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ERCC2 rs13181 and ERCC1 rs11615 polymorphisms in non-small cell lung cancer patients in West Java: towards personalized medicine approaches

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ABSTRACT

Non-Small Cell Lung Cancer (NSCLC) is a disease with a high incidence rate, low survival due to late diagnosis and treatment delays, and varying effectiveness of platinum-based chemotherapy. Individual responses to platinum-based chemotherapy are influenced by genetic polymorphisms in genes affecting pharmacokinetic and pharmacodynamic mechanisms. This study focuses on identifying polymorphisms in the *ERCC2* and *ERCC1* genes, which play a role in platinum pharmacodynamics, and their effects on chemotherapy response. The study involved 23 NSCLC patients conducted at Dr. H.A. Rotinsulu Lung Hospital in Bandung. Polymorphism data were obtained through genotype analysis using sequencing methods from prospective whole blood samples of patients, while chemotherapy effectiveness was assessed by evaluating chemotherapy response using the RECIST 1.1 method, and radiological response prediction and prognostic factors were determined through CYFRA 21-1 levels. The results showed an OR of 0.964 (95% CI: 0.160 - 5.795) for *ERCC2* rs13181 CC + AC vs. AA against chemotherapy response evaluation by RECIST 1.1, and 0.722 (95% CI: 0.062 - 8.464) against CYFRA 21-1 values. Meanwhile, for *ERCC1* rs11615, an OR of 0.268 (95% CI: 0.046 - 1.548) CT + TT vs. CC for RECIST 1.1 and 0.3 (95% CI: 0.026 - 3.427) for CYFRA 21-1 values were obtained. In clinical interpretation, it is known that variant alleles at rs13181 and rs11615 have potential for better chemotherapy response although not statistically significant ($p>0.05$), these results can be considered when assessing patient response to chemotherapy within six cycles. This study provides initial data and forms the basis for future comprehensive cohort observational research.

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1. Introduction

Cancer is the second leading cause of death worldwide with one in six deaths, in 2018 (WHO, 2022). The incidence of new lung cancer cases in Indonesia has increased more than fivefold over the past decade, with the majority (85%) being Non-Small Cell Lung Cancer (NSCLC) (Altekruse et al., 2017; Kemenkes RI, 2017). NSCLC are also known to have low survival rates, with a first-year overall survival rate of 94%, second-year rate of 91%, and third-year rate of 78% (Srikrishnan et al., 2018). The 5-year survival rate for NSCLC overall is only 24% (American Cancer Society, 2019). One of the factors contributing to the low survival rates of NSCLC patients is delayed diagnosis and treatment (Torre et al., 2016). Statistical data indicate that 65% of NSCLC cases are diagnosed at an advanced stage (Kemenkes RI, 2017; Adebonojo et al., 1999), leading to delayed initiation of treatment. Platinum-based (PB) are known to exhibit variability in their effectiveness, with an overall response rate (ORR) ranging from 26% to 63% (Torre et al., 2016; Bahl and Falk, 2001). Studies in the UK have reported rates of 20% to 40%, while a pooled analysis yielded an ORR range of 29.7% to 46.7% for PB regimens (Sirohi et al., 2007; Petrelli et al., 2013). This has emerged as a notable concern, given that PB treatment protocols are integrated into the national healthcare coverage and persist as the predominant choice for initial therapy among Indonesian NSCLC patients with wildtype *Epidermal Growth Factor Receptor (EGFR)* profile (Kemenkes RI, 2017). In contrast, targeted therapies such as *Vascular Endothelial Growth Factor (VEGF)* inhibitors, bevacizumab, or *Tyrosine Kinase* Inhibitor *(TKI)* or *ALK*-inhibitor such as alectinib and/ crizotinib for ALK and *c-ros oncogene 1 (ROS1)*-positive mutations, as well as immunotherapy like atezolizumab for those with high *Programmed Death-Ligand 1 (PD-L1)* expression, are not currently provided by the national healthcare coverage (Kemenkes RI, 2017; Dantoing et al., 2021; Gendarme et al., 2022; Liao et al., 2015; Zugazagoitia et al., 2017; Mortezaee and Majidpoor, 2023; Kemenkes RI, 2021). Consequently, the widespread use of PB regimens in Indonesia stands in contrast to the potential benefits associated with biologic agents, whether used individually or in combination, which are generally regarded as more effective for NSCLC treatment (Zugazagoitia et al., 2017).

Variations in the effectiveness of platinum-based can occur through mechanisms such as the increased activity of DNA repair

pathways, such as *Nucleotide Excision Repair* (NER) or *Base Excision Repair* (BER). These mechanisms also encompass the tolerance of DNA damage caused by the formation of platinum-DNA adducts (Amable, 2016). Tumour markers involved in NER, such as *Excision Repair Cross-Complementing group 1* (ERCC1), *X-Ray Repair Cross Complementing 1* (XRCC1), *Excision Repair Cross-Complementing 2/ Xeroderma Pigmentosum group D* (ERCC2/XPD), and *Xeroderma Pigmentosum Group A-Complementing Protein* (XPA), have been mentioned in several meta-analysis studies as factors related to decreased sensitivity to PB chemotherapy (Song et al., 2017). A meta-analysis study conducted in China indicated that the *ERCC2* rs13181 and *ERCC1* rs11615 genes are the best predictors for evaluating individual responses to PB chemotherapy in patients with NSCLC (Fu et al., 2017; Yang and Xian, 2013; Tang et al., 2017; Wei et al., 2011). However, there have been varied results concerning this matter, such as studies stating that there is no significant correlation between polymorphism in *ERCC1* and *ERCC2* and the clinical outcomes of PB chemotherapy (Qiu et al., 2013; Yin et al., 2010). So that, this study aims to identify polymorphisms in the *ERCC2* rs13181 and *ERCC1* rs11615, which are critical in the pharmacodynamics of platinum-based chemotherapy, and to evaluate their impact on the treatment response in cancer patients, specifically for Indonesian population.

2. Materials and methods

2.1. Study design and population

This research has obtained ethical approval from the Research Ethics Commission of Dr. H.A. Rotinsulu Lung Hospital, Bandung. This is an observational cohort study conducted in November 2019 – March 2020 at Dr. H.A. Rotinsulu Lung Hospital in Bandung, Indonesia which focused on inpatients with inoperable NSCLC treated with PB chemotherapy as first-line and exhibiting wildtype *EGFR* mutations. The study involved the prospective collection of data from patients, including the analysis of genotypes and measurement of *Cytokeratin-19 Fragment 21-1* (CYFRA 21-1) serum level using 3 ml whole blood samples, as well as the retrieval of medical records containing patient profiles, including age, gender, history of alcohol and smoking, histology type, tumor stage, and details of the chemotherapy regimen. To evaluate the effectiveness of the chemotherapy, the study assessed the chemotherapy response using *Response Evaluation Criteria in Solid Tumors version 1.1* (RECIST 1.1) criteria after the completion of six cycles of chemotherapy. Furthermore, the prediction of radiological response and determination of prognostic factors were based on CYFRA 21-1 levels. RECIST 1.1 results were categorized into responders (*Complete Response* (CR) and *Partial Response* (PR)) and non-responders (*Stable Disease* (SD) and *Progressive Disease* (PD)), while CYFRA 21-1 values were divided into two classes using a cut-off value of 10.4 ng/ml, indicating different prognostic outcomes. Patients who has CYFRA 21-1 value below the cut-off value considered has the better prediction related to chemotherapy responses and the disease progression. Conversely, patients with CYFRA 21-1 levels exceeding the cut-off value considered has the poor outcome. Patients who were lost to follow-up, has a comorbidity disease that treated with immunosuppressants or antiviral, had incomplete medical records, or had untraceable RECIST 1.1 results were excluded from the study. The minimum sample size was calculated using the Lemeshow formula. With a total NSCLC population of 147 at Dr. H.A. Rotinsulu Lung Hospital and a population proportion of 7.29%, the minimum required sample size was determined to be 23.

2.2. Genotyping analysis and CYFRA 21-1 measurement

We utilized Vacutainers without anticoagulant to collect 3 ml of whole blood, resulting in the separation of serum and blood clot components. The serum was used for CYFRA 21-1 measurement using the *The Electrochemiluminescence Immunoassay* (ECLIA) method. We set the cut-off value of CFRA 21-1 is 10.4 ng/ml (Said et al., 2015). We isolated DNA from the blood clot and performed PCR before analyzing the polymorphisms using the Sanger sequencing method. The PCR settings were as follows: pre-denaturation at 95°C for 2 minutes, denaturation at 95°C for 1 minute, annealing at 60.4°C for rs113181 and 59.5°C for rs116155 for 1 minute, extension at 72°C for 1 minute, and a final extension at 72°C for 5 minutes. The PCR was carried out for a total of 40 cycles.

For the rs11615 polymorphism, the primer sequences were Forward Primer (F): 5'-AGGACCACAGGACACGCAGA-3' and Reverse Primer (R): 5'-CATAGAACAGTCCAGAACAC-3' with the expected fragment length was 525 bp. While for the rs13181 polymorphism, the primer sequences were Forward Primer (F): 5'-GCC CGC TCT GGA TTA TAC G - 3' and Reverse Primer (R): 5'-CTA TCA TCT CCT GGC CCC C-3' with the expected fragment length was 436 bp.

2.3. Statistical analysis

The statistical data analysis was conducted in two stages. The first stage involved the distribution of genotype frequencies and testing for Hardy-Weinberg genetic equilibrium using the chi-square test with a significance level of P=0.05, indicating H-W equilibrium. Then, analysing the association between polymorphisms and chemotherapy effectiveness using a bivariate approach to estimate the Odds Ratio and 95% Confidence Interval (CI). The presence or absence of a significant relationship between these variables was tested using the Chi-Square (χ^2) method. We use IBM SPSS Statistics 26 version for analysing all of the statistical test.

3. Results and discussion

3.1. Results

3.1.1. Patients characteristic

A total of 46 patients with cytologically or histologically confirmed NSCLC, treated by Platinum-based chemotherapy as first-line were recruited consecutively from November 2019 to March 2022. We followed up with patients until the completion of six cycles of chemotherapy to obtain the RECIST 1.1 data. Finally, there were 23 patients who were appropriate for this study (Fig. 1). In this study, it was observed that the majority of the patients were male (78.2%). In terms of lung cancer risk factors, the majority of male patients (17 out of 18) had a history of smoking, while only 11 of them had a regular alcohol consumption habit. On the other hand, none of the female patients had a history of smoking (p=0,000) or alcohol consumption. It is noteworthy that in this study, all patients, regardless of gender, were majority on stage IVA, with squamous cell carcinoma as the predominant histology type (Table 1). Furthermore, among the total of 8 patients in stage IIIC and IVA were classified into the non-responder category. However, the statistical results did not reveal any significant associations between patient characteristics and RECIST 1.1. Similarly, the CYFRA 21-1 values and their association with patient characteristics did not demonstrate any meaningful correlations or significance (Table 2).

3.1.2. Genetic polymorphism and RECIST 1.1 and CYFRA 21-1

The distribution of all genotypes (wild-type, heterozygous, and homozygous polymorphic variants) with Hardy-Weinberg equilibrium (HWE) is presented in Table 3. Both of rs11615 and rs13181 were indicates no statistically significant differences (p>0.05) on HWE test, therefore we can conclude that the genotype frequencies conform to Hardy-Weinberg equilibrium (HWE) (Table

3). Regardless of gender and genetic polymorphism, out of the 23 patients, 13 were classified as responders (PR and CR), while 10 were classified as non-responders (PD and SD). On the contrary, the majority, 19 patients, had CYFRA 21-1 levels below the cut-off value, indicating a better prediction related to chemotherapy response and disease progression. Polymorphisms in rs13181 and rs11615 is likely to have a chemotherapy response categorized as responder; OR= 0,964 (0,160 – 5,795), p= 1,000, and OR= 0,268 (0,046 − 1,548), p=0,214, respectively (Table 4). Genotypes CT + TT for rs11615, as well as genotypes AC + CC for rs13181, have the potential to predict a better chemotherapy response and disease prognosis based on CYFRA 21-1 value compared to the wildtype (OR = 0,268 (0,046 − 1,548), p= 0,214 and OR= 0,722 (0,062 – 8,464), p= 0.100, respectively). However, based on the statistical analysis results in this study, neither rs11615 nor rs13181 showed a significant association to the chemotherapy response or prognosis prediction (Table 4).

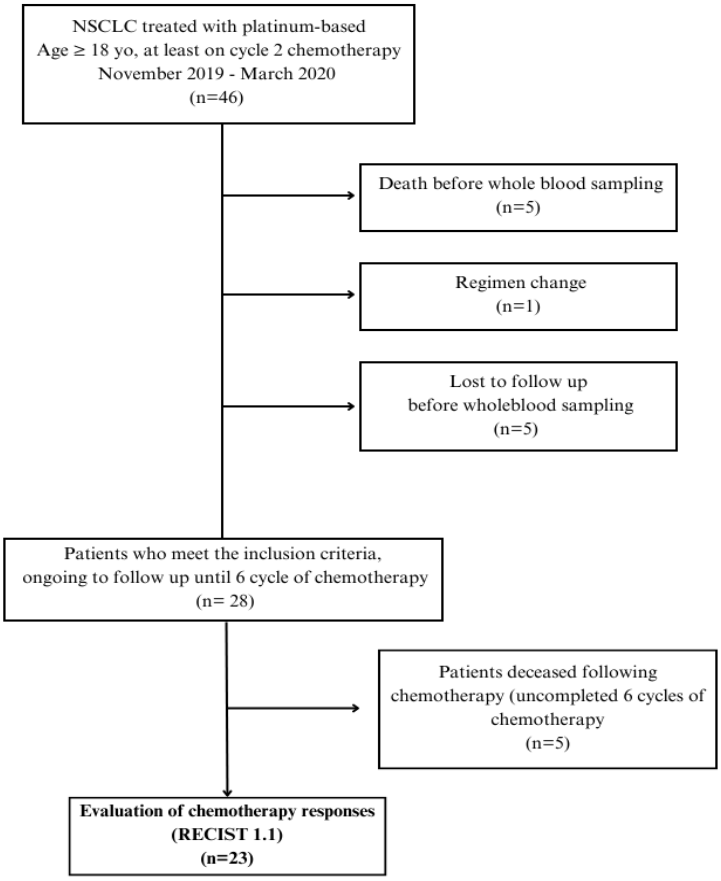

Fig. 1. Research Flowchart

Table 1. Characteristic of patients based on gender

Demography		Gender				
		Female		Male		p-value
		5	(21.7%)	18	(78.2%)	
Smoking History	No	5	(83.33%)	1	(16.67%)	0.000*
	Yes	0	(0)	17	(100%)	
Alcohol Consumption	No	0	(0)	7	(100%)	0.272
	Yes	5	(31.25%)	11	(68.75%)	
Histology	Squamous Cell	2	(16.67%)	10	(83.33%)	0.453
	Adenocarcinoma	2	(22.22%)	7	(77.78%)	
	Large Cell	1	(100%)	0	(0)	
	Unspecified	0	(0)	1	(100%)	
Tumor Stage	II B	0	(0)	1	(100%)	0.323
	III A	1	(25%)	3	(75%)	
	III B	0	(0)	5	(100%)	
	III C	1	(25%)	3	(75%)	
	IV A	2	(33.33%)	4	(66.67%)	
	IV B	1	(33.33%)	2	(66.67%)	
Chemotherapy Regimen	Cisplatin/Paclitaxel	5	(27.78%)	13	(72.22%)	0.545
	Carboplatin/Paclitaxel	0	(0)	5	(100%)	

Chi-square test; Fisher exact test/Mann-Whitney test. *: Statistically Significant

Table 2. Characteristic of patients based on RECIST 1.1 and CYFRA 21-1 value

Demography		RECIST					CYFRA 21-1 Value				
		Responder		Non-Responder		p-value	Better Prediction		Poor Prediction		P-value
Gender	Female	2	(40%)	3	(60%)	0.618	5	(100%)	0	(0)	0.539*
	Male	11	(61.11%)	7	(38.89%)		14	(77.78%)	4	(22.22%)	
Age	62.17 (12.04)										1.000
	≤62	6	(54.55%)	5	(45.45%)	1.000	9	(81.82%)	2	(18.18%)	
	>62	7	(58.33%)	5	(41.67%)		10	(83.33%)	2	(16.67%)	
Smoking History	No	3	(50%)	3	(50%)	1.000	6	(100%)	0	(0)	0.539
	Yes	10	(58.82%)	7	(41.18%)		13	(76.47%)	4	(23.53%)	
Alcohol Consumption	No	4	(57.14%)	3	(42.86%)	1.000	5	(71.43%)	2	(28.57%)	0.557
	Yes	9	(56.25%)	7	(43.75%)		14	(87.5%)	2	(12.5%)	
Histology	Squamous Cell	7	(58.33%)	5	(41.67%)	0.862	9	(75%)	3	(25%)	0.297
	Adenocarcinoma	5	(55.56%)	4	(44.44%)		8	(88.89%)	1	(11.11%)	
	Large Cell	0	(0)	1	(100%)		1	(100%)	0	(0)	
	Unspecified NSCLC	1	(100%)	0	(0)		1	(100%)	0	(0)	
Tumor Stage	II B	0	(0)	1	(100%)	0.569	0	(0)	1	(100%)	0.710
	III A	4	(100%)	0	(0)		4	(100%)	0	(0)	
	III B	4	(80%)	1	(20%)		4	(80%)	1	(20%)	
	III C	0	(0)	4	(100%)		3	(75%)	1	(25%)	
	IV A	2	(33.33%)	4	(66.67%)		6	(100%)	0	(0)	
	IV B	3	(100%)	0	(0)		2	(66.67%)	1	(33.33%)	
Chemotherapy Regimen	Cisplatin/Paclitaxel	10	(55.56%)	8	(44.44%)	1.000	16	(88.89%)	2	(11.11%)	0.194
	Carboplatin/Paclitaxel	3	(60%)	2	(40%)		3	(42.86%)	4	(57,14%)	

Chi-square test; Fisher exact test/Mann-Whitney test

3.2. Discussion

In our study, we observed that the polymorphisms in rs13181 and rs11615 have an odds ratio (OR) that could be interpreted as a risk factor for a better chemotherapy response on RECIST 1.1. and CYFRA 21-1 value compared to the wild-type profile. However, this association was not statistically significant. On the contrary, numerous studies have yielded negative or statistically non-significant results regarding the association between rs13181 and rs11615 and their impact on the clinical outcomes of platinum-based (PB) chemotherapy. The variability in results not only may be influenced by genetic factors such as race, but also the number of samples, quality control of genotyping methods, study design, or variable grouping, can also affect the final outcome of statistical methods. On advanced stages, particularly in the metastasis of lung cancer, there have been varying interpretations of RECIST 1.1 results. For instance, the classification of stable disease as a responder has been a subject of debate. Previous research has suggested that in advanced NSCLC patients who receive a combination of chemotherapy and targeted therapy as their initial treatment and are assessed using RECIST 1.1 criteria, stable disease (SD) demonstrates a comparable overall survival advantage to partial response (PR). This implies that assessing the effectiveness of anti-tumor treatments based solely on RECIST criteria may not always align with overall survival benefits, particularly for patients falling into this group. Consequently, there is a demand for the creation of a more comprehensive assessment approach to enhance the precision of RECIST 1.1 criteria, particularly for patients undergoing chemotherapy combined with targeted therapy for NSCLC (Zhou et al., 2015; Toffart et al., 2014). In addition to RECIST 1.1, CYFRA 21-1 is also utilized as a evaluating marker for chemotherapy. CYFRA 21-1 is a fragment of cytokeratin-19, a protein structure found in intermediate filaments that helps maintain the stability of epithelial cells that expressed in the cytoplasm of tumor epithelial cells, including in Non-Small Cell Lung Cancer (NSCLC) cases (Vollmer et al., 2003). Serum CYFRA 21-1 concentration increases in the presence of malignancies in epithelial cells. Hence, it has long been established that serum CYFRA 21-1 levels can be utilized to predict the effectiveness of chemotherapy. Study on 1997 stated that multivariate analysis identified elevated CYFRA 21-1 levels at any point during the disease progression as an additional indicator of un-favorable survival outcomes (Bréchot et al., 1997). Some studies have also suggested that it can function as a predictor of radiologic-clinical outcomes in response to lung cancer chemotherapy (Said et al., 2015). However, in the end it would be advisable to conduct a two-point measurement to assess the clinical response of chemotherapy with CYFRA 21-1, rather than relying solely on a single baseline measurement for predictive purposes (Park et al., 2013; Fiala et al., 2014). For instance, a study that calculated changes in serum CYFRA 21-1 concentrations measured after the first cycle of chemotherapy could be utilized as an evaluation of the appropriateness of NSCLC chemotherapy selection. By categorizing the results as Disease Control (DC) or Progressive Disease (PD), medical professionals can use a normal threshold value of 17.5% to predict the clinical response of patients and the effectiveness of the administered chemotherapy. An increase in serum levels exceeding 17.5% in NSCLC patients can serve as a basis for making early adjustments to chemotherapy regimens, rather than waiting for the results of thorax CT scans, as per RECIST 1.1 methodology (Zhao et al., 2016).

Around 80% of lung cancer cases in men and 90% in women are attributed to smoking. Among the various types of non-small cell lung cancer (NSCLC), squamous cell carcinoma (SCC) exhibits a particularly strong association with smoking (Sabbula et al., 2024). This study aligns with that pattern, as it includes a majority number of patients with squamous cell histology, and all male patients in the study had a history of smoking. We had a total of 17 male patients who were former smokers with a smoking history of more than 10 years. They had either quit smoking upon being diagnosed with lung cancer or had stopped during the chemotherapy treatment after one or two cycles. Some case with the patients that had a history of alcohol consumption. Smoking and alcohol consumption are well-established as major risk factors for lung cancer. Smoking is directly associated with lung cancer mortality (WHO, 2020). The results of the meta-analysis indicate that there is a linear increase in the risk of cancer associated with

an increase in alcohol consumption compared to non-consumers (Turati et al., 2014). On the other hand, smoking is the primary cause of premature death in cancer patients, especially in lung cancer. Smoking contributes to approximately 30% of total cancer deaths, and nearly 90% of lung cancer deaths (WHO, 2020; Peto et al., 1992). The relationship between alcohol consumption and disease prognosis is also quite significant. For instance, alcohol consumption after cancer diagnosis increases the risk of a second primary cancer, reduces the efficacy and tolerance of radiation therapy, diminishes the effectiveness and tolerance of systemic chemotherapy, lowers quality of life, and increases overall mortality (Jassem, 2019). The reduced effectiveness and tolerance of chemotherapy due to alcohol consumption are associated with the activation of cell growth cycles and the stimulation of survival pathways that manifest as apoptosis resistance (Dasgupta and Chellappan, 2006; Minna, 2003; Xu et al., 2007). Alcohol consumption also influences the prognosis and survival rate of cancer patients. Statistical data from 2002, for instance, indicated that 3.5% of cancer deaths were linked to alcohol (Seitz and Stickel, 2007).

Table 3. Hardy-Weinberg Equilibrium of ERCC1 rs11615 and ERCC2 rs13181

ERCC1 rs11615 Genotype	**Observation (*O*)**	**Expectation (*E*)**	**Proportion**	**Allele Frequency**	**Hardy-Weinberg Equilibrium**	
Wild Type (CC)	12	11.132	0.522	0.696	p^2	0.484
Heterozygote (CT)	8	9.729	0.348		$2pq$	0.423
Homozygote (TT)	3	2.116	0.130	0.304	q^2	0.092
Variation of allele frequency	0.304					
χ^2 value	0.744					
p-value	**0.689**					
ERCC2 rs13181 Genotype						
Wild Type (AA)	16	15.709	0.696	0.8265	p^2	0.683
Heterozygote (AC)	6	6.601	0.261		$2pq$	0.287
Homozygote (CC)	1	0.690	0.043	0.1735	q^2	0.030
Variation of allele frequency	0.1735					
χ^2value	0.149					
p-value	**0.928**					

Table 4. Correlation Between ERCC1 rs11615 and ERCC2 rs13181 with RECIST 1.1 and CYFRA 21-1

ERCC2 rs13181	**RECIST**		**OR (95% CI)**	**p-value**	**CYFRA21-1 Value**			
	Responder	**Non-responder**			**Better Prediction**	**Poor Prediction**	**OR (95% CI)**	**p-value**
Non-mutation	9 (56.25%)	7 (43.75%)	0.964 (0.160 – 5.795)	1.000	13 (81.25%)	3 (18.75%)	0.722 (0.062 – 8.464)	1.000
Mutation	4 (57.14%)	3 (42.86%)			6 (85.71%)	1 (14.29%)		
ERCC1 rs11615								
Non-mutation	5 (41.67%)	7 (58.33%)	0.268 (0.046 – 1.548)	0.214	9 (75%)	3 (25%)	0.300 (0.026 – 3.427)	0.590
Mutation	8 (72.73%)	3 (27.27%)			10 (90.91%)	1 (9.09%)		

The underlying theory regarding the correlation of rs11615 and rs13181 polymorphisms with chemotherapy response is the drug resistance mechanism, which involves the DNA repair mechanisms activity that could inhibit the apoptosis process of cancer cells. The polymorphism in rs13181, which codes for a protein component of the DNA helicase enzyme involved in the recognition of damaged DNA sites caused by platinum agent, and unwinding process that results in alterations in the amino acid Lysine (Lys) to Glutamine (Gln) expressed by that gene. This alteration manifests as changes in Nucleotide Excision Repair (NER) activity, leading to an alteration, decreased or increased in the effectiveness of platinum-based chemotherapy. Conversely, the polymorphism in rs11615 initiates molecular changes by substituting Cytosine (C) with Thymine (T). This alteration does not affect the amino acid sequence (Asn118Asn) but does influence *ERCC1* expression levels. It primarily impacts the incision stage of the NER mechanism, leading to direct changes in NER activity (Song et al., 2017; Zhou et al., 2020; Bowden, 2014; Afifah et al., 2020). From the previous meta-analysis study, *ERCC1* rs11615 and *ERCC2* rs13181 were includes to the best predictors of chemotherapy response (Overall Survival and/ Progression Free Survival) among many other genes involved in the chemotherapy resistance mechanism. Several other polymorphism includes *ERCC1* rs3212986 (ORR), *XPA* rs1800975 (ORR), *ERCC2* rs1052555 (OS, PFS), *XPG* rs2296147 (OS), *XRCC1* rs1799782 (ORR), *XRCC3* rs861539 (ORR), *GSTP1* rs1695 (ORR), *MTHFR* rs1801133 (ORR), and *MDR1* rs1045642 (ORR) (Tang et al., 2017).

Out of a total of 9 genes correlated with chemotherapy response or clinical outcomes, the majority of these genes are associated with DNA repair mechanisms (*EXCC1, XPA, XPD, XPG, XRCC1*, and *XRCC3*). Additionally, genes related to chemotherapy resistance through drug pharmacokinetics mechanisms include drug influx and efflux (MDR1) as well as drug metabolism and detoxification (*GSTP1*). The last gene, *MTHFR*, plays a role in the DNA synthesis process (Tan et al., 2017). Meanwhile, other meta-analysis study stated that *ERCC1* rs13181, along with other Single Nucleotide Polymorphism (SNPs) such as *ERCC1* (rs11615) and *XRCC1* (rs25487, 1799782), are among the top three predictor genes for sensitivity/response to platinum-based chemotherapy. These genes, like others involved in the chemotherapy resistance mechanism, are associated with DNA repair pathways, both in Nucleotide Excision Repair (NER) and Base Excision Repair (BER) (Fu et al., 2017).

As previously mentioned, the observed association between mutant alleles and chemotherapy response should be interpreted cautiously due to the limited sample size and preliminary nature of this study. While the findings suggest a potential trend, further research with larger cohorts is necessary to confirm these results and to better understand the underlying mechanisms. Multivariate analysis to minimize the risk of bias also cannot be performed due to the insufficient sample size. Nevertheless, the findings of this

study can be considered in the evaluation of chemotherapy response especially for patients who have treated by platinum-based chemotherapy of NSCLC in Indonesia, and it could serve as a preliminary study. Additionally, several single nucleotide polymorphisms (SNPs) should be analyzed in relation to resistance mechanisms in platinum-based treatment, including both pharmacodynamic and pharmacokinetic mechanisms.

4. Conclusion

We did not find any statistically significant associations between *ERCC1* rs11615 and *ERCC2* rs13181 polymorphisms and chemotherapy response according to RECIST 1.1 criteria or CYFRA 21-1 values as predictors of disease prognosis. However, in a clinical context, the Odds Ratio can be taken into consideration when assessing a patient's response to chemotherapy after the second cycle. This study provides preliminary data and lays the foundation for future extensive cohort observational research.

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Conflict of interest

The authors declare no conflict of interest in this research.

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