

Original Article

Postpneumonectomy bronchopleural fistula: cohort of patients in a Peruvian National Hospital

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ABSTRACT

Background: Bronchopleural fistula (BPF) is a complication with a great impact on morbidity, mortality and survival in postoperative pneumonectomy patients. Our study aimed to determine the associated clinical-surgical characteristics of the BPF in a Peruvian cohort of patients with BPF following pneumonectomy

Materials and Methods: Cross-sectional, and retrospective study during January 2015-June 2020 in a Peruvian National Hospital. Medical records and operative reports were reviewed, and all patients over age (>18 years) and with all-cause pneumonectomy were considered. The variables were grouped into pneumonectomies with and without BPF, and the characteristics were grouped as a baseline, clinical-surgical and postoperative.

Results: Among fifty-seven patients who underwent pneumonectomy, 28% presented BPF. The mean age was 38.3 ± 15 years, and 62.5% were male. The main pathologies associated with BPF were post-tuberculosis fibrocavitary sequelae (62.5%), pulmonary hydatidosis (18.8%), and post-surgical cavitory sequelae (12.5%). 81.3% were left BPF ($p = 0.342$) and 100% were related to postoperative empyema ($p < 0.05$). The mortality associated with BPF was 6.25%, and in the non-BPF group it was 4.87% ($p = 0.098$). Characteristics that were statistically associated with the presence of bronchopleural fistula were low predicted forced expiratory volume (FEV1) (56.3% vs. 31.7%; $p = 0.046$), preoperative empyema (37.5% vs. 2.4%; $p = 0.001$), postoperative empyema (100% vs. 9.8%; $p = 0.000$) and operative time (450.69 min vs. 367.73 min; $p = 0.032$).

Conclusions: There are a series of factors associated with the presence of patients with BPF following pneumonectomy, many of them mainly related to operative and postoperative events, which is an important predictor of associated complications in our Peruvian population.

Keywords: bronchopleural fistula; pneumonectomy; empyema; tuberculosis; complication.

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Doi: 10.26663/cts.2023.0024

Received 08.04.2023 accepted 01.06.2023

Introduction

Bronchopleural fistula (BPF) is a complication with a great impact on morbidity and mortality (6-71%) in post-operative pneumonectomy patients [1-3], and is defined as the communication of a bronchus into the pleural cavity. Many cases are more frequently associated with patients with BPF following pneumonectomy than with other pulmonary resections [4]. It has been reported in 20% of post-operative patients with complete lung resection due to benign etiology (*Mycobacterium tuberculosis*) and 4.5% in lung cancer [5,6]. The diagnosis of post-pneumonectomy BPF can be early or late and leads to a chronic situation that weakens the patient, leading to malnutrition problems, risk of reactivating tuberculous infections with Multidrug-Resistant germs (MDR), and even leading to death in 10% [1,4,7]. Among the main factors widely described are a history of pulmonary tuberculosis (35%), malnutrition (21%), and right pneumonectomy (15%) [1-3,8-11].

Latin America has with the highest rate of indication of extensive tuberculous pulmonary resections in our environment. This has led to the need to implement operating rooms strictly for this type of surgery such as the one in our institution, with higher rates of BPF than in lung cancer surgeries. Although the surgical technique has progressed, which has generated a decrease in the incidence of BPF, it continues to generate great concern for the thoracic surgeon due to the multifactorial origin of this complication. Therefore, our study aimed to determine the associated clinical-surgical characteristics of the BPF in a Peruvian cohort of patients who underwent pneumonectomy.

Materials and Methods

Design, population, and sample size

A cross-sectional and retrospective study was conducted. Fifty-seven post-pneumonectomy patients previously evaluated by the thoracic surgery service of a Hospital Nacional from Peru during January 2015-June 2020 were studied. Inclusion criteria were the majority of age (>18 years), and pneumonectomy due to different etiologies (tuberculosis, pulmonary hydatidosis, malignant pulmonary tumor, benign pulmonary tumor, severe pulmonary sequelae, and others) and that ended with or without BPF. All patients who underwent pneumonectomy with or without BPF outside the study period and without complete information were excluded.

Data collection and study variables

Data collection was retrospective, and medical records and operative reports were evaluated using a data collection form. Subsequently, the data were tabulated in an orderly manner and respected the chronological order of the patients. A checklist was used, and to avoid any tabulation bias, each of the data obtained was double-checked. The study variables were divided into 2 groups (Pneumonectomies with BPF vs. Pneumonectomies without BPF) and the characteristics evaluated were baseline (age, sex, comorbidities, smoking and alcoholism history), clinical-surgical (pulmonary tuberculosis, type of surgical indication, malnutrition, anemia, hypoalbuminemia, chronic obstructive pulmonary disease (COPD), diabetes mellitus, forced expiratory volume during the first second (FEV1 predicted), overall health (ASA>II), mechanical ventilation greater than 2 hours, pleural empyema pre and post-surgery, pleural empyema pre and post-surgery (pleural empyema pre and post-surgery), mechanical ventilation greater than 24 hours, pre-and postoperative pleural empyema, neoadjuvant therapy and postoperative pulmonary infection, location and type of pneumonectomy, type of suture, operative bronchial closure technique (SWEET, separate loose stitch plication of the cartilaginous bronchial portion over the membranous part, and MABIT, bloc closure of the bronchial stump with arterial and/or venous vessels from the pulmonary hilum), bronchial stump coverage, lymph node dissection, residual tumor in bronchial stump, operative time, intraoperative bleeding and the presence of BPF). The present investigation respected ethical principles, and patient anonymity, and since it was a retrospective study, it was not necessary to implement informed consent. The study protocol was approved by the ethics committee of the Universidad de San Martín de Porres (USMP-00456/2022) and the Hospital Nacional Hipólito Unánue (NIT2309-06/2022), Lima, Peru.

Statistical Analysis

Statistical calculations were based on descriptive analyses with continuous variables (Mean and Standard Deviation) and categorical variables (Counts and percentages). Statistical tests were based on Chi-square, Student's t-test, Fisher's exact test, and the Mann-Whitney U test. The entire statistical analysis of the data was performed with the statistical programs Microsoft Excel 2020 and SPSS v25 for Windows version 10, and values with $p < 0.05$ were considered statistically significant.

Results

Fifty-seven patients who underwent pneumonectomy were evaluated, 28.1% of whom presented BPF. The mean age of the patients with BPF was 38.3 ± 15 years and the male sex prevailed over the female sex (62.5% vs. 37.5%). Twenty-five percent of the patients with BPF had a history of smoking and alcoholism, with no statistically significant relationship (Figure 1).

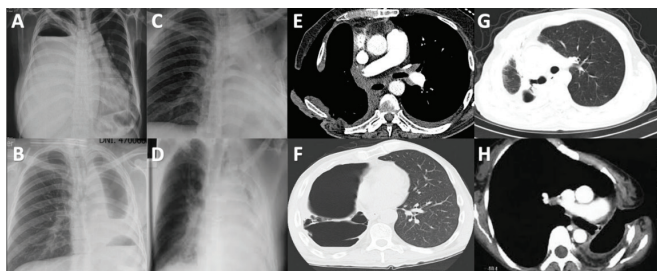


Figure 1. Thoracic radiographs showing various presentations of BPF, including postoperative empyema and collection (A-D), thoracic CT scans show BPF with the presence of postoperative collections and others with thoracic windows (E-H).

About the clinical comparison between the pneumonectomies sample with and without BPF, there was a history of pulmonary tuberculosis in 68.2% vs. 62% (p = 0.225), respectively; however, for patients with BPF, 62.5% had a post-TB fibrocavitary sequela, 18.8% had pulmonary hydatidosis, and 12.5% had a post-surgical cavitory sequela. The mortality associated with BPF was 6.25%, and in the non-BPF group it was 4.87% (p = 0.098). There was malnutrition in 12.5% vs. 2.4% (p = 0.187), both for patients with and without BPF, anemia 51.2% vs. 75% (p = 0.225), hypoalbuminemia 31.3% vs. 14.6% (p = 0.260), Diabetes mellitus 18.8% vs. 7.3% (p = 0.335), predicted low FEV1 56.3% vs. 31.7% (p = 0.046), ASA >II 18.8% vs. 9.8% (p = 0.349), mechanical ventilation >24 hours 6.3% vs. 2.4% (p = 0.486), preoperative pleural empyema 37.5% vs. 2.4% (p = 0.01), preoperative neoadjuvant therapy (100% vs. 100%), postoperative pulmonary infection 18.8% vs. 9.8% and postoperative empyema 100% vs. 9.8% (p = 0.00), respectively for both groups (Tables 1,2). The positive bronchial margins for carcinoma with BPF was 12.5%, and in the non-BPF group it was 7.31% (p = 0.012). Regarding the surgical comparison between the pneumonectomies sample with and without BPF, left pneumonectomy predominated in both groups 81.3% vs. 65.9% (p = 0.342), the main suture thread was polypropylene 56.3% vs. 58.5% (p = 0.430), the main bron-

chial manual closure technique was SWEET 81.3% vs. 97.6% followed by MABIT 18.8% vs. 2.4% (p = 0.063), for bronchial stump used pleural coverage 56.3% vs. 75.6% (p = 0.199), lymph node dissection 6.3% vs. 2.4% (p = 0.486), emergency surgery 87.5% vs. 82.9% (p = 1.00), operative time 450.69 min. vs. 367.73 min. (p = 0.032) and finally intraoperative bleeding 2220.63 ml. vs. 1579.15 ml. (p = 0.145), respectively for both groups (Tables 1,2).

Table 1. Baseline characteristics of patients who underwent pneumonectomy with and without BF.

Variables	Pneumonectomies		P*
	N= 57 (100%)		
	Bronchopleural fistula		
	No (%)	Yes (%)	
	N=41	N=16	
Age, Mean ± SD	42.00 ± 14.65	38.31 ± 15.00	0.400
Gender			
Male	32 (78%)	10 (62.5%)	0.317
Female	9 (22%)	6 (37.5%)	
Antecedents			
Smoking			
No	37 (90.2%)	9 (56.3%)	0.105
Current	1 (2.4%)	2 (12.5%)	
Former smoker	0 (0%)	2 (12.5%)	
Unknown	3 (7.3%)	3 (18.8%)	
Alcoholism			
Yes	1 (2.4%)	4 (25%)	0.08
No	37 (90.2%)	9 (56.3%)	
Unknown	3 (7.3%)	3 (18.8%)	
Pulmonary tuberculosis (TB)			
Sensitive	23 (56.1%)	5 (31.3%)	0.225
MDR	7 (17.1%)	5 (31.3%)	
Pulmonary disease			
Fibrocavitary sequelae post-TB	29 (70.7%)	10 (62.5%)	
Hydatidosis	6 (14.6%)	3 (18.8%)	
Neoplasia	2 (4.9%)	1 (6.3%)	0.848
Bullous lung	1 (2.4%)	0 (0%)	
Post-resection residual cavity	1 (2.4%)	0 (0%)	
Malnutrition	1 (2.4%)	2 (12.5%)	0.187
Anemia	21 (51.2%)	12 (75%)	0.342
Hypoalbuminemia	6 (14.6%)	5 (31.3%)	0.260
COPD	0	1 (6.3%)	0.281
Diabetes Mellitus	3 (7.3%)	3 (18.8%)	0.335

Abbrev.; SD: Standard Deviation, COPD: Chronic obstructive pulmonary disease, MDR: Multidrug-Resistant, *Student's t-test

Table 2. Clinical-surgical characteristics of patients who underwent pneumonectomy with and without BF.

Variables	Pneumonectomies N= 57 (100%)		P
	Bronchopleural fistula		
	No (%) N=41	Yes (%) N=16	
Pneumonectomy			
Right	14 (34.1%)	3 (18.8%)	0.342
Left	27 (65.9%)	13 (81.3%)	
Suture thread			
Black Silk	12 (29.3%)	3 (18.8%)	0.430
Polypropylene	24 (58.5%)	9 (56.3%)	
Vicryl	5 (12.2%)	4 (25%)	
Manual bronchial closure technique			
Sweet	40 (97.6%)	13 (81.3%)	0.063
Mabit	1 (2.4%)	3 (18.8%)	
Positive bronchial margins for carcinoma			
	3 (7.31%)	2 (12.5%)	0.012
Bronchial stump coverage			
Intercostal muscle flap	1 (2.4%)	2 (12.5%)	0.199
Pleural	31 (75.6%)	9 (56.3%)	
Lymph node dissection	1 (2.4%)	1 (6.3%)	0.486
Emergency surgery	7 (17.1%)	2 (12.5%)	1.000
Operative time (Minutes)	367.73 ± 112.76	450.69 ± 169.36	0.032
Intraoperative bleeding (mL)	1579.15 ± 816.85	2220.63 ± 1456.72	0.145
Predicted low FEV1	13 (31.7%)	9 (56.3%)	0.046
ASA >II	4 (9.8%)	3 (18.8%)	0.349
Mechanical ventilation >24 hours	1 (2.4%)	1 (6.3%)	0.486
Preoperative pleural empyema	1 (2.4%)	6 (37.5%)	0.001
Preoperative antibiotic therapy	41 (100.0%)	16 (100.0%)	NC
Postoperative pulmonary infection	4 (9.8%)	3 (18.8%)	0.388
Postoperative empyema	4 (9.8%)	16 (100%)	0.000
Mortality	2 (4.87%)	1 (6.25%)	0.098

Abbrev.; NC: Not calculated, FEV1: Forced expiratory volume during the first second, ASA: American Society of Anesthesiologists

Discussion

BPF is a complication that represents 59% of morbidity and 5.4-71% of mortality in patients who underwent pneumonectomy [1-3]. Our research reported an incidence of 28.1% of BPF, with a higher percentage reported in studies by Mammana (4.5%), Gursoy (10.8%), and La Serna (11%) [6,12,13]. We described a history of sequelae of TB

infection in 68.4%; however, several authors have reported higher rates exceeding 75% [10,12,14,15]. This could be explained by the fact that chronic inflammation due to tuberculosis leads to the deposition of collagen at the hilar level and stiffer anatomical structures; consequently, bronchial tissue is predisposed to impaired healing and a greater risk of BPF [6]. BPF was found to be mainly associated with the male gender (62.5%); being similar to that reported by La Serna, who described that 69% of the population was male [13]. Mammana et al suggested that a possible explanation could be that the diameter of the male bronchus is larger and when closing the bronchial stump this would generate greater tension; on the other hand, Nachira et al reported that the female sex was an associated factor for post-pneumonectomy BPF ($p = 0.03$) [3,6]. The mean age of patients with BPF reported in our study (38.31 ± 15 years) was somewhat different from that reported by Fuso and Ahmet et al as they described 66.1 ± 7.4 years and the latter would be due to the etiology associated with BPF such as neoplasms, unlike our case, mainly young population and with infectious etiologies [9,10,16].

We identified a statistically significant association ($p = 0.015$) between smoking and BPF, similar to that reported by Thomas et al and describing that active smoking was a significant predictor of BPF (OR 1.6; 95%CI, 1.34-1.95, $p = 0.017$) [11]; however, Yazgan and Mazzella et al did not find a clear significant association [8,10]. Likewise, alcoholism was significantly associated with BPF ($p = 0.008$), similar to that described by Thomas et al (OR 2.2; 95%CI, 1.98-2.45, $p = 0.017$), describing alcohol abuse and dependence as a negative predictor for BPF [11]. In Peru, the main indication for pulmonary surgery is for sequelae pulmonary TB, and we report more than 50% incidence of pulmonary TB for both groups; however, without statistically significant association with BPF [14]. Mammana et al also reported no significant association in 20% of their cases [6]; but Gursoy and Ahmet et al reported that 33.3% of patients with pulmonary TB were associated with the presence of post-pneumonectomy BPF ($p = 0.08$) [12, 15].

Among the predictors of BPF development described by Pforr et al the presence of non-malignant pulmonary disease ($p = 0.03$) [10] and among which pulmonary sequelae disease (78%) and hydatidosis (34%), were also described by Birdas, and Ahmet et al [15, 17]. Factors such as malnutrition, underweight, anemia, and hypoalbuminemia have been widely related to BPF and were described by Thomas, Pforr, Haraguchi, and Mazzella et al. However,

the latter highlighted that hypoalbuminemia was present in more than 20% of patients affected by BPF ($p = 0.02$) [8,10,11,18]. COPD and low FEV1 predicted postpneumonectomy have been related to the incidence of BPF, because chronic inflammation of the bronchial mucosa in these patients may contribute to impair healing after lung resection [2]. Algar et al described that low postoperative FEV1 is a predictive factor for postpneumonectomy BPF ($p = 0.012$); however, Yazgan and Thomas et al reported that there is no relationship and that more evidence is needed to accept this [2,11,19]. Nachira ($p < 0.019$) and Mammana et al ($p < 0.001$), reported that prolonged mechanical ventilation causes a higher risk of suture tension and has been associated with the presence of BPF [3,6]; however, we do not report a significant association in this item but we do describe that preoperative empyema is strongly associated with this complication and was described by Haraguchi ($p = 0.002$), stating that preoperative pulmonary infections contribute significantly to BPF in postoperative pneumonectomy patients ($p = 0.002$) [19], stating that preoperative pulmonary infections contribute significantly to BPF in postoperative pneumonectomy patients [19]. We did not find an association between BPF and postoperative pulmonary infection as did Fuso et al [9]. However, Nachira et al concluded that postoperative pulmonary infections were strong predictors of BPF development ($p = 0.008$) [3]. Despite this, it has been described that a mechanism of production of BPF is the infection of the pleural space and the increasing accumulation of infected fluid, resulting in the evacuation of empyema through the bronchial stump and subsequent complication into BPF [20]. That is why we report that 100% of the patients who presented BPF had postoperative pleural empyema ($p = 0.000$), similar to what was described by Nachira et al, who reported that postoperative empyema increases the risk of having BPF by 8 times ($p < 0.001$) [3] and also Somocurcio et al concluded that postoperative complications in patients who underwent surgery for multidrug-resistant pulmonary TB were postoperative empyema followed by BPF [13]. The greater frequency of BPF in right pneumonectomy is due to its blood vascularization which is nourished by one artery, compared to the left bronchus which is perfused by two bronchial arteries; likewise, another protective mechanism would be that in left pneumonectomy, the bronchial stump is covered by the aorta and surrounding tissues [2,18]. All the above described has been reflected in publications by Mammana (OR 4.08; 95%CI, 3.67-4.67, $p = 0.004$), Gursoy (OR 5.90; 95%CI, 4.97-6.32, $p = 0.001$) and Mazzella et al (OR 2.53; 95%CI, 2.11-3.35, $p = 0.023$), concluding

that right pneumonectomy is an associated factor for the development of BPF [6,8,12]. One of the possible causes of BPF is the use of inadequate suture material. Non-absorbable thread (stainless steel, silk, polypropylene) gives better results, the other types are eliminated with the risk of BPF [21]. In the present study; only suture thread was used for bronchial stump closure, no mechanical sutures were used. The most frequent thread used in patients with BPF was polypropylene (56.3%) but no significant association was found. Gursoy et al reported that of the cohort of patients with BPF, automatic suture (74.5%) and manual suture (polypropylene, 25.5%) were used but without significant differences [12]; however, Mammana et al described that the use of vicryl was one of the factors that showed a significant positive trend over time towards BPF ($p < 0.001$) [6]. Ahmet et al reported that of the mechanical and manual suture group (polypropylene), 5% and 1.5% respectively, developed BPF, and it was concluded that mechanical suture was associated with BPF ($p = 0.04$) [15]. The bronchus closure technique with continuous stitches (Mabit Technique) was performed in intraoperative complications such as bleeding, which required quick control of the pulmonary hilum, in sequelae lung, chronic empyema, and in case of previous pulmonary resection, where it was very difficult to separate vascular structures and bronchus. With this technique, 75% BPF was described, in contrast to the sweet technique with 32.5%. This factor was evaluated because, with continuous suturing, one of the basic principles of bronchial stump closure would be affected, that of conserving the blood supply and thus affecting the irrigation of the bronchial stump [1]. In the literature, manual and mechanical closure techniques are compared, and their use in bronchial stump closure is still controversial [3,6,9].

Lymph node dissection in pneumonectomy, especially in right pneumonectomy, has been associated with greater devascularization of the bronchial stump, causing greater vascular damage of the nutrient vessel in surgery and being a risk factor for the presence of BPF [2,18], we did not report a significant association due to the few cases; neither was it described in other studies such as those of Pforr, and Thomas et al [10,11]. Mammana et al reported that residual tumor in the bronchial stump is a risk factor for post-pneumonectomy BPF ($p = 0.018$); however, we did not find any association in the sample studied [6]. La Serna described that the distorted anatomy of patients with sequelae of pulmonary tuberculosis would cause greater intraoperative complications since

pulmonary dissections are difficult and increase the operative time [13]. We described a longer operative time in patients who underwent pneumonectomy and BPF than those who did not present this complication, being a significant and related finding ($p = 0.032$); likewise, Thomas et al also concluded that increased operative time is an associated predictor factor for BPF [11].

Among the limitations of our study was the small sample size of our population; however, despite being one of the leading institutions in the surgical management of TB, we have a small caseload. We also believe that a longer-term follow-up study would be ideal for this group of patients with BPF who underwent pneumonectomy

In conclusion, we have found a series of factors associated with the presence of BPF in patients who underwent pneumonectomy, many of them related to pulmonary tuberculosis infection, which is an important predictor of the associated complications; however, we believe that further multicenter studies with a larger number of patients are needed to identify more factors to be considered during the surgical management of this terrible complication such as BPF.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

Ethics approval

The study protocol was approved by the ethics committee of the Universidad de San Martín de Porres (USMP-00456/2022) and the Hospital Nacional Hipólito Unánué (NIT2309-06/2022), Lima, Peru.

Authors' contribution

KGP, WSC: Concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review, PVZ: Data acquisition, data analysis, manuscript editing and manuscript review.

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