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Factors Associated With Infusion Reactions in Patients With Breast Cancer Receiving Trastuzumab

RYUJI YAMAGUCHI[1], MASANOBU UCHIYAMA[2,3], MOTOYASU MIYAZAKI[4,5], TOSHINOBU HAYASHI[5], KOHEI OYABU[6], TAKAFUMI NAKANO[2,3] and KOICHI MATSUO[2,3]

[1]*Department of Pharmacy, Kyushu Central Hospital, Fukuoka, Japan;*
[2]*Department of Pharmacy, Fukuoka University Hospital, Fukuoka, Japan;*
[3]*Department of Oncology and Infectious Disease Pharmacy, Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka, Japan;*
[4]*Department of Pharmacy, Fukuoka University Chikushi Hospital, Fukuoka, Japan;*
[5]*Department of Emergency and Disaster Medical Pharmacy, Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka, Japan;*
[6]*Department of Drug Informatics and Translational Research, Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka, Japan*

Abstract. *Background/Aim: Trastuzumab (TRA) is a key drug in human epidermal growth factor receptor type 2 (HER2)-positive breast cancer treatment. Infusion reactions (IR) with TRA are frequently observed in practice. Although the efficacy of premedication has been previously reported, it remains uncommon. The probability of severe IR due to TRA is low; however, when it does occur, it is associated with patient discomfort and expenditure of medical resources. This study aimed to analyze the factors associated with the occurrence of IR in patients with breast cancer who received TRA. Patients and Methods: We retrospectively studied 204 patients who underwent TRA for breast cancer treatment between September 2008 and June 2023, identifying factors influencing the occurrence of IR at the time of TRA administration. Results: A total of 182 patients were included in this study, and the incidence of IR was 25.8% (47/182 patients). Multiple logistic regression analysis showed that pertuzumab (PER) use, high alkaline phosphatase (ALP), and low high-density lipoprotein (HDL) cholesterol levels were associated with IR. Conclusion: IR should be considered when PER is combined with TRA. ALP and HDL cholesterol levels may be predictive markers of TRA-induced IR in patients with breast cancer.*

Correspondence to: Koichi Matsuo, Department of Oncology and Infectious Disease Pharmacy, Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1, Nanakuma, Fukuoka Shi Jonan Ku, Fukuoka Ken, 814-0180, Japan. Tel: +81 928716631, Fax: +81 928630389, e-mail: ko1matsuo@fukuoka-u.ac.jp

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Trastuzumab (TRA) is a recombinant humanized monoclonal antibody that selectively binds to the extracellular domain of human epidermal growth factor receptor type 2 (HER2) and is a key drug for HER2-positive breast cancer.

Infusion reaction (IR) is an adverse reaction observed in clinical practice with symptoms including fever, chills, nausea, vomiting, pain, headache, cough, dizziness, rash, and asthenia occurring within 24 h after administering certain medications (1). The mechanisms of IR, including cytokine release syndrome and immunoglobulin E (IgE)- and IgG-mediated responses, have gradually been clarified but are yet to be fully elucidated (2, 3). Although package inserts in Japan and the US indicate that the incidence of IR with TRA is approximately 40%, the incidence of IR reportedly varies from 0.7% to 40%, owing to the different definitions of IR in each clinical trial (4).

Some monoclonal antibody preparations require or recommend the use of corticosteroids, antihistamines, and nonsteroidal anti-inflammatory drugs (NSAIDs) as premedications before administration. However, TRA does not necessarily have a standard method because the efficacy of premedication for IR prevention has not been confirmed.

Tokuda *et al*. reported that the incidence of IR (fever and chills) decreased when NSAID suppositories were administered before TRA administration (5). However, it is difficult to use suppositories as premedication with increasing outpatient treatments.

Takahashi *et al*. reported a low percentage of eosinophils as a risk factor for IR with TRA (6). However, their results were based on univariate analysis, and further analysis adjusting for confounding factors is warranted.

Pertuzumab (PER) is a recombinant humanized monoclonal antibody that specifically binds to domain II of the extracellular region, which is essential for HER2 dimer formation and inhibits ligand-stimulated HER2/HER3 dimerization (7). In metastatic breast cancer and early-stage breast cancer with a high risk of recurrence, PER is combined with TRA; however, few studies have examined whether these combinations contribute to IR.

Understanding the risk factors for IR is important because the incidence of IR is associated not only with patient disadvantage due to treatment interruption, but also with the loss of healthcare resources to address it. This study aimed to analyze the factors associated with the occurrence of IR in patients with breast cancer who received TRA.

Patients and Methods

Eligible patients. Patients with breast cancer who received TRA (Herceptin®; Chugai Pharmaceutical Co., Tokyo, Japan) between September 2008 and June 2023 at Kyushu Central Hospital of the Japan Mutual Aid Association of Public School Teachers were recruited for this study.

Demographic and clinical characteristics of 204 patients, including age, sex, chemotherapy regimen, previous chemotherapy treatment, surgical history, premedication, regular use of antihistamines and NSAIDs, and laboratory parameters before the start of TRA were collected retrospectively from the electronic medical records (EMRs). Of the data for 204 patients extracted from the EMRs, 182 were included in the study, excluding eight patients with a history of TRA administration by a previous physician, 12 patients who discontinued treatment after starting treatment due to side effects from other drugs or refusal of treatment, and two patients who did not receive a third TRA dose during the study period (Figure 1). A total of 182 patients were included in the study and all were females. The order of drugs administered was antibody drugs first, followed by chemotherapy; if PER was administered, it was done before TRA.

Definitions. IRs were defined as any signs or symptoms, including fever, chills, nausea, vomiting, pain, headache, cough, dizziness, rash, and asthenia, occurring within 24 h after the initiation of administration. These data were extracted from the EMRs.

During the study period, these signs and symptoms were observed in outpatient chemotherapy rooms by nurses and pharmacists certified in cancer chemotherapy. At their next visit to our hospital, patients were asked whether these signs or symptoms occurred after returning home.

Patients were divided into two groups: "IR group", including patients who experienced IRs by the third TRA dose, and the "non-IR group", including patients who did not experience IRs by the third dose. IR was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Statistical analysis. Patient characteristics and laboratory parameters were compared between the two groups. In the univariate analysis, categorical data were analyzed using Fisher's direct probability test, and continuous variables were analyzed using the Mann–Whitney *U*-test. The significance level was set at $p<0.05$.

In the multivariate analysis, the presence or absence of IR was used as the objective variable. The explanatory variables were the presence of premedication (5) and eosinophils (6), which have been reported as risk factors for the occurrence of IR in previous reports. Additionally, to search for new risk factors, multiple logistic regression analysis using the forced entry method was performed by adding the concomitant use of PER, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (γ-GTP), high-density lipoprotein (HDL) cholesterol, and CRP levels, which showed $p<0.15$ in the univariate analysis. StatMate V (ATMS Co., Tokyo, Japan) and JMP (SAS Institute Inc., Cary, NC, USA) were used for statistical analyses.

Ethical regulations. This study was conducted following the ethical guidelines for medical research involving human subjects and approved by the Ethical Review Committee of Kyushu Central Hospital (Clinical Research No. 256). All patients were treated following the principles outlined in the Declaration of Helsinki. Accumulated patient data were used after allowing the refusal of patients to participate by publishing an opt-out document. Informed consent was waived because of the retrospective nature of the study.

Results

Patient characteristics. The characteristics of patients in both groups are shown in Table I.

Among the patient characteristics, the PER + TRA regimen was associated with a significantly higher incidence of IR than the TRA regimen in univariate analysis ($p<0.01$). There were significant differences in laboratory parameters prior to TRA administration, particularly ALP and γ-GTP in univariate analysis ($p<0.05$) (Table II).

Incidence of infusion reaction. Most IRs appeared in the early stages of administration ($1^{st}/2^{nd}/3^{rd}$: 43/3/1). IRs included chills (32 cases), fever (25 cases), nausea (seven cases), headache (six cases), vomiting (four cases), pain (two cases), rash (two cases), and cough (one case). Some patients had multiple manifestations. No patient was considered to have serious IR (grade 3 or higher according to the CTCAE version 5.0), and all patients in the IR group continued treatment after the occurrence of IR.

Risk factors for infusion reaction. Use of PER ($p<0.01$), ALP ($p<0.01$), and HDL cholesterol levels ($p<0.01$) were significantly associated factors (Table III).

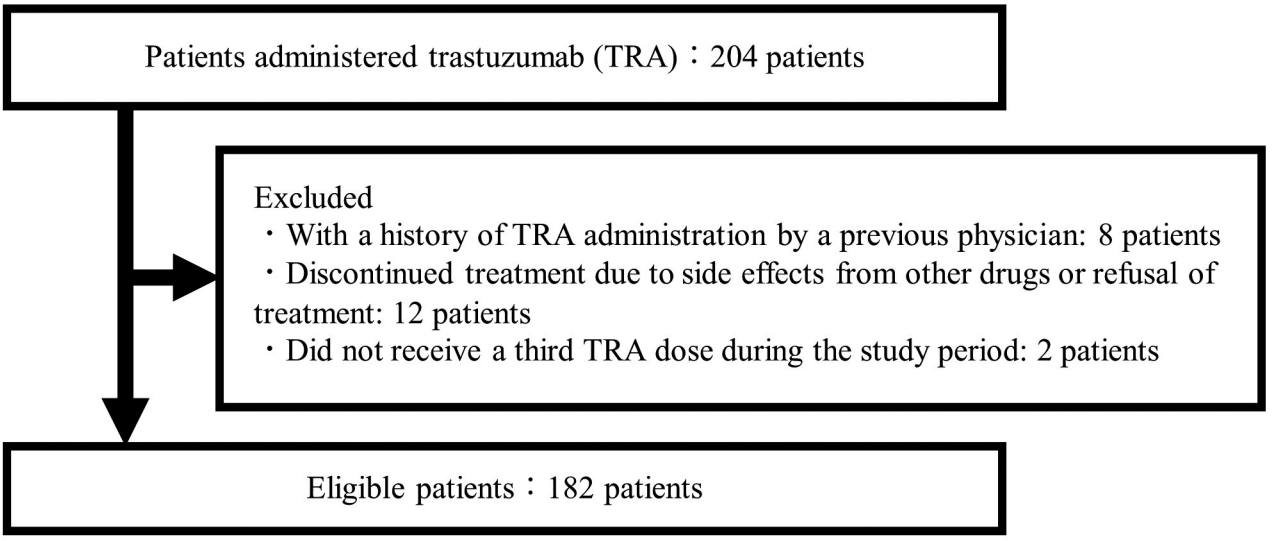

Figure 1. *Patient flow chart and reasons for exclusion. This study included patients who received TRA between September 2008 and June 2023.*

Discussion

This study aimed to analyze the factors associated with the occurrence of IR in patients with breast cancer who received TRA. PER use, ALP, and HDL cholesterol were identified as risk factors for IR among the patient characteristics examined in this study.

The combination of TRA with chemotherapy and PER has been shown to prolong overall survival in metastatic breast cancer (CLEOPATRA study) (8) and improve invasive disease-free survival in early-stage breast cancer (APHINITY study) (9). These results have led to an increase in the combined use of both drugs.

In this study, the overall incidence of IR in patients treated with TRA was 47/182 (25.8%). The incidence of IR at the time of first administration in the aforementioned international clinical study ranged from 9.8% to 20.9% (8, 9), which we believe is comparable to the present results. Furthermore, the incidence of IR in a similar overseas clinical study in Asians, mainly in China and Taiwan, ranged from 9.1-22.0% (10), comparable to the incidence in the present study. In contrast, in the present study, the incidence of IR was as high as 23/47 (48.9%) when only PER-treated patients were included.

In 2022, TRA and PER have been indicated for treating HER2-positive advanced or recurrent unresectable colorectal cancer that has progressed after chemotherapy in Japan. In the study (TRIUMPH study), the incidence of IR was found to be high (21/30, 70%) (11), similar to the incidence in patients treated with PER in this study, although more than half of the patients in the study received premedication. In a similar international clinical trial involving approximately 80% Caucasians, the incidence of IR was 18% (12), lower than that reported in a Japanese clinical trial.

It has been suggested that adverse reactions in TRA may differ depending on race (13); however, as mentioned earlier, there is no difference in the incidence of IR between Caucasians and Asians (Chinese and Taiwanese). To date, there have been no reports of increased incidence of IR with concomitant use of PER, which may be related to the unique circumstances of Asians, including Japanese. Although differences in patient backgrounds and other factors are possible, these details are unknown, and further investigation is needed.

Tokuda *et al*. also reported that premedication with NSAID suppositories at the time of TRA administration decreased the incidence of IR (fever and chills) (5). In this study, although the results were based on univariate analysis, among patients with IR, when symptoms were limited to fever and chills, the presence or absence of premedication tended to be a risk factor for IR (OR=0.399; 95%CI=0.176-0.903; p=0.024). Based on these results, IR, such as fever and chills caused by TRA, may be prevented by NSAIDs. However, other symptoms may not be sufficiently prevented by premedication with NSAIDs. Therefore, premedication with NSAIDs is not uniformly recommended, as there is a risk of overmedication, and the appropriate selection of patients who should be premedicated remains unclear.

Takahashi *et al*. reported a low percentage of eosinophils as a risk factor for IR with TRA (6), which was not observed in this study. However, in the study by Takahashi *et al*., TRA alone was administered on day one, and the other drugs were

Table I. *Clinical characteristics of patients at baseline*.

	Non-IR group (n=135)	IR group (n=47)	*p*-Value
Age			
20s	0	1	0.28
30s	6	3	
40s	25	7	
50s	36	16	
60s	41	16	
70s	22	4	
80s	5	0	
Surgical history			
No	31	11	0.95
Yes	104	36	
Previous chemotherapy treatment			
No	73	27	0.69
Yes	62	20	
AC	40	9	
Dose-dense AC	4	3	
DTX	2	2	
EC	2	0	
FEC	7	3	
Trastuzumab Emtansine	1	1	
Hormone therapy	5	2	
Hormone therapy + Trastuzumab Emtansine	1	0	
Premedication			
No	78	32	0.21
Yes	57	15	
NSAIDs	37	13	
NSAIDs + dexamethasone	1	0	
NSAIDs + H1RA + H2RA + Dexamethasone	3	0	
NSAIDs + H1RA + H2RA + Betamethasone	13	0	
NSAIDs + H2RA + Dexamethasone	1	0	
NSAIDs + Betamethasone	2	0	
Acetaminophen	0	2	
Medications used regularly			
No	119	40	0.59
Yes	16	7	
H1RA	7	2	
H2RA	2	1	
NSAIDs	7	4	
Chemotherapy regimen			
TRA regimen	111	24	<0.01
PER + TRA regimen	24	23	
TRA + DTX	29	5	
TRA + nab-PTX	4	2	
TRA + PTX	38	2	
TRA + S-1	0	1	
TRA + TC	29	9	
TRA monotherapy	11	5	
PER + TRA + DTX	3	6	
PER + TRA + PTX	19	17	
PER + TRA + VNB	1	0	
PER + TRA + ERB	1	0	
Course in which IR occurred			
1st course	0	43	
2nd course	0	3	
3rd course	0	1	

TRA: Trastuzumab; PER: pertuzumab; AC: doxorubicin + cyclophosphamide; DTX: docetaxel; EC: epirubicin + cyclophosphamide; FEC: fluorouracil + epirubicin + cyclophosphamide; nab-PTX: nanoparticle albumin-bound paclitaxel; PTX: paclitaxel; S-1: tegafur/gimeracil/oteracil; TC: docetaxel + cyclophosphamide; VNB: vinorelbine; ERB: eribulin; NSAIDs: non-steroidal anti-inflammatory drugs; H1RA: histamine H1 receptor antagonist; H2RA: histamine H2 receptor antagonist.

Table II. *Laboratory values of patients at baseline.*

		Non-IR group (n=135)	IR group (n=47)	*p*-Value
WBC	10^3/μl	5.0±1.7	5.0±1.5	0.82
RBC	10^6/μl	4.0±0.5	4.0±0.6	0.42
Hb	g/l	12.2±1.5	12±1.7	0.78
Hct	%	36.5±4.6	36.1±5.0	0.82
MCV	fl	92.2±6.3	90.8±5.1	0.24
MCH	pg	30.8±2.4	30.3±1.9	0.22
MCHC	g/dl	33.4±0.9	33.3±0.8	0.67
RDW	%	15.4±3.9	16.0±4.5	0.61
PLT	10^3/μl	264.2±87.5	265.2±82.3	0.74
Neut	%	62.5±9.0	61.7±10.8	0.50
Lymph	%	24.2±9.1	25.0±10.7	0.82
Mono	%	8.9±3.8	9.4±4.8	0.88
Eosino	%	2.3±1.9	2.3±1.9	0.62
Baso	%	0.9±0.6	0.9±0.6	0.40
TP	g/dl	6.9±0.5	6.9±0.5	0.76
Alb	g/dl	4.1±0.3	4.1±0.3	0.56
A/G		1.5±0.3	1.5±0.2	0.38
BUN	mg/dl	13.0±3.5	12.6±4.8	0.41
CRE	mg/dl	0.6±0.1	0.6±0.1	0.34
T-Bil	mg/dl	0.5±0.2	0.5±0.2	0.53
AST(GOT)	U/l	23.2±9.4	29.1±21.9	0.22
ALT(GPT)	U/l	21.0±11.5	27.8±28.3	0.24
ALP	U/l	237.4±80.4	320.8±237.8	<0.01
LDH	U/l	188.9±39.0	207.0±76.6	0.64
γ-GTP	U/l	42.2±54.6	74.6±157.8	<0.05
AMY	U/l	77.2±31.0	72.7±22.6	0.54
ChE	U/l	317.0±102.9	316.8±67.9	0.42
T-Cho	mg/dl	211.5±35.9	216.2±44.3	0.84
HDL-C	mg/dl	68.0±15.7	62.5±14.5	0.06
TG	mg/dl	142.4±109.9	144.7±69.1	0.27
LDL-C	mg/dl	114.2±28.8	121.8±35.6	0.49
non-HDL-C	mg/dl	140.4±35.3	149.2±44.5	0.66
Na	mmol/l	141.4±1.8	141.3±1.9	0.61
K	mmol/l	4.1±0.3	4.1±0.3	0.25
Cl	mmol/l	105.8±2.5	105.6±2.0	0.66
Ca	mg/dl	9.4±0.4	9.5±0.4	0.64
GLU	mg/dl	110.0±26.3	106.3±22.7	0.30
Fe	μg/dl	73.7±27.2	72.0±26.3	0.77
CRP	mg/dl	0.2±0.4	0.2±0.3	0.05

Values are expressed as mean±standard deviation; Mann–Whitney *U*-test results are shown. WBC: White blood cell; RBC: red blood cell; Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red blood cell distribution width; PLT: platelet; Neut: neutrophil; lymph: lymphocyte; Mono: monocyte; Eosino: eosinophil; Baso: basophil; TP: total protein; Alb: albumin; A/G: albumin/globulin ratio; BUN: blood urea nitrogen; CRE: creatinine; T-Bil: total bilirubin; AST(GOT): aspartate aminotransferase (glutamate oxaloacetate transamylase); ALT(GPT): alanine transaminase (glutamic pyruvic transaminase); ALP: alkaline phosphatase; LDH: lactate dehydrogenase; γ-GTP: γ-glutamyl transpeptidase; AMY: amylase; ChE: cholinesterase; T-Cho: total cholesterol; HDL-C: high density lipoprotein cholesterol; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; non-HDL-C: non-high density lipoprotein cholesterol; Na: sodium; K: potassium; Cl: chlorine; Ca: calcium; GLU: glucose; Fe: iron; CRP: C-reactive protein.

Table III. *Multiple logistic regression analysis in factors related to infusion reactions.*

Variables	OR (95%CI)	*p*-Value
Premedication	2.5585 (0.9920-7.4113)	0.06
PER	0.1264 (0.0422-0.3385)	<0.01
Eosino	1.0032 (0.9996-1.0074)	0.10
ALP	0.9930 (0.9874-0.9973)	<0.01
γ-GTP	1.0031 (0.9962-1.0102)	0.39
HDL-C	1.0389 (1.0102-1.0710)	<0.01
CRP	6.1927 (1.2987-57.1920)	0.06

OR: Odds ratio; CI: confidence interval; PER: pertuzumab; Eosino: eosinophil; CRP: C-reactive protein; HDL-C: high density lipoprotein cholesterol; γ-GTP: γ-glutamyl transpeptidase; ALP: alkaline phosphatase.

administered on day two. In this study, PER was administered before TRA; therefore, the administration schedule differed from that of Takahashi *et al*. This may explain the difference in the occurrence of IR since their study investigated the risk factors for IR with TRA alone.

Conversely, a peripheral blood eosinophil count of >3% has been reported as a risk factor for cetuximab-induced infusion reactions in patients with squamous cell carcinoma of the head and neck (14). Eosinophils as a risk factor for monoclonal antibody-induced IR is not a consistent finding, and further validation is required.

ALP and HDL cholesterol levels were identified as independent risk factors for IR induced by TRA in this study. In the IR group, ALP and HDL cholesterol levels were high and low, respectively. Thompson *et al*. reported that body mass index, disease stage, and premedication use were risk factors for IR with TRA (4).

High ALP levels may reflect bone metastases, and the incidence of IR suggests an association with the disease stage. Raza *et al*. reported that HDL cholesterol levels were lower in patients with breast cancer with metastases than in those without metastases (15), suggesting an effect of disease stage. Additionally, peripheral blood tumor cell overgrowth is a known risk factor for IR with anti-CD20 antibodies such as rituximab and obinutuzumab. Therefore, we considered the possibility that the disease stage may also be a risk factor for IR in solid tumors.

However, in this study, surgical history was included as a factor, whereas disease stage was not. This is because TRA and PER are currently used in preoperative chemotherapy, and the tumor volume at the start of treatment is expected to differ between pre- and postoperative chemotherapy, even if the stages are similar. Therefore, establishing a constant relationship between the disease stage and tumor volume is difficult. To address these issues, it is desirable to conduct studies using tumor volume as a factor based on the quantitative estimation of tumor volume and stage.

Also, subcutaneous formulations of PER and TRA with recombinant human hyaluronidase have been in use since 2023. In a global Phase III clinical trial (FeDeriCa study) in patients with HER2-positive early-stage breast cancer, the subcutaneous formulation had a lower incidence of IR compared to the intravenous formulation (16). The authors attributed this to differences in systemic absorption and lower maximum serum concentrations associated with subcutaneous administration. Patients at high risk of IR may be able to avoid IR by choosing the subcutaneous formulation. However, the incidence of IR in advanced or recurrent breast cancer with subcutaneous formulations is unknown and awaits future reports.

Study limitations. First, this was a single-center retrospective study, and it cannot be denied that there is a certain bias among the physicians, pharmacists, and nurses involved in this study, which limits the generalizability of the results. Second, laboratory values may be confounding factors, such as infectious diseases and dyslipidemia.

Conclusion

This study suggests that the incidence of IR increased in Japanese females when PER was administered compared with TRA alone. In clinical practice, it is important to closely monitor the occurrence of IR during the first administration of PER and consider premedication such as NSAIDs.

Additionally, ALP and HDL cholesterol levels may be predictive markers of TRA-induced IR in patients with breast cancer. Although ALP and HDL cholesterol levels may reflect stage and tumor volume, this study could not determine this association. Future studies are needed to indicate a correlation between IR incidence and tumor volume after estimating the tumor volume in solid tumors.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, RY, MU, MM, KM; Data curation, RY, MU, TH, KO, TN; Formal analysis, RY, MU, MM, TH, KO, TN; Investigation, RY, MU, MM, TH, KO, TN, KM; Methodology, RY, MU, MM, TH, KO, TN, KM; Visualization, RY, MU, MM, TH, KO, TN, KM; Writing – review and editing, RY, MU, MM, TH, KO, TN, KM; Supervision, MU, MM, KM; Funding acquisition, KM; Project administration, KM.

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