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Risk Factors for Adverse Events of Nanoliposomal Irinotecan Plus 5-Fluorouracil and L-leucovorin

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Abstract. *Background/Aim: The regimen with nanoliposomal irinotecan plus 5-fluorouracil and L-leucovorin (nal-IRI/FL) is used for metastatic pancreatic cancer. A clinical study has indicated that the uridine diphosphate-glucuronosyltransferase (UGT) 1A1 polymorphism is associated with neutropenia during nal-IRI/FL treatment; however, no studies have reported risk factors for the occurrence of adverse events in the clinical setting. This study aimed to explore the risk factors for adverse events of nal-IRI/FL. Patients and Methods: This study included patients with metastatic pancreatic cancer who started nal-IRI/FL treatment. Patient information, including laboratory data before nal-IRI/FL initiation and adverse events during nal-IRI/FL treatment, was retrospectively obtained from medical records. Results: This study consisted of 36 patients, including 16, 16, and 4 with UGT1A1*6 or *28 wild-type (–/–), heterozygous (+/–), and homozygous (+/+), respectively. Patients with UGT1A1*6 or *28 (+/+) exhibited significantly lower nadir counts of white blood cells (p=0.033) and neutrophils (p=0.043). Multiple regression analyses revealed that the decreased white blood cell count was significantly associated with the genotype of UGT1A1*6 or *28 (+/+) (p=0.009), high aspartate aminotransferase (AST) value before the therapy (p=0.019), and pancreatic head cancer (p=0.030). Also, the decreased neutrophil count was significantly related to the genotype of UGT1A1*6 or *28 (+/+) (p=0.017). Conclusion: Patients with UGT1A1*6 or *28 (+/+) should be especially concerned about neutropenia and leukopenia during nal-IRI/FL treatment. Additionally, high AST value and pancreatic head cancer may be risk factors for leukopenia during nal-IRI/FL treatment.*

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Metastatic pancreatic cancer is one of the most lethal malignancies, with very limited treatment options (1). Nanoliposomal irinotecan (nal-IRI) is mainly used for patients with metastatic pancreatic cancer (1), because NAPOLI-1, the global randomized phase 3 trial, has revealed a survival benefit with the regimen consisted of nal-IRI plus 5-fluorouracil (5-FU) and leucovorin for patients with metastatic pancreatic cancer after previous gemcitabine-based therapy (2). Based on this trial result, the regulatory agency in Japan has approved the nal-IRI plus 5-FU and L-leucovorin (nal-IRI/FL) combination therapy. Particularly interesting studies focused on predictors of treatment-response by nal-IRI-based therapy in patients with pancreatic cancer have indicated that C-reactive protein/albumin ratio (CAR), neutrophil/lymphocyte ratio (NLR), Glasgow prognostic score (GPS), total bilirubin, carcinomatosis, and previous irinotecan treatment are significantly associated with overall survival (3-8).

The most common grade ≥3 treatment-emergent adverse event reported in Asian patients is neutropenia (54.5%) in the subgroup analysis of NAPOLI-1 study (9). Leukopenia/neutropenia (76.1%/71.7%) and diarrhea (58.7%) are commonly seen nal-IRI/FL treatment-emergent adverse events in the Japanese randomized phase 2 trial (10).

Irinotecan released from nal-IRI in the body is converted to SN-38, which is demonstrated up to 1000-fold higher topoisomerase I inhibitory activity *versus* irinotecan (11). SN-38 is inactivated by uridine diphosphate-glucuronosyltransferase (UGT) 1A1 (11). Patients with *UGT1A1*6* and **28* genotypes

have demonstrated decreased metabolic activity (12, 13). Allele frequencies of *UGT1A1*6* and **28* are 0.157 and 0.097, respectively, in Japanese, and 0.007 and 0.388, respectively, in Caucasians (14). The initial dose of nal-IRI has to be adjusted according to the *UGT1A1* genotype (15). This is consistent with NAPOLI-1 trial, in which patients homozygous for the *UGT1A1*28* allele initially receive nal-IRI at a 20 mg/m^2 dose reduction from the usual 70 mg/m^2 (2). In the Japanese clinical study, all patients with *UGT1A1* (*UGT1A1*6/*6* or **6/*28*) mutations in the nal-IRI/FL arm exhibited grade ≥3 decreased neutrophil count in spite of the dose reduction (15). A previous study in Taiwan has revealed a significantly higher incidence of grade ≥3 neutropenia and diarrhea in patients with *UGT1A1*6* or **28* homozygosity/compound heterozygosity than in those with single heterozygosity/wild type (16). However, no study has reported the risk factors for the adverse events during nal-IRI/FL treatment based on analysis of factors other than the *UGT1A1* polymorphism in clinical settings.

The present study aimed to investigate the risk factors for leukopenia, neutropenia, and diarrhea during nal-IRI/FL treatment in Japanese patients based on their characteristics, such as *UGT1A1* polymorphism, laboratory data before nal-IRI/FL initiation, and tumor location.

Patients and Methods

Ethics. This study was designed and implemented under the Declaration of Helsinki and its amendments, and was approved by the Wakayama Medical University Ethics Committee (No. 3,828). Information regarding the conduct of the study was disclosed on the website, and the research participants were given the option to refuse study participation.

Patient and safety evaluation. Patients with metastatic pancreatic cancer, who started nal-IRI/FL treatment at Wakayama Medical University Hospital, were retrospectively recruited from June 2021 to May 2022. Patient backgrounds, including the laboratory data before nal-IRI/FL initiation, were collected from the electronic medical records. White blood cell count nadir, neutrophil count nadir, and onset of diarrhea were evaluated during nal-IRI/FL treatment and graded according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis. Statistical Package for the Social Sciences (SPSS® Statistics 28.0; IBM Japan, Tokyo, Japan) was used for all statistical analyses. Data are expressed as the number of patients or the median with an interquartile range. Kruskal–Wallis tests and the post hoc Mann–Whitney *U*-tests with a Bonferroni correction were used to compare the medians of continuous values among groups, whereas chi-square tests were utilized to test categorical data distribution. Multivariate logistic regression analysis was conducted to identify factors affecting the onset of diarrhea, in which the onset of diarrhea was the dependent variable and all the independent variables with *p*-values of <0.2 defined in the univariate logistic regression analysis were tested. Multiple regression analyses were performed to identify factors related to the nadir count of white blood cell and neutrophil, in which the nadir count was the dependent variable and the independent variables with *p*-values of <0.2 defined in the single regression analysis were selected and tested. *p*-values of <0.05 were considered statistically significant.

Results

Thirty six patients with metastatic pancreatic cancer were recruited in this study. Table I summarizes the characteristics of patients who received nal-IRI/FL treatment. There were 16, 16, and four patients with *UGT1A1*6* or **28* wild-type (–/–), heterozygous (+/–), and homozygous (+/+) genotypes, respectively. The *UGT1A1*6* and **28* alleles were detected in three and 12 patients in the *UGT1A1*6* or **28* (+/–) group, respectively, and the allele detail of one patient was unknown. The *UGT1A1*6/*6*, **6/*28*, and **28/*28* genotypes were detected in one, one, and two patients in the *UGT1A1*6* or **28* (+/+) group, respectively. Patients with *UGT1A1*6* or **28* (+/+) showed higher total bilirubin levels in their pretreatment stages. The initial nal-IRI doses of patients with *UGT1A1*6* or **28* (–/–), (+/–), and (+/+) were 56 (56-56), 56 (48-67), and 48 (40-49) mg/m^2 (median with the interquartile range), respectively. The prescribed nal-IRI doses for patients with *UGT1A1*6* or **28* (+/+) were lower than those for other patients (p=0.011). Conversely, factors other than total bilirubin level and initial nal-IRI dose were not significantly different among the *UGT1A1* genotype groups.

Diarrhea during nal-IRI/FL treatment was observed in seven (24.1%) of 29 patients, who had not been prescribed any antidiarrhea medication at the commencing time of nal-IRI. The rest of seven patients were excluded, since they received loperamide for diarrhea symptoms at the start of therapy. The incidence of grade ≥1 diarrhea in patients with *UGT1A1*6* or **28* (–/–), (+/–), and (+/+) were 27.3%, 21.4%, and 25.0%, respectively (Figure 1). Multivariate analysis did not extract any risk factors, which significantly affected the development of diarrhea possibly induced by nal-IRI/FL (Table II).

The nadir counts of white blood cells in patients with *UGT1A1*6* or **28* (–/–), (+/–), and (+/+) were 3,340 (2,950–5,120), 3,220 (2,520-3,923), and 2,050 (1,550-2,513)/mm^3, respectively (median with the interquartile range) (Figure 2A). The nadir counts of neutrophil in patients with *UGT1A1*6* or **28* (–/–), (+/–), and (+/+) were 1,930 (1,540-2,782), 1,285 (1,093-2,113), and 860 (407-1,616)/mm^3, respectively (median with the interquartile range) (Figure 2B). The nadir counts of white blood cells and neutrophils were significantly lower in patients with *UGT1A1*6* or **28* (+/+) (p=0.033, 0.043, respectively) (Figure 2A and B). Grade 3 or 4 leukopenia and neutropenia in the *UGT1A1*6* or **28* (+/+) group demonstrated an incidence rate of 50.0%, indicating a higher tendency than those in *UGT1A1*6* or **28* (–/–) and (+/–) groups at 7.1% and 12.5%, respectively (p=0.085 for each) (Figure 2C and D). Multiple regression

Table I. *Patient characteristics*.

	*UGT1A1*6* or **28*			
	(−/−) (n=16)	(+/−) (n=16)	(+/+) (n=4)	*p*-Value
Age (years)	74 (65-78)	72 (61-75)	75 (71-79)	0.412[a]
Sex: female/male	8/8	7/9	3/1	0.535[b]
Body weight (kg)	44.5 (37.0-51.7)	52.2 (48.2-57.7)	50.6 (35.0-59.3)	0.075[a]
Body surface area (m^2)	1.42 (1.27-1.53)	1.55 (1.43-1.62)	1.49 (1.21-1.60)	0.135[a]
History of surgical resection: +/−	7/9	4/12	1/3	0.495[b]
Location: Head/Not head	10/6	11/5	3/1	0.869[b]
Number of prior systemic therapy: 1/≥2	10/6	12/4	3/1	0.721[b]
Initial nal-IRI dose (mg/m^2)	56 (56-56)	56 (48-67)	48 (40-49)	0.011[a]
Initial L-leucovorin dose (mg/m^2)	160 (160-190)	160 (160-191)	150 (120-160)	0.144[a]
Initial 5-fluorouracil dose (mg/m^2)	1,856 (1,786-1,920)	1,920 (1,840-1,920)	1,757 (1,470-1,891)	0.244[a]
Laboratory data before nal-IRI/FL initiation				
AST (U/l)	28 (21-34)	25 (20-32)	19 (18-23)	0.128[a]
ALT (U/l)	22 (12-49)	19 (12-36)	12 (9-17)	0.164[a]
Serum albumin (g/dl)	3.3 (3.1-3.7)	3.7 (3.2-3.8)	3.5 (3.0-3.9)	0.552[a]
Total bilirubin (mg/dl)	0.5 (0.3-0.7)	0.6 (0.4-0.9)	1.0 (0.8-1.4)	0.018[a]
Serum creatinine (mg/dl)	0.61 (0.53-0.77)	0.74 (0.60-0.90)	0.66 (0.59-0.73)	0.173[a]
eGFR ($ml/min/1.73\ m^2$)	81 (71-94)	75 (63-81)	72 (64-77)	0.269[a]

Data are expressed as the number of patients or median with interquartile range in parentheses. [a]Kruskal-Wallis test. [b]Chi-square test. UGT: Uridine diphosphate-glucuronosyltransferase; nal-IRI: nanoliposomal irinotecan; nal-IRI/FL: nanoliposomal irinotecan plus 5-fluorouracil and L-leucovorin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; eGFR: estimated glomerular filtration rate.

Table II. *Predictive factors for diarrhea during nal-IRI/FL treatment*.

Factors	Odds ratio	95%CI	*p*-Value
Body weight	0.89	0.78-1.03	0.108
Serum albumin	0.11	0.01-1.42	0.091

The predictive factors for diarrhea during nal-IRI/FL treatment were evaluated by multivariate logistic regression analysis using patient characteristics with *p*-values of <0.2 in the univariate logistic regression analyses. 95%CI: 95% confidence interval.

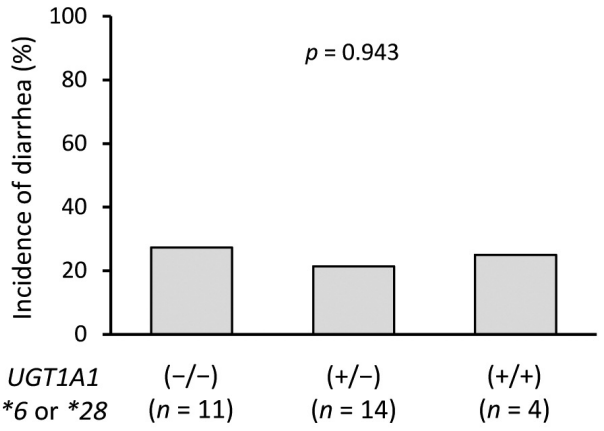

Figure 1. *Influence of UGT1A1 genotype on diarrhea during nal-IRI/FL treatment. Seven cases were excluded, since they received loperamide for diarrhea symptoms at the start of nal-IRI/FL treatment. The chi-square test was used to test categorical data distribution.*

analyses revealed that the *UGT1A1*6* or **28* (+/+) genotype, high AST value before the nal-IRI/FL therapy, and pancreatic head cancer were significantly associated with decreased white blood cell count (p=0.009, 0.019, and 0.030, respectively) (Table III), and that of *UGT1A1*6* or **28* (+/+) was significantly related to decreased neutrophil count (p=0.017) (Table IV).

Discussion

This study revealed the risk factors for leukopenia and neutropenia during nal-IRI/FL treatment in Japanese patients based on patient characteristics such as *UGT1A1* polymorphism, laboratory data before nal-IRI/FL initiation, and tumor location.

This study did not extract any risk factors that significantly influenced the development of diarrhea during nal-IRI/FL treatment (Table II). A previous study has revealed a significantly higher incidence of grade ≥3 diarrhea in patients with *UGT1A1*6* or **28* homozygosity/compound heterozygosity than in those with single heterozygosity/wild type at 33.3% *versus* 9.5%, respectively (16). This study surveyed the incidence of grade ≥1 diarrhea, and we excluded seven cases because of regular loperamide administration from the start of nal-IRI/FL. This exclusion

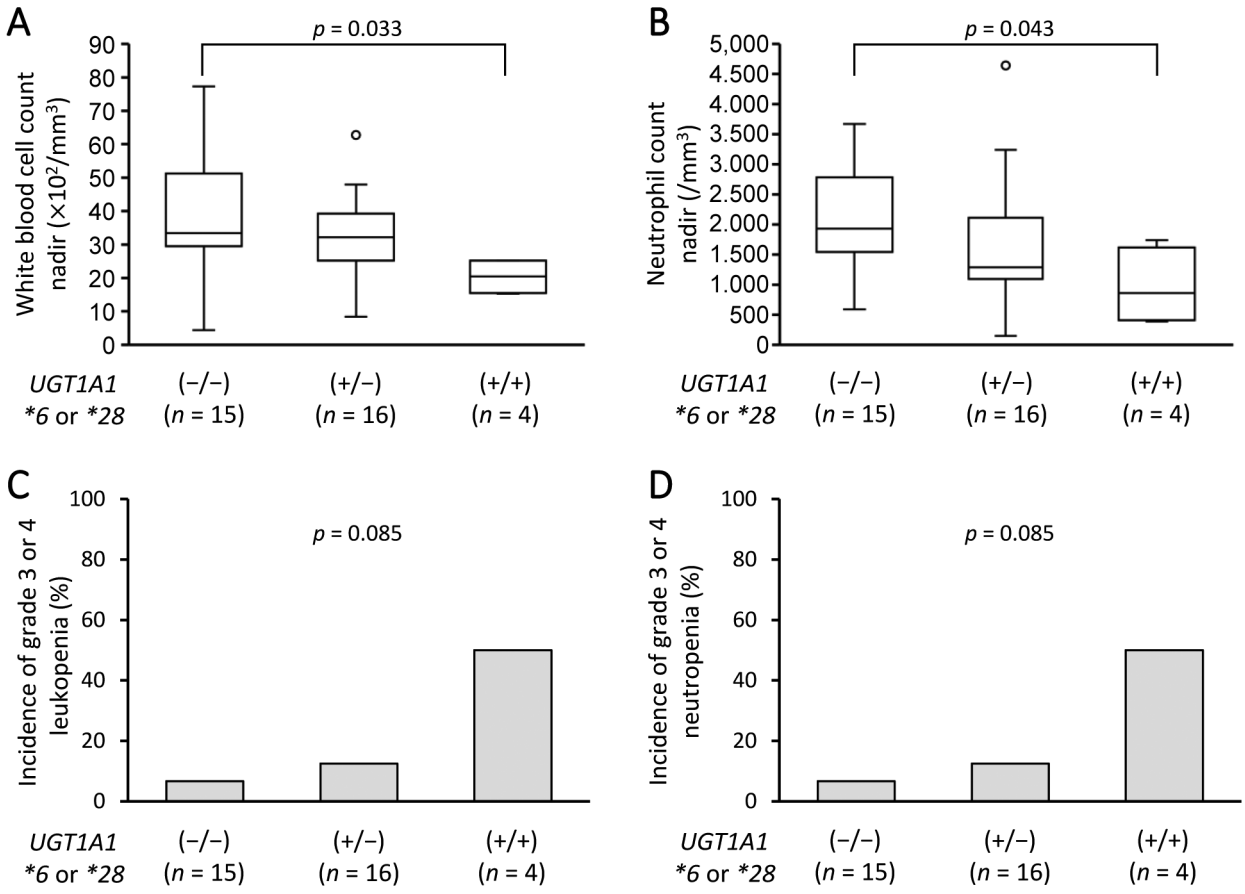

Figure 2. *Influence of UGT1A1 genotype on leukopenia and neutropenia during nal-IRI/FL treatment. (A) White blood cell count nadir, (B) neutrophil count nadir, (C) incidence of grade 3 or 4 leukopenia, (D) incidence of grade 3 or 4 neutropenia. One case was excluded because of missing information on the laboratory data after nal-IRI/FL-initiation. The box plot shows minimum, first quartile, median, third quartile, and maximum. The central rectangle spans the first quartile to the third quartile (the interquartile range). An outlier between 1.5 and 3 times the interquartile range is indicated as an open circle. Kruskal–Wallis tests and the post hoc Mann–Whitney U-tests with a Bonferroni correction were used to compare the medians of continuous values among groups, whereas chi-square tests were utilized to test categorical data distribution.*

is necessary to accurately assess the adverse effects of nal-IRI/FL, but the influence of the *UGT1A1* polymorphism might not have been detected due to the small sample size.

By this study, we identified a 14.7% incidence rate of grade ≥3 neutropenia during nal-IRI/FL treatment, although an incidence of 45.7% of grade ≥3 neutropenia has been reported by a Japanese phase 2 trial (10). The standard nal-IRI/FL regimen consists of 70 mg/m^2 nal-IRI, 200 mg/m^2 L-leucovorin, and 2,400 mg/m^2 5-FU, and patients with *UGT1A1*6* or **28* (+/+) should be prescribed nal-IRI at a 20 mg/m^2 dose reduction (15). However, as shown in this study, the dose and its reduction were at the attending physician's discretion rather than the standard reduction rule (Table I). Thus, the lower incidence of grade ≥3 neutropenia found in this study might be associated with a reduced treatment dose. The incidence of grade ≥3 neutropenia in a previous study has been reported to be significantly higher in patients with *UGT1A1*6* or **28* homozygosity/compound heterozygosity than in those with single heterozygosity/wild type; occurrence rates are 73.3 and 38.1%, respectively (16). Patients with *UGT1A1*6* and **28* genotypes have demonstrated decreased metabolic activity (12, 13). In particular, the phase 1 studies of nal-IRI-based therapy have indicated that patients with *UGT1A1*6/*28* show a higher area under the plasma concentration–time curve of SN-38 than that of the other patients and experience grade 4 neutropenia (17, 18). The neutropenia is associated with unencapsulated SN-38 maximum plasma concentration (C_{max}), and Asians show higher unencapsulated SN-38 C_{max} compared with Caucasians in a pharmacokinetic analysis (19). Nal-IRI is less toxic than conventional irinotecan *in vivo* (20). The grade ≥3 neutropenia and leukopenia in the *UGT1A1*6* or **28* (+/+) group exhibited a high incidence (Figure 2), indicating that unencapsulated SN-38 C_{max} might have been increased in this group.

Table III. *Predictive factors for leukopenia during nal-IRI/FL treatment.*

Factors	B	Standard error	*p*-Value
*UGT1A1*6* or **28* (+/+)	–19.32	6.97	0.009*
Age	0.36	0.25	0.169
AST	–0.28	0.11	0.019*
Head pancreatic cancer	–10.49	4.61	0.030*

The predictive factors for leukopenia during nal-IRI/FL treatment were evaluated by multiple regression analysis using patient characteristics with *p*-values of <0.2 in the single regression analyses. Total bilirubin level was excluded from the analysis because it is associated with the *UGT1A1* genotype (Table I). The *F* score of this model was 4.709 (p=0.005) with adjusted R^2=0.304. B: Unstandardized coefficients; UGT: uridine diphosphate-glucuronosyltransferase; AST: aspartate aminotransferase. *p<0.05 was considered statistically significant.

Table IV. *Predictive factors for neutropenia during nal-IRI/FL treatment.*

Factors	B	Standard error	*p*-Value
*UGT1A1*6* or **28* (+/+)	–1,242.7	491.3	0.017*
AST	–15.8	7.8	0.051
Serum creatinine	–1,785.4	913.7	0.060

The predictive factors for neutropenia during nal-IRI/FL treatment were evaluated by multiple regression analysis using patient characteristics with *p*-values of <0.2 in the single regression analyses. Total bilirubin level was excluded from the analysis because it is associated with the *UGT1A1* genotype (Table I). The *F* score of this model was 4.103 (p=0.015) with adjusted R^2=0.215. B: Unstandardized coefficients; UGT: uridine diphosphate-glucuronosyltransferase; AST: aspartate aminotransferase. *p<0.05 was considered statistically significant.

The results of this study revealed that increased AST value before the nal-IRI/FL therapy and pancreatic head cancer were significantly associated with leukopenia (Table III). A previous study on FOLFIRINOX, which includes conventional irinotecan and provides similar prognoses to nal-IRI/FL as second-line therapy (21), has revealed the significant risk factor of grade 4 neutropenia: tumor location in the head of the pancreas (odds ratio=1.96) (22). Biliary obstruction due to a tumor in the head of the pancreas increases bilirubin levels, and total bilirubin higher than the upper limit of normal range is also a risk factor for grade 4 neutropenia (23). We believe that biliary obstruction and decreased liver function before nal-IRI/FL initiation might be associated with developing leukopenia through elevated unencapsulated SN-38 C_{max}. There are many reports on predictors of treatment-response by nal-IRI-based therapy. In particular, CAR, NLR, GPS, total bilirubin, carcinomatosis, and previous treatment with irinotecan have been significantly associated with overall survival (3-8). However, no study has reported the risk factors for the adverse events during nal-IRI/FL treatment based on the analysis of factors other than the *UGT1A1* polymorphism in clinical settings. The results of this study indicated that *UGT1A1*6* or **28* (+/+), high AST value before the nal-IRI/FL therapy and pancreatic head cancer may be risk factors for myelosuppression during nal-IRI/FL treatment (Table III, Table IV).

This study has several limitations. This is a retrospective study based on medical records. Further, we did not measure the plasma concentration of irinotecan and its active metabolite SN-38. Therefore, a prospective study with a larger number of patients needs to clarify the influence of factors affecting the pharmacokinetics of nal-IRI.

Conclusion

Patients with *UGT1A1*6* or **28* (+/+) should be especially concerned about neutropenia and leukopenia during nal-IRI/FL treatment. Further, high AST value and pancreatic head cancer may be risk factors for leukopenia during nal-IRI/FL treatment.

Conflicts of Interest

The Authors declare no competing interests in relation to this study.

Authors' Contributions

Conceptualization: T.I. and M.S.; Data curation: T.I., H.E., S.H., K.K., and S.S.; Formal analysis: T.I. and M.S.; Supervision: R.A., M.K., and K.M.; Writing – original draft: T.I., M.S., and K.M.; Writing – review & editing: R.A. and M.K.; All Authors read and approved the final manuscript.

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