RESEARCH PAPER

Survival Outcomes of Lung Adenocarcinoma Patients with Malignant Pleural Effusion According to EGFR Mutation Status and First-Line Therapy

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ABSTRACT

Background: Malignant pleural effusion (MPE) is a common sign of more severe lung cancer that has a poor prognosis. EGFR mutations have shown a favorable response to EGFR tyrosine kinase inhibitors (EGFR-TKIs). However, data on the survival outcomes of patients with lung adenocarcinoma and malignant pleural effusion (MPE) depend on the EGFR mutation status and the treatment methods used, especially in real-world clinical practice. This study investigates the survival of patients with EGFR mutant tumors treated with EGFR-TKIs and patients with wild-type EGFR tumors treated with chemotherapy. They also found predictor variables related to survival.

Methods: At Rotinsulu Pulmonary Hospital, Bandung, West Java, Indonesia., we conducted a retrospective cohort analysis on 144 patients diagnosed with lung adenocarcinoma and malignant pleural effusion. Retrospectively, data from medical records were used to determine clinicopathological characteristics, EGFR mutation status, treatment choices, and survival. The probability of survival was calculated using the Kaplan-Meier method and compared with the log-rank test. Independent prognostic factors were identified using Cox proportional hazards regression analysis.

Results: Out of 144 patients, 84 (58.3%) had EGFR mutations and received EGFR-TKI treatment, while 60 (41.7%) had wild-type EGFR tumors and received chemotherapy. The main mutant subtypes consist of exon 19 deletions (57.1%) and L858R exon 21. Although this difference is not statistically significant (log-rank P=0.717), patients with EGFR mutant tumors have a longer median overall survival compared to patients with wild-type EGFR tumors (13 months versus 9 months). According to the multivariate Cox regression analysis, increasing age (hazard ratio [HR] 1.027, 95% confidence interval [CI] 1.006 to 1.049; P = 0.011) and advanced metastatic stage (hazard ratio [HR] 1.526, 95% confidence interval [CI] 1.049 to 2.220; P = 0.027) are two independent predictors of shorter overall survival. Although not statistically significant, the overall survival trend supports improved survival for EGFR mutation status (HR 0.802, 95% CI 0.544–1.183).

Conclusions: Patients with EGFR mutant lung adenocarcinoma with malignant pleural effusion who receive EGFR-TKI therapy have clinically longer OS compared to EGFR wild-type tumors receiving chemotherapy, although this is not statistically significant. Two important components of survival are age and metastatic burden. Our findings provide real-world evidence for the use of molecular profiling in prognostic assessment and personalized therapeutic regimens for more severe lung adenocarcinoma with malignant pleural effusion.

Keywords: *lung adenocarcinoma; malignant pleural effusion; EGFR mutation; EGFR tyrosine kinase inhibitor; overall survival; Kaplan–Meier.*

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INTRODUCTION

Lung adenocarcinoma is classified as the most common type of non-small cell lung cancer. (NSCLC), commonly results in malignant pleural effusion (MPE) that is linked to poor prognosis and shortened survival. MPE occurs in about 15% of cancer patients and adversely reduces quality of life because of its debilitating symptoms [1]. The presence of malignant pleural effusion (MPE) is a major prognostic indicator for decreased overall survival (OS) and progression-free survival (PFS) in cancer patients, since hazard ratios demonstrate much inferior outcomes for those with pleural effusion relative to those without [2].

Despite advancements in systemic therapies for lung adenocarcinoma, the presence of malignant pleural

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effusion introduces significant variability in clinical outcomes, indicating that traditional clinicopathological characteristics are insufficient for accurate prognosis prediction. Recent studies have explored several molecular biomarkers to improve prognostic stratification in lung adenocarcinoma, including endoplasmic reticulum stress-, cuproptosis-, and metabolism-related signatures [3,4]. Although these biomarkers demonstrate promising prognostic performance, most remain investigational and have not yet been widely incorporated into routine clinical practice. In contrast, EGFR mutation testing has become the most clinically established molecular biomarker for guiding treatment selection and prognostic assessment in advanced lung adenocarcinoma.

The key oncogenic driver in lung adenocarcinoma is the EGFR mutation. This mutation has a significant impact on tumor biology, metastasis patterns, treatment response, and patient survival. EGFR mutations occur in more than 50% of advanced-stage lung adenocarcinomas, especially in the Asian population, and have revolutionized therapy using EGFR tyrosine kinase inhibitors (TKI)[5]. In contrast, drug resistance to these inhibitors, such as the development of the T790M mutation, presents a substantial problem, although third-generation TKIs like osimertinib have shown success in overcoming this resistance[5,6]. Sequential treatment methods combining first or second-generation TKIs with osimertinib have shown promising survival outcomes, with an average survival of up to fifty months in clinical settings[6]. Immune profiles and reactions to PD-1/PD-L1 inhibitors vary among EGFR mutation subtypes. Rare EGFR variations had stronger immune activation and better responses than common mutations (e.g., L858R and exon 19 deletions) [7].

As shown in several studies with varying results, the predictive utility of EGFR mutation status in patients with malignant pleural effusion (PE) remains inconsistent. Osimertinib is the standard drug for non-small cell lung cancer (NSCLC) with EGFR mutations and performs differently in patients with pleural effusion (PE) with or without EGFR T790M mutations. Patients who are EGFR T790M positive have much shorter PFS and OS compared to patients without PE, indicating that PE has a detrimental effect on their health. In this case, PE does not have a significant effect on the[8].

Adding EGFR mutation status to the therapeutic regimen provides a better insight into the survival patterns of lung adenocarcinoma patients, especially with malignant pleural effusion. Mutations such as EGFR p.T790M are critical to response and resistance to therapy. by EGFR mutations (such as p.T790M). The results have demonstrated that patients with the p.T790M mutation present better survival rates following sequential treatment with first/second generation EGFR tyrosine kinase inhibitors (TKIs) with an average overall survival up to fifty months[6]. With a median overall survival of 54.3 months, sequential treatment with afatinib and osimertinib was very successful in patients with Del19 mutations[9].

Previous studies mostly analyzed the efficacy of EGFR-TKI treatment without directly comparing it to overall survival in patients with malignant pleural effusion. However, the results are promising. Also, there is still a lack of evidence of real-world clinical practice in Indonesia. As far as we know, this study is the first to assess overall survival in a real patient cohort with complex lung adenocarcinoma due to malignant pleural effusion. This differs from previous studies that focused more on treatment efficacy or progression-free survival. This technique offers therapeutically relevant evidence from a population that is still under-represented in the current research. Therefore, this study compared the overall survival of patients with malignant pleural effusion and lung adenocarcinoma based on EGFR mutation status and treatment modality, and to identify clinicopathological factors related to survival at Rotinsulu Pulmonary Hospital, Bandung, West Java, Indonesia.

METODE PENELITIAN

Study Design

A retrospective observational cohort study was conducted to compare the survival of patients with lung adenocarcinoma with malignant pleural effusion (MPE) according to epidermal growth factor receptor (EGFR) mutation status and their treatment modalities at Rotinsulu Pulmonary Hospital, Bandung, West Java, Indonesia. The study sought to investigate the difference in survival treatment between patients with EGFR mutations treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and wild-type EGFR patients treated with platinum-based chemotherapy. Clinicopathological factors associated with patient survival were also investigated.

Study Setting and Participants

Patients treated at Rotinsulu Pulmonary Hospital in Bandung for lung adenocarcinoma complicated by malignant pleural effusion were included in this study. Eligible individuals were selected from hospital medical records and institutional databases from January 2021-December 2023.

Patients were eligible if they had histologically or cytologically proven lung adenocarcinoma with malignant pleural effusion, EGFR mutation testing results, complete therapy information and appropriate follow-up data for survival analysis. Patients having incomplete clinical data, uncertain EGFR mutation status, or insufficient follow-up data were eliminated from the analysis.

Variables and Data Collection

Clinicopathological data were collected from patient medical records retrospectively using a standardized data collection form. Age, gender, smoking status, EGFR mutation status, treatment modality, and survival outcomes are all variables that were collected. According to the molecular diagnostic results found in the medical records, the EGFR mutation status was identified as mutant or wild type. For patients with EGFR mutant tumors, the treatment methods consisted of EGFR-TKI and chemotherapy. Overall survival (OS), defined as the time from the date of diagnosis to death from any cause or the last available follow-up, is the primary endpoint of this trial.

Statistical Analysis

While categorical variables are represented by frequency and percentage, continuous variables are represented by appropriate descriptive statistics. The median survival time and survival probability were calculated using the Kaplan-Meier survival analysis. To assess the survival distribution between the study groups, the log-rank test was used. Prognostic variables independently associated with overall survival were identified thru Cox proportional hazards regression analysis. To measure the degree of association between clinicopathological factors and survival outcomes, hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Age, gender, smoking status, EGFR mutation status, and therapy modality are the variables in the Cox regression model. Each statistical analysis was performed using IBM SPSS Statistics Version 31. Statistically, a two-sided P value of less than 0.05 is considered significant.

Ethical Considerations

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the appropriate Institutional Review Board or Health Research Ethics Committee in Rotinsulu Pulmonary Hospital. Research permission was obtained from Rotinsulu Pulmonary Hospital No: PL.02.03/D.XLI/11001/2024. Because this study retrospectively analyzed anonymized medical records, the requirement for medical record access was obtained from Hospital Director.

RESULT

Patient Characteristics

A total of 144 patients with lung adenocarcinoma and malignant pleural effusion (MPE) were included in the analysis. Of them, 84 patients (58.3%) had EGFR mutations and received EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy, and 60 patients (41.7%) had EGFR wild-type tumors and received chemotherapy.

The mean age of the study population was 57.2 years (range, 28 to 81 years), with most patients (56.9%) between 40 and 59 years of age. The percentage of female patients was higher in the EGFR-mutant group (57.1%) compared with the EGFR wild-type group (60.0% male patients). In terms of extent of disease, 87 patients (60.4%) had pleural metastasis only (M1a), while 57 patients (39.6%) had pleural metastasis plus distant organ metastases (M1b/M1c). The median overall survival for the whole cohort was 12 months and the mean survival was 13.1 months.

Table 1. Baseline Clinicopathological Characteristics of Patients with Lung Adenocarcinoma and Malignant Pleural Effusion

Variables	N=144	Percentage
Age (Years)		
20-39	4	2.78%
40-59	82	56.94%
>=60	58	40.28%
Mean	57.21	
Median	58.00	
Minimum	28	
Maximum	81	
Gender		
Male		
EGFR Mutation	36	42.90%
EGFR Wild type	36	60%
Female		
EGFR Mutation	48	57.10%
EGFR Wild type	24	40%
Stadium		
M 1A	87	60.40%
M 1B/1C	57	39.60%

Survival status (months)		
Mean	13.08	
Median	12.00	
Minimum	1	
Maximum	36	
EGFR mutation status		
Mutation	84	58.3
Wild type	60	41.7

Distribution of EGFR Mutation Subtypes

In 84 individuals with EGFR-mutant malignancies, 81 patients (96%) had a single mutation and only 3 patients (3%) had compound EGFR mutations (Table 3). The most prevalent mutant subtype was exon 19 deletion (57%) followed by exon 21 L858R (39%) (Table 2). Compound mutations were rare, including exon 19 deletion plus exon 20 T790M (1%) and exon 18 G719X plus exon 20 S768I (3%).

Table 2. Characteristics of EGFR Mutations in Patients with Lung Adenocarcinoma and EPG.

EGFR Mutation Sites	**N=84**	**Percentage**
Delesi exon 19	48	57%
Exon 21 L858R	33	39%
Delesi exon 19 and exon 20 T790M	1	1%
Exon 18 G719X and S768I Exon 20	2	3%

Table 3. EGFR Mutation Types in Patients with Lung Adenocarcinoma and EPG.

Mutation Type	**N=84**	**Presentase**
Single Mutation	81	96%
Double Mutation	3	4%

Overall Survival According to EGFR Mutation Status

The median overall survival was longer for EGFR-mutant tumor patients treated with EGFR-TKIs than for EGFR wild-type tumor patients treated with chemotherapy (13 vs. 9 months). The estimated mean survival time was 14.3 months (95% CI, 12.4 to 16.3) in the EGFR-mutant group compared to 13.4 months (95% CI, 10.4 to 16.3) in the EGFR wild-type group. Kaplan–Meier survival curves demonstrated that survival probabilities were significantly greater in patients with EGFR mutations over the first 15 months of follow-up. After this point, survival curves converged and crossed, indicating equivalent long-term survival trends across treatment groups.

Table 4. Overall Survival According to EGFR Mutation Status and Treatment Modality

Variable	**EGFR mutation + TKI**	**EGFR wild type + Chemotherapy**
Median survival (months)	13	9
Mean survival (months)	14.35	13.36
95% CI	12.35–16.34	10.43–16.28

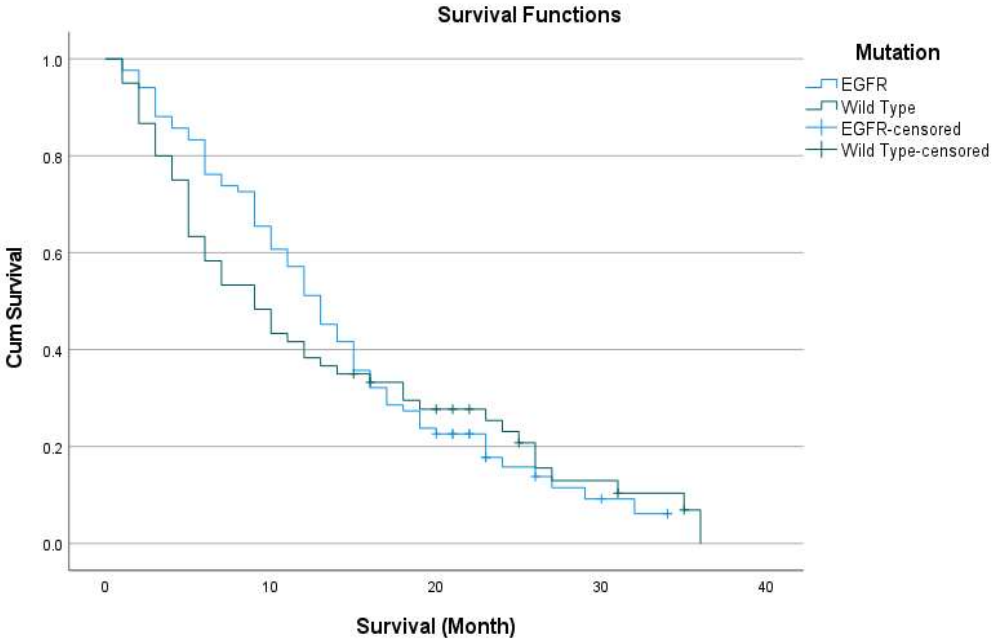

Figure 1. Kaplan–Meier Overall Survival Curves According to EGFR Mutation Status and Treatment Modality

Comparison of Survival Between Study Groups

Patients with EGFR mutant tumors had numerically longer survival . However, there was no statistically significant difference in overall survival between EGFR mutation patients who received EGFR-TKI therapy and EGFR wild-type tumors who received chemotherapy (log-rank χ^2 = 0.131, P = 0.717).

Table 5. Comparison of Survival Between Study Groups

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	0.131	1	0.717

Prognostic Factors Associated with Overall Survival

Independent prognostic factors linked with overall survival were identified by doing Cox proportional hazards regression analysis. Age was independently linked with poorer survival (HR 1.027, 95% CI 1.006–1.049; P = 0.011), meaning each extra year of age raised the hazard of death by roughly 2.7%. Patients with M1b/M1c disease also had a significantly greater risk of mortality than those with M1a disease (HR 1.526, 95% CI 1.049–2.220; P = 0.027). EGFR mutation status was related with a 20% decreased hazard of mortality versus EGFR wild-type disease (HR 0.802, 95% CI 0.544-1.183) but did not reach statistical significance (P = 0.266). Likewise, there was a nonsignificant tendency toward better survival in females (HR 0.823, 95% CI 0.566-1.197; P = 0.309).

Table 6. Multivariable Cox Proportional Hazards Regression Analysis of Factors Associated with Overall Survival

Variable	HR	95% CI	P value
EGFR mutation	0.802	0.544–1.183	0.266
Age	1.027	1.006–1.049	**0.011**
Female sex	0.823	0.566–1.197	0.309
M1b/M1c metastasis	1.526	1.049–2.220	**0.027**

DISCUSSION

Patients with EGFR-mutant lung adenocarcinoma with malignant pleural effusion treated with EGFR-TKI therapy have a longer median survival than patients with wild-type EGFR tumors treated with chemotherapy, but this difference is not statistically significant. Two independent factors that still function as independent predictors are age and stage of metastasis. This is consistent with findings from several trials that have demonstrated the efficacy of EGFR-TKIs in patients with EGFR mutations. For example, Wu et al. found that EGFR-TKIs such as afatinib were associated with good survival outcomes in patients with low performance status, and that dose modification was an important factor indicating overall survival[10].

Additionally, Wang et al., like Gijtenbeek et al., showed that erlotinib increased PFS more than erlotinib alone but also increased toxicity[11]. Chen et al. also validated the predictive value of the Amplified Refractory Mutation System for EGFR-TKI efficacy and found that lower CT values were associated with better outcomes[12]. Additionally, Wang et al. and Gu et al. showed that the addition of chemotherapy to EGFR-TKIs may prolong progression free survival in EGFR-mutant patients, particularly in co-altered patients, but the overall survival benefit was not uniformly statistically significant[13,14]. In summary, the results of these studies underscore the limited benefits of EGFR-TKI therapy in specific patient subgroups and propose age and metastatic stage as independent prognostic factors.

The epidemiological pattern of EGFR-mutant lung adenocarcinoma is well-known and consistent with clinicopathological aspects that predominantly affect females and patients of middle age, as proven in several investigations. In a real-world multicenter investigation, most patients with EGFR-mutated advanced non–small cell lung cancer (NSCLC) were female (56%) and had a mean age of 65.6 years [15]. In addition, a study on the identification of the CT features that might predict EGFR mutations revealed that female sex and nonsmoke status were significant independent prognostic variables for EGFR mutations, which further supported the gender and age distribution in EGFR-mutant lung adenocarcinoma [16]. Moreover, the association between EGFR mutations and certain clinical parameters, such as the decrease of progression-free survival in patients with bone metastases, underlines the clinical significance of these mutations for prognosis and treatment [17]. In addition, long-term survival analyses validate the demographic trends already described in this population [18] , with female sex and younger age being associated with longer OS in patients with EGFR-mutated NSCLC. In summary, our results are consistent with the usual epidemiological characteristics of EGFR-mutant lung adenocarcinomas, which are mainly diagnosed in middle-aged women.

The frequency of exon 19 deletion, followed by exon 21 L858R mutations in lung adenocarcinoma is in line with the spectrum of mutations in Asian patients, especially in non-small cell lung cancer (NSCLC) . In the study by Xi et al , the most common EGFR mutation was deletion of exon 19 in Chinese NSCLC patients, suggesting that this alteration is common in this population [19]. This is consistent with the general consensus that EGFR mutations including exon 19 deletions and exon 21 L858R mutations are common in Asian patients with lung adenocarcinoma. Wang et al. EGFR mutations are reported to occur in over 50% of patients with late stage lung adenocarcinoma in Asian patients [5]. This is further corroborated by the work of Stratmann et al who evaluate the clinical management of lung cancer with mutations of EGFR and highlight the importance of these mutations in guiding treatment options [6]. Moreover, these mutations are necessary for the effectiveness of EGFR tyrosine kinase inhibitors (TKIs), the mainstay of treatment in EGFR mutant NSCLC, as reviewed in the context of resistance mechanisms and treatment sequencing [5,6]. In conclusion, the spectrum of mutations described in these investigations emphasize the importance of exon 19 deletions and exon 21 L858R mutations in Asian patients with lung adenocarcinoma.

EGFR-targeted therapy may provide a survival advantage for patients with EGFR-mutant cancers, particularly in cases of malignant pleural effusion (PE), while several trials failed to reach statistical significance. Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI) and is the mainstay treatment of advanced non-small-cell lung cancer (NSCLC) with EGFR mutations. But its effectiveness in PE patients is determined by the status of the EGFR T790M mutation. In EGFR T790M-negative patients, PFS was similar with or without PE, but T790M-positive patients had significantly shorter PFS and OS when PE was present [8]. The first- and second-generation TKIs, afatinib vs gefitinib and erlotinib, have shown longer OS, suggesting a possible survival benefit, but need to be directly compared with osimertinib [20]. Immune checkpoint inhibitors (ICIs) have also been studied in the context of EGFR-TKI failure with combination therapies showing improved outcomes in individuals with certain EGFR mutations including exon 19 deletions [21]. In real-world data, most EGFR-mutant NSCLC patients get TKI therapy and disease progression is a frequent reason for discontinuation [15]. Overall, the findings indicate that EGFR-targeted therapies (e.g. osimertinib and afatinib) may provide a survival benefit to patients with malignant pleural effusion, especially when combined with genetic profiling and other treatments, although the benefit may not always be statistically significant.

Kaplan-Meier survival curves demonstrated early differences and late similarities between the two groups, indicating a survival benefit of EGFR-targeted therapy that was more pronounced in the first few months after starting treatment. Another study showed median OS of 36.9 months for individuals with EGFR mutations and survival curves plateaued at 72 months for patients with EGFR mutations or ALK rearrangements, demonstrating the importance of days to months of survival advantage [18]. Multivariate Cox regression analysis revealed that advanced metastatic stage and older age were independent predictors of poor overall survival in patients with NSCLC. This is confirmed by data from the German CRISP registry which demonstrated significantly lower OS and PFS for patients with advanced metastatic illness, in particular with liver metastases or multiple metastatic

organ systems, compared to those with less metastatic sites [22].

The EGFR mutation status is linked with better prognosis due to the efficacy of EGFR-directed therapies such as EGFR-tyrosine kinase inhibitors (TKIs) [23]. However, the statistical significance of this trend for the improvement of overall survival remains uncertain in particular studies. The presence of EGFR mutations has been linked with better treatment outcomes, especially with the surgical removal of the original tumour, greatly prolonging longevity. Moreover, patients with EGFR mutations or ALK rearrangements have improved survival with a distinct plateau in survival curves beyond five years, suggesting a possible long-term benefit from targeted therapy [18]. On the contrary, KRAS mutations, especially G12C, do not confer equivalent improvements in survival, and co-mutations with STK11 and KEAP1 result in poor prognosis, an example of the complex effect of genetic factors on NSCLC prognosis [24]. In conclusion, age and metastatic stage are very strong predictors of survival, but the role of EGFR mutations, although beneficial, needs to be researched to discover statistical significance in multivariable models.

The results of the evaluated publications show the clinical relevance of genetic diagnostics and personalised therapy approaches for patients with lung adenocarcinoma with malignant pleural effusion (MPE). The detection of specific mRNA markers, such as DUSP6, MDM2, RNF4 and WEE1, represents a promising diagnostic approach to distinguish MPE from benign pleural effusions, which is crucial for a timely and accurate diagnosis at the advanced stage of malignancies [25]. Also, the combination of radiomics models and clinical features, especially with [18F]FDG PET/CT, improved the prediction of EGFR mutation status, which is useful in personalised management for lung adenocarcinoma, especially at the advanced stages [26]. MicroRNAs (miRNAs) are also involved in lung cancer, and the association of some miRNAs with tumour suppression and oncogenesis, as well as therapy response and survival outcomes, provides the basis for personalised medicine [27]. Together, these studies support the application of molecular diagnostics and personalized treatment options for improved clinical outcomes in lung adenocarcinoma with MPE. The construction of endoplasmic reticulum stress-related gene model helps prognosis and therapeutic decisions and emphasizes the importance of molecular profiling in treatment planning for lung adenocarcinoma patients [3].

The present study has several important strengths, including the evaluation of real-world survival outcomes in Indonesian patients; however, several methodological limitations should also be considered when interpreting the findings. Future multicentre prospective studies incorporating comprehensive molecular profiling and newer generations of EGFR-TKIs are warranted to further clarify prognostic determinants and optimize treatment strategies for patients with malignant pleural effusion.

CONCLUSION

While categorical variables are represented by frequency and percentage, continuous variables are represented by appropriate descriptive statistics. The median survival time and survival probability were calculated using the Kaplan-Meier survival analysis. To assess the survival distribution between the study groups, the log-rank test was used. Prognostic variables independently associated with overall survival were identified thru Cox proportional hazards regression analysis. To measure the degree of association between clinicopathological factors and survival outcomes, hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Age, gender, smoking status, EGFR mutation status, and therapy modality are the variables in the Cox regression model. Each statistical analysis was performed using IBM SPSS Statistics Version 31. Statistically, a two-sided P value of less than 0.05 is considered significant.

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