

A Retrospective Analysis of the Presentation, Outcomes and Determinants of Severity of Postoperative Pneumonia in Upper Abdominal Oncological Surgeries

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Abstract

Context: Postoperative pneumonia (POP) is a major cause of morbidity following upper abdominal oncological surgeries. **Aims:** To estimate the incidence of POP following upper abdominal oncological surgeries and to identify its clinical and microbiologic features and the risk factors for the development of severe pneumonia. **Settings and Design:** Retrospective analysis of patients with POP at a regional cancer center. **Patients and Methods:** Patients' preoperative and intraoperative details and data on clinical and radiological features and pathogens isolated were collected. Patients with severe pneumonia were identified on the basis of Infectious Disease Society of America/American Thoracic Society criteria and their predictors were estimated. The types of respiratory support required and their outcomes were analysed. **Statistical Analysis Used:** Parametric Student's *t*-independent test was used to compare two groups' means. Categorical data are presented as frequency and percentage values. $P < 0.05$ was considered statistically significant. **Results:** Incidence of POP was 15.24% with 48% developing severe pneumonia. There was a significant difference in the mean age (59.5 ± 8.62 vs. 50.15 ± 10.53 years, $P = 0.024$), duration of surgery (315.77 ± 107.29 vs. 432.92 ± 177.18 min, $P = 0.055$), blood loss (446.15 ± 260.18 ml vs. 712.5 ± 326.22 ml), time to empiric antibiotic (15.69 ± 5.77 vs. 42 ± 38.12 h, $P = 0.022$), and symptom resolution ≥ 3 days (23.1% vs. 72.7%) between patients with nonsevere and severe pneumonia. Patients presenting with cough (odds ratio = 0.06, 95% confidence interval: 0.006–0.618) were more likely to have nonsevere pneumonia. **Conclusions:** Predictors of severe pneumonia are elderly, prolonged surgical duration, higher blood loss, delayed empiric antibiotic and delayed symptom resolution.

Keywords: Cancer surgeries, high-flow oxygen therapy, postoperative pneumonia, upper abdominal surgeries

INTRODUCTION

Postoperative pneumonia (POP) is considered the second most important predictor of long-term survival following oncological surgeries next only to tumor grade.^[1] Patients undergoing upper abdominal surgeries for cancer possess a multitude of risk factors predisposing them to POP.^[2-5] POP increases hospitalization and treatment costs.^[6,7] POP delays initiation of adjuvant chemotherapy and lowers survival.^[8-10] While there are literature aplenty on ventilator-associated pneumonia (VAP), there is limited knowledge on POP. The aim of this study is to estimate the incidence, identify the clinical and microbiologic features of POP and to identify the risk factors for the development of severe pneumonia.

PATIENTS AND METHODS

We conducted a retrospective single-center study at a regional cancer center. Data from the hospital records of patients who

underwent elective upper abdominal oncological surgeries over a period of 2 years (April 2017 to March 2019) were analyzed and those who developed POP within 15 days after surgery were included in the study. The investigating team included specialists in anesthesia and intensive care medicine. Upper abdominal oncological surgeries included surgeries for stomach, liver, esophageal and periampullary cancers. We excluded patients with preexisting pulmonary or

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cardiac disease, patients who received elective postoperative ventilation and patients who required re-intubation for a nonpulmonary cause. The diagnosis of pneumonia was made in accordance with the Centers for Disease Control and Prevention (CDC) guidelines.^[11] In patients with recurrent episodes of pneumonia, only the first episode was taken into account.

The age, gender, body mass index, comorbidities, preoperative length of stay, nutritional risk screening (NRS 2002), diagnosis, surgery done, duration of surgery, and perioperative blood transfusion details were collected. The time to development of initial symptom following surgery and the time to empiric antibiotic after symptom onset were noted. The Infectious Diseases Society of America (IDSA) major and minor scores were noted for each patient and severe pneumonia was defined by the presence of at least one major criterion or three or more minor criteria.^[12] The chest radiographic infiltrates were classified as localized, multiple unilateral, multiple bilateral and diffuse. The culture reports were classified into single or multiple organisms. The antibiotic susceptibility was categorized into penicillin sensitive or resistant for *Streptococcus pneumoniae* and extended-spectrum beta-lactamase producer or not for Gram-negative aerobic bacteria. The presence of multiple drug-resistant (MDR) pathogens was noted. Appropriateness of the empiric antibiotic was based on the culture reports and in accordance with the antibiotic prescription guidelines.^[13] The number of patients who required high-flow oxygen therapy (HFOT), noninvasive ventilation (NIV), endotracheal intubation (ETT), time to intubation from symptom onset, duration of respiratory support, presence of confusion, hypotension and requirement of vasopressors were noted. Systemic bacteremia was considered positive if the patient had positive blood culture with the same organism within 2 days of symptom onset. Delayed intubation was defined as time to intubation >72 h after symptom onset. Time to resolution of symptoms was defined by SpO₂ >92% in room air and respiratory rate <30/min without the need for respiratory support for 24 h. The highest Sequential Organ Failure Assessment (SOFA) score during the course of pneumonia was noted. Concomitant intra-abdominal infection was defined as computerized tomography evidence of intra-abdominal collection and organisms isolated from an aseptically obtained culture from the abdominal collection.

Statistical analysis

Data analysis was carried out using statistical software STATA version 12.0, StataCorp LLC 4905 Lakeway Drive, College Station, Texas 77845-4512, USA. Continuous variables were tested for normality assumptions using the Kolmogorov–Smirnov test. For normally distributed data, descriptive statistics such as mean, standard deviation and range values were calculated. Parametric Student's *t*-independent test was used to compare two groups' means. For skewed data, median and interquartile range values were calculated. Nonparametric Wilcoxon rank-sum test was used to compare two medians. Categorical data were presented as frequency and percentage

values. Unadjusted odds ratio with a 95% confidence interval (CI) was calculated to assess significant risk variables for the primary outcome. A two-sided probability of $P < 0.05$ was considered for statistical significance.

RESULTS

Of the 165 patients eligible for inclusion, 25 developed POP with an incidence rate of 15.24%. Twelve (48%) patients had severe pneumonia, of which 66.66% were male and 33.3% were female. The types of surgeries included are shown in Figure 1. The incidence of pneumonia and severe pneumonia is shown in Figure 2. Patients undergoing Whipple's surgery had the highest incidence of severe pneumonia (41.6%), followed by transhiatal esophagectomy (THE; 25%) and extended total gastrectomy (16.6%).

Hypoxia was the most common presenting symptom seen in 22 (88%) patients, followed by cough in 17 (68%) patients and tachypnea in 14 (56%) patients. Time from symptom onset to starting empiric antibiotic was <12 h in 11 (44%) patients, 12–24 h in 10 (40%) patients, 24–48 h in 2 (8%) patients, and >48 h in 2 (8%) patients. Three (12%) patients had associated systemic bacteremia. Eighteen (72%) patients had localized infiltrate in the chest X-ray and 6 (24%) patients had multiple bilateral infiltrates. Good-quality sputum sampling was obtained in 19 (76%) patients. Single organism was isolated in 16 (64%) patients and two organisms were isolated in 8 (32%) patients. One patient had negative culture. *Streptococcus pneumoniae* was the most common organism (50%) isolated in infections with single organism, followed by *Klebsiella pneumoniae* (25%) and *Pseudomonas aeruginosa* (18.75%). The type of organism isolated in relation to time to onset of pneumonia is shown in Figure 3. Nine (36%) patients had infection with extended-spectrum beta-lactamase pathogens and 5 (20%) had infection with MDR pathogens. Sixteen (64%) patients required respiratory support. Seven (43.75%) patients were managed with HFOT. Of these, one patient required NIV after 3 days of HFOT and recovered 3 days later. Eight (50%) patients were started on NIV, of which 4 (50%) required subsequent ETT and 1 (25%) died due to multiorgan failure. One (6.25%) patient was directly intubated at onset of respiratory failure due to hemodynamic instability. The time to intubation was <72 h in 3 (60%) patients and >72 h in 2 (40%) patients. Patients on HFOT required it for a mean period of 2.84 days. Patients on NIV required support for a mean of 2.33 days and patients with ETT required support for a mean period of 2.6 days. Four (16%) patients received inappropriate empiric antibiotic. The time to symptom resolution was ≤48 h in 9 (36%) patients, 48–72 h in 6 (24%) patients, and >72 h in 6 (24%) patients.

The predictors of severe pneumonia are shown in Tables 1 and 2.

The mean SOFA scores in patients with mild and severe pneumonia were 2.38 ± 0.65 and 7.92 ± 3.655 ($P < 0.0001$), respectively.

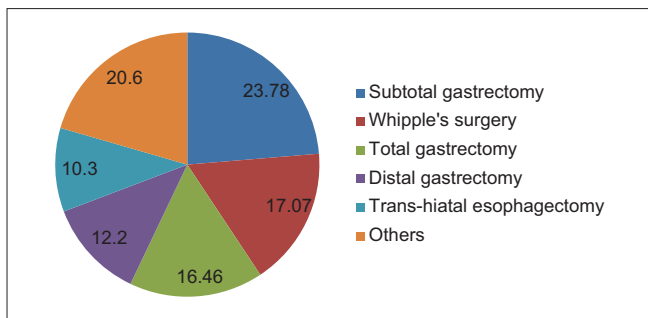


Figure 1: Types of surgeries (%)

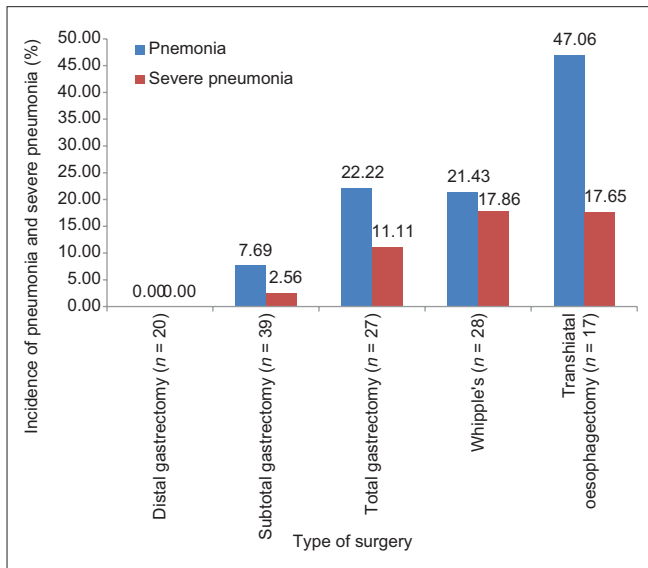


Figure 2: Incidence of pneumonia and severe pneumonia among various surgeries

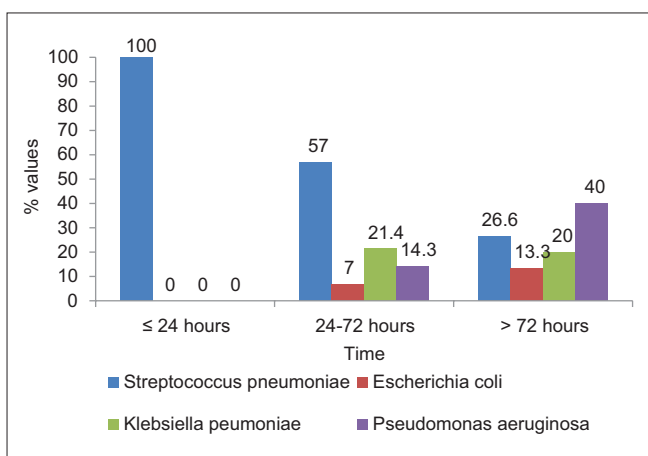


Figure 3: Pathogens isolated in relation to onset of postoperative pneumonia

Four (33.33%) patients with severe pneumonia had concomitant intra-abdominal infection, of which one patient died.

DISCUSSION

There is limited literature on the presentation and outcomes of

Table 1: Predictors of severe pneumonia - continuous variables

Parameter	Mean ± SD		P
	Nonsevere pneumonia	Severe pneumonia	
Age (years)	50.15 ± 10.53	59.5 ± 8.62	0.024
Hemoglobin (g/dL)	11.15 ± 1.69	10.63 ± 2.43	0.537
Nutritional risk screening score	4 ± 0.91	3.92 ± 0.99	0.829
Charlson comorbidity index	2.69 ± 0.95	3.42 ± 1.38	0.137
Smoking (pack years)	3.85 ± 6.50	1.67 ± 3.89	0.325
Time since smoking cessation (years)	0.87 ± 2.75	0.02 ± 0.05	0.299
Duration of surgery (min)	315.77 ± 107.29	432.92 ± 177.18	0.055
Intraoperative blood loss (ml)	446.15 ± 260.18	712.5 ± 326.22	0.033
Onset of symptoms (days)	2.77 ± 1.74	3.33 ± 3.39	0.602
Time to empiric antibiotics (h)	15.69 ± 5.77	42 ± 38.12	0.022
Postoperative urea (mg/dL)	22.46 ± 6.35	34 ± 19.24	0.052

SD: Standard deviation

Table 2: Predictors of severe pneumonia - discrete variables

Parameter	Incidence in nonsevere pneumonia, n (%)	Incidence in severe pneumonia, n (%)	P
Cough as initial presentation	12 (92.3)	5 (41.7)	0.011
No P/F improvement at 72 h	1 (7.7)	6 (50)	0.030
Patients with symptom resolution ≥ 3 days	3 (23.1)	8 (72.7)	0.038
Multiple bilateral chest X-ray infiltrates	4 (30.8)	2 (16.7)	0.645
Multiple organisms	3 (23.1)	5 (45.5)	0.390
ESBL organisms	5 (38.5)	8 (66.7)	0.238
MDR organisms	1 (7.7)	3 (25)	0.322
Inappropriate empiric antibiotic	1 (7.7)	3 (25)	0.322

P/F: PaO₂/FiO₂, ESBL: Extended-spectrum beta-lactamase, MDR: Multidrug resistant

POP in upper gastrointestinal oncological surgeries. Knowledge on the presentation, causative organisms, severity prediction, management modalities and outcomes will help in allocation of appropriate resources in limited availability settings.

Postoperative oncological patients are at increased risk of pneumonia due to multitude of predisposing factors which increase the exposure to hospital-acquired pathogens, impairment in immunity and surgical stress.

Data are limited on the incidence of HAP excluding VAP. In a retrospective study of 1053 gastrectomy patients, the incidence of POP was 2.2% with nil mortality. Fifty-five percentage of these patients underwent laparoscopic gastrectomy, 5.3% had proximal gastrectomy and 72% had distal gastrectomy.^[4] In

our study, all patients had open surgeries with 17.68% (29) proximal gastrectomy, 10.37% (17) THE and 35.37% (58) distal gastrectomy. This could explain the 15.24% incidence of POP in our study. We found a higher incidence of pneumonia in general and severe pneumonia, in particular in patients undergoing Whipple's surgery and THE. Prolonged duration of these surgeries, constant diaphragmatic retraction and risk of recurrent laryngeal nerve injury predisposing to aspiration could be the putative factors.

We followed the CDC definition of POP in accordance with the recommendation by the core outcome measures in perioperative and anaesthetic care (COMPAC) group.^[10] The IDSA/American Thoracic Society criteria was used severity assessment. Intensive care unit (ICU)-level care is needed in the presence of one or more major criteria. The presence of three or more minor criteria indicates severe pneumonia and the likely need of ICU-level care.^[12,14]

Among the presenting features, hypoxia was the most common (88%), which could be attributed to atelectasis and diaphragmatic splinting. Fever was seen less commonly in 44% of patients underscoring the need for high index of suspicion to identify POP. In patients with severe pneumonia, it was found that cough was the presenting symptom in 41.7% of patients, whereas it was seen in 92.3% of patients with nonsevere POP ($P = 0.011$, odds ratio [OR] = 0.06, 95% CI: 0.006–0.618). This could be due to early identification and treatment of POP in patients presenting with cough and hence avoiding a severe pneumonia.

The sampling method predominantly used was sputum cultures in 76% of patients. In nonventilated patients with ICU-acquired pneumonia, it was found that spontaneous sputum cultures had 82% sensitivity and 94% specificity.^[15] In a retrospective study comparing the sample of patients who underwent broncho-alveolar lavage (BAL) and sputum collection, it was found that the rate of concurrent positive cultures in paired specimens obtained within 1 or 7 days was 93.7% and 96.5%, respectively. BAL may be helpful in isolating organisms missed by sputum cultures.^[16] According to British Thoracic Society (BTS), bronchoscopy may be considered for patients with nonresolving or slowly resolving pneumonia if they are current or ex-smokers and >50 years of age. Its role early in the course of pneumonia is limited.^[17]

Four patients received inappropriate empiric antibiotic and three of them had severe pneumonia. However, there was no statistically significant difference in severity of pneumonia and appropriateness of antibiotic. This could be due to the small sample size of our study. The main pathogens isolated in patients with inappropriate antibiotic were multidrug-resistant (MDR) *K. pneumoniae*, followed by *Escherichia coli* and *P. aeruginosa*. *P. aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) are the most common cause of initial inappropriate empiric antibiotic in patients undergoing intra-abdominal surgeries.^[18]

Incidence of nosocomial pneumonia was 28% in patients with intra-abdominal infection with a mortality rate of 66%.^[19] In our study, 33.33% (4) of patients with severe pneumonia had concomitant intra-abdominal infection and mortality was 25% (1). In experimental studies, the presence of intra-abdominal abscess is known to decrease the ability of pulmonary macrophages to clear the bacteria. Prolonged antibiotic treatment and hospitalization would favor the development of high-risk pathogens causing pneumonia in these patients.^[19] Concomitant intra-abdominal abscess, prolonged duration of surgery >400 min, isolation of MRSA, and inadequate initial antibiotic therapy were determinants of death.^[18]

There was a significant difference in the mean age of patients with severe and nonsevere pneumonia, 59.5 ± 8.62 versus 50.15 ± 10.53 years, $P = 0.024$. Pneumonias differ in their presentation due to modified host response in elderly patients. They are also functionally dependent, immunocompromised, and have impaired airway reflexes predisposing them to severe disease.^[20]

The duration of surgery between patients with nonsevere and severe pneumonia was 315.77 ± 107.29 and 432.92 ± 177.18 min, respectively, $P = 0.055$. Prolonged duration of anesthesia and surgery are independent predictors of death from pneumonia due to suppression of cell-mediated immunity by the surgical stress.^[21]

Six (37.5%) patients were successfully managed on HFOT. One patient required subsequent NIV after 3 days of HFOT due to worsening PaO₂/FiO₂ (P/F) ratios and subsequently recovered after 3 days on NIV. In a retrospective review of *Pneumocystis carinii* pneumonia treated with HFOT, it was found that P/F ratios significantly improved in HFOT as compared to mechanical ventilation group. PaO₂ improved in survivors as compared to nonsurvivors within 3 h of initiation of HFOT. Less than 57% increase in baseline PaO₂ had a sensitivity of 87% in predicting mortality. The 60-day mortality was 52% in the high-flow and subsequent mechanical ventilation group, 13% in the high-flow group, and 30% in the mechanical ventilation group.^[22] The use of HFOT in acute respiratory failure helps in rapid amelioration of dyspnea, improves hypoxemia, improves management of respiratory secretions, and lowers the need for mechanical ventilation. The early predictors of failure of HFOT are persistence of tachypnea, thoracoabdominal discordance, and lack of improvement in oxygenation.^[23] Intubation rates did not differ between HFOT, standard oxygen, and NIV group. The 90-day mortality was significantly less in HFOT. The incidence of septic shock was also higher in the NIV group as compared to the HFOT group (30.9% vs. 17.9%), and this could explain the improved 90-day mortality in the HFOT group.^[24] On comparing patients intubated early (<48 h) and late (>48 h) after HFOT due to lack of improvement, it was found that the mortality was less in patients intubated early. The possible explanation could be delay in diagnosis due to lack of

definitive airway access, inadequate clearance of secretions and uncontrolled lung stretch contributing to lung injury.^[25] Hence, HFOT is of great worth and applicability in the management of hypoxia in pneumonia, but it needs continuous vigilance to assess nonimprovement and need for mechanical ventilation.

There was a significant difference in time to starting empiric antibiotic after symptom onset among patients with nonsevere and severe pneumonia, 15.69 ± 5.77 h versus 42 ± 38.12 h, $P = 0.022$. Delay in starting empiric antibiotic could be due to atypical presentation such as altered sensorium and incorrect attribution of hypoxia to atelectasis or other noninfective causes. Patients presenting with cough (OR = 0.06, 95% CI: 0.006–0.618) were more likely to have nonsevere pneumonia due to early treatment. In a study on HAP and VAP, it was observed that patients receiving antibiotics within 24 h after a culture had a significantly shortened length of stay in ICU, 5.62 days compared to those receiving antibiotics at 24–48 h (9 days) and >48 h (15.8 days), $P < 0.001$.^[26]

Patients with severe pneumonia had a higher mean intraoperative blood loss, 712.5 ± 326.221 ml versus 446.15 ± 260.177 , $P = 0.033$. This could be due to prolonged duration of surgery or extensive dissections. Large-volume blood loss can predispose to prolonged systemic hypoperfusion which can activate the stress response mechanism and enhance the catabolic effects of inflammation.^[27] Blood loss can cause direct immune dysfunction due to significant loss of leukocytes and can further suppress cell-mediated immunity through depression of T-lymphocytes, macrophage antigen presentation capacity, and reduced B cell function.^[21,28] Hemorrhagic stress response mediated by antidiuretic hormone-aldosterone and renin angiotensin systems (ADH-aldosterone and RAS) system enhance retention of fluids given for managing hypovolemia and by increasing alveolar capillary hydrostatic pressure and facilitating abnormal capillary permeability can lead to alveolar dysfunction.^[29] These factors work in unison in the pathogenesis of POP.

Patients with severe pneumonia had a lack of improvement in P/F ratio at 72 h in 50% as compared to 7.7% in nonsevere pneumonia, $P = 0.030$. The time to symptom resolution was >3 days in 72.7% of patients with severe pneumonia as compared to 23.1% in patients with non-severe pneumonia, $P = 0.038$. Due to low P/F ratios, there was a need to supplement oxygen therapy for prolonged period in patients with severe pneumonia. Worsening P/F could be due to filling up of the alveoli with inflammatory exudate compromising the functional residual capacity and due to reduced surfactant activity.^[30]

Perioperative blood transfusion, preoperative hemoglobin, malnutrition as assessed by NRS, comorbidities, duration, and time since cessation of smoking were not significant predictors of severe pneumonia despite being known risk factors for the development of pneumonia. The limitations of this study are the limited sample size, as we chose to focus on a relatively high-risk population for the development of POP and its retrospective design.

CONCLUSIONS

One in two patients developing POP following upper abdominal oncological surgeries is likely to have severe pneumonia with the need of respiratory or hemodynamic support. Predictors of severe pneumonia are elderly, prolonged surgical duration, higher intraoperative blood loss, delay in starting empiric antibiotic, lack of improvement in oxygenation within 72 h, and time to symptom resolution more than 3 days. HFOT is a valuable tool in the armamentarium of POP, but it needs vigilance in identifying worsening pneumonia and the need for mechanical ventilation when required.

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Conflicts of interest

There are no conflicts of interest.

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