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The Chemotherapy Use and Adverse Effects of Patients with Lung Cancer at Regional General Hospital in Surabaya, Indonesia

Rika Yulia[1], Aguslina Kirtishanti[1*], Heru Wijono[2], Eko Setiawan[1,3], Bobby Presley[1,3], Tjie Kok Go[4,5], Ni Putu Irma Mayani[6], Anna Febriani[7], Halim Priyahau Jaya[7], Fauna Herawati[1,3]

[1]Department of Clinical and Community Pharmacy, Faculty of Pharmacy, University of Surabaya 60293, Surabaya, East Java, Indonesia
[2]Faculty of Medicine, University of Surabaya, Surabaya, East Java, Indonesia
[3]Centre for Medicines Information and Pharmaceutical Care, University of Surabaya, Surabaya, East Java, Indonesia
[4]Faculty of Biotechnology, University of Surabaya 60293, Surabaya, East Java, Indonesia
[5]Center of Excellence for Food Products and Health Supplements for Degenerative Conditions, University of Surabaya, Surabaya, East Java, Indonesia
[6]Faculty of Pharmacy, University of Surabaya, Surabaya, East Java, Indonesia
[7]Department of Pulmonology and Respiratory, Dr. Soetomo General Hospital, Surabaya, East Java, Indonesia

ABSTRACT

In Indonesia, lung cancer is the leading cause of death related to cancer, according to Global Cancer Observatory. Chemotherapy is the most common treatment since it works systemically and can prevent cancer cells from spreading to other organs. Cytotoxicity of chemotherapy can also put patients at high risk of experiencing adverse effects. This study aimed to evaluate the congruity of chemotherapy use with treatment recommendations and the profile of adverse effects, not only acute but also delayed adverse drug reactions. This prospective observational study involved 41 adult patients with lung cancer who received chemotherapy. Data is collected through patients' medical records, brief patient interviews, and analyzed descriptively. The majority of the patients received first-line chemotherapy (87.80%). Pemetrexed-cisplatin (39.02%) and pemetrexed-carboplatin (19.51%) are the most common first-line therapy, followed by docetaxel (12,20%) as the second-line chemotherapy commonly used by patients. The chemotherapy regimens used in patients were 100% appropriate based on treatment guidelines. 61.11% and 60% of patients experience adverse effects with the first and second line of chemotherapy, respectively. Anemia (63,89%) was the most common delayed adverse effect in the first-line chemotherapy and hair loss (60%) was the most common one in the second-line chemotherapy. The platinum-based chemotherapy is a standard treatment for lung cancer, but its tolerability limits its uses. These findings showed chemotherapy-related adverse effects that need to be considered in choosing the best choice of therapy to optimize the treatment. Therefore, prophylaxis therapy to manage chemotherapy-related adverse effects may be considered in patients with chemotherapy.

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**corresponding author*
Email: aguslina@staff.ubaya.ac.id

INTRODUCTION

Immobilized cells in lung tissue cause lung cancer, also known as lung carcinoma, which is one of the most frequent types of cancer around the globe. According to Global Burden of Cancer (GLOBOCAN) figures for 2020 (Sung et al., 2021), the incidence of lung cancer is 2.2 million people (11.4%) worldwide, and the mortality rate from lung cancer is the highest, reaching 1.79 million people (18.0%) in both sexes compare with breast and cervix cancer. Data in Indonesia in 2022, lung cancer is the most common cancer in males and ranks number 2 in both sexes. The mortality rate of lung cancer is also considered to be the highest number in males and the second highest mortality rate among males and females (Ferlay J, 2024). Due to the high mortality rate from lung cancer, the patient's therapy plays an essential role in minimizing mortality. Chemotherapy is one of the most often used treatments for patients with lung cancer because chemotherapy medicines disrupt the cell cycle to limit the growth of cancer cells and spread to other organs (Yuliandra, Nasif, Ermayanti, Sulistyowati, & Juwita, 2019).

Chemotherapy is one of the modalities of cancer therapy that works systemically. Chemotherapy can attack cells during cell division and development. Chemotherapy is cytotoxic, which means that it does not specifically attack cancer cells but can also attack normal cells in the body (Fernandes & Saini, 2023; Lewandowska et

al., 2020). Chemotherapy often attacks cells in the bone marrow, hair follicles, mouth lining, and intestines. Damage that occurs to normal cells due to chemotherapy can cause adverse effects (Burke & Rashdan, 2021; Hines et al., 2023; Lustberg, Kuderer, Desai, Bergerot, & Lyman, 2023; Rashdan, Minna, & Gerber, 2018; Wang et al., 2019; Zhou, Li, Wang, An, & Li, 2022). The dose of chemotherapy administered depends on the clinical status. An excessively high dosage in the body can raise the risk of further cell damage. Giving a lower-than-usual dose (under-dose) can reduce the efficacy of therapy, while giving a higher-than-usual dose can raise the likelihood of adverse effects (Prapa et al., 2021). Muthu et al. previously reported that the most prevalent adverse effects observed by lung cancer patients at North Indian referral hospitals were diarrhea, vomiting, and constipation (Muthu, Mylliemngap, Prasad, Behera, & Singh, 2019). Yuliandra et al. investigated the hematological adverse effects of chemotherapy at Dr. M. Djamil Padang Hospital (Yuliandra et al., 2019). They discovered that patients experienced anemia due to the treatment with carboplatin and paclitaxel (50%), carboplatin and gemcitabine (66.7%), and carboplatin and vinorelbine (50%). While leucopenia found in 31.3% of patients receiving the carboplatin-paclitaxel combination. Chemotherapy can also cause psychological adverse effects in patients, such as increased anxiety, low self-acceptance, and feelings of exclusion from their surroundings (Prapa et al., 2021; Semenenko, Banerjee, Olver, & Ashinze, 2023). Many combinations of chemotherapy can be used as treatment in patients with lung cancer, which produce different efficacy and adverse effects with various dosages. This can affect the quality of life of patients.

There is an urgent need for data analysis on the use of chemotherapy in lung cancer patients due to the high number of lung cancer cases in Indonesia in terms of prevalence and mortality. Furthermore, data on the profile and adverse effects of chemotherapy treatment in lung cancer patients in Indonesia are currently limited. These data can help health professionals measure the therapeutic tolerance of chemotherapy and adapt supportive care to patients, including appropriate approaches or supplementation to minimize chemotherapy-related adverse effects, especially in Indonesia setting. The study aimed to identify and analyze patients' sociodemographics, chemotherapy profiles, and any chemotherapy-related adverse effects. The study also examined how well the chemotherapy schedules and doses followed the Clinical Practice Guidelines of KSM Pulmonology and Respiratory Medicine at Dr. Soetomo Regional General Hospital Surabaya. The setting used is Dr. Soetomo Regional General Hospital Surabaya, a class A government-owned hospital that operates as a referral hospital for cancer patients in East Java. Therefore, most cancer patients within the East Java Province will be referred to the hospital.

METHODS

This descriptive observational study was conducted in November and December 2022 at KSM Pulmonology and Respiratory Science at Dr. Soetomo Regional General Hospital Surabaya. The study was conducted following the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of RSUD Dr. Soetomo (No. 1150/LOE/301.4.2/XI/2022). Data of this study were collected from patients' medical records and brief interviews with lung cancer patients at Dr. Sutomo Surabaya. Data collected from medical records includes sociodemographics, chemotherapy profiles, and data on chemotherapy-related adverse effects. The brief interview was conducted to collect additional data to complete the data from medical records, i.e., risk factors of lung cancer and chemotherapy-related adverse effects. The sequential sampling approach was used. This study involved adult patients with lung cancer over 18 with or without comorbidities who received chemotherapy as inclusion criteria; patients who received chemotherapy but declined to participate in the study and patients who were unable to be interviewed due to certain conditions or communication problems were excluded from the study. Total sampling was used during data collection in this study.

Patients who completed the inclusion and exclusion criteria and agreed to participate in the study were asked to sign the informed consent letter. Data collected during the study were reviewed descriptively for sociodemographic data, chemotherapy profiles, and chemotherapy-related adverse effects, including the appropriateness of chemotherapy administration. Treatment guidelines utilized at KSM Pulmonology and Respiratory Medicine at Dr. Soetomo Regional General Hospital Surabaya were used to assess the appropriateness of chemotherapy because clinicians in the hospital use it to choose the chemotherapy. Patients will be monitored for the adverse effect within the data collection period by using brief interviews. Data on chemotherapy-related adverse effects was analysed descriptively and quantitatively using Excel based on the type of acute (<24 hours after chemotherapy), delayed (1-7 days after chemotherapy), and continued delayed adverse effects (Mustian et al., 2008).

RESULTS AND DISCUSSION

Sociodemographic Characteristics

A total of 41 patients with lung cancer were involved in this study. Sociodemographic information (Table 1) showed thirty-four percent of patients in this research

Table 1. Sociodemographics

Category	Number (N = 41)	Percentage (%)
Age		
Late teens (17-25 years)	0	0
Early adulthood (25-35 years)	0	0
Late adulthood (36-45 years)	5	12.20
Early elderly (46-55 years)	11	26.83
Late elderly (56-65 years)	14	34.15
Seniors (>65 years)	11	26.83
Gender		
Male	34	82.93
Female	7	17.07
Education		
Primary school	13	31.71
Junior high school	5	12.20
Senior high school	19	46.34
Diploma	1	2.44
Bachelor	3	7.32
Occupation		
Entrepreneur	13	31.72
Pensioner	7	17.07
Farmer	5	12.20
Housewife	4	9.76
Bureaucrat	2	4.88
Factory employee	1	2.44
Lecturer	1	2.44
Others	8	19.51
Marital Status		
Married	41	100
Not married	0	0
Region		
Surabaya	15	36.59
Sidoarjo	5	12.20
Madura	3	7.32
Tulung Agung	2	4.88
Lumajang	2	4.88
Banyuwangi	2	4.88
Madiun	1	2.44
Lamongan	1	2.44
Mojokerto	1	2.44
Gresik	1	2.44
Bojonegoro	1	2.44
Tuban	1	2.44
Sumenep	1	2.44
Pasuruan	1	2.44
Out of East Java	4	9.76

were in their late old years (56–65 years) (34.15%). This finding is similar to the study of Chairudin et al., which found that most patients with lung cancer are between 51 and 60 (35.50%) (Chairudin, Marhana, & Erawati, 2019). The high number of patients with lung cancer in this age category can be influenced by the decline of body function and immunity in the elderly, which can potentially increase the risk of cancer. The impairment of the cell's ability to repair itself can cause unnatural growth of cells, which generate tumor masses that can spread to other tissues (Kobayashi et al., 2018; Steendam et al., 2023).According to the study's findings, most patients with lung cancer are dominated by males (82.93%). Study by Chairudin et al. also reported similar findings (Chairudin et al., 2019).

Table 2. Risk factor and clinical condition profile

Risk factor		
Category	**Number (N = 41)**	**Percentage (%)**
Smoking status		
Smoking history	29	70.73
Never smoked	12	29.27
Family History of Cancer		
No	33	80.49
Yes	8	19.51
Lung Disease History		
No	35	85.37
Yes	6	14.63
Clinical Condition Profile		
Category	**Number (N = 41)**	**Percentage (%)**
Cancer Stage		
NSCLC		
IIIA	1	2.44
IIIB	0	0.00
IIIC	4	9.76
IVA	26	63.41
IVB	6	14.63
SCLC		
Limited	0	0
Extensive	4	9.76
Histological Type		
NSCLC		
Adenocarcinoma	30	73.17
Squamous cell	7	17.07
Large cell	0	0
SCLC	4	9.76

Risk Factors

We classified patients based on three risk factors (Table 2): smoking history, history of lung disease, and family history of cancer. The findings showed that 70.73% of patients had a smoking history, while 29.27% had never smoked but were passive smokers. Muthu et al. discovered similar history of smoking behavior data among patients with lung cancer, revealing that 55% were active smokers and 20% were passive smokers (Muthu et al., 2019). The finding in Table 2 can be related to the sociodemographic data that males are the dominant number of patients with lung cancer. Males, on average, smoke more than females. Societal, environmental, and psychological factors can all influence smoking behavior among males. The Central Statistics Agency (BPS) predicts that by 2022, the percentage of Indonesians above 18 years old who smoke will be 6.54% for men and 0.16% for women. Smoking behaviour can increase the risk of lung cancer due to tobacco use is the leading cause of lung cancer. There are more than 4,500 chemicals in cigarettes, and more than 60 of them are known to cause cancer. These include polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines, aldehydes, benzene, and aromatic amines. In cigarettes, cytochrome P-450 enzymes help start a metabolic process that changes cancer-causing chemicals into forms that can bind and add to DNA (Holme et al., 2023). This finding shows that smoking behavior needs special attention from healthcare professionals, as the number of people who smoke tends to increase, even though the danger of smoking is already mentioned in the cigarette box.

The data finding from the study (Table 2) showed that most patients (85.37%) had no history of lung disease. According to the data, 14.63% patients had been diagnosed with TB and had taken oral antituberculosis drugs (OAT). Dutkowska et al. found that 56% of lung cancer patients had no comorbidities, 35% had COPD, and 3% had residual tuberculosis (Dutkowska & Antczak, 2016). Combination of lung cancer and a history of tuberculosis may put patients in danger. Patients who have received TB treatment may have delayed lung inflammation due to the extended duration of TB medication and the manifestation of TB symptoms several months before lung cancer detection. This condition can result in genetic damage and changes (Cheng et al., 2019).

Another risk factor for lung cancer is a family history of cancer, as shown in many studies (Abe et al., 2023; Coté et al., 2012; Ji, Sundquist, Sundquist, & Zheng, 2022; Yin, Chan, Seow, Yau, & Seow, 2021). Risk factors in Table 2 found that 80.49% of patients had no family history of cancer and 19.51% of patients had a family history of cancer. Patients' family histories are derived from a single lineage (grandparents, father, mother, and siblings). Most lung cancer patients have no family history of cancer, according to Kanwal et al. (Kanwal, Ding, & Cao, 2017). This condition is caused by somatic genetic changes that occur only in cancer cells and are not passed down through the germline cell lineage. In contrast, Cote et al. discovered that having a family history of cancer increased the probability of developing lung cancer (Coté et al., 2012). This might be attributable to inherited characteristics; however, the key factors that lead to the development of lung cancer are environmental factors and lifestyle factors such as smoking habits. Patients who live in a smoker's environment may absorb carcinogenic compounds from cigarette smoke, which is still the main cause of lung cancer. Further study might be needed to find the association between family history of cancer and lung cancer to explain the reason for the disparity in the findings.

Clinical Conditions

We categorized the clinical conditions of the patients (Table 2) based on the number of chemotherapy cycles they received, the histological kind of lung cancer, the disease stage, and their EGFR (The epidermal growth factor receptor) status. Based on immunohistochemistry, the World Health Organization (WHO) classifies lung cancer into two types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (Nicholson et al., 2022). Table 2 found that 90.24% of patients had NSCLC and SCLC was found in four patients (9.76%). Adenocarcinoma was the most prevalent histological type among patients diagnosed with non-small cell lung cancer (NSCLC) (73.17%). The histological type of lung cancer is critical in its therapy. According to the American Cancer Society, SCLC accounts for 10%-15% of all lung cancer cases, while NSCLC accounts for 80-85% of instances (Wolf et al., 2023).

Patients with NSCLC were more likely to be in stage IVA (63.41%), whereas all patients with SCLC were in the advanced stage. During the study period, most chemotherapy was administered in cycles 1–3 (70.73%), whereas 29.27% was administered in cycles 4–6. A period of rest time between cycles might boost the efficiency of chemotherapy in killing cancer cells by allowing cancer cells to have an inactive period, during which they are not impacted by chemotherapy, and an active phase, during which they proliferate and grow (Michael, Ainsley, Joseph, & Jahan, 2020). All patients in this study had a negative EGFR status. EGFR is an ErbB family tyrosine kinase receptor, namely ErbB1. These receptors are important for cell development and death. EGFR mutations cause uncontrolled cell proliferation and death. The presence of EGFR alters the therapeutic options. Patients with positive EGFR mutations can receive targeted therapy, such as tyrosine kinase inhibitors. In contrast, patients with negative EGFR mutations are treated with first-line chemotherapy, which includes a combination of platinum-based and non-platinum chemotherapy (Cabanero et al., 2017; Passaro et al., 2022; Pecci et al., 2022).

Chemotherapy Profiles

The chemotherapy profile (Table 3) shows that pemetrexed-cisplatin is the most common combination (39.02%), followed by pemetrexed-carboplatin (19.51%), and 12.20% of patients received docetaxel monotherapy. All patients had palliative chemotherapy and none of them had any surgery or radiation. Palliative chemotherapy attempts to prolong patients' lives and relieve symptoms when recovery is not possible.

Table 3. Chemotherapy Profiles

Name	Number (N = 41)	Percentage (%)
Pemetrexed-cisplatin	16	39.02
Pemetrexed-carboplatin	8	19.51
Paclitaxel-carboplatin	6	14.63
Docetaxel	5	12.20
Etoposide-carboplatin	2	4.88
Gemcitabine-carboplatin	2	4.88
Vinorelbine-carboplatin	1	2.44
Etoposide-cisplatin	1	2.44

Table 4. Acute side effects of first-line regimens

Acute side effects		Delayed side effect		Continued delayed side effect	
Side Effects	**Number (N = 36) Percentage (%)**	**Side Effects**	**Number (N = 36) Percentage (%)**	**Side Effects**	**Number (N = 36) Percentage (%)**
None	14 (38.89)	Anemia	23 (63.89)	Hepar Disorders	4 (11.11)
Nausea	12 (33.33)	Nausea	19 (52.78)	Kidney Disorder	3 (8.33)
Constipation	7 (19.44)	Vomiting	18 (50.00)	Diarrhea	3 (8.33)
Cough	6 (16.67)	Hair Loss	11 (30.56)	Body Aches	3 (8.33)
Vomiting	5 (13.89)	Constipation	10 (27.78)	Joint Pain	2 (5.56)
Hypersensitivity Reaction	3 (8.33)	Fever	6 (16.67)	Headache	1 (2.78)
Headache	3 (8.33)				
Joint Pain	2 (5.56)				
Chest Pain	2 (5.56)				
Diarrhea	1 (2.78)				
Fever	1 (2.78)				

Table 5. Acute side effects of second-line regimens

Acute side effects		Delayed side effect	
Side Effects	**Number (N = 5); percentage (%)**	**Side Effects**	**Number (N = 5); percentage (%)**
None	2 (40)	Hair Loss	3 (60)
Nausea	2 (40)	Anemia	2 (40)
Diarrhea	1 (20)	Nausea	2 (40)
Hypersensitivity Reaction	1 (20)	Vomiting	2 (40)
Cough	1 (20)	Diarrhea	1 (20)
Body aches	1 (20)	Fever	1 (20)
Chest pain	1 (20)	Joint Pain	1 (20)
Vomiting	1 (20)		

Most patients (87.80%) with lung cancer received the first-line regimen, while 12.20% of patients with the second-line regimen based on the guidelines used by clinicians in the hospitals (KSM Pulmonology and Respiratory Medicine at Dr. Soetomo Regional General Hospital Surabaya). Pemetrexed-cisplatin (39.02%) and pemetrexed-carboplatin (19.51%) are the most common first-line chemotherapy. The second-line chemotherapy was docetaxel monotherapy. Monotherapy can be used as an alternate regimen if there is a consideration of an elevated risk of toxicity with two combination chemotherapy and if there is no substantial benefit for patient survival (Rashdan et al., 2018). The assessment showed that all patients received the appropriate choice of chemotherapy. Two patients (5,56%) with the first-line regimen received inappropriate doses: one had a paclitaxel regimen with a lower dose than usual and the other had a higher dose than usual for carboplatin regimen. Chemotherapy dosages can differ based on the clinical condition of the patient. Several factors, including the patient's comorbidities, absolute neutrophil count, and other therapeutic modalities, determine the dosage of paclitaxel (Goldschmidt et al., 2021). If the patient experiences severe adverse effects or is having radiation therapy, the healthcare professional may reduce, postpone, or cancel chemotherapy.

Chemotherapy-Related Adverse Effects

This study classified chemotherapy-related adverse effects based on the timing of the onset of adverse effects, especially acute (<24 hours after chemotherapy administration) and delayed (1-7 days after chemotherapy) (Table 4 & 5). We reclassified each category based on the samples that got first- and second-line regimens. 38.89% and 40.00% of patients who got the first-line and second-line regimens did not experience any acute adverse effects, respectively. This is because each patient's adverse effects can differ; not all patients who receive chemotherapy experience any adverse effects in a short time.

In patients who received the first-line chemotherapy combination, the most common acute adverse effect experienced was nausea (33.33%). Chemotherapy can cause the release of 5-hydroxytryptamine (5-HT) in the lining of the digestive tract and set off an emetic reflex through dorsal stimulation that results in nausea. Chemotherapy agents can also induce the postrema region (the chemoreceptor trigger zone) as a regulator of nausea and vomiting. Pemetrexed-cisplatin is the most common chemotherapy with the adverse effect of nausea, which accounts for as much as 50% of the total number of patients who use the regimen. According to the literature, intravenous cisplatin has a >90% risk of causing nausea, while pemetrexed has a 10–30% risk of causing nausea (Jahn et al., 2022). Patients taking docetaxel monotherapy as the second-line therapy encounter vomiting as a adverse effect (20.00%) because intravenous docetaxel increases the incidence of emesis by 10–30% (Gubens & Wakelee, 2010).

According to the study's findings, the most common delayed adverse effects encountered were anemia, nausea, and vomiting. Anemia developed in 63,89% of patients who received the first-line chemotherapy. This result is similar to another study that the most prevalent hematological toxicity (50%) encountered following chemotherapy was anemia. Suppression of the bone marrow and damage to erythroid stem cells, which play a key role in erythrocyte creation, cause anemia in chemotherapy patients (Kang et al., 2020). Anemia is prevalent in patients taking pemetrexed-cisplatin regimens. A similar finding to one case report showed that a lung cancer patient who got pemetrexed-cisplatin experienced anemia 21 days after treatment. The patient's lab findings revealed a rapid decrease in hemoglobin levels from 127 g/L two weeks before treatment to 68 g/L three weeks later. Pemetrexed suppresses the synthesis of folic acid, which the body requires to make red blood cells. Cisplatin-induced damage to the renal tubules is linked to the generation of erythropoietin hormone (EPO), which plays a role in erythropoiesis. Cisplatin usage can result in anemia owing to EPO insufficiency (Souilah et al., 2018). Hair loss is the most prevalent delayed adverse effect in second-line regimen patients. Cell damage in the hair follicles causes hair loss. After chemotherapy is discontinued, hair restoration typically begins 1-2 months later. According to the research, docetaxel has a high chance of inducing hair loss (Saraswat, Chopra, Sood, Kamboj, & Kumar, 2019). Chemotherapy-related adverse effects from this study need to be addressed by healthcare professionals to optimize the treatment in patients, as chemotherapy is one of the main treatments for lung cancer. Monitoring for the adverse effects is an important aspect of the treatment that needs attention from the healthcare provider. The use of prophylactic medication needs to be considered for patients with chemotherapy to minimize the risk of adverse effects, optimize the therapy, and improve adherence to chemotherapy.

Some limitations need to be acknowledged in this study. First, researchers cannot be certain that patients' concerns are genuine adverse effects of chemotherapy. The researcher documented the symptoms of patients following chemotherapy use and conceptually linked them. Second, there is a possibility of recall bias to the delayed adverse effects based on patient interviews because the data is based on the patient's recollection.

CONCLUSIONS

This study shows that most patients already received first-line chemotherapy, which indicates the appropriate choice of chemotherapies already implemented in practice for patients with lung cancer. Anemia and hair loss are the most common delayed adverse effects in first and second-line chemotherapy regimens, respectively. Chemotherapy-related adverse effects must be anticipated during therapy by considering the additional use of prophylaxis medication or supplementation to help minimize the risk and improve the quality of life, including the need for routine monitoring. Further study can be done to explore the suitable prophylaxis medication in patients with chemotherapy.

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Author contribution
"Conceptualization, A.K. and F.H.; methodology, R.Y.; software, N.I.; validation, A.K. and N.I.; formal analysis, A.F, E.S, and B.P.; investigation, N.I.; resources, H.P.J.; data curation, N.I.; writing—original draft preparation, A.K.; writing—review and editing, F.H. H.W, R.Y, T.K, A.K, E.S, and B.P; visualization, N.I.; supervision, F.H.; project administration, R.Y. All authors have read and agreed to the published version of the manuscript."

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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