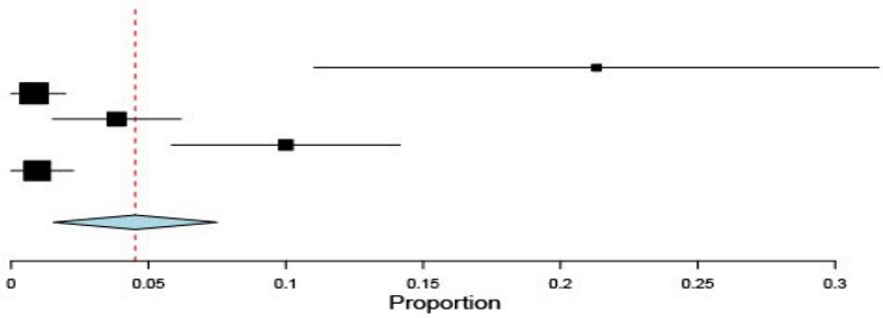


Studies	Estimate	(95% C.I.)	Ev/Trt
Aramesh et al. 2018	0.180	(0.084, 0.277)	11/61
Norero et al. 2019	0.007	(0.000, 0.016)	2/289
Reichert et al. 2020	0.252	(0.181, 0.323)	36/143
Shirinzadeh et al. 2011	0.150	(0.101, 0.199)	30/200
Uchihara et al. 2017	0.115	(0.089, 0.142)	63/546
Linden et al. 2019	0.030	(0.027, 0.033)	361/11943
Overall (I^2=96.17 % , P< 0.001)	0.099	(0.064, 0.133)	503/13182

Fig 5: Forest plot of Ventilator dependency.

Hospital Mortality

Hospital mortality due to postoperative respiratory problems was studied in five trials Aramesh et al. stated 13 patients from 61 patients, Wan et al. 2 patients from 240 patients, Vrba et al. 10 patients from 260 patients, Shirinzadeh et al. 20 patients from 200 patients and Nozaki et al. 2 patients from 210 patients there was no significant heterogeneity among trials (P 0.001, I2 = 88.88%), OR 0.045, 95% CI (0.015, 0.075). **(Fig. 6)**

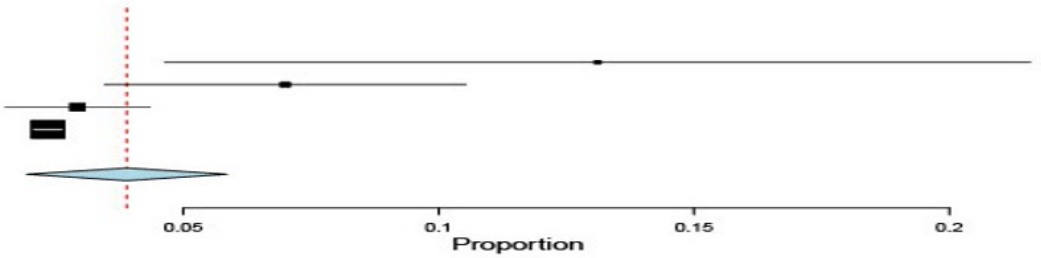


Studies	Estimate	(95% C.I.)	Ev/Trt
Aramesh et al. 2018	0.213	(0.110, 0.316)	13/61
Wan et al. 2016	0.008	(0.000, 0.020)	2/240
Vrba et al. 2019	0.038	(0.015, 0.062)	10/260
Shirinzadeh et al. 2011	0.100	(0.058, 0.142)	20/200
Nozaki et al. 2017	0.010	(0.000, 0.023)	2/210
Overall (I^2=88.88 % , P< 0.001)	0.045	(0.015, 0.075)	47/971

Fig 6: Forest plot of Hospital mortality.

Chylothorax

Chylothorax was stated in four trials Aramesh et al. stated 8 patients diagnosed with chylothorax from 61 patients, Shirinzadeh et al. 14 patients diagnosed with chylothorax from 200 patients, Uchihara et al. 16 patients diagnosed with chylothorax from 546 patients and Linden et al. 281 patients from 11943 patients, there was no significant heterogeneity among trials (P 0.004, I2 = 77.44%), OR 0.039, 95% CI (0.019, 0.059). **(Fig. 7)**



Studies	Estimate	(95% C.I.)	Ev/Trt
Aramesh et al. 2018	0.131	(0.046, 0.216)	8/61
Shirinzadeh et al. 2011	0.070	(0.035, 0.105)	14/200
Uchihara et al. 2017	0.029	(0.015, 0.043)	16/546
Linden et al. 2019	0.024	(0.021, 0.026)	281/11943
Overall (I^2=77.44 % , P=0.004)	0.039	(0.019, 0.059)	319/12750

Fig 7: Forest plot of Chylothorax.

Table 1: Characteristics and quality assessment of the enrolled studies

	Selection				Comparability		Outcome		Results
Study	**Is the Case Definition Adequate?**	**Selection of Controls**	**Representativeness of the Cases**	**Definition of Controls**	**Comparability of Cases and Controls on the Basis of the Design or Analysis**	**Assessment of Outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow-up of cohorts**	**GOOD \Fair \Poor**
Aramesh[6] et al. 2018	Yes	unclear	Yes	unclear	Yes	Yes	Yes	Yes	(6) Fair
Wan[7] et al. 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	(8) Good
Takesue[8] et al. 2019	Yes	unclear	Yes	Yes	unclear	Yes	Yes	Yes	(6) Fair
Tamagawa[9] et al. 2019	Yes	unclear	Yes	unclear	unclear	Yes	Yes	Yes	(5)Fair
Goense[10] et al. 2018	Yes	unclear	Yes	Yes	unclear	Yes	Yes	Yes	(6) Fair
Vrba[11] et al. 2019	Yes	unclear	Yes	unclear	unclear	Yes	Yes	Yes	(5) Fair
Reichert[12] et al. 2020	Yes	unclear	Yes	unclear	unclear	Yes	Yes	Yes	(5) Fair
Norero[13] et al. 2019	Yes	unclear	Yes	unclear	unclear	Yes	Yes	Yes	(5) Fair
Tsujimoto[14] et al. 2012	Yes	unclear	Yes	Yes	Yes	Yes	Yes	Yes	(7) Good
Shirinzadeh[15] et al. 2011	Yes	Yes	unclear	Yes	Yes	unclear	Yes	Yes	(6) Fair
Nozaki[16] et al. 2017	Yes	Yes	unclear	Yes	Yes	Yes	Yes	Yes	(7) Good
Uchihara[17] et al. 2017	unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	(7)Good
Amari[18] et al. 2021	Yes	Yes	Yes	Yes	Yes	unclear	Yes	Yes	(7) Good
Tanaka[19] et al. 2021	Yes	unclear	Yes	Yes	Yes	Yes	unclear	unclear	(5) Fair

Table 2: Characteristics and quality assessment of the enrolled meta-analysis study

Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Free of selective reporting	Free of other bias
Linden[20] et al. 2019	Yes	Yes	Yes	Yes	unclear	Unclear

Table 3: **Outcome parameters:**

1: Pneumonia.
2: Acute respiratory distress syndrome.
3: Atelectasis.
4: Ventilator dependency.
5: Hospital mortality.
6: Chylothorax.

Study	Study Design	Sample Size	Types of operation	Outcome
Aramesh[6] et al. 2018	Retrospective cohort	254	121 underwent transhiatal and 133 transthoracic osophagectomy	1,2,3,5,6
Wan[7] et al. 2016	Retrospective cohort	240	132 Thoraco-laparoscopic osophagectomy and 108 Mckeown	1,2,4,5
Takesue[8] et al. 2019	Retrospective cohort	124	open osophagectomy	1
Tamagawa[9] et al. 2019	Retrospective cohort	122	open osophagectomy	1
Goense[10] et al. 2018	Retrospective cohort	4096	open osophagectomy	1
Vrba[11] et al. 2019	Retrospective cohort	260	open gastrectomy	1,2,5
Reichert[12] et al. 2020	Retrospective cohort	143	38 Thoracoscopic osophagectomy and 105 open approach	1,3
Norero[13] et al. 2019	Retrospective cohort	289	open gastrectomy	1,3,4,5
Tsujimoto[14] et al. 2012	Retrospective cohort	27	Thoracoscopic osophagectomy	1,2
Shirinzadeh[15] et al. 2011	Retrospective cohort	200	Open osophagectomy	1,2,3,4,5,6
Nozaki[16] et al. 2017	Retrospective cohort	210	Thoracoscopic osophagectomy	1,2,5
Uchihara[17] et al. 2017	Retrospective cohort	546	184 Minimally invasive esophagectomy and 362 thoracotomy	1,2,3,6
Linden[20] et al. 2019	Meta-analysis	11943	Open Ivor Lewis 4035,minimally invasive Ivor Lewis 2722, transhiatal 2530, open three-hole 1093, minimally invasive threehole,703, minimally invasive transhiatal 497 and thoracoabdominal 363	1,2,3,6
Amari[18] et al. 2021	Retrospective cohort	51	Gastrectomy	1
Tanaka[19] et al. 2021	Retrospective cohort	312	Open osophagectomy	1

Discussion

Esophageal cancer is the seventh most common cause of cancer-related death globally. The overall five-year survival is below 20%.[20] The main course of treatment is surgical resection, which is usually combined with chemotherapy or chemo-radiotherapy for locally advanced tumors. Conventional surgical treatment involves open esophagectomy (OE) using transthoracic or transhiatal approaches which are associated with high morbidity and mortality. Respiratory complications (RCs) are common with OE and can increase the risk of death up to 20%.[21]

Atelectasis and pneumonia are the most frequent postoperative complications that occur after thoracic surgery, and they are usually caused and worsened by retention of secretion.

Chest physiotherapy for airway clearance after thoracic surgery is recommended to improve reduced lung volume, assist secretion clearance, and improve mobility. Conventional chest physiotherapy (CCP) involves deep breathing exercises and manual chest percussion (clapping) to assist patients in clearing sputum from the airways.[22]

However, CCP is labor-intensive and can potentially cause patient discomfort. Patients are reluctant to cough deeply and are incapable of effectively clearing their airway secretions by themselves. Active cycle of breathing technique (ACBT) is an alternative airway clearance technique. A typical ACBT cycle consists of breathing control, three to four thoracic expansion exercises, and a forced expiratory technique (huffing). ACBT has been shown to improve short-term secretion clearance in patients with chronic lung disease. It is also flexible, tolerated, and accepted well by patients. Although ACBT is widely used in patients with respiratory conditions characterized by chronic sputum production, such as cystic fibrosis and bronchiectasis, current literature on perioperative chest physiotherapy involving ACBT after thoracic surgery is limited.[23]

The current meta-analysis showing the respiratory complications after major upper gastrointestinal surgeries we have comprehensively searched and assessed the published literature regarding this topic.

This study includes fifteen trials with the following outcomes pneumonia, ARDS, atelectasis, ventilator dependency, hospital mortality and chylothorax.

Regarding pneumonia it was assessed in fifteen included studies 2976 out of 18624 patients were included with 15.9 percent.

Many risk factors contribute to the development of postoperative pneumonia. The most common were older age, aspiration, and diabetes.

Pneumonia was more with patients that were not well prepared and with bad general and nutritional conditions and smoking was a major risk factor for developing post-operative pneumonia.

While ARDS it was assessed in 8 included studies 424 out of 13489 patients were included with 3.1 percent.

Regarding ARDS No major pre-operative risk factor was noticed except for cardiac patients, multiple transfusions or TRALI were the major perioperative risk factors for ARDS.

Regarding Atelectasis it was assessed in 4 included studies 194 out of 939 patients were included with 20.6 percent.

Atelectasis was noticed to be one of the commonest respiratory complications especially following upper GI malignancy surgeries due to prolonged surgery duration and general anesthesia and delayed post-operative ambulation.

Regarding ventilator dependency was assessed in 6 included studies 503 out of 13182 patients were included with 3.8 percent.

Ventilator dependency was noticed in patients who were smokers and weren't well prepared and with bad general condition preoperatively

Regarding Hospital mortality due to respiratory complications was assessed in five included studies 47 out of 971 patients were included with 4.8 percent.

Regarding chylothorax it was assessed in 4 included studies 319 out of 12750 patients were included with 2.5 percent.

Chylothorax was noted in patients with increase in tumor size, T4 staging, bad general condition and patients with co-morbidities.

The length of hospital stay varies from country to country because of cultural aspects and reimbursement, why no final conclusions on the effect of postoperative physiotherapy on LOS were drawn in this study. However, it seems that postoperative physiotherapy has the potential to reduce the postoperative length of hospital stay, which is in accordance with prior investigations in ERAS (Enhanced Recovery after Surgery) settings Our limitation is few number of studies meeting our eligibility criteria, In addition to 14 of our 15 studies are retrospective studies.

Conclusion

Our meta-analysis is done on 15 studies including 18,817 patients. Pneumonia, ARDS, ventilator

dependency, atelectasis and chylothorax are statistically significant post-operative respiratory complications and are significant causes that lead to hospital mortality. Those complications are found more in patients with increase in tumor size, T4 staging, bad general condition and patients with co-morbidities. In addition to, prevention of those complications by early intervention, early ambulation and well preparation of the patients pre-operatively are significant cause in decreasing the post-operative pulmonary complications post-operative.

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