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The relationship of lactate dehydrogenase, pH, glucose and protein pleural fluids with one year life of patients with non-small cell lung carcinoma with malignant pleural effusion in Prof. Dr IGNG Ngoerah Denpasar

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***Abstract*---**Malignant pleural effusion (MPE) is one of the most common metastases in Non-Small Cell Lung Carcinoma (NSCLC). Some part of the pleural fluid analysis affects the patient's survival. A retrospective cohort study using medical record data of 76 patients was done in Prof. Dr. IGNG Ngoerah General Hospital. The one-year survival was 36.6%, with a median survival of 240 days or 8 months (95% CI 110.94–369.05). The cut-off point for pleural fluid protein was 5 g/dL (sensitivity 33.3%, specificity 32.1%), glucose 47.5 mg/dL (sensitivity 81.3%, specificity 32.1%), lactate dehydrogenase (LDH) 978.5 IU/L (sensitivity 41.7%, specificity 46.4%) and pH 7.3 (sensitivity 62.5%, specificity 35.7%). Bivariate analysis showed that only protein was associated with survival. Protein < 5 g/dL had a median survival of 116 days (95% CI 67.96 – 164.05, p = 0.001). Multivariate analysis showed pleural fluid protein < 5gr dL, best supportive care therapy, and non-adenocarcinoma histology were independent risk factors for death {HR 2,345,95% CI: 1,055-5,214; p= 0.037; HR 5,332. 95% CI: 2.109 – 13.478; p = 0.000; HR 2,635, 95% CI 1,096 – 6,335; p = 0.30). There is a relationship between pleural fluid protein and one-year survival of NSCLC patients with MPE, so it is hoped that pleural fluid protein can be used as one of the considerations in estimating survival and patient management.

***Keywords*---**Pleural effusion, LDH, pH, Protein, Glucose, Survival.

Introduction

Primary lung cancer is cancer or malignant cells originating from the airway epithelium (Zaini et al., 2018). Lung cancer is the leading cause of death from cancer in America. In 2019 there were an estimated 228,150 new cases with an estimated lung cancer mortality rate of 142,670 deaths, and only 18% of patients with lung cancer can survive five years after being diagnosed(NCCN, 2019). Data from the Dharmais Cancer Hospital show that lung cancer consistently ranks third most common after breast and cervical cancer. The incidence also increased by 45% in 3 years, with a mortality rate of 32% in 2010 and 37.5% in 2013 (Ministry of Health Data and Information Center, 2015).

A high LDH value indicates that there has been an extensive inflammatory process, there is acute inflammation, necrosis, and cell death in the pleural cavity so that the LDH value of pleural fluid can be used to assess the severity of damage due to tumor cell infiltration in the pleural cavity. A high pleural LDH

(>1500IU/L) predicts shorter survival (less than one year) in patients with lung adenocarcinoma with MPE at initial diagnosis (Verma et al., 2016).

Pleural fluid hypoprotein status is divided into patients who experience pleural fluid hypo protein and do not experience pleural fluid hypo protein. It is called pleural fluid hypo protein if the pleural fluid protein level is <3,600 ml/dL. Patients who died were dominated by patients with pleural fluid hypo protein (72.7%) than patients who lived (13.0%) (Bielsa, 2008). These results are consistent with the study of Abrao et al., which stated that pleural fluid protein levels of less than 3.6 g/dL were associated with high mortality in MPE patients (Abrao et al., 2015).

Low glucose levels in MPE are associated with impaired glucose transport from the blood to the pleural fluid. Increased use of glucose by tumors in the pleura may also cause low glucose levels (Good, 2005). Other investigators also showed that the glucose concentration and low pH in Pleural effusion predict shorter survival and less successful pleurodesis (Edward, 2008).

A decrease in the pH of the pleural fluid occurs due to an increase in intrapleural cellular metabolic activity or an abnormality of the pleural membrane, which inhibits the release of protons and organic acids from the pleural cavity into the circulation (Steven et al., 2008). A low pleural fluid pH can be used as a marker of increased intrapleural tumor metabolic activity. Several studies have reported that the pH value of pleural fluid in malignancy is related to life expectancy. Sahn and Good said that patients with a pleural fluid pH < 7.30 had a shorter life expectancy when compared to patients with a pleural fluid pH ≥ 7.30 (Heffner et al., 2000)

Researchers wanted to know the relationship between LDH, pH, glucose, and pleural fluid protein parameters and the survival of NSCLC patients with MPE. This research is expected to be a reference for determining the best therapeutic options. In addition, the results of the study are expected to form the basis for developing a scoring system to predict patient survival. Moreover, studies on the relationship between pleural fluid analysis levels as a prognostic factor in patients with advanced lung cancer are still limited.

Method

This study is an observational analytic study using a retrospective cohort design. This study was initiated by assessing the levels of LDH, pH, glucose and protein in the pleural fluid when the diagnosis of NSCLC with malignant pleural effusion was made. Furthermore, after the diagnosis, follow-up or survival observation were carried out for one year since January 2018. Overall variable assessment and follow-up for one year using medical records from Dr. IGNG Ngoerah Hospital Denpasar analysis with ROC, Kaplan Meier, log-rank test, and a Cox regression model were performed.

This study was approved by the Udayana University ethical committee. All patients aged over 18 years who were diagnosed with Lung Cancer Non-Small Cell Carcinoma with malignant pleural effusion and treated at Prof. Dr IGNG Ngoerah

Denpasar Bali since January 2018 were included. Exclusion criteria: (1) Incomplete or missing medical records, (2)Have a primary malignancy other than lung cancer, (3) Infectious diseases, namely bacterial pneumonia, pulmonary tuberculosis or the discovery of bacteria in pleural fluid cultures, (4) Comorbid diseases such as congestive heart failure, kidney failure, diabetes mellitus and hepatic cirrhosis.

Cancer therapy is defined as using tyrosine kinase inhibitors (TKI) for more than one month, or undergoing at least 2 cycles of chemotherapy, or receiving only the best supportive care. Multisite metastases were defined as metastases in 2 or more organs other than the brain. All patients were diagnosed with brain metastases based on imaging, such as MRI or Brain CT Scan.

Results and Discussion

A total of 76 patient were included I this study, subjects diagnosed with NSCLC with MPE who received services at Prof. Dr. IGNG Ngoerah Denpasar Bali from January 2018. The sociodemographic and clinical characteristics of the subjects can be seen in table 1, and table 2.

Table 1
Sociodemographic Characteristics of NSCLC Patients with MPE

Characteristics	Frequency (n = 76)	Per cent %
Gender		
Man	32	42,1
Woman	44	57,9
Age (years)a mean ± SB	60.45±12.60	
< 65 years	47	61.8
≥ 65 Years	29	38,2
Regency		
Badung	11	14.5
Bangli	3	3,9
Buleleng	8	10.5
Denpasar	17	22,4
Gianyar	9	11,8
Karangasem	9	11,8
Klungkung	3	3,9
Negara	6	7,9
Tabanan	4	5,3
NTB	4	5,3
Central Sulawesi	1	1,3
North Sumatra	1	1,3
Education		
No education	12	15,8
Elementary school	19	25.0
Junior high school	4	5,3
Senior High School	27	35.5
College	14	18,4

Occupation		
Government employees	12	15,8
Entrepreneur	16	21.0
Farmer	21	27,6
Private sector employee	10	13,2
Housewife	17	22,4
Smoking history		
Yes	28	36,8
Not	48	63,2
History of family with cancer		
Yes	5	6,6
Not	71	93.4

Table 2
Clinical Characteristics of NSCLC Patients with MPE

Characteristics	Frequency (n = 76)	Per cent %
Body Mass Index		
Underweight	32	42,1
Normal	35	46,1
Overweight	6	7,9
Obesity	3	3,9
ECOG		
ECOG 1	2	2,6
ECOG 2	48	63,2
ECOG 3	24	31,6
ECOG 4	2	2,6
Histology		
Adenocarcinoma	65	85.5
SCC	8	10.5
Large cell carcinoma	1	1.3
Another type	2	2,6
Cancer treatment		
TKI	32	42,1
Chemotherapy	26	34,2
BSC	18	23,7
Multi site		
Yes	7	9,2
Not	69	90.8
Brain metastases		
Yes	13	17,1
Not	63	82.9
Die		
Yes	48	63,2
Not	28	36,8

Information: ECOG (Eastern Cooperative Oncology Group), DM (Diabetes Mellitus, COPD (Chronic Obstructive Pulmonary Disease), SCC (Squamous Cell Carcinoma) TKI (Tyrosine Kinase Inhibitor), BSC (Best Supportive Care)

Lung cancer is the most common cause of malignant pleural effusion (MPE) and accounts for approximately 40% of all cases. Approximately 8-20% of lung cancer patients have malignant pleural effusion. Malignant pleural effusion is known to reduce the survival of cancer patients(Porcel et al., 2015; Shojaee et al., 2019). Previous studies have shown that the average survival in patients with MPE associated with lung cancer is 3-4 months and can increase to 13 months in patients with better conditions.(Kasapoglu, et al., 2016; Morgensztern, et al., 2012; NCCN, 2019).

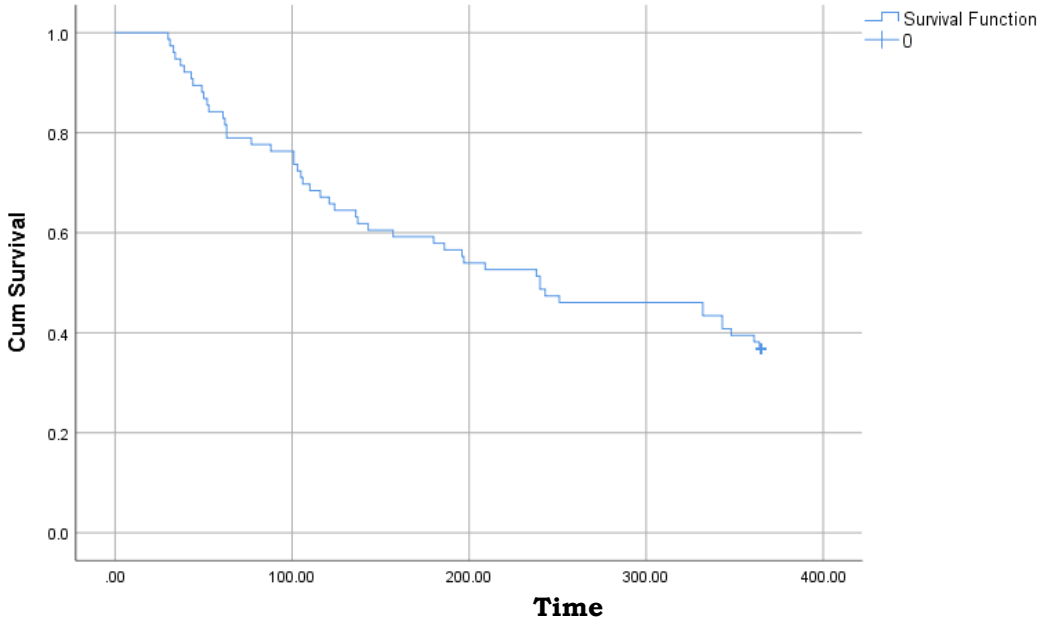

Figure 1. Kaplan Meier curve for survival analysis of NSCLC with MPE patients

In this study, the median survival was 240 days or 8 months (95% CI 110.94 – 369.05), and the one year survival is 36,6% in NSCLC patients with MPE at Prof. Dr IGNG Ngoerah Denpasar, which in the Kaplan Meier curve (Figure 1). These results are not much different from the study by Kasapoglu et al. (2016), NSCLC patients with MPE obtained a median survival of 6 months and a 1-year survival rate of 27.1%. In addition, a retrospective study by Sugiura et al. (1997) in Nagoya, Japan, also concluded that there is a difference in survival between advanced lung cancer patients with and without pleural effusion. The median longevity of lung cancer patients with effusion was 7.5 months and 5.5 months without effusion.(Froudarakis et al., 2012; Wang, et al., 2010).

In this study, a total sample of 76 people was obtained. The number of male samples was 32 people (42.1%), with a female sample of 44 people (57.9%). This is consistent with a retrospective cohort study with an observational-analytic nature that examined lung cancer patients with malignant pleural effusion at Dr. Hasan Sadikin in 2018 and found that the majority of the female sex was 82.4% (Hendro et al., 2019). There is a worldwide trend of increased lung cancer incidence and mortality in women, which has been reported in many studies. This was

attributed to the progressive increase in smoking among women, which began during the second world war. The study's results were compared with men and adjusted for the smoking burden; women are twice as likely to develop lung cancer. In addition to hormonal characteristics, there are molecular differences, differences in DNA damage repair, growth factor receptors, and cytochrome P450 enzymes in women at risk for lung cancer. Several genetic mutations were found to be more prevalent in women who smoke, including overexpression of the CYP1A1 gene (Cytochrome P450 Family 1 Subfamily A Member 1), mutation of glutathione S-transferase Enzyme M1, mutation of the tumor suppressor gene p53, and overexpression of X-linked gastrin-releasing peptide. Receptors that may influence the development of lung cancer in women. Women also had a higher family risk of developing lung cancer, even after adjusting for smoking status (Rodriguez et al., 2012)

The age group in this study was < 65 years, namely 47 people (61.8%), with a group of ≥ 65 years of 29 people (38.2%). This is by previous NSCLC research at Prof. Hospital. Dr. IGNG Ngoerah found patients aged <65 years in 71 samples (74%) (Andikayasa et al., 2021). This is also in line with the study of KPKBKSK patients with MPE at RSUP Dr. Kariadi Semarang. Most of the research subjects were <60 years old, 62 people (75.6%) and > 60 years, 20 people (24.4.%) (Supartono et al., 2012). More samples with age < 65 years can be caused by earlier exposure to carcinogens, such as smoking or occupational factors that increase the risk of exposure to carcinogens(Eguchi, et al., 2017; Kasapoglu et al., 2016; Wang et al., 2012). The number of cigarettes smoked per day in young subjects compared to older subjects, regardless of case-control status, was more at a young age. This was due to changes in nicotine content and filter use over the last two decades (Jemal et al., 2003). Since the 1960s, the nicotine content in the market share has decreased from 1.14 to 0.78 mg. Studies in the United States and Germany show that smokers compensate for a lower nicotine content by increasing the amount smoked and deeper inhalation. In addition, genetic predisposition combined with smoking can play a role in the occurrence of lung cancer at a young age (Kreuzer et al., 1998).

In this study, 28 people (36.8%) were smokers and the remaining 48 (63.2%) were non-smokers. This is in line with research at Prof. Hospital. Dr. IGNG Ngoerah previously found 55 people (68.8%) who did not smoke (Ekaruna et al., 2021). Even though more subjects did not smoke, passive smoking bias still could not be ruled out in this study. The study by Fleiss and Gross also showed that non-smokers exposed to tobacco smoke had a higher risk of developing lung cancer than smokers. Although tobacco smoke is the leading cause of lung cancer, environmental carcinogens, such as arsenic, asbestos and radon, air pollution, the presence of lung diseases such as chronic bronchitis, emphysema, tuberculosis, pneumonia, and asthma also play an increasingly important role in the development of malignancy, either independently or through additive or multiplicative effects (Akhtar et al., 2017).

The occupations in the most research samples were farmers, with 21 people (27.6%), and as housewives, with 17 people (22.4%). This is by research at Prof. Hospital. Previously, IGNG Ngoerah had 17 NSCLC patients (21.3%) as farmers (Ekaruna, et al., 2021). Some jobs, such as farmers dealing with pesticides, and

work dealing with solvents, or materials that can be easily inhaled, are known to increase a person's risk of developing work-related lung cancer.(Consonni, et al., 2010; Neuberger, et al., 2003).

The risk of developing lung cancer can be inherited due to genetic defects. Someone with a history of vertical heredity with lung cancer has an increased risk of developing lung cancer that is greater than those who do not. As more and more studies focus on the genome of lung cancer, especially non-small cell lung carcinoma, the understanding that this disease is heritable has deepened.(Sacher, et al., 2016). A total of 5 people (5.6%) in the study sample had genetic risk factors, while 71 people (93.4%) did not have genetic risk factors. This is also under research at Prof. Dr. I.G.N.G Ngoerah Hospital previously found that 65 people (81.2%) had no family history of cancer (Ekaruna et al., 2021). This is also by the research by Sinaga et al. (2022) in Dr H. Abdul Moeloek Hospital, Lampung Province, in 2018-2021, the results for lung cancer were not had a family history of 190 patients (77.9%) and a family history of 54 patients (22.1%). Not all lung cancers have a genetic basis because some occur sporadically or without a family history of cancer. The cancer is not caused by mutations in the germline or cancer-susceptible genes but rather due to acquired somatic genetic changes (Myrnasari et al., 2017).

Place of residence or environmental factors with high pollution is also associated with an increased incidence of lung cancer. Areas where most of the population work in the mining, plantation, industrial, or traffic-heavy sectors may experience an increased risk of lung cancer(Consonni et al., 2010; Neuberger et al., 2003). In this study, 17 people (22.4%) had their addresses in Denpasar. Denpasar City is one of the busiest city centres in Bali. The city of Denpasar is very vulnerable to environmental issues such as environmental sanitation, environmental pollution and environmental damage that disturb nature's beauty and sustainability. For Denpasar City, the primary source of air pollution is from moving pollutant sources, namely from the transportation sector, for example, motorized vehicles, followed by other pollutant sources. (Sugiarta, 2019).

In this study, the majority of the sample had a high school education (high school), 27 people (35.5%). Previous research at the Dharmais Cancer Hospital in Jakarta shows that most NSCLC patients with MPE have a high school education of 35.5% (Ramadhaniah et al., 2010). In a study conducted by Radkiewicz et al. (2019) found a relationship between a low level of education and a higher risk of lung cancer. Smoking was much more common in individuals with less than a high school education, 32.1%, compared to 9.1% among college graduates. Individuals with higher education are more likely not to start smoking and are easier to quit; smokers with low levels of education are not even likely to try to leave (Beril et al., 2013). However, this study did not draw a relationship between education level and lung cancer because it did not use a control group.

Most of the nutritional status of the study sample with normal nutrition as many as 35 people (46.1%). These results are similar to the results of previous studies at Prof. Dr. I.G.N.G Ngoerah Hospital was found in 50 people (62.5%) with normal nutritional status in NSCLC patients (Ekaruna et al., 2021). In some studies, weight loss is associated with a poorer prognosis. Weight loss is associated with a

more severe course of the disease. However, this is still contradictory in several other studies, where there was no relationship between weight loss and patient survival (Kasapoglu et al., 2016). Further studies are needed to determine whether the association between low body mass and lung cancer is due to the influence of further related factors in prospective data with repeated weight measurements in individuals over time, as well as information on smoking, diet, and other body-related factors mass index (Goodman, et al., 1992).

Performance status (PS) of the subjects in this study was mainly with an ECOG score of 2, as many as 48 people (63.2%) indicating that patients experienced a decrease in their ability to carry out their daily activities. This is by the study of NSCLC patients at Mangunkusumo Hospital and Dharmais Cancer Hospital Jakarta in January 2007-April 2013obtained the most significant sample with an ECOG score of 2, as many as 116 (50%) people (Fawziah et al., 2014). In another research study, it was stated that there was a significant negative correlation between the ECOG score and the patient's quality of life ($r = -0.71$, $p < 0.05$). PS strongly correlates with the quality of life in general, including psychological, psychological, and existing symptoms. PS is also related to the number and degree of patient complaints (Beril et al., 2013).

Guidelines for managing lung cancer in Indonesia state systemic lung cancer treatment is chemotherapy and targeted therapy. For chemotherapy, one of the principles for choosing a regimen is to use platinum-based therapy (cisplatin or carboplatin).(Syahruddin and Jusuf, 2016). In this study,58 people (76.3%) received treatment among tyrosine kinase inhibitors(TKI), as many as 32 people (42.1%) and chemotherapy platinum-based therapy as many as 26 people (34.2%). This is in line with previous research at Prof. Hospital. Dr IGNG Ngoerah, as many as 55% of the samples received systemic chemotherapy, and TKI was the most widely used treatment (Ekaruna et al., 2021). The current study shows that chemotherapy provides a significant advantage in survival in lung cancer patients. For NSCLC, chemotherapy was associated with a 0.38-fold risk of death compared to no treatment (adjusted HR = 0.38; 95% CI: 0.37 - 0.39) (Musika et al., 2021). For TKI administration, the median and 2-year progression-free survival (PFS) and overall survival (OS) rates in patients receiving targeted therapy were nearly double those obtained in patients. Finally, TKI reduces the risk of recurrence or progression, as well as the risk of death in more than 50% of NSCLC patients (Aguilar, et al., 2022).

Metastasis is the ability of cells to escape from the primary tumor and then enter the circulation to distant tissues and form secondary tumors. Metastatic cells can leave the primary tumor if they can escape, circulate, and invade. In this study, 69 samples (90.8%) of NSCLC patients with malignant pleural effusion did not have multisite metastases, seven samples (9.2%) had multisite metastases, and 13 samples (17.1%) had brain metastases. This is almost the same as my previous research on the prognostic value of metastases in NSCLC patients; it was found that 38% of patients with NSCLC had one metastasis, and only 19% had two or more metastases even in the current study, 63.8% of all cohorts showed one-site metastases (Xu et al., 2019). Previous research on KPKPBSK patients at Prof. Hospital Dr. IGNG Ngoerah also found 3.8% with brain metastases (Ekaruna et al., 2021). Lung cancer also most often metastasizes to

the brain, around 30% -60% of all brain metastases, and has a 10:1 ratio with primary brain tumors. One study found the incidence of brain metastases to be 11.1 per 100,000. The survival rate of untreated brain metastatic lung cancer patients ranges from 1-3 months. Ali et al.'s study of NSCLC patients who experienced brain metastases obtained an average survival rate of 7.8 months, whether the metastases were known from the initial diagnosis or known as the disease progressed (Febriani et al., 2018).

Among the types of non-small cell lung cancer, adenocarcinoma is the most common type causing malignant pleural effusion. The findings of this study support this: 65 people (85.5%) had an adenocarcinoma subtype, eight people (10.5%) had a squamous cell carcinoma subtype, one person (1.3%) had a giant cell subtype, and two people (2.6%) with other subtypes. This is to the results of a study at the Jakarta Darmais Cancer Hospital; the morphological types of lung cancer in the non-small cell carcinoma group with pleural effusion in that study were adenocarcinoma (73.5%), squamous cell carcinoma (19.4%) and large cell carcinoma (4.5%). In line with research at Persahabatan Hospital, the most common types of cancer cells were adenocarcinoma (90.4%), squamous cell carcinoma (6.6%), and large cell carcinoma (2.5%).

Relationship between Pleural Fluid LDH and One-Year Survival of NSCLC Patients with MPE

In this study, pleural fluid LDH levels had no association with one-year survival in non-small cell lung cancer patients with malignant pleural effusion at Prof. Dr IGNG Ngoerah Denpasar. Pleural fluid Lactate Dehydrogenase (LDH) levels obtained a cut point of 978.5 IU/ (41.7% sensitivity and 46.4% specificity) (Figure 2 and Table 3). Median survival for pleural fluid LDH levels ≥ 978.5 IU/L was 343 days (95% CI 199.27 – 486.72), longer than the median survival at < 978.5 IU/L, which was 143 days (95% CI 61.44 – 224.55) but not significant statistically (p=0.198) (Figure 3 and Table 4).

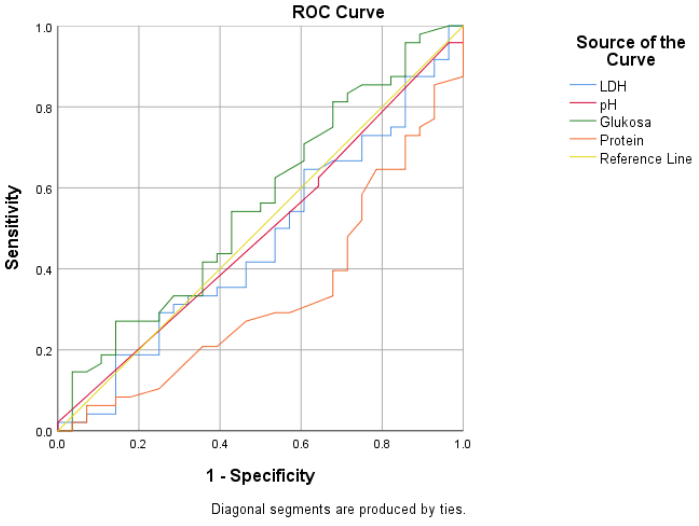

Figure 2. ROC curve

Table 3
The area under the curve (area under the curve / AUC)

	AUC	95% CI		Significance
		Lower limit	Upper limit	
Proteins	.335	.210	.461	.017
Glucose	.561	.425	.697	.377
LDH	.466	.331	.601	.624
pH	.490	.355	.624	.880

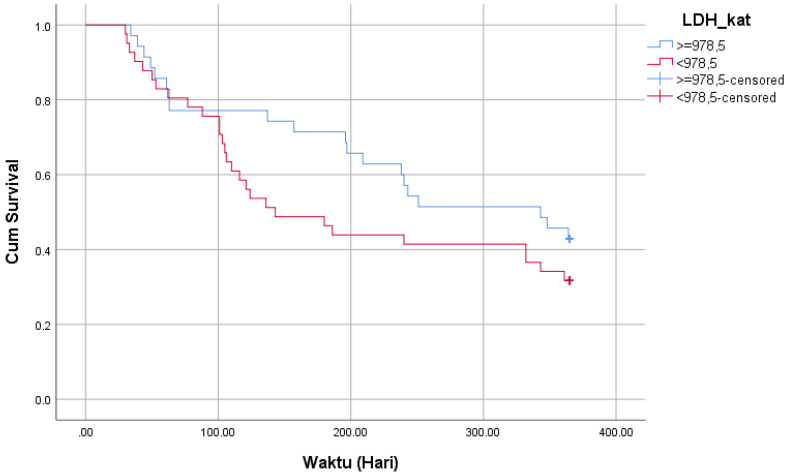

Figure 3. Kaplan Meier LDH curve pleural fluid on survival of NSCLC patients with EMP

Table 4
Mean and median LDH of pleural fluid on survival of NSCLC patients with MPE

LDH	Means	95% CI		Median	95% CI	
		Lower limit	Upper limit		Lower limit	Upper limit
≥ 978.5IU/L	251.5	208.9	294.0	343	199.2	486.7
< 978.5IU/L	207.0	165.8	248.2	143	61.4	224.5

A theoretically high pleural fluid LDH (>1500IU/L) predicts shorter survival (less than one year) in patients with lung adenocarcinoma with MPE at initial diagnosis. A high LDH value indicates that there has been an extensive inflammatory process and the presence of acute inflammation, necrosis, and cell death in the pleural cavity. Thus the LDH value of pleural fluid can be used to assess the severity of damage due to the infiltration of tumor cells in the pleural cavity. High levels of pleural LDH in the pleural space and its association with poor survival have been described in mixed cancer cohorts, although the underlying mechanisms are not fully understood. Upregulation of LDH enzymes to allow more preferential use of glycolysis rather than oxidative phosphorylation for energy by tumor cells. The high rate of glycolysis benefits growing cells by

producing adenosine triphosphate (ATP) much more rapidly than oxidative phosphorylation(Verma et al., 2016; Magy et al., 2012). There was no relationship between pleural fluid LDH and survival in this study because the obtained pleural fluid LDH cut point had a poor predictive value (ROC curve close to the diagonal line). The difference in results between this study and theory can also be explained by the low cut point value below 1500 IU/L.LDH is a marker of inflammation or cellular injury, so it is sensitive but a non-specific pathological marker. Besides that, in Vermal et al. (2016), LDH values can also be affected by therapy, i.e. EGFR-TKI, which contributes to more prolonged survival. In this study, no grouping of samples who received EGFR-TKI therapy was carried out, which could affect the study results.

Relationship between Pleural Fluid pH and One-Year Survival of NSCLC Patients with MPE

In this study, pleural fluid pH levels had no relationship with the one-year survival of NSCLC patients with MPE. The pH level in this study used a cut point value of 7.30 (sensitivity 62.5% and specificity 35.7%). Median survival pleural fluid pH level < 7.30 was 238 days (95% CI 100.58 – 375.42) which did not differ much from median survival at ≥ 7.30, namely 240 days (95% CI 62.33 – 417.66)but not statistically significant (p = 0.864) (figure 4 and table 5). Burrows et al. (2000) also found that there was no correlation between pleural fluid pH and survival with a cut point of 7.20 (HR, 95% CI0.99 0.97–1.01, p = 0.34). This study was similar with Heffner et al. (2000) that stated the pH of the pleural fluid did not have a sufficient level of accuracy or cannot be used to determine the prognosis and survival of lung cancer patients. In a study conducted by Pantazopoulos et al. (2014) also did not recommend the used of pleural fluid pH because of poor sensitivity.

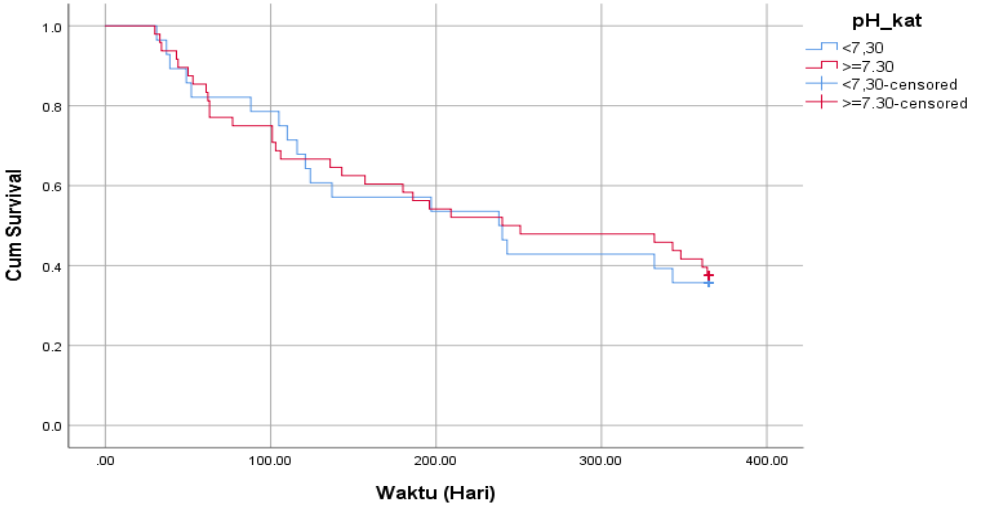

Figure 4. Kaplan Meier pH curve pleural fluid on survival of NSCLC patients with MPE

Table 5
Mean and median pH of pleural fluid on survival of NSCLC patients with MPE

pH	Means	95% CI		Median	95% CI	
		Lower limit	Upper limit		Lower limit	Upper limit
< 7.30	223.2	174.8	271.6	238	100.5	375.4
≥ 7.30	230.0	191.6	268.3	240	62.3	417.6

In some literature, the pH level of pleural fluid in MPE is low; according to Fisher's statistical test, there is a significant relationship between the pH level of pleural fluid and the high mortality rate in MPE patients. Low pleural fluid pH values can be caused by malignancy or by infection. In MPE, a low pleural fluid pH is usually associated with a significant tumor burden. The pH value of pleural fluid is affected by the balance between the production and efflux of CO2 and lactate (Hendro et al., 2019). The process of glycolysis in the pleural cavity produces CO2 and lactate, while its efflux is disturbed due to tumor invasion covering the lymphatic stoma. If the production of CO2 and lactate is normal or high, but the efflux is not disturbed, the pH value will not decrease. On the contrary, although the production is average, if the efflux is disturbed, the accumulation of CO2 and lactate will cause local acidosis or decrease the pleural fluid's pH value. Because the tumor cells cover the lymphatic stoma, the efflux will continue to be disturbed, so MPE patients will not experience improvement, resulting in high mortality (Hendro et al., 2019).

A potential explanation for this discrepancy is that in this study, the pH cut point of the pleural fluid obtained also has a poor predictive value (the ROC curve is close to the diagonal line). Furthermore, the range of pH values in the literature indicates uncertainty about what the critical value for pH is across the observed range (Burrows et al., 2000).difference in results can also be related to problems logistics or mishandling of specimens, variations in collection and analysis methods are susceptible and possible clot formation in blood gas analysis. Some centres do not even have access to blood gas analyzers to measure pH and rely on litmus paper or a pH meter, which is inaccurate (Fitzgerald et al., 2019). The measured pleural fluid pH accuracy highly depends on the sample collection method. Residual air, lidocaine, and delayed analysis significantly change pH and can impact clinical management (Rahman et a ., 2008)

Relationship of pleural fluid protein with one-year survival of NSCLC patients with MPE

Analysis of protein levels of pleural fluid found a relationship with a one-year survival of lung cancer patients with non-small cell carcinoma with malignant pleural effusion at Prof. Dr. IGNG Ngoerah Denpasar. Survival rates with protein values < 5 g/dl were lower than those with protein values ≥ 5 g/dl, with the median survival time of NSCLC patients with MPE having protein levels < 5 g/dL was 116 days (95% CI 67.96 – 164.05), and this was statistically significant (p = 0.001) (Fig. 5 and Table 6).

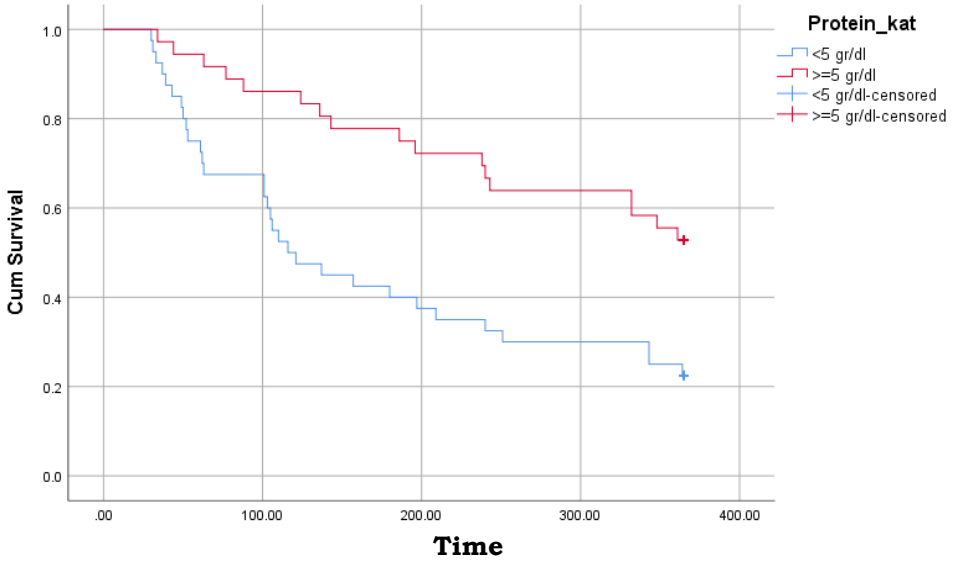

Figure 5. Kaplan Meier curve of pleural fluid protein on survival of NSCLC patients with MPE

Table 6
Mean and median pleural fluid protein on survival of NSCLC patients with MPE

Proteins	Means	95% CI		Median	95% CI	
		Lower limit	Upper limit		Lower limit	Upper limit
< 5 gr/dL	179.3	138.8	219.7	116	67.96	164.03
≥ 5 gr/dL	281.1	243.4	318.8	-	-	-

These results are in line with research conducted by Kasapoglu et al. (2019) with a peak point of 4.7 g/dL, the median survival time of NSCLC patients with MPE was 1.8 months (95% CI 0.78-2.82, p <0.0001) at protein levels ≤ 4.7 g /dL lower when compared with pleural fluid protein levels > 4.7 g/dL (95% CI 8.72-12.67, p < 0.0001). This is similar with a study in DR. Hasan Sadikin hospital which reported that the patients who died were more dominated by patients who had pleural fluid hypoprotein (protein <3.6 g/dL) (72.7% vs 13.0 %) than patients who lived (Hendro et al., 2019). Pleural fluid hypoprotein, according to Fisher's statistical test, showed a significant relationship between pleural fluid hypoprotein and a high mortality rate in MPE patients who underwent CTT. This was, possibly due to plasma hypoproteinemia accompanying advanced disease. Tumor patients with advanced stages will have a lower life expectancy (Hendro et al., 2019). This is also confirmed in the research of Bielsa., et al. (2008) stated that lower pleural fluid protein concentrations were associated with lower survival due to plasma hypoproteinemia, which often occurs in malnourished patients at an advanced stage.

Relationship of pleural fluid glucose with one-year survival of NSCLC patients with MPE

In this study, pleural fluid glucose levels had no relationship with the one-year survival of NSCLC patients with MPE at Prof. Dr. IGNG Ngoerah Denpasar Hospital. Pleural fluid glucose levels were obtained with a cut point of 47.5 mg/dL (sensitivity 81.3% and specificity 32.1%). Median survival of NSCLC patients with malignant pleural effusion who had glucose levels ≥ 47.5 g/dL was 209 days (95% CI 134.36 – 283.63), median survival at < 47.5 g/dL was 364 days with p-value = 0.199 (log-rank), this was not statistically significant (Figure 6 and Table 7).

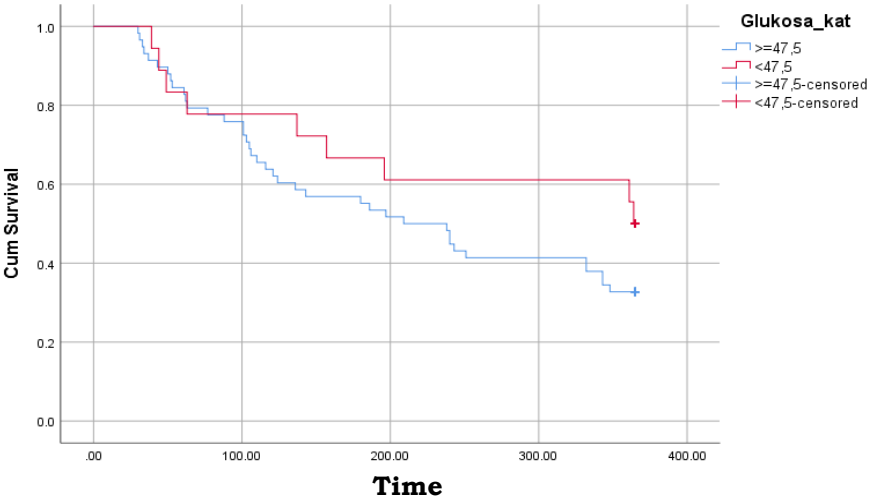

Figure 6. Kaplan Meier curve of pleural fluid glucose on survival of NSCLC patients with MPE

Table 7
Mean and median glucosepleural fluid on survival of NSCLC patients with MPE

Glucose	Means	95% Confidence Interval (CI)		Median	95% Confidence Interval (CI)	
		Lower limit	Upper limit		Lower limit	Upper limit
≥ 47.5 mg/dL	217.1	183.3	251.0	209	134.3	283.6
< 47.5 mg/dL	260.8	198.3	323.2	364	-	-

Burrows et al. (2000) also found no correlation between pleural fluid glucose and survival using the 60 mg/dL cut point (HR = 0.99, 95% CI 0.99–1.00, p = 0.22). However, different things were reported in the studies of Sahn and Good, Rodriquez-Panadero and Lopez-Mejias, and Sanchez-Armen goal and Rodriguez-Panadero (Burrows et al., 2000). Differences in results were also found in Pantazopoulos's study et al. (2014) with pleural fluid glucose values <65 mg/dL and were associated with a higher risk of pleurodesis failure. This is due to increased metabolism of the pleural membrane by malignant cells or other

involved cells, which means that the higher the severity of cancer, the lower the glucose level.(Pantazopoulos, et al., 2014).

A potential explanation for this discrepancy is due to population bias in previous studies with different outcomes, in which incomplete data, small numbers of patients with low glucose values, and enrollment of patients with symptomatic and asymptomatic effusions were noted (Burrows et al., 2000). In this research, the obtained pleural fluid glucose cut point has a poor predictive value (the ROC curve is close to the diagonal line). Besides, pleural effusion glucose levels are susceptible to changes in blood glucose levels(Pantazopoulos et al., 2014). Blood glucose levels can be influenced by many things, such as dietary factors, physical activity, stress, drug intake, age, and body mass index (Hasanah & Helma, 2019). All of these things could not be controlled by the retrospective cohort design in this study.

Factors affecting mortality of NSCLC patients with MPE

The results of multivariate analysis (Table 8) found that the factors that most influenced the one-year survival of NSCLC patients with MPE were protein < 5 g/dl, best supportive care therapy and non-adenocarcinoma NSCLC histology.

Table 8
Results of Analysis of Factors Influencing Mortality

Variable	Adjutant HR	95% CI	P value
Protein < 5 gr/dL	2,345	1.055 – 5.214	0.037*
Glucose ≥ 47.5 mg/dL	1,250	0.490 – 3.185	0.640
LDH ≥ 978.5 IU/L	0.765	0.369 – 1.582	0.469
pH < 7.30	0.698	0.334 – 1.459	0.340
Age < 65 years	0.896	0.470 – 1.710	0.740
Gender	1,785	0.663 – 4.808	0.252
Man			
Smoker	0.522	0.173 – 1.572	0.248
ECOG >2	1,456	0.721 – 2.940	0.295
Underweight	0.567	0.272 – 1.179	0.129
BSC	5,332	2.109 – 13.478	0.000*
Multi site	1.129	0.348 – 3.668	0.840
Brain metastases	1,221	0.487 – 3.061	0670
Non adenocarcinoma	2,635	1.096 – 6.335	0.030*

Description: LDH (Lactate Dehydrogenase), ECOG (Eastern Cooperative Oncology Group), BSC (Best Supportive Care)
* Has a significant effect (p-value <0.05)

In this study, protein levels <5 g/dl had a risk of death of 2.3 times in 1 year in NSCLC patients with MPE at Prof. Dr. IGNG Ngoerah Denpasar. Previous studies in patients with malignant pleural effusion who had undergone chest tube thoracostomy defined pleural fluid hypo protein if the pleural fluid protein level was <3,600 ml/dL. In that research, It was found that patients who died were dominated by patients with pleural fluid hypoprotein (72.7%) than patients who were alive (13.0%). These results are also to the research of Abrao et al. (2015),

which stated that pleural fluid protein levels of less than 3.6 g/dL were associated with a high mortality rate in MPE patients. Pleural fluid hypoprotein levels that affect mortality are possibly associated with plasma hypoproteinemia accompanying the advanced disease. Tumor patients with advanced stages have a lower life expectancy (Hendro et al., 2019).

The effect of plasma hypo protein on pleural fluid has been explained in the theory of pleural fluid filtration in the experimental determination of variables and coefficients in the Starling equation. Pleural fluid is filtered at the parietal pleural level from the systemic microvessels to the extrapleural interstitium and into the pleural cavity down a large pressure gradient. Relatively small (Hamm & Light, 1997). In addition, pleural mesothelial cells (PMC) are the most common cells found in the pleural space and are the primary cells that respond to noxious stimuli. Malignant cells in the mesothelial cells cause protein and fluid leakage from the plasma. Malignant cells also produce large amounts of VEGF, which alters the permeability of the mesothelial monolayer (Batra et al., 2015). Plasma protein can be affected by the condition of NSCLC patients with advanced stages where there is a decrease in body protein synthesis called "cancer cachexia", which is a form of severe malnutrition characterized by anorexia, early satiety, weight loss, anaemia, weakness, muscle loss. Under starvation conditions, the use of energy for the brain by glucose is replaced with ketone bodies which are the result of the breakdown of fat. Muscle and visceral protein are used as precursors for gluconeogenesis, resulting in decreased protein catabolism and gluconeogenesis from amino acids in the liver. In cancer, there is an imbalance between pro-inflammatory cytokines such as TNF-α, IL-2, IL-6, and interferon-gamma and anti-inflammatory cytokines such as IL-4, IL-12, and IL-15. Activation of pro-inflammatory cytokines activates nuclear transcription factor NF-B, resulting in the inhibition of muscle protein synthesis and a decrease in pro-Myelin D. This transcription factor modulates the signal darling pathway of muscle development. Patients who experience cachexia will cause a decrease in survival time four times lower than the ability of patients who do not experience weight loss (Deans & Wigmore, 2009).

The choice of therapy is also related to patient survival, and patients who are not treated have shorter median survival than patients who receive cancer therapy. In this study, patients with BSC had 5.3 times the risk of death within 1 year. These results are consistent with studies that found a significant difference in median survival between the chemotherapy and non-chemotherapy groups (7.1 months vs 2.5 months, $p<0.001$). However, survival was slightly better for the chemotherapy group in this study (Daniel et al., 2019). Research conducted at RSCM and Dharmais Hospital also found a relationship between patients undergoing chemotherapy and those not undergoing chemotherapy with one-year survival. Patients undergoing chemotherapy had a better one-year survival (7.1 months vs 2.5 months).(Fawziah, et al., 2014). Another study also showed that patients with palliative therapy had a lower median survival of 1.8 months compared to patients with chemotherapy and radiotherapy for 11 months (95% CI 8.55-13.44, $p<0.0001$).(Kasapoglu, et al., 2016).

Strengths and weaknesses of research

This study was the first in Bali to examine the LDH, pH, glucose and protein values of pleural fluid and its relationship with the one-year survival of NSCLC patients with MPE. Restrospective cohort design made the data collection easier and reduce the chance of loss to follow up. This study was based on routine settings for the management of NSCLC patients with MPE so that it can be used as an evaluation and the results obtained are easy to apply. Our limitation was the use of secondary data has variable measurements that cannot be standardized due to differences in place, time, tools and methods in examining variables.

Conclussion

Protein level in pleural fluid was related to one-year survival of NSCLC patients with MPE. This can be a consideration for estimating survival and management of NSCLC patients with MPE.

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