Augmented Renal Clearance of Vancomycin in Hematologic Malignancy Patients

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SUMMARY

The pharmacokinetics of vancomycin (VAN) was retrospectively examined based on trough concentrations at large scale to identify pharmacokinetic differences between Japanese hematologic malignancy and non-malignancy patients. Data from 261 hematologic malignancy patients and 261 non-malignancy patients, including the patient’s background, VAN dose, and pharmacokinetics of VAN estimated by an empirical Bayesian method, were collected and analyzed. Our results showed significantly higher values for VAN clearance and shorter elimination half-lives in patients with hematologic malignancies than non-malignancy patients. In addition, multiple regression analysis under adjusting for confounding factors by propensity score, showed that VAN clearance significantly increased in relation to hematologic malignancies. In conclusion, since in hematologic cancer patients VAN clearance is increased, the blood concentration of VAN becomes lower than expected and this may contribute to the survival of resistant bacteria when VAN is administered at low doses. These results suggest that early monitoring of VAN levels in hematologic cancer patients might be recommended to maintain desired effects without side-effects.

Key words: vancomycin, pharmacokinetics, hematologic malignancy, non-malignancy
INTRODUCTION

Methicillin-resistant Staphylococcus aureus (MRSA) is known to be particularly at high risk of causing infections in compromised patients, such as the elderly and immunosuppressive or postoperative patients. It has been reported that the rate of hospital-acquired MRSA infection is high in cancer patients, due to reduced immune function and the side effects of anticancer drugs. Vancomycin (VAN) is a glycopeptide antibiotic that has been the first choice in the treatment of MRSA infections. However, VAN is known to have a high incidence of nephrotoxicity when the existing serum concentration of VAN before administration is $\geq 20 \, \mu g/mL$. Therefore, when administering VAN, it is necessary to perform therapeutic drug monitoring (TDM) to assure effective and safe dosing and to maintain the trough concentration from 10 $\mu g/mL$ to 20 $\mu g/mL$. Pharmacokinetic studies of VAN in MRSA-infected patients have been reported and there are also reports of population pharmacokinetic parameters in adult Japanese patients. Recently, an empirical Bayesian method was widely applied to TDM data and the predictability of the Bayesian forecasting methods using population pharmacokinetic parameters of Japanese patients has been examined.

There is a phenomenon of increased of renal clearance, known as augmented renal clearance (ARC). An underlying mechanism of ARC involves administration of vasoactive drugs and fluid, which increases cardiac output. In the absence of complicating multiple organ failure, including renal and liver dysfunction, this results in elevated drug clearance as a result of increased renal blood. Among risk factors associated with ARC are sepsis, systemic inflammatory response syndrome (SIRS), surgery, and burn. A precise definition of ARC has yet to be made, although several studies have shown that ARC is characterized by creatinine clearances (CLcr) ranging from $>120$ mL/min to $>150$ mL/min.
VAN is primarily excreted in the urine, and variations in its pharmacokinetic parameters depend on renal function.\textsuperscript{24} There are additional factors known to affect VAN concentration. Differences have been reported in VAN pharmacokinetics associated with malignant and non-malignant adult and pediatric patients.\textsuperscript{25-27} In adult neutropenic patients administered VAN, the distribution volume (Vdss) has been shown to increase and the elimination half-time ($t_{1/2}$) to decrease.\textsuperscript{28} VAN clearance (CL\textsubscript{VAN}) is significantly elevated in elderly malignant tumor patients,\textsuperscript{29} while in Japanese patients CL\textsubscript{VAN} is affected by renal function, while the morbidity of underlying malignancy is not related.\textsuperscript{30}

There is a risk that the effectiveness of VAN might be reduced because it is administered at inappropriately low doses. Additionally, VAN trough concentrations may be too great in patients with specific underlying diseases, potentially resulting in nephrotoxicity. Unfortunately, there are few large-scale reports on CL\textsubscript{VAN} for Japanese adults. Therefore, we performed a large scale investigation directed specifically toward the effects of hematologic malignancies on the pharmacokinetic parameters of VAN. This is the first time that we have performed such a study by multiple regression analysis adjusted for confounding factors using propensity scores.
MATERIALS AND METHODS

Data source and patient characteristics

This study was conducted in accordance with the Declaration of Helsinki and its amendments, and the protocol was approved by the Ethics Committee of Tokyo Jikei University (approved number: 30-213(9234)) and Hoshi University (approved number: 30-026). The data were collected retrospectively from patients who were treated longer than 3 days with VAN following initial administration. VAN serum concentrations were measured during hospitalization from January 2015 to December 2018 in Jikei University Kashiwa Hospital (Chiba, Japan). However, patients were excluded who were under 18 years of age, were renal replacement therapy patients, or were patients with a change in serum creatinine (Scr) of \( \geq 0.5 \text{ mg/dL} \) or \( \geq 50\% \) from the start time of VAN administration to time of blood VAN concentration measurement.

Basic patient characteristics (sex, age, body weight, and cancer type) were extracted from data in the Electronic Medical Record system. The following laboratory test values were extracted; blood urea nitrogen (BUN), Scr, CLcr, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil), direct bilirubin (D-Bil), \( \gamma \)-glutamyl transpeptidase (\( \gamma \)-GTP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), serum albumin (Alb), white blood cell (WBC), neutrophils (Neutro), and C-reactive protein (CRP). In addition, the dose and interval of VAN administration and the trough blood concentration of VAN at steady state were extracted. Serum concentrations were measured by a latex immunoturbidimetric assay using a Nanopia\textsuperscript{®} TDM Vancomycin (SEKISUI MEDICAL, Tokyo, Japan). The VAN blood trough concentration value was taken after \( \geq 3 \) days following the start of administration. When data were more than one point, the last-measured value was used if the exclusion criteria were not met. When the VAN dose was changed in the
middle of administration, the trough value measured before the dose change was used if it was after $\geq 3$ days from the start of administration, and if not, the trough value measured after $\geq 3$ days from the dose change was used.

**Data analysis**

Relationships among trough concentrations, dose, values of clinical laboratory tests, and other patient characteristics were investigated. Statistical comparisons were made between patients with hematologic malignancies and non-malignancy patients. CLcr was calculated by the method of Cockcroft-Gault.\(^{31}\) Using observed trough concentration data, an empirical Bayesian method\(^{32}\) was applied to obtain the individual estimated values of $\text{CL}_{\text{VAN}}$, $\text{Vdss}$, and $t_{1/2}$. Bayesian estimation was carried out for VAN using TDM analysis software Ver. 3.3 (Meiji Seika Pharma Co., Ltd., Tokyo, Japan) based on a linear two-compartment model. A population pharmacokinetic parameter set for Japanese adult patients\(^{33}\) was adopted, wherein when the calculated CLcr is greater than 85 mL/min, the population average clearance was set to 3.83 L/hr, otherwise an equation of $\text{CL (L/hr)}=0.537\times\text{CLcr (L/hr)}+0.32$ was adopted. All available trough concentration data for each patient was simultaneously used for the Bayesian estimation.

Patients were divided into the following groups: Group A with $60 \leq \text{CLcr} < 120$ mL/min and Group B with $\text{CLcr} \geq 120$ mL/min (Fig. 1). For both Group A and Group B, statistical comparisons of VAN trough values, dose, laboratory test values, $\text{CL}_{\text{VAN}}$ values, $\text{Vdss}$, and $t_{1/2}$ were made between patients with hematologic malignancies and non-malignancy patients.

**Statistical analysis**

Differences in patient characteristics, VAN doses, observed trough concentrations, $\text{CL}_{\text{VAN}}$,
Vdss, $t_{1/2}$, and values of clinical laboratory tests in patients with hematologic malignancies and non-malignancy patients, were statistically compared by the Mann–Whitney $U$ test or chi-square test. In addition, multiple regression analysis was performed on non-malignancy and hematologic malignancy patients using propensity scores. Logistic regression analysis was used to calculate the propensity score. The propensity scores were calculated from BUN, Scr, CLcr, AST, ALT, T-Bil, D-Bil, $\gamma$-GTP, ALP, LDH, Alb, WBC, Neutro and CRP. Factors contributing to CLVAN were then investigated using multiple regression analysis. All values for each variable are expressed as mean ± standard deviation (SD) unless otherwise indicated. A $P$-value of $<0.05$ was considered statistically significant. Data analysis was performed using R software Ver. 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).
RESULTS

Patient characteristics

Of the 990 patients who received VAN during the study period, 684 patients met the necessary criteria (Fig. 1). These consisted of 261 non-malignancy patients and 261 hematologic malignancy patients. A total of 136 non-malignancy patients and 170 hematologic malignancy patients had CLcr: $\geq 60$ mL/min. There were 107 non-malignancy patients and 148 hematologic malignancy patients in Group A (CLcr: $60\sim 120$ mL/min), and 29 non-malignancy patients and 22 hematologic malignancy patients in Group B (CLcr: $\geq 120$ mL/min) (Fig. 1). A summary of data used in this study is presented in Tables 1 and 2. In all 522 subjective patients (Table 1), BUN, AST, T-Bil, D-Bil, Alb, WBC, and Neutro in the non-malignancy group were significantly different from the hematologic malignancy group. In Group A (Table 2), a significant difference in Alb was found between the non-malignancy group and the hematologic malignancy group, and in Group B (Table 2), a significant difference was observed in body weight, Scr, and Alb. These results indicated that there were significant differences between non-malignancy and hematologic malignancy patient data, including CLcr.

Comparison of VAN dose and observed trough concentration

A summaries of VAN daily doses and observed trough concentrations are shown in Tables 1 and 2. In all subjective patients (Table 1), the VAN daily dose was $31.6\pm 10.0$ mg/kg in the hematologic malignancy group and $28.1\pm 11.2$ mg/kg in the non-malignancy group, with VAN trough concentrations being $13.3\pm 6.0$ μg/mL and $11.8\pm 5.7$ μg/mL, respectively. Both the VAN daily dose and the trough concentration were significantly higher in the
hematologic malignancy group than in the non-malignancy group. In Group A (Table 2), the VAN daily dose was 34.2±7.9 mg/kg in the hematologic malignancy group and 33.4±8.8 mg/kg in the non-malignancy group, with the trough concentrations being 13.4±5.8 μg/mL and 11.5±5.0 μg/mL, respectively. While there were no significant differences in the VAN daily doses, the trough concentrations had significant differences. In Group B (Table 2), the VAN daily dose was 31.5±5.4 mg/kg in the hematologic malignancy group and 28.0±5.3 mg/kg in the non-malignancy group, with the trough concentrations being 7.7±4.5 μg/mL and 8.0±4.2 μg/mL, respectively. The VAN daily dose, but not the trough concentration, was significantly higher in the hematologic malignancy group. Thus, while the VAN-administration dose per body weight was significantly higher in the hematologic malignancy patients of Group B (Table 2), there were no significant difference in the trough concentration level between the hematologic malignancy group and the non-malignancy group. This suggested that CL_{VAN} might increase in the hematologic malignancy patients.

**Comparison of VAN pharmacokinetic parameters**

Summaries of the VAN pharmacokinetic parameters are given in Table 3. In all subjective (All) patients, the CL_{VAN} value was 0.055±0.017 L/hr/kg in the hematologic malignancy group and 0.051±0.019 L/hr/kg in the non-malignancy group, while the t_{1/2} values were 32.7±13.0 hr and 37.1±18.8 hr, respectively. The value of CL_{VAN} was significantly higher and t_{1/2} was significantly shorter in the hematologic malignancy group than in the non-malignancy group. In contrast, the Vdss value was 1.81±0.57 L/kg in the hematologic malignancy group and 1.84±0.62 L/kg in the non-malignancy group, indicating a lack of significant difference between the two groups.

In Group A (Table 3), the CL_{VAN} value was 0.060±0.016 L/hr/kg in the hematologic
malignancy group and 0.062±0.016 L/hr/kg in the non-malignancy group; t\(_{1/2}\) values were 28.5±11.0 hr and 31.0±14.3 hr and the values of Vdss were 1.73±0.44 L/kg and 1.84±0.49 L/kg, respectively. There were no significant differences between the two groups.

In Group B, the CL\(_{\text{VAN}}\) value was 0.070±0.001 L/hr/kg in the hematologic malignancy group and 0.063±0.014 L/hr/kg in the non-malignancy group. The value of CL\(_{\text{VAN}}\) was significant higher in the hematologic malignancy group than in the non-malignancy group. In contrast, t\(_{1/2}\) was 33.7±12.5 hr in the hematologic malignancy group and 37.2±35.0 hr in the non-malignancy group, with Vdss being 1.63±0.36 L/kg and 1.58±0.34 L/kg, respectively. There were no significant differences between the two groups in their t\(_{1/2}\) and Vdss values. These results indicate that CL\(_{\text{VAN}}\) values in All and Group B patients increased and the t\(_{1/2}\) for VAN in All patients was significantly shortened between the hematologic malignancy group and the non-malignancy group.

**Factors contributing to CL\(_{\text{VAN}}\) values**

Multiple regression analysis was performed in both the non-malignancy and hematologic malignancy groups (261 patients each) using propensity scores. As shown in Table 4, significant differences were found in the partial regression coefficients of the hematologic malignancy group, with CL\(_{\text{VAN}}\) (95% confidential interval: 0.015 to 0.140, \(P\)-value = 0.015). Under adjusting by propersity scores, these results suggest that CL\(_{\text{VAN}}\) is affected by the presence or absence of hematologic malignancies.
DISCUSSION

In this study, we investigated factors contributing to VAN pharmacokinetic parameters. Of 522 subjective patients, CL\textsubscript{VAN} was found to be 0.051±0.019 L/hr/kg for the non-malignancy group and 0.055±0.017 L/hr/kg for the hematologic malignancy group (Table 3). This indicates a significant increase in the hematologic malignancy group as compared with the non-malignancy group. In addition, the t\textsubscript{1/2} values were 37.1±18.8 hr and 32.7±13.0 hr, respectively, which were significantly shorter for the non-malignancy group versus the hematologic malignancy group (Table 3), while the Vdss values were not significant different. There were significant differences in the patients' background between the non-malignancy and hematological malignancy groups in regards to BUN, AST, T-Bil, D-Bil, Alb, WBC, and Neutro (Table 1). In addition, multiple regression analysis under adjusting for propensity scores showed that the presence or absence of hematological malignancies affected the CL\textsubscript{VAN} values (Table 4).

A previous study dealing with CL\textsubscript{VAN} has shown that adult patients with neutropenia showed increased Vdss of VAN and shortened t\textsubscript{1/2} of VAN.\textsuperscript{28} In contrast, Omote et al.\textsuperscript{30} reported that in Japanese patients of mixed background, CL\textsubscript{VAN} values were affected by renal function, but not by the morbidity of the malignancy in 22 kinds of cancers (leukemia, lung, esophageal, bladder, lymphoma, etc). In the current study, we examined CL\textsubscript{VAN} values for the non-malignancy group versus the hematologic malignancy group and found a significant increase in CL\textsubscript{VAN} in hematologic malignancy patients as compared with the non-malignancy patients. Fernandez et al. showed that CL\textsubscript{VAN}, but not Vdss or t\textsubscript{1/2}, was significantly greater in patients with hematologic malignancies as compared to those with nonmalignancies, although the results were not adjusted to reflect confounding factors, including patient backgrounds.\textsuperscript{11} While the increase in CL\textsubscript{VAN} values in hematological malignancy patients was in agreement with our current results (Table 3), we found a significant shortening of t\textsubscript{1/2} of VAN in
hematological malignancy patients. Additionally, by performing multiple regression analysis using propensity scores, we found that $\text{CL}_{\text{VAN}}$ values were affected by the presence of hematological malignancies (Table 4). As a consequence, administration of higher doses of VAN was necessary to reach the target serum concentration in hematologic malignancy patients as compared to non-malignancy patients, regardless of renal function. It would be interesting to examine $\text{CL}_{\text{VAN}}$ values for individual cancers to ascertain whether other cancers, particularly solid malignancies, affect $\text{CL}_{\text{VAN}}$ values.

Next, statistical comparisons were performed on patient backgrounds and VAN pharmacokinetic parameters. In Group A (Table 3), VAN pharmacokinetic parameters were not significantly different between the non-malignancy group and the hematologic malignancy group in terms of $\text{CL}_{\text{VAN}}$, $t_{1/2}$, and $\text{Vdss}$ values. However, in Group B (Table 3), $\text{CL}_{\text{VAN}}$ showed a significant increase in the hematologic malignancy group, which was $0.070 \pm 0.001 \text{ L/hr/kg}$ as compared to $0.063 \pm 0.014 \text{ L/hr/kg}$ in the non-malignancy group. These results indicate that patients with hematologic malignancies and normal renal function with $\text{CL}_{\text{Cr}} \geq 120 \text{ mL/min}$ might need higher doses administered than under the usual regimen.

Factors associated with ARC are known to include sepsis, trauma, surgery or brain surgery, burns and admission to the intensive care unit (ICU). ARC has been reported in approximately 30-65% of ICU patients, in spite of normal Scr values. In these compromised patients, the occurrence of ARC was affected by administering a variety of agents, including crystalloids and vasopressors. In this study, 42 patients in the non-malignancy group and 7 patients in the hematologic malignancy group were admitted to the ICU, with more patients in the non-malignancy group having been admitted to the ICU (data not shown). Although there were only a small number of cases of ICU admission in the hematologic malignancy group, there was a significant increase in $\text{CL}_{\text{VAN}}$ values for this group (Table 3). It is possible that the presence or absence of hematologic malignancies can have a significant relationship to ARC expression, regardless of whether ICU admission is
involved.

In this study, we found that the presence or absence of hematologic malignancies affects the pharmacokinetics of VAN. However, one limitation of this study is that it was not possible to arrive at an appropriate calculated starting VAN dose for administration to patients with hematologic malignancies in clinical practice. Further study will be required to resolve this issue.

Since VAN clearance occurs primarily through renal excretion, increases observed in total clearance, even with malignancies occurring at sites other than the excretory organ, may indicate that extrarenal clearance is affected in malignancy patients. However, it is difficult to reconcile such a mechanism with previous reports showing that the contributions of extrarenal clearance of VAN are low. In our current study, we have found a significant difference in Alb levels between the non-malignancy group and the hematologic malignancy group (Tables 1 and 2). In addition, Sun et al. reported that the binding rate of Alb, which is a major VAN-binding serum protein, was as low as approximately 30%. Therefore, it is reasonable that the influence of changes in the protein binding rate of VAN accompanying albuminemia is also small. Further studies are required to elucidate the key factors giving rise to increased VAN clearance and decreased t1/2 in hematological malignancy patients.

As described above, in patients with hematologic malignancies, increases in CL\textsubscript{VAN} values can lead to VAN blood concentrations being lower than target concentrations, such that the effectiveness of VAN is diminished. It is possible that having concentrations of VAN below target levels, may facilitate the generation of resistant bacteria. The mechanisms by which ARC arises in patients with hematologic malignancies are still unclear and further work is needed in this area.
CONCLUSION

In conclusion, we have shown that monitoring of VAN levels may be particularly important for hematologic cancer patients in clinical settings so that appropriate intervention can be undertaken when indicated.
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Conflict of Interest

The authors declare no conflict of interest.
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Fig. 1. Flowchart of selection of target patients in the study.

VAN, vancomycin; Scr, serum creatinine; CLcr, creatinine clearance (Cockcroft-Gault equation).
Table 1. Patients characteristics and demographic data on all subject patients.

|                          | Non-malignancy | Hematologic malignancy | P-value |
|--------------------------|----------------|-------------------------|---------|
| Number of patients       | 261            | 261                     |         |
| Sex (male/female)        | 175/86         | 146/115                 | 0.012*  |
| Age (years old)          | 67.2 ± 16.9    | 65.6 ± 13.6             | 0.480*  |
| Body weight (kg)         | 56.2 ± 13.1    | 55.0 ± 10.3             | 0.379*  |
| Daily dose (mg/kg)       | 28.1 ± 11.2    | 31.6 ± 10.0             | <0.001* |
| Trough concentration (μg/mL) | 11.8 ± 5.7    | 13.3 ± 6.0              | 0.002*  |
| BUN (mg/dL)              | 20.0 ± 15.2    | 16.7 ± 10.2             | 0.006*  |
| Scr (mg/dL)              | 0.82 ± 0.43    | 0.76 ± 0.23             | 0.173*  |
| CLcr (mL/min)            | 74.1 ± 35.6    | 77.0 ± 29.2             | 0.100*  |
| AST (U/L)                | 34.8 ± 32.8    | 34.5 ± 75.1             | <0.001* |
| ALT (U/L)                | 35.9 ± 45.0    | 35.5 ± 55.0             | 0.099*  |
| T-Bil (mg/dL)            | 0.64 ± 0.66    | 0.78 ± 0.71             | <0.001* |
| D-Bil (mg/dL)            | 0.33 ± 0.45    | 0.44 ± 0.69             | 0.003*  |
| γ-GTP (U/L)              | 68.1 ± 81.5    | 95.9 ± 220.5            | 0.097*  |
| ALP (U/L)                | 304.4 ± 237.2  | 308.9 ± 261.7           | 0.846*  |
| LDH (U/L)                | 252.4 ± 176.9  | 319.0 ± 597.5           | 0.179*  |
| Alb (g/dL)               | 2.50 ± 0.63    | 2.63 ± 0.55             | 0.006*  |
| WBC (10^3/μL)            | 10.3 ± 6.8     | 5.54 ± 16.30            | <0.001* |
| Neuto (10^3/μL)          | 7.80 ± 4.66    | 1.47 ± 2.46             | <0.001* |
| CRP (mg/dL)              | 10.9 ± 9.88    | 9.77 ± 7.56             | 0.999*  |

Numerical variables are summarized as mean ± standard deviation (SD).

BUN, blood urea nitrogen; Scr, serum creatine; CLcr, creatinine clearance (Cockcroft-Gault equation); AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Bil, total bilirubin; D-Bil, direct bilirubin; γ-GTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; Alb, serum albumin; WBC, white blood cell; Neuto, neutrophils; CRP, C-reactive protein.

*chi-square test; *Mann-Whitney U-test.
## Table 2. Patients characteristics and demographic data on Group A and B.

|                        | Group A                      | Group B                      |   |   |
|------------------------|------------------------------|------------------------------|---|---|
|                        | Non-malignancy | Hematologic malignancy | P-value | Non-malignancy | Hematologic malignancy | P-value |
| Number of patients     | 107 | 148 | | 29 | 22 | | |
| Sex (male/female)      | 68/39 | 111/37 | 0.067<sup>a</sup> | 23/6 | 19/3 | 0.777<sup>a</sup> |
| Age (years old)        | 60.5 ± 14.0 | 63.1 ± 11.5 | 0.149<sup>b</sup> | 42.2 ± 12.3 | 43.9 ± 9.7 | 0.761<sup>b</sup> |
| Body weight (kg)       | 57.6 ± 9.2 | 58.0 ± 8.5 | 0.728<sup>b</sup> | 75.1 ± 11.6 | 65.8 ± 7.2 | 0.001<sup>b</sup> |
| Daily dose (mg/kg)     | 33.4 ± 8.8 | 34.2 ± 7.9 | 0.726<sup>b</sup> | 28.0 ± 5.3 | 31.5 ± 5.4 | 0.008<sup>b</sup> |
| Trough concentration (µg/mL) | 11.5 ± 5.0 | 13.4 ± 5.8 | 0.011<sup>b</sup> | 8.0 ± 4.2 | 7.7 ± 4.5 | 0.827<sup>a</sup> |
| BUN (mg/dL)            | 15.0 ± 6.6 | 15.0 ± 7.9 | 0.429<sup>b</sup> | 12.0 ± 5.4 | 10.3 ± 4.9 | 0.155<sup>b</sup> |
| Scr (mg/dL)            | 0.70 ± 0.14 | 0.71 ± 0.14 | 0.438<sup>b</sup> | 0.69 ± 0.11 | 0.64 ± 0.09 | 0.012<sup>b</sup> |
| CLcr (mL/min)          | 87.0 ± 17.1 | 85.5 ± 17.1 | 0.540<sup>b</sup> | 143.9 ± 24.3 | 135.8 ± 19.5 | 0.162<sup>b</sup> |
| Alb (g/dL)             | 2.50 ± 0.64 | 2.68 ± 0.50 | 0.006<sup>b</sup> | 2.71 ± 0.65 | 3.06 ± 0.59 | 0.035<sup>b</sup> |
| CRP (mg/dL)            | 8.26 ± 8.28 | 8.92 ± 7.12 | 0.122<sup>b</sup> | 8.69 ± 8.12 | 7.35 ± 5.43 | 0.992<sup>b</sup> |

Numerical variables are summarized as mean ± standard deviation (SD).

BUN, blood urea nitrogen; Scr, serum creatinine; CLcr, creatinine clearance (Cockcroft-Gault equation); Alb, serum albumin; CRP, C-reactive protein.

<sup>a</sup>chi-square test; <sup>b</sup>Mann-Whitney U-test.
Table 3. Comparison of vancomycin pharmacokinetic parameters.

|                | All          | Group A          | Group B          |
|----------------|--------------|------------------|------------------|
|                | Non-malignancy | Hematologic malignancy | Non-malignancy | Hematologic malignancy | P-value<sup>a</sup> | Non-malignancy | Hematologic malignancy | P-value<sup>a</sup> |
| **CL<sub>VA N</sub> (L/hr/kg)** | 0.051 ± 0.019 | 0.055 ± 0.017 | 0.009 | 0.062 ± 0.016 | 0.060 ± 0.016 | 0.440 | 0.063 ± 0.014 | 0.070 ± 0.001 | 0.013 |
| **t<sub>1/2</sub> (hr)** | 37.1 ± 18.8 | 32.7 ± 13.0 | 0.005 | 31.0 ± 14.3 | 28.5 ± 11.0 | 0.189 | 37.2 ± 35.0 | 33.7 ± 12.5 | 0.140 |
| **V<sub>dss</sub> (L/kg)** | 1.84 ± 0.62 | 1.81 ± 0.57 | 0.692 | 1.84 ± 0.49 | 1.73 ± 0.44 | 0.063 | 1.58 ± 0.34 | 1.63 ± 0.36 | 0.278 |

Numerical variables are summarized as mean ± standard deviation (SD).

CL<sub>VA N</sub>, total body clearance of vancomycin; t<sub>1/2</sub>, elimination half-life; V<sub>dss</sub>, volume of distribution.

<sup>a</sup>Mann-Whitney U-test.
Table 4. Factors contributed to CLV\textsubscript{N} using multiple regression analysis

|                                | Coefficient (β) | 95% CI       | \( P \)-value |
|--------------------------------|-----------------|--------------|---------------|
| Intercept                      | 0.047           | 0.013-0.075  | 0.005         |
| Hematologic malignancy         | 0.085           | 0.015-0.140  | 0.015         |
| Propensity score               | 0.018           | -0.050-0.109 | 0.469         |

Propensity score: BUN, Scr, AST, ALT, T-Bil, D-Bil, \( \gamma \)-GTP, ALP, LDH, Alb, WBC, Neutro and CRP. CI, confidential interval.