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ORIGINAL ARTICLE

COMPREHENSIVE CLINICO-DEMOGRAPHIC ANALYSIS OF MALIGNANT PLEURAL EFFUSIONS IN THE BULGARIAN POPULATION: INSIGHTS FROM AN OBSERVATIONAL CASE-CONTROL STUDY

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Abstract. *Malignant pleural effusions represent a significant problem both from a clinical perspective and from a socioeconomic standpoint. They constitute a substantial burden on the healthcare system. Affecting approximately 1 million people each year, malignant pleural effusions are a leading cause of debilitating dyspnea and decreased quality of life for many patients. Distant metastasis to the pleural layers is one of the most common complications in many malignancies, with approximately 20% of cancer patients experiencing pleural effusions during treatment. The average survival after diagnosis varies between 4 and 9 months, depending on the type and stage of neoplasm. This underscores the necessity for proper understanding of this pathology and the development of an appropriate diagnostic and therapeutic algorithm to address its consequences. To clarify the clinico-demographic aspects of malignant pleural effusions, we carried out a one-year case-control observational study, which included patients of varying ages, clinical manifestations and primary etiologies. A total of 151 patients were included in the analysis. The control group consisted of 72 patients, all of whom were diagnosed with benign disease, confirmed by subsequent biopsy. Of these, 38 cases were confirmed as inflammatory, and 34 were verified as pleural effusions of non-inflammatory origin. Malignant pleural involvement was confirmed in 79 patients. These two groups are representative of the main types of pleural pathology. We aimed to define the main characteristics of pleural malignancies and correctly recognize patients at risk.*

Key words: *malignant pleural effusion, pleural carcinomatosis, hydrothorax, demographic, clinical manifestation*

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INTRODUCTION

To delve into the pathophysiological mechanisms underlying the development of hydrothorax, we must first understand how a pleural effusion is formed, thereby gaining a better understanding of the consequent symptoms. Any disturbance of pleural fluid accumulation or clearance leads to fluid retention in the pleural cavity. In cases of congestive heart failure, the increased hydrostatic pressure leads to fluid filtration through the vascular wall, causing the transudation of fluid between the two pleural layers [1-2]. Respectively, a reduction in endovascular oncotic pressure may contribute to the inability to retain fluid within the vasculature, leading to its accumulation in the pleural cavity. One such cause is decreased plasma protein content, specifically albumin, in liver cirrhosis, where albumin plays a critical role in maintaining oncotic pressure and homeostasis.

Increased vascular permeability is significant in infectious diseases of the lung. Increased vascular permeability, resulting from the toxic effects of certain endotoxins, may occur when the compliance of the extracellular matrix is altered. It then becomes rigid, and endogenous lysyl oxidase activity, a key damaging mediator in vascular permeability disturbances, increases.

Impaired lymphatic drainage through the mediastinal lymph nodes or the thoracic duct is another cause of fluid stasis, leading to increased hydrostatic pressure and the formation of a pleural effusion.

Malignant pleural diseases, such as pleural mesothelioma and pleural carcinomatosis, are classified as combined pathologies and require complex treatment. On the one hand, morphological changes in the pleural layers hinder pleural fluid drainage, while on the other, neoplasms disrupt vascular permeability through various damaging mediators, creating a predisposition to pleural effusions. Additionally, cancer patients are often cachectic, and malnutrition further contributes to decreased oncotic pressure.

The clinical presentation of hydrothorax varies and is largely dependent on the underlying disease. A detailed medical history is crucial in uncovering the etiopathogenesis of the pleural effusion. The patient should be questioned about any past pulmonary infections, which would direct the diagnostic process toward parapneumonic pleural effusion. If the patient reports ongoing episodes of fever, this suggests the presence of an active infection. Comorbidities such as congestive heart failure, renal impairment, or liver cirrhosis may indicate a transudative nature of the pleural effusion. A history of wasting syndrome, paraneoplastic syndrome, and severe dyspnea with minimal physical exertion, coupled with a confirmed neoplasm, point towards a malignant etiology of the effusion.

The patient should be thoroughly questioned about occupational and environmental hazards, with particular attention to smoking history (measured in pack-years) and potential asbestos exposure, which is linked to the development of pleural mesothelioma. Recent alcohol abuse, ingestion of corrosive agents, or episodes of forceful vomiting raise the likelihood of pleural effusion due to esophageal rupture. A history of chest trauma followed by the sudden appearance of fluid in the pleural cavity is indicative of a hemothorax, supported by the fact that a rib fracture can result in a blood loss of 120-150 mL.

The presence of pleural effusion alongside ascites is observed in severe peritoneal carcinomatosis and Meigs syndrome. If hydrothorax is accompanied by symmetrical edema of the lower extremities, a cardiogenic pleural effusion is suspected. Unilateral edema, along with a history of varicose veins, limb pain, and dyspnea at rest, raises suspicion of hydrothorax caused by pulmonary thromboembolism. If the patients have undergone a coronary intervention within the past three weeks, they are at risk for developing pleural effusion, as is the case with exposure to certain medications like amiodarone [3-7].

MATERIALS AND METHODS

To achieve the stated goals and objectives, a cross-sectional, observational case-control study was conducted in a Bulgarian population of patients with pleural effusions.

The screened male and female participants for this study were recruited from patients hospitalized at the Department of Thoracic Surgery at UMHAT “Kaspela”.

The choice of statistical methods was made in accordance with the objectives of the study, the type of variables, and established practices in scientific research in the field of thoracic surgery. The systematization, processing, and analysis of primary data were carried out using the IBM SPSS Statistics software package. The analysis and conclusions from the study were derived from a summarized presentation of the empirical results in tabular form, accompanied by corresponding graphs. The graphical analysis was conducted using MS Office 365. To clarify the results of the conducted analyses, the following statistical-mathematical methods were used:

Pearson's Chi-Square Test: A non-parametric statistical analysis used to measure the differences between observed and expected frequencies in categorical data.

Mann-Whitney Wilcoxon Test: A non-parametric statistical analysis used to compare two independent groups. It aims to determine whether the distributions of the two populations differ significantly from one another.

RESULTS

Between March 2023 and April 2024, 151 patients with pleural effusions were studied. For the purposes of this study, the patients were divided into two groups: the first group consisted of 79 patients with a histologically confirmed malignant pleural effusion, and the second group consisted of 72 patients with a confirmed non-malignant hydrothorax. The second group was further subdivided into 38 patients with inflammatory pleural effusions and 34 with non-inflammatory pleural effusions, based on surgical biopsy results and the clinical presentation of the disease.

Data from 91 men (60.3%) and 60 women (39.7%) were analyzed (Figure 1). It was found that in the malignant group, 51.8% (N=41) of patients were female, while 48.2% (N=38) were male. In comparison, in the non-malignant group, this distribution was 26.39% (N=19) females and 73.1% (N=53) males. Using Pearson's Chi-Square Test, a statistically significant difference was observed between the malignant and non-malignant groups (p=0.001, X^2=10.237a) (Table 1).

The age of the studied patients varied greatly, with a mean age of 67.5 (Figure 2). The mean age in the malignant group was 70.5 years, while in the non-malignant group, it was 82 years. The youngest patient was 30 years old, and the oldest was 88. The most affected age group was 71-80 years, with the least affected being 30-40 years. According to the Mann-Whitney test, there was no statistically significant difference between the age groups (p=0.094) (Table 2).

Table 1. The results of several Chi-Square tests used to assess the relationship between our two groups. The Pearson Chi-Square and Likelihood Ratio tests yielded significant values ($p < 0.01$), indicating a strong association. The Continuity Correction is used to adjust for continuity in small samples. Fisher's Exact Test confirms significance in cases where expected counts are low. The Linear-by-Linear Association test further supports a trend between variables. Degrees of freedom (df) = 1 in each case

Chi-Square Tests					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	10.237[a]	1	0.001		
Continuity Correction[b]	9.199	1	0.002		
Likelihooc Ratio		1	0.001		
Fisher's Exact Test				0.002	0.001
Linear-by-Linear Association	10.169	1	0.001		
N of Valid Cases	151				

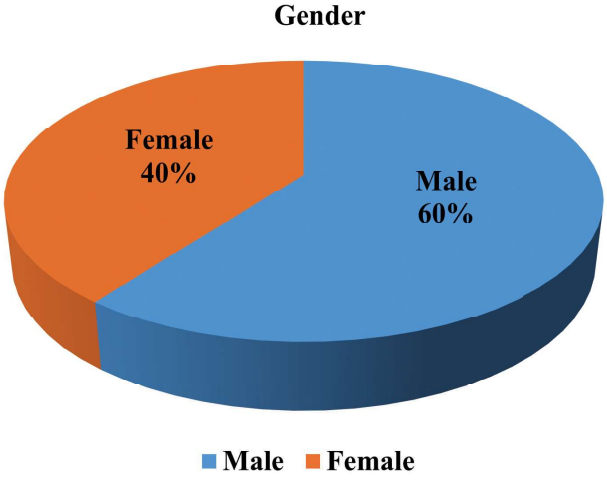

Fig. 1. Distribution of groups by gender

Table 2. A Mann–Whitney U test was conducted to compare age between the two groups. The results showed no significant difference, U = 2402.50, Z = -1.646, p = 0.100 (2-tailed). The Wilcoxon W value (5562.50) represents the rank sum for one group. These results suggest that age distributions are similar between the groups

	Year
Mann-Whitney U	2402.500
Wilcoxon W	5562.500
Z	-1.646
Asymp. Sig. (2-tailed)	0.100

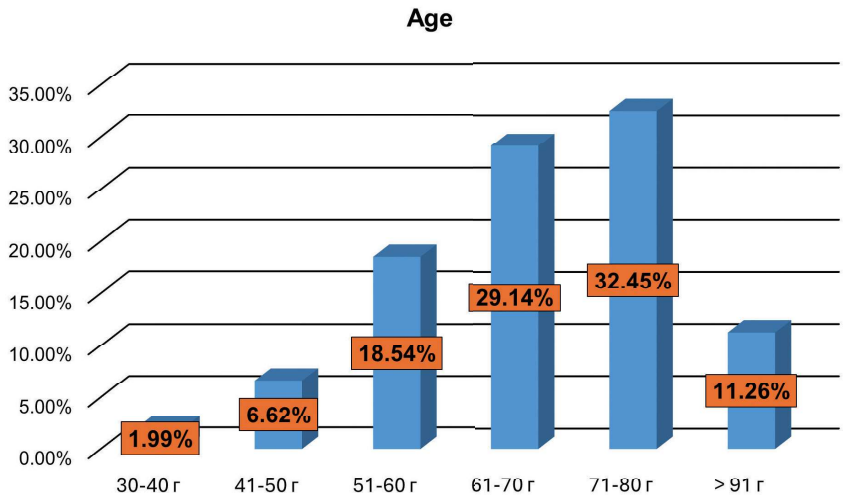

Fig. 2. Distribution of groups by age

Among the studied patients, 72 cases (47.7%) of pleural effusion were not associated with a malignant condition (Figure 3). In contrast, 45 patients (29.8%) had a history of known oncological disease. Interestingly, in 34 patients (22.5%), malignant pleural effusion was the first manifestation of a previously undiagnosed cancer.

Analyzing the affected side of the thoracic cavity, it was observed that in 53.64% of cases, the left hemithorax was involved (Figure 4). Right-sided effusions were observed in 31.79% of cases, and bilateral pleural effusions were seen in 13.57% of patients. Among patients in the non-malignant group, left-sided involvement was seen in 38.9% of cases, right-sided in 38.9%, and both hemithoraces were diseased in 22.2%. In the malignant group, malignant pleural effusions predominantly affected the left side in 67.1% of cases (N=53), the right side in 25.3% (N=20), and both sides in 7.6% (N=6). Applying Pearson's chi-squared test, a statistically significant difference was observed between the groups (X^2=13.299a; p=0.001) (Table 3).

Based on the clinical presentation, we can observe the distribution of patients shown in Figure 5. Further breaking down this analysis, 63.3% (N=50) of cases with malignant pleural effusion exhibited clinical symp-

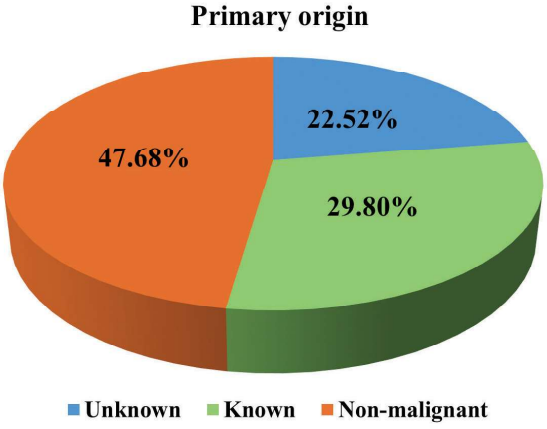

Fig. 3. Patient distribution according to primary site of origin

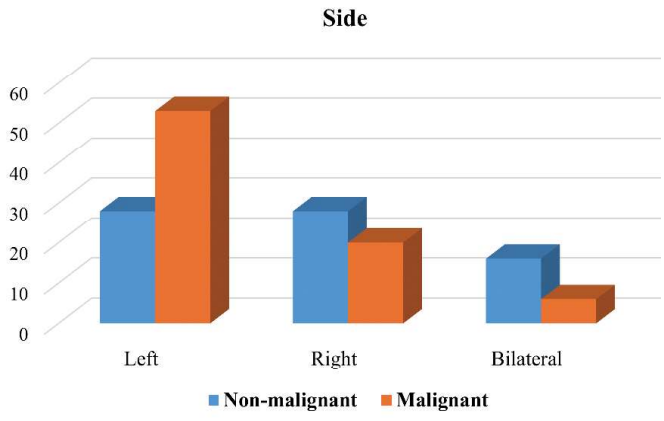

Fig. 4. Distribution of Groups by Affected Side

Table 3. A Chi-Square analysis was conducted to examine the association between our two groups. The Pearson Chi-Square test was significant, $\chi^2(2) = 13.299$, $p = 0.001$, suggesting a meaningful relationship. This finding was supported by the Likelihood Ratio test, $\chi^2(2) = 13.575$, $p = 0.001$. A significant Linear-by-Linear Association, $\chi^2(1) = 12.963$, $p < 0.001$, indicates a possible ordinal trend between the variables. The analysis included 151 valid cases

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	13.299[a]	2	0.001
Likelihooc Ratio	13,575	2	0.001
Linear-by-Linear Association	12,963	1	0.000
N of Valid Cases	151		

toms, compared to 78.8% (N=30) with inflammatory pleural effusion and 64.7% (N=22) with non-inflammatory pleural effusion. Pearson's Chi-Square test showed no statistically significant difference between the compared groups (p=0.242; X^2=1.371a) (Table 4).

Furthermore, we classified patients based on their primary oncological disease. Of the 79 malignant pleural effusions with histologically verified pleural carcinomatosis, the distribution was analyzed based on histological type (Figure 6).

The largest group consisted of patients with metastatic lung carcinoma (N=31), followed by women with confirmed breast carcinoma (N=17). Clear cell renal carcinoma accounted for the third-largest group (N=6), followed by endometrial carcinoma (N=5) and ovarian carcinoma (N=5). Colorectal carcinoma was the most common metastatic carcinoma among gastrointestinal malignancies (N=4), followed by gastric carcinoma (N=2) and pancreatic carcinoma (N=2). Mesothelioma was diagnosed in 2 patients. There was also 1 patient, each with metastatic urothelial carcinoma, testicular carcinoma, sarcoma, and chronic lymphocytic leukemia invading the pleura.

DISCUSSION

1. Gender

Analyzing the results of the distribution of pleural effusions by gender, we can conclude that the per-

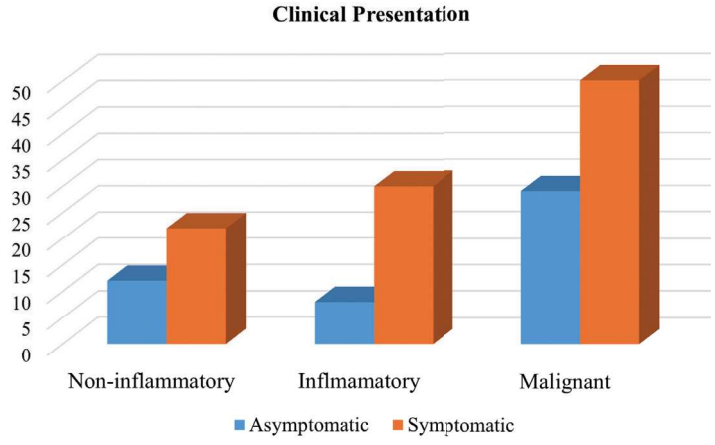

Fig. 5. Symptom Distribution Across Groups

Table 4. Pearson's Chi-Square Test applied for clinical manifestation

Chi-Square Tests					
	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.371[a]	1	0.242		
Continuity Correction[b]	0.994	1	0.319		
Likelihooc Ratio	1.377	1	0.241		
Fisher's Exact Test				0.297	0.159
Linear-by-Linear Association	1.362	1	0.243		
N of Valid Cases	151				

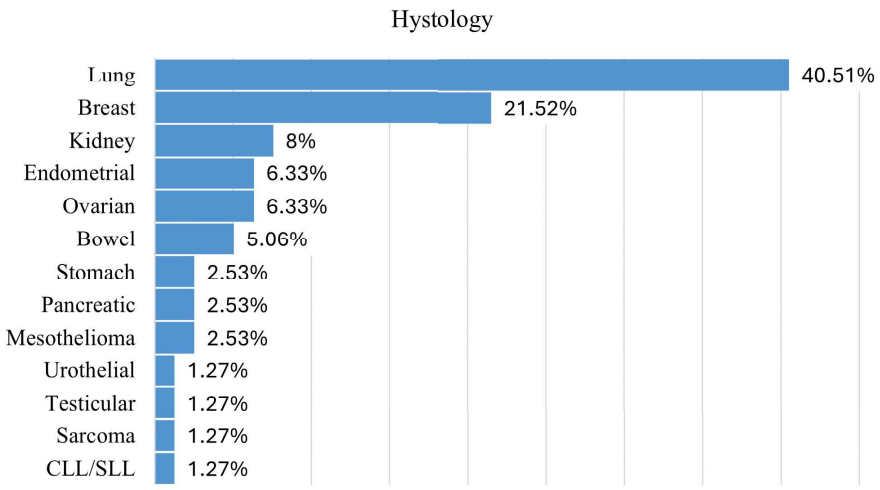

Fig. 6. Distribution of Groups by Histological Type

centage of men is significantly higher compared to women (N=90/N=41). In the non-malignant group, 73.1% (N=53) of the patients were men, and 26.39% (N=19) were women. On the other hand, malignant pleural effusions seem to show a predilection to the female gender (p=0.001). In the malignant group, 51.8% (N=41) of the patients were women, and 48.2% (N=38) were men. This may be related to the fact that a significant percentage of secondary malignant diseases of the pleura result from malignant diseases of the female reproductive system [8].

In support of this hypothesis, we present a study conducted by Foote [9]. In his work, he observed 686 patients with malignant pleural effusions, 281 (41%) of whom were men. He found that women were more at risk, reporting 405 (59%) affected women, with 351 of them having a verified non-gynecological cancer (p=0.0049). These gender differences persist even after eliminating factors such as comorbidities (p = 0.0017). Furthermore, women showed better survival outcomes (p=0.0004).

2. Age

When we distributed the studied patients by gender, we noticed that the most vulnerable group in our sample were patients between 71 and 80 years of age. However, this did not result in a statistically significant difference between the malignant and non-malignant groups. Warnisher et al. [10] present a similar study investigating 241 men and 161 women with malignant pleural effusions. They found that patients around 70 years old were the most affected, which is consistent with our data. The most common cause of malignant pleural effusions in their sample was adenocarcinoma, but they did not find a statistically significant difference between age groups.

3. Oncological History

Of all the patients we observed, 29.8% (N=45) of those with malignant pleural effusions reported a known oncological disease, which had been verified histologically. Meanwhile, 22.5% (N=34) of the patients were admitted with a confirmed pleural effusion and were later diagnosed with secondary pleural malignancy without having a known cancer. Looking at global data, we found an analysis conducted by Fashoyin-Aje et al. [11], who estimated that in 30% of patients, symptoms related to pleural effusion were the first sign of malignancy. Furthermore, approximately 7-10% of malignant pleural effusions are caused by neoplasms of unknown primary origin (UPO).

4. Affected Side

According to our analysis, we observed a statistically significant difference between the malignant and non-malignant groups in relation to the affected hemithorax. In 67.1% (N=53) of patients with malignant pleural effusions, it was left-sided. Therefore, we can hypothesize that pleural carcinomatosis occurs more often on the left side. Global literature provides evidence suggesting that the side on which hydrothorax occurs is largely determined by the primary disease. Banarjee et al. [12] stated that in patients with breast cancer, 70% of pleural effusions occur on the same side as the affected breast, 20% on the contralateral side, and 10% bilaterally. In our observations, lung carcinoma also predominantly affects the pleura on the same side before metastasizing to the opposite side. The occurrence of non-malignant pleural effusions depends on the pathogenesis and mechanism of occurrence. Cardiogenic pleural effusions are the most common and are often bilateral or right-sided [13]. This is related to increased pressure and right-sided congestion. Additionally, several anatomical factors exist. While the thoracic duct drains most of the body's lymphatic fluid, the right lymphatic duct drains the right side of the face and neck, part of the right hemithorax, the right shoulder, and the right arm [14]. Its smaller diameter is a reason why, under increased venous pressure, lymphatic drainage into the venous circulation is impaired. This ultimately leads to the accumulation of pleural fluid in the right hemithorax. We also hypothesize that the position of the heart and most of the mediastinum in the left hemithorax, leading to a reduced pleural sur-

face area on that side, as well as the position and dynamics of the diaphragm, may be potential causes for changes in hydrostatic pressure and occurrence of cardiogenic effusion on the opposite side.

5. Symptoms

According to our observations, the highest percentage of asymptomatic cases were in the malignant group (36.7%). They are diagnosed incidentally during routine check-ups or re-staging imaging. Non-malignant effusions presented with symptoms in 64.7% of cases, while inflammatory effusions in 78.8% of cases. The most common symptoms we observed were dyspnea during physical exertion and cough with white or clear expectoration. Patients also reported pain in the affected side. Despite our data, we did not find a statistically significant difference between the sample groups, and therefore, we cannot conclude that the clinical presentation can classify malignant and non-malignant pleural effusions.

6. Histology

When analyzing malignant pleural effusions by histology on pleural biopsy, we conclude that lung carcinoma is the leading cause of pleural carcinomatosis in 40.51% (N=31) of the patients. Breast carcinoma is the second most common tumor metastasizing to the pleura in 21.51% (N=17). This correlates with data from other studies on similar issues [15]. A study conducted by Migliore et al. [16] provides data on pleural involvement in extrathoracic tumors. He states that 40% of the patients had primary lung carcinoma. In 25% of cases, it was due to breast carcinoma, followed by lymphoma in 10% of patients. The remaining cases were secondary malignant pleural tumors originating from the ovary (5%), gastrointestinal tract (5%), and unknown primary origin (5%). His study confirms that among extrathoracic tumors, breast carcinoma (39.1%) is the most common cause of pleural metastases.

CONCLUSION

This observational case-control study provides significant insights into the clinico-demographic characteristics of malignant pleural effusions in the Bulgarian population. The findings highlight the critical importance of recognizing malignant pleural effusions as a substantial clinical challenge that not only affects patients' quality of life but also poses a considerable burden on the healthcare system.

Our findings advocate for the development of more effective diagnostic and therapeutic algorithms tailored to malignant pleural effusions, thereby enabling clinicians to address the complexities of this condition more effectively. Future studies should continue to explore the multifactorial aspects of pleural effusions, integrating larger sample sizes and diverse populations to enhance the generalizability of the results.

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Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

Informed Consent from Participants: *Informed consent was obtained from all participants included in the study.*

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