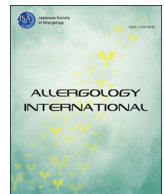




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Original Article

The thymus and activation-regulated chemokine (TARC) level in serum at an early stage of a drug eruption is a prognostic biomarker of severity of systemic inflammation

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List of abbreviations used:

TARC, Thymus and activation-regulated chemokine; DIHS, drug-induced hypersensitivity syndrome; DRESS, Drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; MPE, maculopapular exanthema; EM, erythema multiforme; NLR, neutrophil to lymphocyte ratio; GPS, Glasgow prognostic score; SIRS, systemic inflammatory response syndrome; mSIRS, modified systemic inflammatory response syndrome; WBC, white blood cell; Alb, albumin; CRP, C-reactive protein; BT, body temperature; PR, pulse rate; sBP, systolic blood pressure; dBP, diastolic blood pressure; ROC curve, receiver-operator characteristic curve

ABSTRACT

Background: In severe drug eruptions, precise evaluation of disease severity at an early stage is needed to start appropriate treatment. It is not always easy to diagnose these conditions at their early stage. In addition, there are no reported prognostic biomarkers of disease severity in drug eruptions. The aim of this study was to test whether the thymus and activation-regulated chemokine (TARC) level in serum at an early stage of a drug eruption can serve as a prognostic biomarker of systemic inflammation.

Methods: Study participants included 76 patients who received a diagnosis of a drug eruption, one of the following: drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, maculopapular exanthema, and erythema multiforme. Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) was eliminated in this study because scoring system for evaluating the severity was established. Correlation coefficients between serum TARC levels and indicators of systemic inflammation, including the neutrophil-to-lymphocyte ratio, Glasgow prognostic score, modified systemic inflammatory response syndrome (mSIRS) score, and C-reactive protein in serum were evaluated. **Results:** Serum TARC levels positively correlated with the neutrophil-to-lymphocyte ratio, Glasgow prognostic score, mSIRS score, C-reactive protein, albumin, white blood cell count, body temperature, and pulse rate. TARC levels negatively correlated with systolic blood pressure. Among these parameters, the mSIRS score showed strong correlation (correlation coefficient: 0.68).

Conclusions: Serum TARC levels correlate well with indicators of systemic inflammation and of disease severity among patients with a drug eruption except SJS/TEN. Serum TARC may be a prognostic biomarker of severity of inflammation in drug eruptions.

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Introduction

Because drug rash with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) is life-threatening drug eruptions, precise evaluation of disease severity

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at an early stage is needed to start appropriate treatment and to improve the prognosis. However, it is not always easy to diagnose these conditions at early stages.^{1–3}

Several indicators are known as a useful scoring system for systemic inflammation, including the neutrophil-to-lymphocyte ratio (NLR),⁴ Glasgow prognostic score (GPS),^{5,6} and systemic inflammatory response syndrome (SIRS) score.^{7,8} Especially, worsened vital signs, which are included in the SIRS score, can lead to mortality in patients with DRESS.⁹ Although the scoring system for evaluating severity of Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) was reported,¹⁰ there are no reported biomarkers that can predict severity of drug eruptions.

Thymus and activation-regulated chemokine (TARC; i.e., CC chemokine ligand 17) recruits Th2-polarized T lymphocytes into local inflammation sites, thus leading to a Th2-type immune reaction.^{11–13} Recently, TARC has been given a lot of attention as a potential biomarker of drug eruptions.^{14–17} Serum TARC levels are elevated preferentially in patients with DRESS/DIHS,^{14,15} reflecting a Th2-type immune response in these patients.¹⁶ On the other hand, we recently demonstrated that serum TARC levels increase in association with eosinophilia in patients with a drug eruption, regardless of DRESS/DIHS.¹⁷

In the present study, we aimed to test whether serum TARC at an early stage of a drug eruption can serve as a prognostic biomarker of systemic inflammation.

Methods

Patients

Study participants included 76 patients (10–99 years old; mean age 61.1) who received a diagnosis of a drug eruption in Shimane University Hospital from April 2014 to October 2016. Of the 76 patients, 28 were males (10–89 years old; mean age 65.1), and 48 were females (19–99 years old; mean age: 59.1). Diagnoses of DRESS/DIHS were made according to the respective clinical criteria.^{2,18} Final diagnoses were made as follows: DRESS/DIHS in 12 patients, maculopapular exanthema (MPE) in 18 patients, and erythema multiforme (EM) in 46 patients. SJS/TEN was eliminated in this study because scoring system for evaluating the severity was established.

The details of the study were fully explained to each patient or his/her guardian, and written informed consent was obtained. This study's protocol was approved by the ethics committee of Shimane University Faculty of Medicine (approval No. 1746).

Laboratory tests and evaluation of clinical scores

The following clinical parameters were evaluated in the patients during a medical examination: the white blood cell (WBC) count, neutrophil count, lymphocyte count, serum albumin (Alb) level, and C-reactive protein (CRP) level. The NLR was defined as a neutrophil count divided by lymphocyte count. GPS was evaluated in combination with cutoff values of CRP >1.0 mg/dL and Alb <3.5 g/dL, with the highest score of 2 and lowest score of 0 (Table 1). In addition, the following vital signs were evaluated during the

examination in these patients: body temperature (BT), pulse rate (PR), systolic blood pressure (sBP), and diastolic blood pressure (dBP). The modified SIRS (mSIRS) score was used for evaluating the WBC count, BT, and PR, with the highest score of 3 and lowest score of 0 (Table 2), where the respiratory rate was omitted from the original SIRS scoring system because such data were scarce. The worst levels of respective clinical parameters or clinical scores during a medical examination were used for evaluation of a correlation with serum TARC levels.

Measurement of serum TARC levels

Serum TARC levels were quantified by a chemiluminescent enzyme immunoassay using the HISCL® system (Sysmex, Hyogo, Japan) and a TARC Assay Kit (Shionogi, Osaka, Japan).¹⁹ Serum TARC levels were examined at first visit to Shimane University Hospital. The mean lag of TARC measurement after onset was 7.1 ± 8.3 days.

Data analysis

The data are presented as mean $\pm$ standard deviation. Statistical analysis was conducted in the R software (version 3.3.1, Vienna, Austria). The Mann–Whitney *U* test was used for analysis between two groups. The Kruskal–Wallis test was performed for comparison among three or more groups. The Spearman's rank correlation test was carried out for analysis of correlations. Statistical significance was assumed when a *P* value was less than 0.05.

Results

The NLR, GPS, and mSIRS score in the groups of patients stratified by diagnosis

When the NLR was evaluated during the disease course in the respective groups, the values were 18.5 ± 21.0 in the DRESS/DIHS ($n = 11$), 4.5 ± 2.8 in MPE ($n = 18$), and 12.0 ± 28.0 in EM ($n = 46$). The NLR was higher in the DRESS/DIHS than in MPE ($P = 0.001$) (Fig. 1A). GPS was 1.70 ± 0.48 in the DRESS/DIHS ($n = 10$), 0.44 ± 0.51 in MPE ($n = 16$), and 1.02 ± 0.85 in EM ($n = 44$). GPS in the patients with the DRESS/DIHS was higher than GPS in the patients with MPE and EM ($P < 0.001$ and $P = 0.018$, respectively) (Fig. 1B). The mSIRS score was 2.20 ± 0.63 in DRESS/DIHS ($n = 10$), 0.58 ± 0.79 in MPE ($n = 12$), and 1.09 ± 1.13 in EM ($n = 34$). The mSIRS scores in the patients with DRESS/DIHS were higher than these scores in the patients with MPE and EM, ($P = 0.002$ and $P = 0.003$, respectively) (Fig. 1C).

Laboratory and physical parameters in the groups of patients stratified by diagnosis

The data on laboratory and physical parameters are presented in Table 3, including the WBC count, neutrophil count, lymphocyte count, CRP, Alb, BT, PR, sBP, and dBP in the groups of patients stratified by diagnosis. When these values were compared among the groups, the CRP level was higher in the patients with DRESS/DIHS than in patients with MPE and EM ($P = 0.001$ and $P = 0.042$,

Table 1
Evaluation of Glasgow prognostic score (GPS), with highest score 2 and lowest score 0.

GPS score	0	1	2
Cut-off values	Alb ≥ 3.5 mg/dL and CRP ≤ 1.0 g/dL	Alb <3.5 mg/dL or CRP >1.0 g/dL	Alb <3.5 mg/dL and CRP >1.0 g/dL

Alb, albumin; CRP, C-reactive protein.

Table 2
Evaluation of modified systemic inflammatory response syndrome (mSIRS) score, with highest score 3 and lowest score 0.

mSIRS score	+1	+1	+1
Cut-off values	WBC count >12,000/ μ L or <4000/ μ L	BT > 38 °C or <36 °C	PR > 90/min

WBC, white blood cell; BT, body temperature; PR, pulse rate.

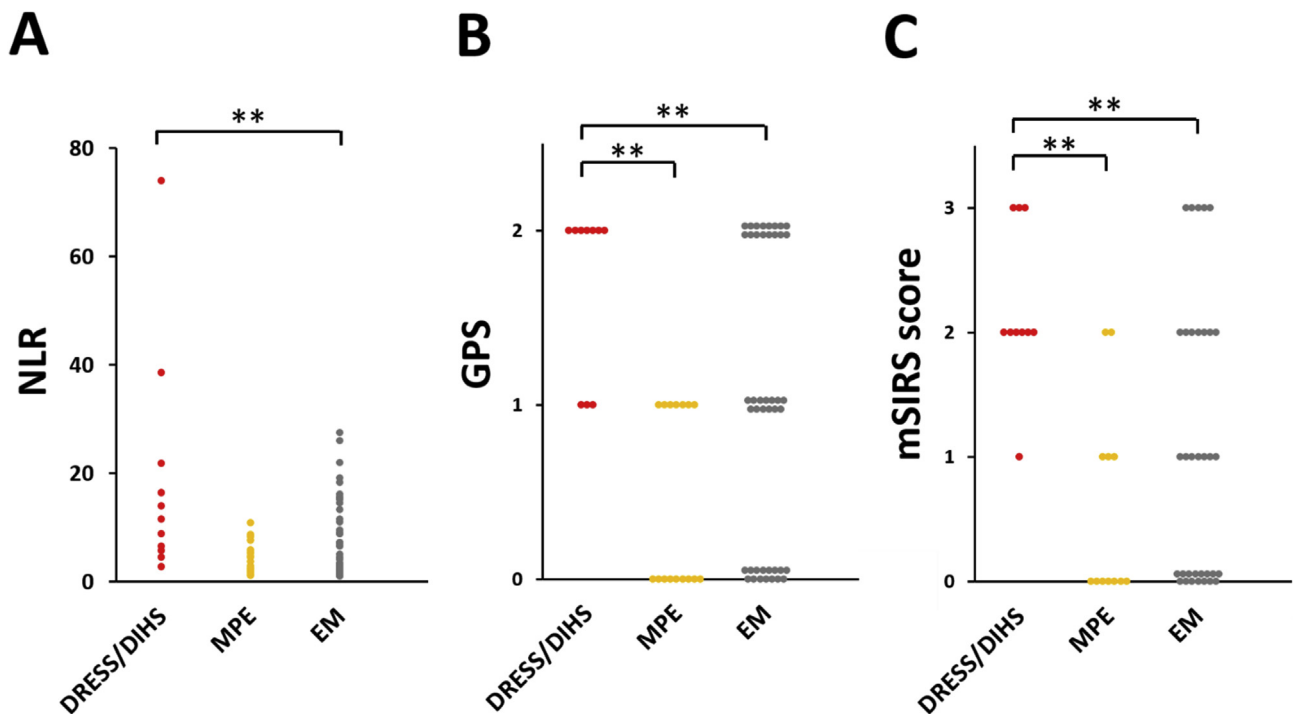


Fig. 1. Evaluation of inflammatory scores in patient groups stratified by diagnosis. (A) The respective values of NLR, with 11 cases of DRESS/DIHS, 18 cases of MPE, and 46 cases of EM ($n = 75$). (B) The respective values of GPS, with 10 cases of DRESS/DIHS, 16 cases of MPE, and 44 cases of EM ($n = 70$). (C) The respective values of mSIRS score, with 10 cases of DRESS/DIHS, 12 cases of MPE, and 34 cases of EM ($n = 56$). Statistical significance was evaluated using the Mann–Whitney U-test (* $P \leq 0.05$ and ** $P \leq 0.02$).

Table 3

Laboratory and clinical parameters in patient groups stratified by diagnosis.

Diagnosis	NLR			GPS			mSIRS score				Blood pressure		
	n	Neutrophil count (/μL)	Lymphocyte count (/μL)	n	CRP (g/dL)	Alb (mg/dL)	n	WBC count (/μL)	BT (°C)	PR (/min)	n	sBP (mmHg)	dBp (mmHg)
DRESS/DIHS	11	6634 ± 2478	1334 ± 905	10	6.35 ± 4.25	2.74 ± 0.82	10	9982 ± 3460	38.5 ± 1.0	95.3 ± 13.7	10	91.4 ± 11.3	53.8 ± 11.0
MPE	18	4638 ± 3265	1337 ± 612	16	1.91 ± 2.94	3.76 ± 0.61	12	6967 ± 3139	37.0 ± 0.9	81.1 ± 18.2	12	111.3 ± 16.9	66.3 ± 12.4
EM	46	5703 ± 3435	1458 ± 705	44	3.72 ± 4.03	3.41 ± 0.71	34	7959 ± 3238	37.3 ± 0.98	86.2 ± 20.0	34	108.1 ± 15.7	62.6 ± 7.9
Total	75	5951 ± 3332	1442 ± 670	70	3.92 ± 4.12	3.38 ± 0.78	56	8215 ± 3631	37.6 ± 1.1	88.8 ± 19.6	56	104.3 ± 16.0	61.9 ± 11.0

NLR, neutrophil to lymphocyte ratio; GPS, Glasgow prognostic score; mSIRS score, modified systemic inflammatory response syndrome score; CRP, C-reactive protein; Alb, albumin; WBC, white blood cell; BT, body temperature; PR, pulse rate; sBP, systolic blood pressure; dBp, diastolic blood pressure; DRESS, Drug reaction with eosinophilia and systemic symptoms; DIHS, drug-induced hypersensitivity syndrome; MPE, maculopapular exanthema; EM, erythema multiforme. Data are presented as mean ± standard deviation.

respectively); BT was higher in the patients with DRESS/DIHS than in patients with MPE and EM ($P = 0.004$ and $P = 0.005$, respectively); sBP was lower in the patients with DRESS/DIHS than in patients with MPE, and EM ($P < 0.001$, and $P = 0.005$, respectively); dBp was lower in the patients with DRESS/DIHS than in patients with MPE ($P = 0.041$).

Correlations between serum TARC levels and indicators of systemic inflammation

When serum TARC levels were evaluated at the first examination, the data in the groups of patients stratified by diagnosis were as follows: $32,156 \pm 22,566$ pg/mL in DRESS/DIHS, 2033 ± 4548 pg/mL in MPE, and 3461 ± 5681 pg/mL in EM. The serum TARC level was higher in DRESS/DIHS than in MPE, and EM (respective P values were all less than 0.001) (Supplementary Fig. 1).

Positive correlations were found between serum TARC levels and WBC count, neutrophil count, CRP, BT, and PR, whereas negative correlations were detected between serum TARC levels and Alb, and sBP (Fig. 2). A significant correlation was observed

between serum TARC levels and NLR, GPS, and mSIRS score, all of which were positive correlations (Fig 3). Among these parameters, the mSIRS score showed strong correlation (correlation coefficient: 0.68). In addition, most of these correlations remained significant even if we included only patients with MPE, and EM, omitting patients with DRESS/DIHS (Supplementary Fig. 2, 3). And most of these tendencies were observed in the respective patient groups (Supplementary Fig. 4, 5)

Receiver-operator characteristic curve (ROC) analysis

To assess the utility of serum TARC measurements for prognosis of systemic inflammation, a receiver-operator characteristic curve (ROC) analysis was conducted. Serum TARC measurements were found to have sensitivity 72% and specificity 70% for the GPS of 2 with a cutoff value of 2000 pg/mL ($n = 69$). Serum TARC levels had sensitivity 83% and specificity 64% for the mSIRS score more than 2 with a cutoff value of 850 pg/mL, and sensitivity 75% and specificity 79% for the mSIRS score of 3 with a cutoff value of 6000 pg/mL ($n = 56$) (Fig. 4).

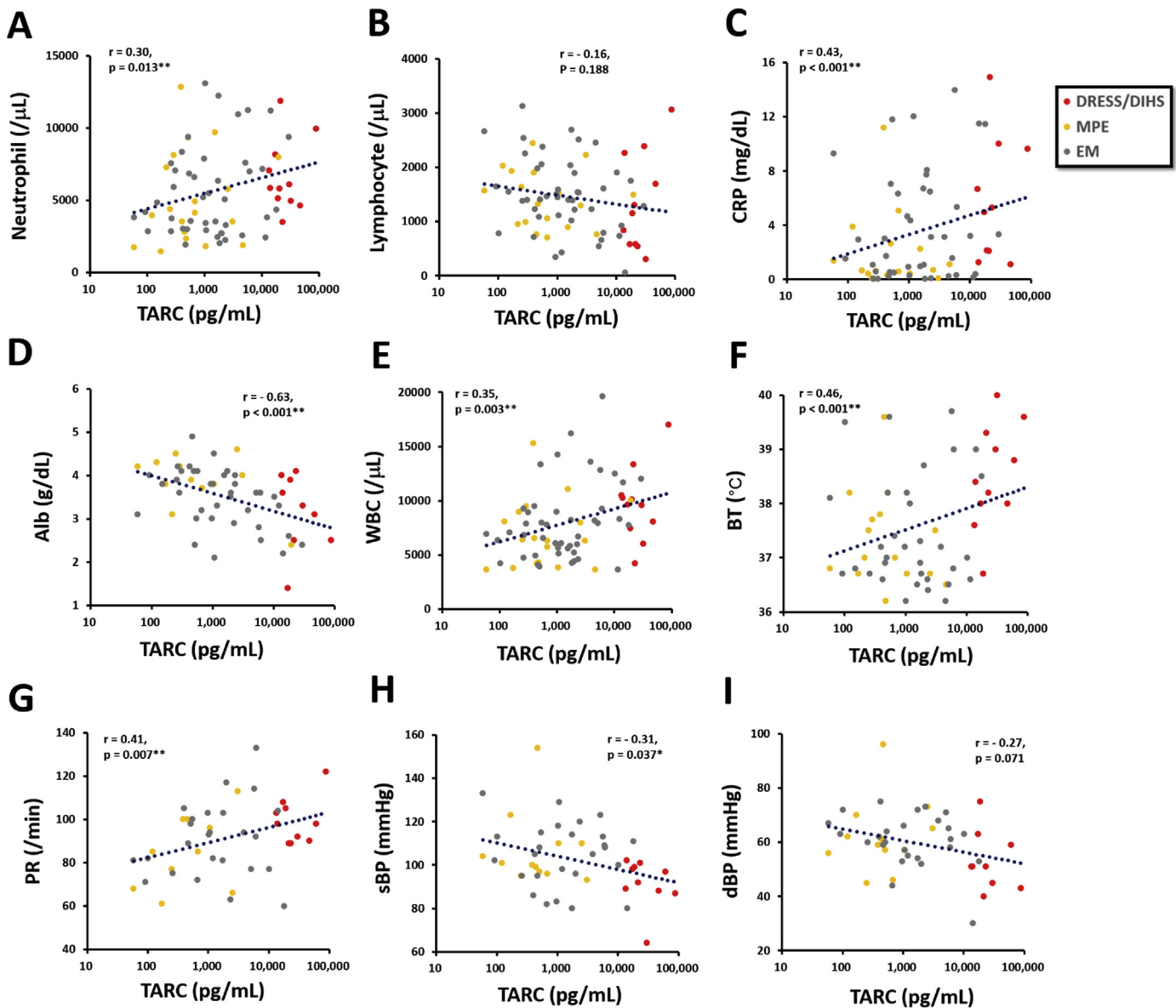


Fig. 2. Correlation between serum TARC levels and parameters of clinical and laboratory tests. Correlation between serum TARC levels and (A) Neutrophil count, (B) Lymphocyte count, (C) CRP, (D) Alb, (E) WBC count, (F) Body temperature, (G) Pulse rate, (H) Systolic blood pressure, and (I) Diastolic blood pressure. Statistical significance was evaluated using the Spearman's rank correlation test (* $P \leq 0.05$ and ** $P \leq 0.02$).

Discussion

This study shows that serum TARC measurement in patients at an early stage of a drug eruption can predict the maximal grade of systemic inflammation regardless of the type of drug eruption: DRESS/DIHS, MPE, or EM. The serum TARC levels were found to significantly correlate with all indicators of systemic inflammation—the NLR, GPS, and mSIRS score—when serum TARC levels were measured at the first consultation in our department. Among these three scores, mSIRS showed the best correlation with serum TARC levels: the correlation coefficient of 0.68 (Fig. 3). The NLR, GPS, and SIRS score have been reported to be useful for predicting mortality in various diseases. The NLR helps to predict mortality and short-term outcomes in infectious diseases, acute coronary syndrome, and heart failure.^{4,20–22} GPS testing can predict mortality in patients with heart failure or cancer.^{5,6} The SIRS score can predict mortality among the patients in intensive care units.²³ It

was reported that worsened vital signs that are included in the SIRS score can lead to death in patients with DRESS.⁹ Our finding is also supported by other reports, which indicate that the serum TARC level is associated with eosinophilia in patients with drug eruptions,¹⁷ and eosinophilia is related to the SIRS score.^{8,24,25} In addition, a receiver-operator characteristic curve analysis revealed that serum TARC measurement had high sensitivity and specificity in predicting GPS and mSIRS score, suggesting the utility of serum TARC measurement for prognosis of systemic inflammation (Fig. 4).

Other reports have suggested that serum TARC is upregulated preferentially in patients with DRESS/DIHS, reflecting a Th2-type immune reaction in DRESS/DIHS.^{14–16} Even if we had analyzed only the data on groups MPE, and EM, omitting the patients with DRESS/DIHS, most of these correlations between serum TARC levels and indicators of systemic inflammation would have been validated (Supplementary Fig. 2, 3). And most of these tendencies were observed in the respective patient groups (Supplementary Fig. 4, 5).

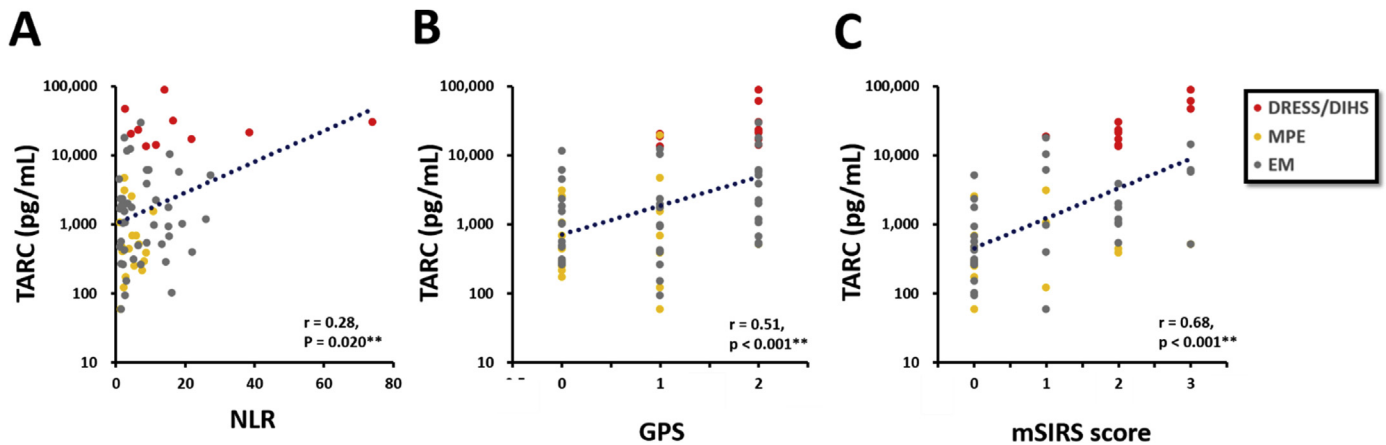


Fig. 3. Correlation between serum TARC levels and indicators of systemic inflammatory condition. (A) Correlation between serum TARC levels and NLR. (B) Correlation between serum TARC levels and GPS. (C) Correlation between serum TARC levels and mSIRS score. Statistical significance was evaluated using the Spearman's rank correlation test (* $P \leq 0.05$ and ** $P \leq 0.02$).

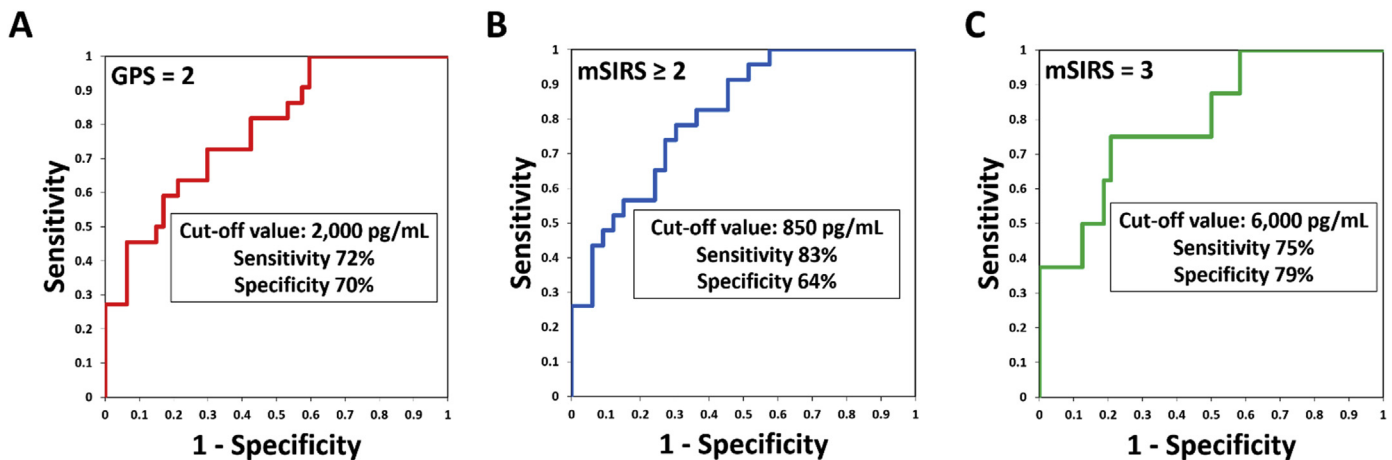


Fig. 4. A receiver-operator characteristic curve analysis. (A) Sensitivity and specificity of serum TARC level in evaluating GPS = 2 ($n = 69$). (B) Sensitivity and specificity of serum TARC level in evaluating mSIRS score ≥ 2 ($n = 56$). (C) Sensitivity and specificity of serum TARC level in evaluating mSIRS score = 3 ($n = 56$).

This result suggests that these findings are robust and not strongly tied to the type of drug eruption.

The limitation of our study is that we used mSIRS scores instead of the SIRS score because we could not calculate the respiratory rate, which is needed to calculate the SIRS score. Because mSIRS scores in the patients with DRESS/DIHS were found to be significantly higher than those in the patients with MPE or EM as shown in Figure 1, the mSIRS score appears to reflect disease severity in drug eruptions. Another limitation of the study is that SJS/TEN was not included in the study because scoring system for evaluating the severity was well established and serum TARC level was known not to increase as high as DRESS/DIHS.^{10,14–17}

Although we showed a correlation between serum TARC levels and indicators of systemic inflammation in drug eruptions, the mechanism underlying the increase in serum TARC levels during drug eruptions remains unclear. Furthermore, although increased serum TARC levels are also seen in atopic dermatitis,²⁶ they do not always lead to worsened vital signs in patients with atopic dermatitis. Connections between TARC production and systemic clinical parameters have yet to be elucidated.

In conclusion, we showed that serum TARC levels significantly correlate with indicators of systemic inflammation and of disease severity among patients with drug eruptions except SJS/TEN. Our

results suggest that serum TARC at an early stage of a drug eruption may be a prognostic biomarker of severity of inflammation.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2017.06.001>.

Conflict of interest

The authors have no conflict of interest to declare.

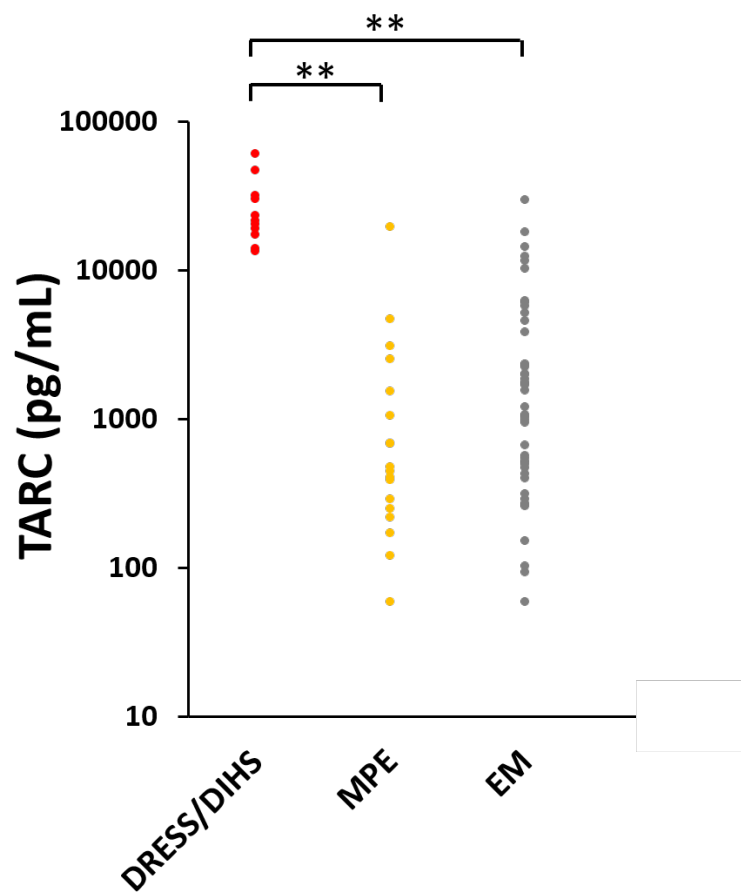
Authors' contributions

TKF and EM designed the study and wrote the manuscript. YC, HN, KH, MO and SK confirmed diagnoses and collected the peripheral-blood samples. RO conducted the laboratory tests.

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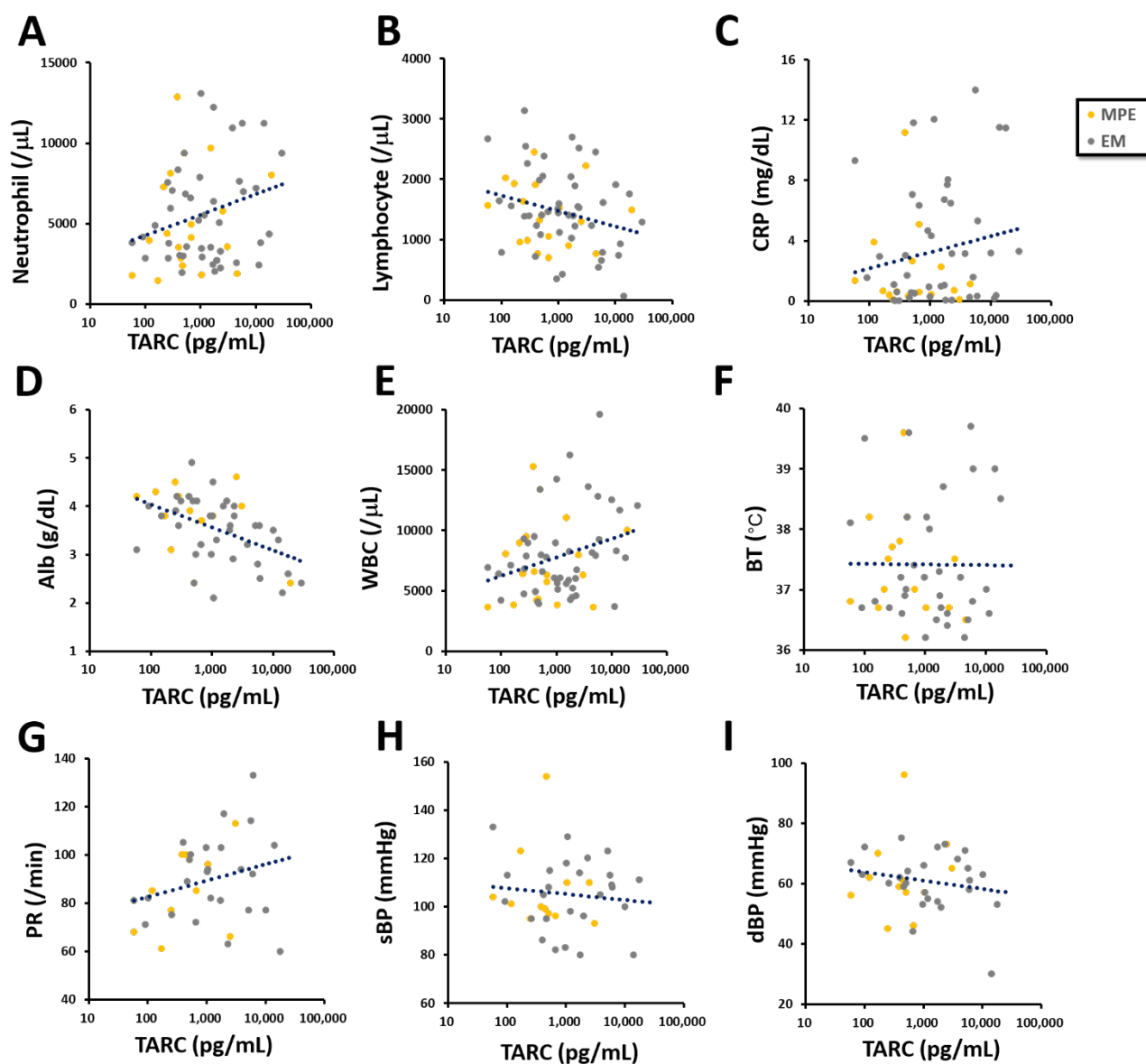
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Supplementary Fig. 1



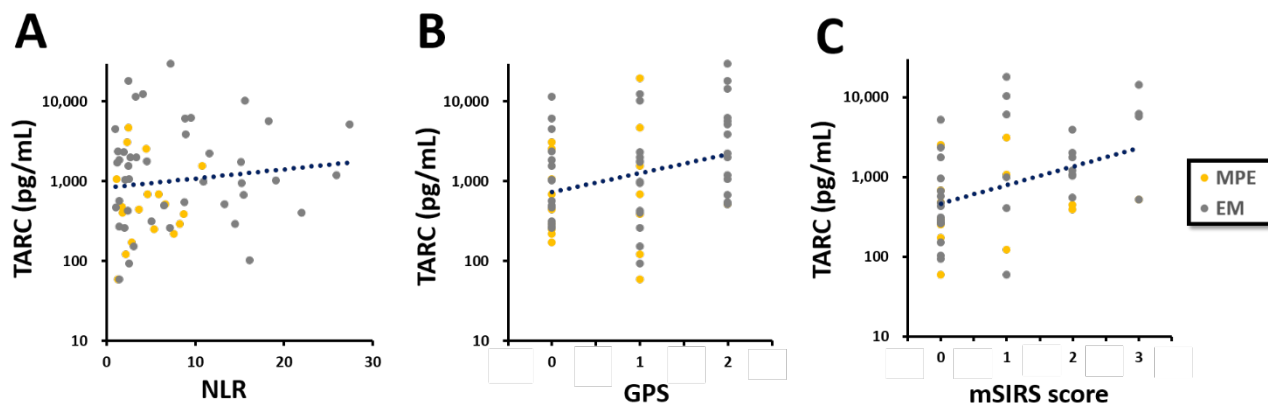
Serum TARC levels in patient groups stratified by diagnosis. DRESS/DIHS ($n = 12$), MPE ($n = 18$), and EM ($n = 46$). Statistical significance was evaluated using the Mann-Whitney U-test (** $P \leq 0.02$).

Supplementary Fig. 2



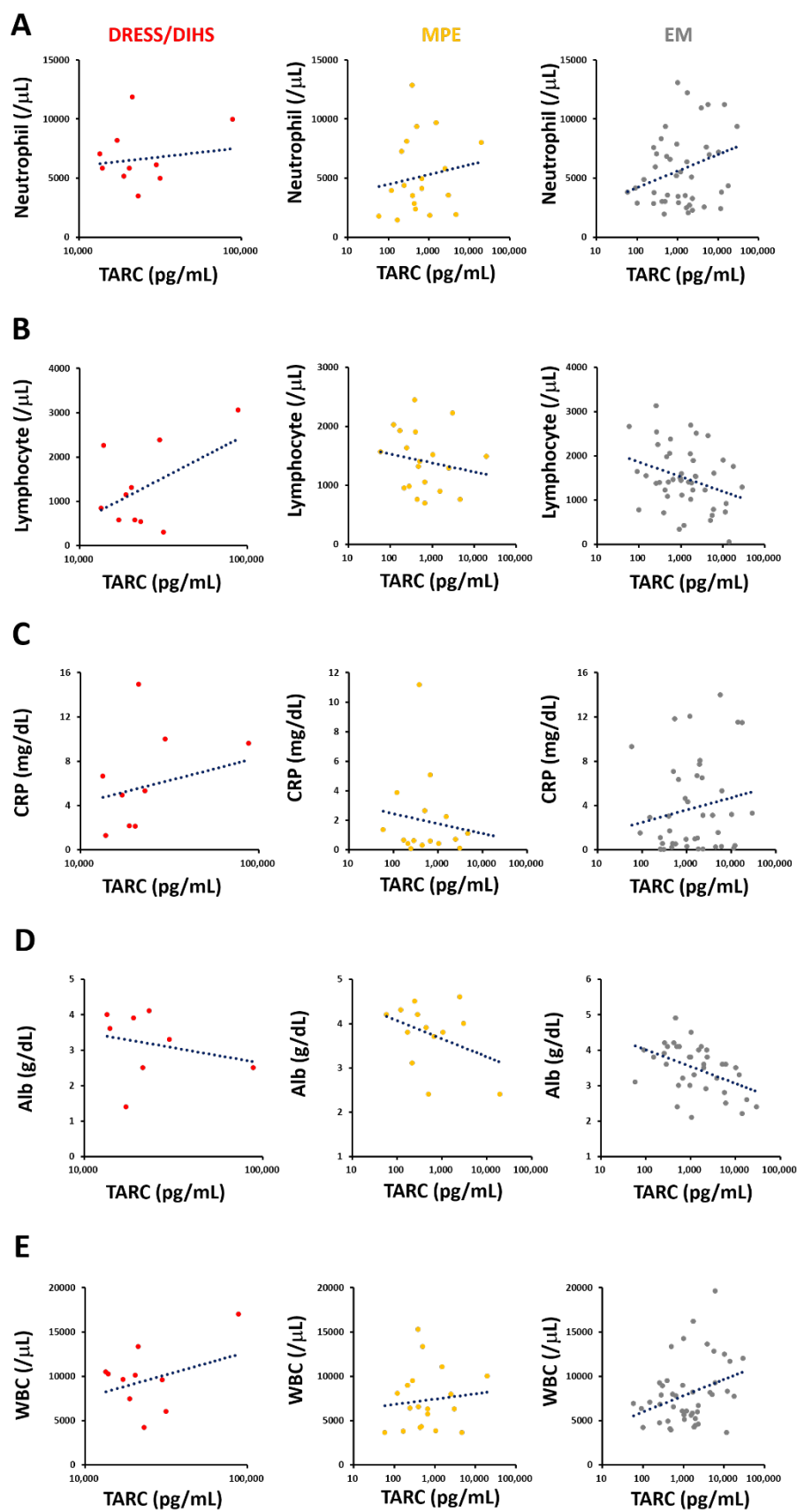
Correlation between serum TARC levels and parameters of clinical and laboratory tests. Correlation between serum TARC levels and (A) Neutrophil count, (B) Lymphocyte count, (C) CRP, (D) Alb, (E) WBC count, (F) Body temperature, (G) Pulse rate, (H) Systolic blood pressure, and (I) Diastolic blood pressure.

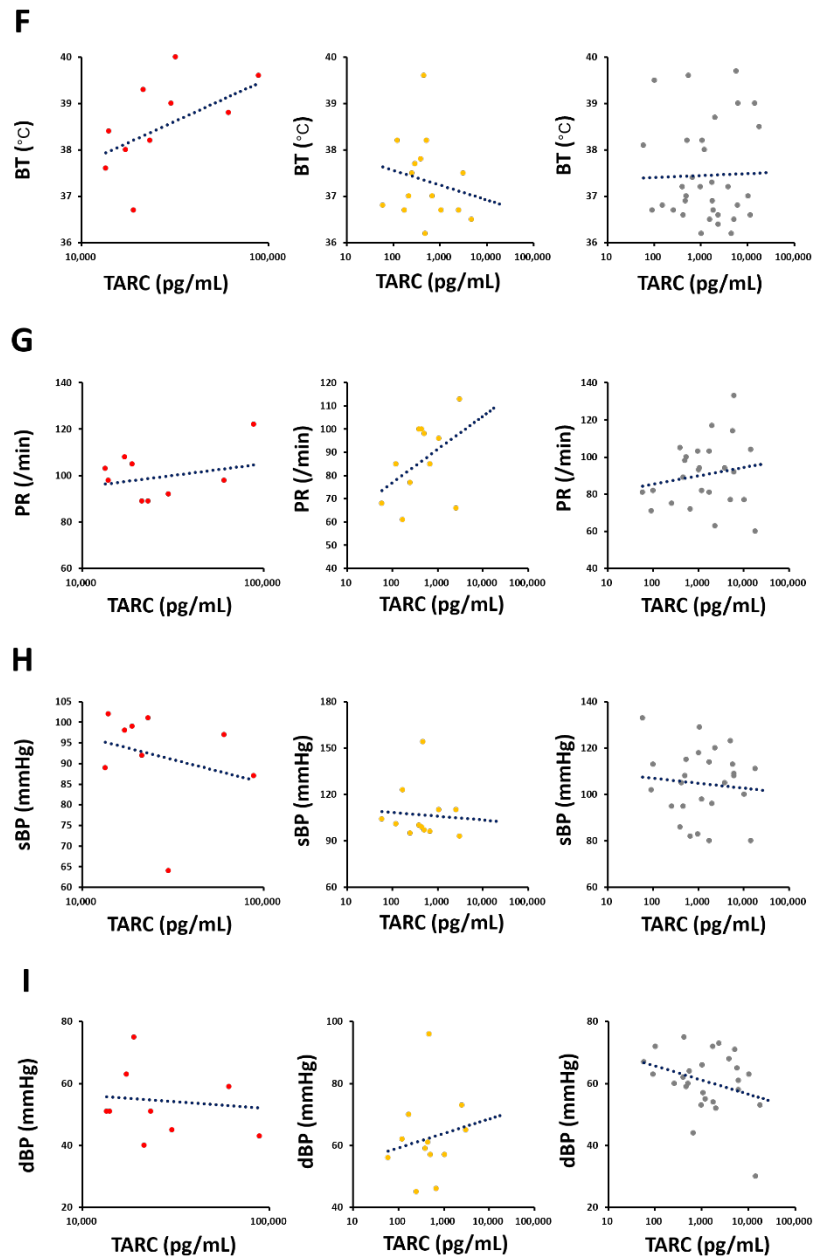
Supplementary Fig. 3



Correlation between serum TARC levels and NLR, GPS and mSIRS, omitting patients with DRESS/DIHS. Correlation between serum TARC levels and (A) NLR, (B) GPS, and (C) mSIRS score.

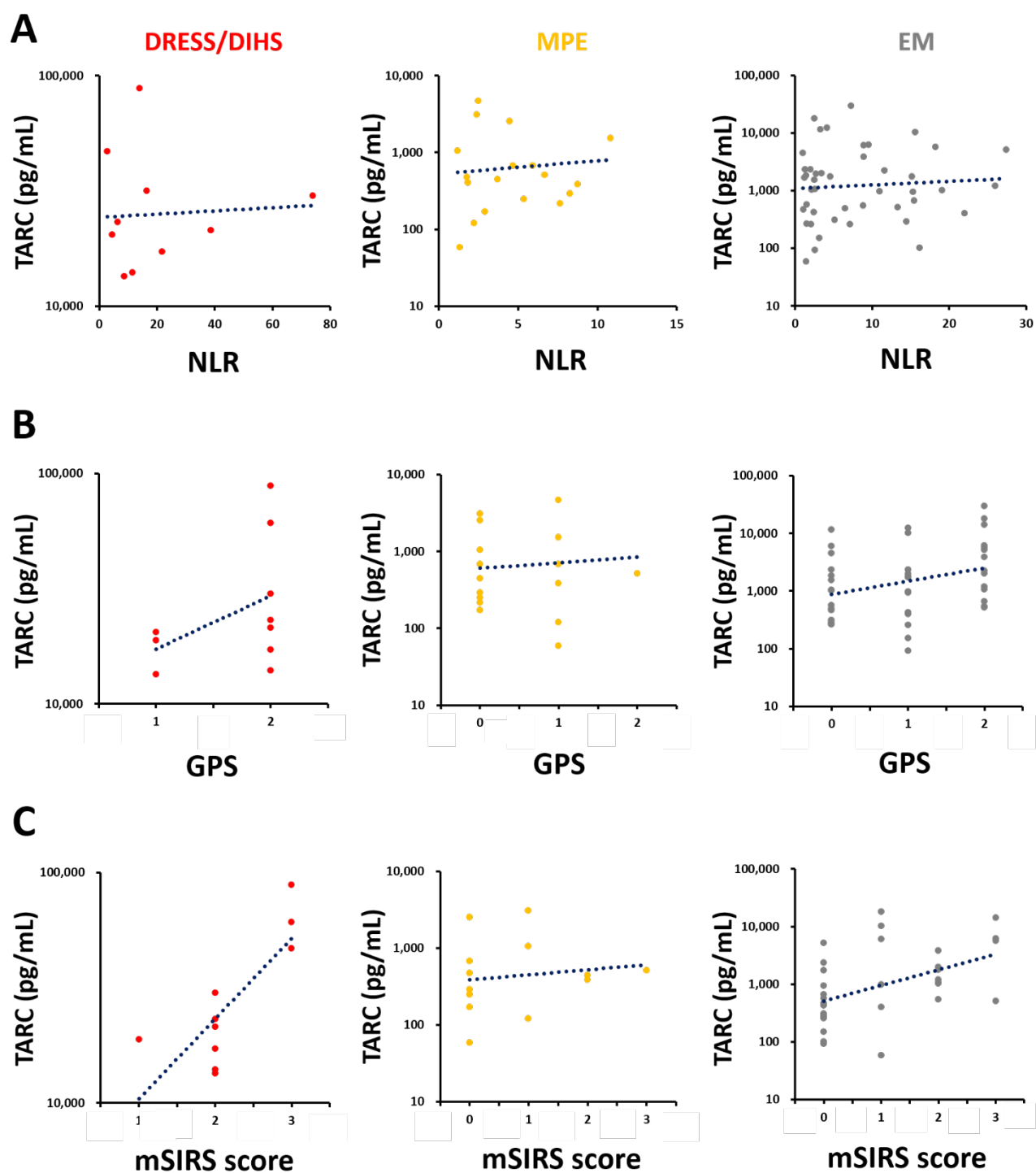
Supplementary Fig. 4





Correlation between serum TARC levels and parameters of clinical and laboratory tests. Correlation between serum TARC levels and (A) Neutrophil count, (B) Lymphocyte count, (C) CRP, (D) Alb, (E) WBC count, (F) Body temperature, (G) Pulse rate, (H) Systolic blood pressure, and (I) Diastolic blood pressure.

Supplementary Fig. 5



Evaluation of (A) NLR, (B) GPS and (C) mSIRS score in patient groups stratified by diagnosis.