

## Persistent Air Leaks in Spontaneous Pneumothorax: Risk Factors and The Role of Autologous Blood Pleurodesis

Dashab Hannan<sup>1\*</sup> Md. Ataur Rahman<sup>2</sup> Md. Resalat Chowdhury<sup>3</sup> Mainul Hasan Sohel<sup>4</sup>  
Sowrabh Biswas<sup>5</sup> Muhammad Karim Hossain<sup>6</sup>

### Abstract

**Background:** Persistent Air Leaks (PAL) complicate Spontaneous Pneumothorax (SP) prolonging hospitalization and morbidity. Autologous Blood Pleurodesis (ABP) is a minimally invasive option, but its efficacy versus chemical pleurodesis needs evaluation. The purpose of the study is to identify PAL risk factors in SP and compare ABP with tetracycline pleurodesis.

**Materials and methods:** In this prospective study at NIDCH, Dhaka, 176 SP patients requiring chest tube drainage were enrolled and equally divided into PAL (Air leak >5 days) and non-PAL groups. Clinical, radiological and procedural factors were analyzed. PAL patients received ABP or tetracycline. Outcomes included leak resolution, cessation time, complications, hospital stay and recurrence. Analysis used SPSS v26, p 0.05 was significant.

**Results:** PAL was associated with older age, low BMI, COPD, smoking, bullae and lung collapse >50%. Independent predictors were BMI <20 (OR=2.94) COPD (OR=2.72) bullae (OR=2.59) and collapse >50% (OR=2.87). ABP showed comparable resolution to tetracycline (95.45% vs. 88.64%, p=0.361) but faster cessation (2.4±1.3 vs. 3.6±1.7 days, p=0.003) and fewer complications (4.55% vs. 59.09%, p<0.001).

**Conclusion:** PAL in SP is linked to clinical and radiological factors. ABP is safe, effective, and better tolerated, ensuring faster resolution and fewer complications.

**Key words:** Autologous blood pleurodesis; Chest tube drainage; Persistent air leak; Risk factors; Spontaneous pneumothorax; Tetracycline pleurodesis.

### Introduction

Spontaneous Pneumothorax (SP) is a common thoracic emergency characterized by the presence of air in the pleural space without antecedent trauma or intervention, leading to partial or complete lung collapse.<sup>1</sup> Globally, the incidence of spontaneous pneumothorax ranges from 17 to 24 cases per 100,000 individuals annually, making it a relevant clinical concern across diverse healthcare settings.<sup>2</sup> While initial management with oxygen supplementation and intercostal tube drainage is often effective, a significant number of patients experience complications, the most prominent of which is Persistent Air Leak (PAL).<sup>3</sup> Defined as an ongoing escape of air from the lung parenchyma into the pleural cavity beyond the usual healing period—commonly accepted as five to seven days—PALs pose substantial clinical challenges.<sup>4</sup> They not only prolong hospital stay and delay recovery but also increase the risk of infection, patient discomfort and resource utilization.<sup>5,6</sup> PALs are more frequently observed in individuals with underlying structural lung disease or secondary spontaneous pneumothorax, though they may also complicate primary cases, particularly in smokers or those with subpleural blebs and bullae.<sup>7</sup> The identification of factors predisposing to PAL is therefore critical in tailoring early interventions, selecting appropriate therapeutic modalities and anticipating prolonged clinical courses. Risk factors may be intrinsic—such as age, body habitus, smoking history, and pre-existing lung pathology—or extrinsic, including procedural techniques, timing of intervention, and tube size or position.<sup>8</sup> In clinical practice, timely resolution of PAL is a priority, yet surgical intervention is not always feasible, especially in patients with comorbidities, limited pulmonary reserve, or surgical reluctance. In such cases, alternative, non-surgical methods of

1. Registrar (Surgery) of Thoracic Surgery

□ NIDCH, Dhaka.

2. Assistant Professor of Thoracic surgery

□ Mainamoti Medical College, Cumilla.

3. Thoracic Surgeon

□ Bangladesh Specialized Hospital, Dhaka.

4. Associate Professor of Orthopedics

□ Central Medical College, Dhaka.

5. Junior Consultant of Thoracic Surgery

□ Chattogram Maa Shishu-O-General Hospital, Chattogram.

6. Assistant Professor of Thoracic Surgery

□ Bangladesh Medical University, Dhaka.

**\*Correspondence:** Dr. Dashab Hannan

□ Cell : 01817 58 34 20

□ E-mail: drdashab@gmail.com

Submitted on □□02.02.2026

Accepted on □: □03.03.2026

promoting pleural adhesion and sealing air leaks become necessary. Among these, Autologous Blood Pleurodesis (ABP) has emerged as a simple, minimally invasive and cost-effective option.<sup>9</sup> This technique involves instillation of a patient's own venous blood into the pleural cavity via the existing chest tube, with the aim of forming a fibrin clot or initiating an inflammatory reaction that encourages pleurodesis and closure of the alveolar-pleural fistula.<sup>10</sup> Unlike chemical pleurodesis, which often involves sclerosing agents that can induce systemic side effects or intense pleuritic pain, ABP offers a more physiologic and generally well-tolerated approach, making it especially suitable for high-risk or debilitated patients.<sup>11,12</sup> Furthermore, the ease of administration at the bedside without the need for general anesthesia adds to its appeal in resource-limited environments or in patients unfit for surgery.<sup>13</sup> Despite its apparent benefits, ABP remains underutilized and lacks standardized protocols, with considerable variation in clinical practice regarding timing of administration, volume of blood used and patient positioning.<sup>14</sup> This study aimed to investigate the risk factors associated with persistent air leaks in spontaneous pneumothorax and to evaluate the therapeutic role of autologous blood pleurodesis in their management.

### Materials and methods

This prospective study was conducted in the Department of Thoracic Surgery, NIDCH, Dhaka, Bangladesh, from 15 May 2022 to 30 June 2023, including 176 patients with spontaneous pneumothorax requiring chest tube drainage. Patients were divided into PAL (Air leak >5 days, n=88) and non-PAL groups (Air leak ≤5 days, n=88). Inclusion criteria were age ≥18 years, primary or secondary spontaneous pneumothorax and chest tube treatment. Exclusion criteria included traumatic/iatrogenic pneumothorax, active infection or malignancy, prior pleurodesis or thoracic surgery, immunosuppression or refusal to consent.

Data collected included age, sex, smoking, BMI, COPD, previous pneumothorax, lung collapse, bullae on CT, chest tube size, re-expansion time, air leak and tube duration, and suction use. PAL patients received pleurodesis after conservative

management: ABP (50–100 mL autologous blood, 2-hour clamping) or tetracycline (500 mg in 20 mL saline). Outcomes assessed were air leak resolution, chest tube removal, hospital stay, 30- and 90-day recurrence, and complications. Ethical approval and informed consent were obtained. SPSS v26 was used for analysis; continuous data were mean ± SD, categorical as frequencies/percentages, compared using t-test, chi-square, or Mann–Whitney U. Multivariate logistic regression identified independent PAL predictors;  $p \leq 0.05$  was significant. Ethical clearance was obtained from the institutional review board and all participants provided written informed consent before enrollment.

### Results

A total of 176 patients were included, evenly split into PAL and non-PAL groups (n=88 each). The PAL group was older ( $52.6 \pm 10.8$  vs.  $48.3 \pm 11.2$  years) and predominantly male (98.9% vs. 93.2%). Smoking history was higher in PAL patients (76.1% vs. 59.1%,  $p=0.018$ ) while mean BMI was lower ( $19.6 \pm 2.7$  vs.  $21.3 \pm 2.5$  kg/m<sup>2</sup>,  $p=0.005$ ). Comorbid COPD was more common in PAL patients (70.5% vs. 44.3%,  $p=0.001$ ). (Table I). Radiologically, PAL patients had greater lung collapse (>50%, 68.18% vs. 43.18%,  $p=0.002$ ) and more bullae on CT (63.64% vs. 37.50%,  $p=0.001$ ). They required larger chest tubes ( $32.0 \pm 0.0$  vs.  $28.0 \pm 2.0$  Fr,  $p<0.001$ ) and had longer lung re-expansion times ( $3.6 \pm 1.8$  vs.  $2.1 \pm 1.0$  days,  $p<0.001$ ) (Table II). Table III showed PAL patients had longer air leak ( $4.1 \pm 1.7$  vs.  $1.8 \pm 0.7$  days) and chest tube duration ( $3.93 \pm 2.45$  vs.  $2.12 \pm 1.04$  days,  $p<0.001$ ) higher suction use (70.5% vs. 32.95%) and all required intervention (100% vs. 13.64%). Table IV identified BMI <20 kg/m<sup>2</sup> (OR 2.94), COPD (OR 2.72) bullae on CT (OR 2.59) and lung collapse >50% (OR 2.87) as independent predictors of PAL. In PAL patients receiving ABP or tetracycline pleurodesis (n=44 each) ABP shortened air leak cessation ( $2.4 \pm 1.3$  vs.  $3.6 \pm 1.7$  days,  $p=0.003$ ) and had fewer minor complications (4.5% vs. 59.1%,  $p<0.001$ ) (Table V). Table VI presented longer hospital stay in PAL patients ( $13.58 \pm 4.4$  vs.  $6.82 \pm 2.75$  days,  $p<0.001$ ). Recurrence at 30 and 90 days was higher in PAL (5.7% and 7.9%) but not statistically significant.

**Table I** Baseline Demographic and Clinical Characteristics of Patients (n=176)

| Characteristics          | PAL (n=88)       |                   | Non-PAL (n=88)   |                   | p value |
|--------------------------|------------------|-------------------|------------------|-------------------|---------|
|                          | Frequency<br>(n) | Percentage<br>(%) | Frequency<br>(n) | Percentage<br>(%) |         |
| Age (Years)              |                  |                   |                  |                   |         |
| Mean ± SD                | 52.6 ± 10.8      |                   | 48.3 ± 11.2      |                   | 0.019   |
| Gender                   |                  |                   |                  |                   |         |
| Male                     | 87               | 98.86             | 82               | 93.18             | 0.092   |
| Female                   | 1                | 1.14              | 6                | 6.82              |         |
| Smoking history          | 67               | 76.14             | 52               | 59.09             | 0.018   |
| BMI (kg/m <sup>2</sup> ) |                  |                   |                  |                   |         |
| Mean ± SD                | 19.6 ± 2.7       |                   | 21.3 ± 2.5       |                   | 0.005   |
| COPD                     | 62               | 70.45             | 39               | 44.32             | 0.001   |
| Previous pneumothorax    | 17               | 19.32             | 9                | 10.23             | 0.09    |

**Table II** Radiological and Procedural Findings (n=176)

| Findings                         | PAL (n=88)       |                   | Non-PAL (n=88)   |                   | p value |
|----------------------------------|------------------|-------------------|------------------|-------------------|---------|
|                                  | Frequency<br>(n) | Percentage<br>(%) | Frequency<br>(n) | Percentage<br>(%) |         |
| Pneumothorax side (Right)        | 49               | 55.68             | 46               | 52.27             | 0.686   |
| Lung collapse >50%               | 60               | 68.18             | 38               | 43.18             | 0.002   |
| Bullae on CT                     | 56               | 63.64             | 33               | 37.50             | 0.001   |
| Chest tube size (Fr)             |                  |                   |                  |                   |         |
| Mean ± SD                        | 32.0 ± 0.0       |                   | 28.0 ± 2.0       |                   | <0.001  |
| Time to lung re-expansion (Days) |                  |                   |                  |                   |         |
| Mean ± SD                        | 3.6 ± 1.8        |                   | 2.1 ± 1.0        |                   | <0.001  |

**Table III** Duration and Management of Air Leak (n=176)

| Parameters                  | PAL (n=88)       |                   | Non-PAL (n=88)   |                   | p value |
|-----------------------------|------------------|-------------------|------------------|-------------------|---------|
|                             | Frequency<br>(n) | Percentage<br>(%) | Frequency<br>(n) | Percentage<br>(%) |         |
| Duration of air leak (Days) |                  |                   |                  |                   |         |
| Mean ± SD                   | 4.1 ± 1.7        | 1.8 ± 0.7         |                  |                   | <0.001  |
| Chest tube duration (Days)  |                  |                   |                  |                   |         |
| Mean ± SD                   | 3.93 ± 2.45      |                   | 2.12 ± 1.04      |                   | <0.001  |
| Use of suction              | 62               | 70.45             | 29               | 32.95             | <0.001  |
| Intervention needed         | 88               | 100.00            | 12               | 13.64             | <0.001  |

**Table IV** Predictors of Persistent Air Leak (Multivariate Logistic Regression) (n=176)

| Variables                 | Adjusted OR | 95% CI    | p value |
|---------------------------|-------------|-----------|---------|
| BMI <20 kg/m <sup>2</sup> | 2.94        | 1.32–6.54 | 0.008   |
| COPD                      | 2.72        | 1.35–5.49 | 0.005   |
| Bullae on CT              | 2.59        | 1.24–5.43 | 0.011   |
| Lung collapse >50%        | 2.87        | 1.42–5.82 | 0.003   |

**Table V** Outcomes of Autologous Blood Pleurodesis (ABP) in PAL Patients (n=176).

| Outcomes                          | ABP Group (n=44) |                   | Tetracycline Group (n=44) |                   | p value |
|-----------------------------------|------------------|-------------------|---------------------------|-------------------|---------|
|                                   | Frequency<br>(n) | Percentage<br>(%) | Frequency<br>(n)          | Percentage<br>(%) |         |
| Resolution of air leak            | 42               | 95.45             | 39                        | 88.64             | 0.361   |
| Time to air leak cessation (Days) | 2.4 ± 1.3        |                   | 3.6 ± 1.7                 |                   | 0.003   |
| Time to chest tube removal (Days) | 3.65 ± 2.93      |                   | 4.20 ± 1.91               |                   | 0.312   |
| Recurrence within 30 days         | 1                | 2.27              | 4                         | 9.09              | 0.361   |
| Minor complications               | 2                | 4.55              | 26                        | 59.09             | <0.001  |

**Table VI** Hospital Stay and Recurrence Rates (n=176)

| Outcome                        | PAL (n=88)       |                   | Non-PAL (n=88)   |                   | p value |
|--------------------------------|------------------|-------------------|------------------|-------------------|---------|
|                                | Frequency<br>(n) | Percentage<br>(%) | Frequency<br>(n) | Percentage<br>(%) |         |
| Length of hospital stay (Days) |                  |                   |                  |                   |         |
| Mean ± SD                      | 13.58 ± 4.4      |                   | 6.82 ± 2.75      |                   | <0.001  |
| Recurrence within 30 days      | 5                | 5.68              | 1                | 1.14              | 0.213   |
| Recurrence within 90 days      | 7                | 7.95              | 2                | 2.27              | 0.089   |

## Discussion

Persistent air leaks represent a challenging complication in spontaneous pneumothorax, with varying etiologies and clinical presentations that significantly impact management strategies.<sup>15</sup> This prospective analysis highlights key demographic, clinical, radiological, and procedural predictors of Persistent Air Leak (PAL) in Spontaneous Pneumothorax (SP) and evaluates the efficacy of Autologous Blood Pleurodesis (ABP) compared to tetracycline pleurodesis. In our study the PAL group were significantly older ( $p=0.019$ ) with lower BMI ( $p=0.005$ ) higher prevalence of COPD ( $p=0.001$ ) and a more frequent smoking history ( $p=0.018$ ). These findings align with prior studies where aging lung parenchyma, nutritional status and smoking-related lung damage—especially COPD—were identified as predisposing factors for delayed healing and alveolar-pleural fistula formation.<sup>16,17</sup> The association of low BMI with PAL is consistent with Drewbrook et al. who found that underweight status impairs tissue healing and predisposes to prolonged leaks.<sup>18</sup> Radiological assessments revealed that the Persistent Air Leak (PAL) group exhibited a significantly higher prevalence of bullae on Computed Tomography (CT) scans ( $p=0.001$ ) and more frequent lung collapse exceeding 50% ( $p=0.002$ ). These results mirror the previous studies which showed that large bullae and greater collapse extent impair visceral pleural apposition, increasing the likelihood of prolonged air leaks.<sup>7,19</sup> Additionally, larger chest tube sizes and delayed re-expansion in PAL patients ( $p<0.001$  for both) suggest a more severe parenchymal compromise and the need for more aggressive drainage strategies.<sup>9</sup> PAL patients had significantly prolonged air leak duration ( $4.1 \pm 1.7$  vs.  $1.8 \pm 0.7$  days), extended chest tube use ( $3.93 \pm 2.45$  vs.  $2.12 \pm 1.04$  days), and higher suction requirement (70.45% vs. 32.95%,

$p < 0.001$ ). This aligns with the study of Lazarus et al. that PAL increases intervention needs, hospital costs, and patient morbidity.<sup>20</sup> Multivariate analysis identified BMI  $< 20 \text{ kg/m}^2$  (OR 2.94) COPD (OR 2.72) bullae (OR 2.59) and lung collapse  $> 50\%$  (OR 2.87) as independent predictors of PAL. These are consistent with previous studies which showed pre-existing lung pathology and anatomical distortion from bullae were found to independently prolong leak duration.<sup>7,18,21</sup> The therapeutic efficacy of Autologous Blood Patch Pleurodesis (ABP) was comparable to that of tetracycline, achieving resolution rates of 95.45% and 88.64%, respectively ( $p = 0.361$ ) but superior in faster air leak cessation ( $2.4 \pm 1.3$  vs.  $3.6 \pm 1.7$  days,  $p = 0.003$ ) and markedly lower complication rates (4.55% vs. 59.09%,  $p < 0.001$ ). These findings echo the experience of Apilio ulla et al. who described ABP as a safe and effective bedside method that avoids the pain, fever and systemic symptoms often associated with chemical agents.<sup>22</sup> Our study showed PAL significantly prolongs hospitalization ( $13.58 \pm 4.4$  vs.  $6.82 \pm 2.75$  days,  $p < 0.001$ ) although recurrence rates at 30 and 90 days did not reach statistical significance. Still, the numerical trend toward higher recurrence in the PAL group supports close post-discharge monitoring. The shorter hospital stays with ABP support its practical advantage, especially in resource-constrained settings.<sup>7,23</sup>

### Limitations

This single-center study may limit generalizability across populations and healthcare settings. The sample size, though adequate, restricted subgroup analyses. Variations in timing and volume of autologous blood pleurodesis were not standardized, possibly influencing outcomes. Follow-up beyond 90 days was lacking, limiting late recurrence assessment. The observational design may also introduce selection bias.

### Conclusion

Persistent air leaks in spontaneous pneumothorax are linked to low BMI, COPD, bullae, and extensive lung collapse, leading to longer leaks and hospital stay. Autologous blood pleurodesis matched tetracycline in efficacy but achieved faster leak cessation with fewer complications. It is a safe, effective, minimally invasive option, especially for patients unfit for surgery or in resource-limited settings. Early risk factor recognition and timely ABP can improve outcomes and reduce healthcare burden.

### Recommendation

Autologous blood pleurodesis should be considered a preferred option for managing persistent air leaks in spontaneous pneumothorax due to its safety, faster resolution and fewer complications. Early identification of risk factors such as low BMI, COPD, bullae and extensive lung collapse can help optimize patient outcomes.

### Acknowledgement

We are deeply grateful to our parents for their constant encouragement and support throughout this study. We also sincerely thank our teachers, colleagues and all who contributed to the successful completion of this research.

### Contribution of authors

DH-Conception, acquisition of data, manuscript drafting, data analysis & final approval.

MAR-Data analysis, manuscript drafting & final approval.

MRC-Design, acquisition of data, manuscript drafting & final approval.

MHS-Acquisition of data, drafting & final approval.

MKH-Acquisition of data, data analysis, interpretation of data & final approval.

SB-Data analysis, manuscript drafting, critical revision of content & final approval.

### Disclosure

All the authors declared that there is no conflict of interest.

### References

1. Shorthose M, Barton E, Walker S. The contemporary management of spontaneous pneumothorax in adults. *Breathe*. 2024;19(4).
2. Hallifax RJ, Goldacre R, Landray MJ, Rahman NM, Goldacre MJ. Trends in the incidence and recurrence of inpatient-treated spontaneous pneumothorax, 1968-2016. *Jama*. 2018;320(14):1471-1480.
3. Thachuthara-George J. Pneumothorax in patients with respiratory failure in ICU. *Journal of thoracic disease*. 2021;13(8):5195.
4. Duron G, Backer E, Feller-Kopman D. Evaluation and management of persistent air leak. *Expert Review of Respiratory Medicine*. 2023;17(10):865-872.
5. Varela G, Jiménez MF, Novoa N, Aranda JL. Estimating hospital costs attributable to prolonged air leak in pulmonary lobectomy. *European Journal of Cardio-Thoracic Surgery*. 2005;27(2):329-333.

6. Mueller MR, Marzluf BA. The anticipation and management of air leaks and residual spaces post lung resection. *Journal of thoracic disease*. 2014;6(3):271.
7. Cheng HS, Lo YT, Miu FP, So LK, Yam LY. Prevalence, risk factors, and recurrence risk of persistent air leak in patients with secondary spontaneous pneumothorax. *European Clinical Respiratory Journal*. 2023;10(1):2168345.
8. Pischik VG, Maslak OS, Osborne AD, Zinchenko EI, Kovalenko AI. Risk factors and outcomes of prolonged air leak after pulmonary resections. *Indian Journal of Thoracic and Cardiovascular Surgery*. 2019;35:564-568.
9. Wong J, Dincer HE. Challenges in the treatment of persistent air leak. *Current Challenges in Thoracic Surgery*. 2025;7.
10. Qiang Cao G, Kang J, Wang F, Wang H. Intrapleural instillation of autologous blood for persistent air leak in spontaneous pneumothorax in patients with advanced chronic obstructive pulmonary disease. *The Annals of thoracic surgery*. 2012;93(5):1652-1657.
11. Trivedi SB, Niemeyer M. Treating recurrent Pleural Disease: A review of indications and Technique for Chemical Pleurodesis for the Interventional Radiologist. In *Seminars in interventional radiology* 2022;39(03):275-284.
12. Keerattichananont W, Kaewdech A, Keerattichananont S. Efficacy and safety profile of autologous blood versus talc pleurodesis for malignant pleural effusion: A randomized controlled trial. *Therapeutic Advances in Respiratory Disease*. 2018;12:1753466618816625.
13. North Tees and Hartlepool NHS Foundation Trust. Autologous Blood Patch Treatment for Pneumothorax With a Persistent Air Leak. University Hospital of North Tees. 2024.  
<https://www.nth.nhs.uk/resources/autologous-blood-patch-treatment-for-pneumothorax-with-a-persistent-air-leak>.
14. Shakir S, Choo-Kang B, Ross C, Conroy K, Thorley R, Walker S, Bhatnagar R, Aujayeb A. Autologous blood patch pleurodesis for secondary spontaneous pneumothorax: A narrative review, a retrospective case series and state of play in the UK. *Pulmonary Therapy*. 2023;9(1):165-172.
15. Adeyinka A, Pierre L. Air leak. *StatPearls*. 2025.
16. Louw EH, Shaw JA, Koegelenberg CF. New insights into spontaneous pneumothorax: A review. *African Journal of Thoracic and Critical Care Medicine*. 2021;27(1):18-22.
17. Ma Q, Tarabrin EA, Berikkhanov ZG, Ivanova MY. Risk factors and clinical impact of prolonged air leak following video-assisted thoracoscopic surgery: A retrospective cohort study. *Frontiers in Medicine*. 2025;12:1549765.
18. Drewbrook C, Das S, Mousadoust D, Mousadoust D, Mousadoust D, Nasir B, Yee J, McGuire A. Incidence risk and independent predictors of prolonged air leak in 269 consecutive pulmonary resection patients over nine months: A single-center retrospective cohort study. *Open Journal of Thoracic Surgery*. 2016;6(04):33.
19. Shen KR, Cerfolio RJ. Decision making in the management of secondary spontaneous pneumothorax in patients with severe emphysema. *Thoracic surgery clinics*. 2009;19(2):233-238.
20. Lazarus DR, Casal RF. Persistent air leaks: A review with an emphasis on bronchoscopic management. *Journal of thoracic disease*. 2017;9(11):4660.
21. Cerfolio RJ, Bass CS, Pask AH, Katholi CR. Predictors and treatment of persistent air leaks. *The Annals of thoracic surgery*. 2002;73(6):1727-1731.
22. Apilio ullah B, Dumanl A, Ceran S. Application of autologous blood patch in patients with non-expanded lungs and persistent air leak. *Turkish Journal of Thoracic and Cardiovascular Surgery*. 2020;28(3):521.
23. Ibrahim IM, Abd Elaziz ME, El-Hag-Aly MA. Early autologous blood-patch pleurodesis versus conservative management for treatment of secondary spontaneous pneumothorax. *The Thoracic and Cardiovascular Surgeon*. 2019 ;67(03):222-226.