Using Japanese big data to investigate novel factors and their high-risk combinations that affect vancomycin-induced nephrotoxicity

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What is already known about this subject:

- **Several factors such as higher serum concentration and the long-term duration associate with vancomycin (VCM)-induced nephrotoxicity (VIN).**
- **It has not been clarified whether factors such as some concomitant medications (e.g., ramelteon and piperacillin) and ward pharmacy service affect VIN.**

What this study adds:

- **Concomitant ramelteon use, ward pharmacy service, duration of VCM <7 days, and trough concentrations 10–15 mg/L reduce the risk of VIN.**
- **Concomitant piperacillin-tazobactam and piperacillin use increase the risk.**
- **Combination of 'VCM trough concentrations ≥20 mg/L and concomitant piperacillin-tazobactam use' is associated with the highest risk.**

Abstract

Aims

Several factors related to vancomycin-induced nephrotoxicity (VIN) have not yet been clarified. In the present study, we used Japanese big data to investigate novel factors and their high-risk combinations that influence VIN.

Methods

We employed a large Japanese electronic medical record database and included patients who had been administered intravenous vancomycin between June 2000 and December 2020. VIN was defined as an increase in serum creatinine ≥0.5 mg/dL or 1.5-fold higher than the baseline. The outcomes were: (1) factors affecting VIN that were identified using multiple logistic regression analysis, and (2) combinations of factors that affect the risk of VIN according to a decision tree analysis, which is a typical machine learning method.

Results

Of the 7,306 patients that were enrolled, VIN occurred in 14.2% of them (1,035). A multivariate analysis extracted 22 variables as independent factors. Concomitant ramelteon use (odds ratio; 0.701, 95% confidence interval; 0.512–0.959), ward pharmacy service (0.741, 0.638–0.861), duration of VCM <7 days (0.748, 0.623–0.899) and trough concentrations 10–15 mg/L (0.668, 0.556–0.802) reduce the risk of VIN. Meanwhile, concomitant piperacillin-tazobactam use (2.056, 1.754–2.409) and piperacillin use (2.868, 1.298–6.338) increase the risk. The decision

tree analysis showed that a combination of vancomycin trough concentrations ≥20 mg/L and concomitant piperacillin-tazobactam use was associated with the highest risk.

Conclusions

We revealed that the concomitant ramelteon use and ward pharmacy service may decrease the risk of VIN, while the concomitant use of not only piperacillin-tazobactam but also piperacillin may increase the risk.

1 INTRODUCTION

Nephrotoxicity is a common side effect of vancomycin (VCM) treatment against gram-positive bacterial infections such as methicillin-resistant *Staphylococcus aureus*. Vancomycin-induced nephrotoxicity (VIN) occurs in 5–43% of all patients and often causes treatment interruption.[1]

The risk factors of VIN have been reported in several previous studies. They include trough concentrations >20 mg/L or >15 mg/L, area under the concentration-time curve (AUC) >600, long-term duration, concurrent medications (such as non-steroidal anti-inflammatory drugs (NSAIDs), amphotericin B, loop diuretics, aminoglycosides, piperacillin-tazobactam (PIPC-TAZ), calcineurin inhibitors (CNI), intravenous radiocontrast dyes, and vasopressors), and certain diseases (such as chronic kidney disease, obesity, and diabetes mellitus).[2–5]

However, there are certain unresolved issues. First, a recent study revealed that concomitant melatonin use shows protective efficacy against VIN as it reduces oxidative stress in the proximal tubules.[6, 7] Though melatonin itself has antioxidant properties, the stimulation of melatonin receptors also attenuates the effects of oxidative stress.[8–10] The oral melatonin receptor agonist ramelteon mitigates oxidative stress and inflammation in multiple organs.[8, 11, 12] Hence, the concomitant use of ramelteon may decrease the risk of VIN. Second, multiple studies reported that concomitant PIPC-TAZ use increases the risk of VIN.[13–15] However, the

interaction between piperacillin (PIPC) and VCM remains unclear. Recently, Contejean *et al*. used a spontaneous database (VigiBase, the WHO global database of individual case safety reports) and found that a combination of VCM plus PIPC increased the risk of VIN. Nevertheless, their findings were based on signal detection.[16] Thus, population-based studies adjusting for the confounding factors are required. Third, our previous study demonstrated via a claims database that ward pharmacy service is associated with the active implementation of therapeutic drug monitoring (TDM) for VCM.[17] As Japanese claims databases lack laboratory data, we could not determine whether ward pharmacy service contributes to VIN reduction.

In single- and multi-centre studies, it is difficult to resolve these issues except on a large scale because VCM and PIPC are seldom used concomitantly. Institutional bias is unavoidable in evaluating the contributions of ward pharmacists. In the present study, we employed a large Japanese electronic medical record (EMR) database containing information on numerous subjects and abundant clinical laboratory data.[18, 19] An EMR database can assess both VCM serum concentrations and the presence of VIN based on serum creatinine (Scr) concentration elevation. In these respects, the EMR database markedly differs from the Japanese claims database.[17]

In this study, we evaluated factors affecting VIN including the foregoing unresolved issues. We also used machine learning to evaluate combinations of factors influencing VIN risk. To the best of our knowledge, this study is the first to employ a Japanese EMR database in the evaluation of VIN risk. We also confirmed whether known risk factors for VIN could be extracted from this database.

2 METHODS

2.1 Data source

We implemented the large Japanese EMR database named the RWD database maintained by the Health, Clinic, and Education Information Evaluation Institute (HCEI; Kyoto, Japan) with support from the Real World Data Co., LTD (Kyoto, Japan).[18, 19] The RWD database includes information about 20 million individuals within approximately 160 Japanese medical institutions. These patient data were collected from 2000. It contains patient demographics, drug prescriptions, diagnoses, laboratory results, and procedures. The data were collected from the EMR of each medical institution and anonymised. Individual patient numbers were assigned to each patient.

2.2 Study population

Patients who had been intravenously administered VCM between June 2000 and December 2020 were included. VCM was identified by the Anatomical Therapeutic Chemical (ATC) system code No. J01XA01. Patients meeting the following criteria were excluded: (1) duration of VCM therapy <3 days; (2) baseline Scr concentrations not measured; (3) Scr concentrations not measured during VCM therapy; (4) serum VCM concentrations not measured; (5) serum VCM concentrations measured <3 days after the initiation of VCM; (6) first serum VCM

concentration measured after VIN occurrence; (7) surgery during VCM therapy; (8) age <18 years; (9) renal replacement therapy such as haemodialysis or peritoneal dialysis; and (10) other missing values.

2.3 Definition of VIN

VIN was detected based on Scr concentration elevation because collection of urine output data from the RWD database was difficult. The occurrence of VIN was defined as an elevation in Scr concentration of ≥0.5 mg/dL or at least 1.5-fold higher Scr concentration than the baseline according to the 2009 Vancomycin Consensus Statement of the Infectious Diseases Society of America.[20] To account for the possibility that Scr concentration might rise following VIN,[21] we observed until the second day after the end of VCM therapy.

2.4 Outcomes

The following outcomes were evaluated: (1) factors affecting VIN; (2) combinations of factors altering the risk of VIN according to a decision tree (DT) analysis, which is a typical machine learning method; and (3) comparison of the proportions of the following VIN patterns 'before and after propensity score matching': (i) patients undergoing concomitant ramelteon use vs. those not using ramelteon; (ii) concomitant PIPC-TAZ use vs. PIPC use; and (iii) patients with ward pharmacy service vs. those without it. Patients who received both PIPC-TAZ and PIPC

were excluded. VCM trough concentrations were compared between patients with and without ward pharmacy service.

2.5 Data collection

Patient age, sex, body weight, comorbidities, infection type, baseline laboratory data (creatinine clearance (CrCl), white blood cell counts, blood urea nitrogen, total bilirubin, aspartate aminotransferase, alanine aminotransferase, and C-reactive protein), concomitant medications, VCM data (daily dose, duration, serum concentration, and days to initial serum concentration collection), implementation of ward pharmacy service, and numbers of hospital beds prescribed VCM were evaluated. Scr concentrations at baseline and during VCM therapy were extracted. Days to VIN occurrence were evaluated from the day on which VCM administration was initiated. Comorbidities, infection types, and concomitant medications are shown in Tables S1 and S2. Concomitant medications were selected based on previous reports.[2–5] Concomitant use of PIPC or ramelteon was also evaluated. If the medication prescription periods overlapped by ≥1 day during VCM therapy, it was regarded as the drugs were concomitantly administered.[5] Concomitant medications prescribed after VIN were deemed 'non-concomitant use'. In Japan, melatonin preparations only be administered for the treatment of 'difficulty in falling asleep, associated with neurodevelopmental disorders in childhood'. Therefore, we did not evaluate the concomitant use of melatonin. Age was calculated on the day of VCM initiation. Baseline

laboratory data were extracted from the day on which VCM therapy was started or within a maximum of 14 days from that time. The Cockcroft-Gault equation was used to calculate CrCl.[22] BMI could not be assessed as the RWD database lacked body height information. Thus, body weight ≥100 kg served as an index of overweight.[2] In the RWD database, the timing of VCM serum concentration (trough or peak value) collection could not be determined. Hence, trough values were considered because TDM for VCM was performed according to the trough value for Japan even though the new guideline recommends AUC-guided dosing.[23, 24] If multiple serum VCM concentrations were obtained on the same day, the lowest value was considered as the trough concentration. Since serum VCM concentrations may be measured multiple times during VCM therapy, the initial, average, and maximum values were evaluated (trough concentrations after VIN were not evaluated). In addition, the median numbers of measurement of trough concentration during the VCM therapy were collected. The database contained only daily VCM dose data. Therefore, we could not determine whether the initial loading dose was administered. For example, if an initial loading dose of 1000 mg was performed on the first night of VCM administration and the maintenance dose was 500 mg twice daily, both daily doses were 1000 mg. This also explains why we excluded patients whose serum VCM concentrations were measured <3 days after the initiation of VCM. Nevertheless, this practice does not increase the risk of VIN.[25]

Ward pharmacy service implementation was detected by calculating 'drug management and guidance fee' and/or 'in-patient pharmaceutical services' during or within one week before or after VCM administration.[17, 26] The 'drug management and guidance fee' can be calculated by performing the patient compliance instruction and pharmaceutical management, e.g., evaluation of the drug dosage, route of administration, and drug-drug interactions. It can be calculated up to once per week for the inpatients. The 'inpatient pharmaceutical services premium' is similar to a 'hospital fee'. For calculating this medical fee, ward pharmacists are required to perform pre-defined pharmaceutical services by staying at each ward for more than 20 h/week. For example, one of the requirements is the description of 'the ward pharmacist should set the appropriate dosage before administration, especially for the drugs that required to be safely managed and need calculation of flow proportion or dosage'.

2.6 Statistical analysis

A univariate analysis was performed to select the variables for the multiple logistic regression analysis. The characteristics of patients described in the data collection statement were used. Factors were selected according to their reliability, correlation, and clinical importance regardless of *P* values. A multiple logistic regression analysis was then performed based on the results of the univariate analysis. To evaluate the combinations of factors changing the risk of VIN, a DT analysis was conducted using the chi-squared (χ^2) automatic interaction detection

(CHAID) algorithm.[27, 28] The DT model, which has a framework resembling a flowchart, is used to construct predictive models by using structured nonparametric approach. The DT model is commonly used to establish classification systems based on multiple factors. It classifies populations into segments, i.e., 'branches', which form an inverted tree and can easily handle large and complicated datasets. Therefore, construction of a DT model enables users to estimate combinations of factors that increase or decrease the risk of adverse events. The CHAID algorithm procedure was as follows: (1) construct multiple 2 × 2 contingency tables between the dependent variables (VIN occurrence) and each independent variable (factors affecting VIN occurrence); (2) extract the most significant factor via a χ^2 test; (3) branch the DT; (4) repeat steps 1–3; and (5) finish DT branching when the stop criteria are met. The branch stop criteria were: (1) attainment of three depth levels; (2) parent nodes ≤100 patients and/or child nodes ≤50 patients; or (3) no significant differences among factors affecting VIN. A weakness of the CHAID algorithm is that it cannot adjust for confounding factors because it simply repeats the χ^2 test. Therefore, in the present study, the independent variable was obtained among the factors identified in the multiple logistic regression analysis.

Pearson's χ^2 or Fisher's exact test was performed to compare the proportions of VIN between variable pairs such as concomitant use of PIPC-TAZ vs. PIPC. Fisher's exact test was employed if >20% of the cells in the contingency table had fewer than five expected frequencies. A Mann-

Whitney *U* test was used to compare continuous valuables. For comparison of the proportions of VIN, we employed the propensity score-matching method to avoid confounding. The potential factors affecting the selection of ramelteon, PIPC-TAZ, or PIPC (demographics, comorbidities, VCM durations, concomitant medications, and number of hospital beds), as well as those affecting performance of the ward pharmacy service (demographics, comorbidities, concomitant medications, number of hospital beds) were analysed using a multivariate logistic model. Then, the propensity scores were calculated using the significant factors. Pairs of patients were matched using the nearest neighbour pair matching algorithm within a specified calliper by standard deviation of the logit of the propensity score is 0.2.[29] A standardised difference of less than 0.1 was considered an adequate variable balance.[30]

The DT analysis was performed using SPSS Decision Trees V. 24 (IBM Corp., Tokyo, Japan). JMP v. 14 (SAS Institute Inc., Cary, NC, USA) was implemented for all other statistical analyses. $P < 0.05$ indicated statistically significant difference.

2.7 Model evaluation

To evaluate the misclassification risk of the DT model, we employed a 10-fold cross validation method,[27, 31] for which we (1) randomly separated the data sets for analysis into 10 data sets of equal sample size, (2) constructed the DT model using a training data set, (3) used the remaining

nine data sets as testing data to verify model effectiveness, and (4) repeated 10 empirical tests by using each subset as the test data.

2.8 Ethical approval

The Institutional Review Board of the Faculty of Pharmaceutical Sciences of Hokkaido University approved the study protocol (No. 2020-006).

3 RESULTS

3.1 Patient characteristics and univariate analysis

Of the 47,697 patients administered VCM between June 2000 and December 2020, 7,306 were enrolled in the present study (Figure 1). VIN occurred in 14.2% (1,035) of the patients. The median time (interquartile: IQR) to onset was 8 (5–13) days. The median times (IQR) to initial serum concentration collection of VCM were 4 (3–5) and 4 (3–6) days in patients with and without VIN, respectively. The median numbers (IQR) of measurement of trough concentration during the VCM therapy were 1 (1–2) in both groups.

Results of the univariate analysis of patient characteristics are shown in Table 1. To evaluate the odds ratios for each stratification, we entered age, CrCl, VCM duration, and trough concentration into the multivariate analysis as categorical data rather than continuous variables. For converting categorical data, the cut-off values were referenced and partially modified from previous reports.[1, 3–5] Considering that VCM trough concentrations were measured multiple times in some patients, the average values were employed for multivariate analysis.[1, 3] Body weight ≥100 kg was applied as an alternative overweight index but was not regarded as a continuous variable. Cirrhosis and chronic kidney disease comorbidities are usually correlated with laboratory values such as total bilirubin and CrCl. Hence, we employed clinical laboratory

values because they provide specific information. Infection type could not be specified in >30% of all patients. Patients with infectious endocarditis (IE) were at high risk for VIN. IE may be correlated with high trough concentrations, concomitant aminoglycoside use, and long-term duration.[32] Thus, we excluded all infectious diseases from the multivariate analysis.

3.2 Multivariate analysis

The results of the multivariate logistic regression analysis are shown in Table 2. Twenty-two variables, including concomitant use of ramelteon, concomitant use of PIPC, and ward pharmacy service were extracted as independent factors affecting VIN.

In addition, we performed sensitivity analyses on five patterns (Tables S3–S7): (1) age, CrCl, duration, and trough concentrations were entered as continuous variable; (2) cut-off values for age, CrCl, and duration of VCM were sequentially changed; and (3) the definition of concomitant medication was changed to prescription during VCM administration. We confirmed attainment of similar results. In particular, the results of concomitant use of ramelteon, concomitant use of PIPC, and ward pharmacy service were unchanged. For age, significant differences were observed by modifying continuous variables or cut-off values, but trends remained unchanged (Tables S3 and S4).

3.3 DT analysis

Factors significantly differing in the multivariate analysis were entered into the DT analysis. Significant differences were partially determined for CrCl and the number of hospital beds. Therefore, we applied all categories of these factors.

Figure 2 shows that DT branched into seven subgroups. Patients with trough concentrations ≥20 mg/L and concomitant PIPC-TAZ use were classified in the highest VIN risk group. Patients with trough concentrations <20 mg/L, without concomitant use of PIPC-TAZ and loop diuretic were categorized as the lowest VIN risk group.

The misclassification risk of the DT model estimated by 10-fold cross validation was 14.3 ± 0.4%.

3.4 Comparison of proportions of VIN between patients 'treated with ramelteon and those not, 'treated with PIPC-TAZ and PIPC', and 'with ward pharmacy service and those without'

The proportion of VIN was significantly lower in patients treated with ramelteon than in those without only after propensity score matching (Figures 3a and 3d). This trend did not change even when the analysis was limited to patients continuously receiving ramelteon for at least one to two weeks prior to VCM initiation but statistical significance was not obtained (data not

shown). Although a standardised difference less than 0.1 was not observed for only two variables, the statistical balance between the ramelteon and non- ramelteon groups was obtained by propensity score matching (Table S8). In 97.9% (424/433) of the patients, the daily dose of ramelteon was 8 mg.

The proportion of VIN was higher in patients treated with PIPC than in those treated with PIPC-TAZ. However, the difference was not significant (Figure 3b). The median overlapping durations of VCM and PIPC-TAZ or PIPC were both four days. Six patients who received both PIPC-TAZ and PIPC were excluded. Daily PIPC-TAZ and PIPC doses are listed in Table S9. Due to the small sample size, propensity score matching was not performed.

The proportions of VIN were lower in patients receiving ward pharmacy service than in those without it before and after propensity score matching (Figures 3c and 3e). The statistical balance between with and without ward pharmacy service groups was confirmed by propensity score matching in all variables (Table S10). The proportion of VCM trough concentrations (initial, average, and maximum) ≥20 mg/L was significantly lower in patients with ward pharmacy service than in those without it regardless of the propensity score matching. A high proportion of VCM trough concentrations <10 mg/L (initial, average, and maximum) was determined for

these group. Only after matching, a higher proportion of 10–15 mg/L (only average) was obtained in patients with ward pharmacy service than in those without (Table 3).

4 DISCUSSION

To the best of our knowledge, this study is the first to use the large Japanese EMR database to investigate the factors affecting VIN. We collected data for 7,306 patients. This population is the largest of all those in related studies performed in Japan.[1, 3, 27, 33] Serum VCM concentrations registered in the RWD database were assumed (but not proven) to be trough values. The proportion of average VCM concentrations ≥20 mg/L was only 15.7% (1,146/7,306 patients) and was not as high as those previously reported.[34, 35] The median averages of VCM concentrations were 17.0 and 13.7 mg/L for patients with and without VIN, respectively. These values resembled those of our previous studies.[27, 33] Hence, even if certain collected VCM concentrations were not trough values, they would not influence our conclusions. Most of the independent factors extracted from the multivariate analysis were consistent with those previously reported.[2–5] Our results showed that short-term duration (<7 days) and trough concentrations 10–15 mg/L were protective factors for VIN compared to the reference variables (i.e., 7–14 days and 15–20 mg/L).[1, 2, 4, 5] These factors are already known, but a large database reinforced the information on these key treatment optimisation characteristics. Thus, the RWD database may be used to analyse adverse reaction factors and applied to other drugs as well.

In the present study, we focused on three unresolved issues. First, the odds ratio of concomitant ramelteon use was significantly lower in the multivariate analysis. Additionally, the proportion of VIN was significantly lower in patients treated with ramelteon than in those without after propensity score matching. This finding partially supports that of a previous study wherein the use of a melatonin preparation reduced the risk of VIN.[6] Although no significant difference was obtained before adjustment for confounding factors, our findings demonstrate potential therapeutic value; however, they merit further verification.

Second, concomitant PIPC use was extracted as a VIN risk factor along with concomitant PIPC-TAZ use. Comparison of these groups revealed that patients receiving PIPC tended to have non-significantly higher proportions of VIN than patients receiving PIPC-TAZ. As the sample size of the PIPC group was small, it could not be concluded that concomitant PIPC use causes a higher risk of VIN than PIPC-TAZ use. In the multivariate analysis, we demonstrated in clinical studies that PIPC was, at the very least, a VIN risk factor. A potential mechanism of this drug-drug interaction is the competitive inhibition of organic anion transporters (OATs). PIPC and tazobactam are substrates for both OAT1 and OAT3.[36, 37] VCM suppresses mRNA and protein expression of OAT1 and OAT3.[38] These OATs mediate creatinine transit by inhibiting available pumps.[39] Toxicological synergy may occur, increasing Scr concentration; thus, our results are reasonable.

Third, the present work revealed that ward pharmacy service is a VIN suppression factor by multivariate analysis. This conclusion is reliable because the proportions of VIN were lower in patients with ward pharmacy service before and after propensity score matching. Ward pharmacists foster the appropriate use of VCM by monitoring VIN, making TDM recommendations, and setting doses.[40-43] As most of the screened studies were single-centre, institutional bias could not be entirely avoided. Although the medical fee calculation requirements related to ward pharmacy services include setting and evaluating drug dosages, [17, 26] we could not clearly show which interventions were actually performed (i.e., ward pharmacy service is not specific for VCM). Regardless, the furnished big data provided evidence that ward pharmacists contributed to VIN reduction.

Patients receiving ward pharmacy service had relatively lower proportions of average, initial and maximum VCM trough concentrations ≥20 mg/L than those without ward pharmacy service. This may have contributed to reduce the proportion of VIN. Nevertheless, the proportions reaching therapeutic range (10–20 mg/L) did not significantly differ between patient groups except for average trough concentration 10–15 mg/L after propensity score matching. Thus, we could not provide sufficiently strong data that ward pharmacists intervened to optimise the VCM dose. Andrew *et al*. reported that pharmacist intervention reduces the

proportion of trough concentrations ≥20 mg/L and occurrence of VIN, but it did not improve the proportion of reaching the therapeutic range.[44] In addition, several nomograms and dose-setting softwares have been reported to optimise VCM dosing; however, the proportions of reaching the therapeutic range have not been 100%.[45-47] Thus, our results are consistent with these previous reports.

We used DT analysis to identify the combinations of factors that may increase or decrease the risk of VIN. However, one disadvantage of this machine learning method is that the number of cases available for analysis decreases with increasing tree branching.[27, 28] The use of big data overcame this limitation because sufficient numbers of patients could be collected even in the smallest subgroup (n = 156). The misclassification risk of our DT model indicated favourable.[27, 48] The proportions of VIN in the seven subgroups branched by DT analysis were in the range of 7.74–42.2%. We determined that the combination of VCM trough concentration ≥20 mg/L and concomitant PIPC-TAZ use were associated with the highest VIN risk. Therefore, frequent VIN monitoring is vital for high-risk patients. However, since the present study did not address AUC-guided dosing,[24] further studies are required.

Our study has certain limitations. The causal relationship between VCM and Scr concentration elevation could not be evaluated as Scr concentrations fluctuate for many reasons. Moreover, it

is unclear whether high VCM trough concentrations are the cause or effect of VIN. The same limitation was also reported for prior studies. Infection type could not be identified in >30% of all patients. Information regarding pathogen type and infectious disease severity could not be evaluated because there was a lack of data for these factors. As drug administration was determined from prescriptions, actual use could not be evaluated. However, our findings regarding concomitant use of ramelteon, concomitant use of PIPC, and ward pharmacy service were unchanged when the definition of concomitant use was modified to 'prescriptions during the VCM therapy'. Since strict inclusion criteria were essential to accurately assess VIN, we were only able to include 15.3% of the study population (7,306 out of 47,697), which limits its extrapolation. In fact, some comorbidities and infection types differed between patients who were included (n=7,306) and who were excluded (only patients ≥18 years, n=37,685) (Table S11). Additionally, our study included patients who received VCM between June 2000 and December 2020, and the role of ward pharmacists may have changed over time. We also assessed the proportion of VIN before and after 15 May 2013, when the Japanese TDM guidelines were published online.[23] As a result, these proportions were 3.92% (2 out of 51) and 11.9% (337 out of 2,823), respectively; thus, the developmental impact of the TDM guideline could not be evaluated due to the small sample size. Since most Japanese reports on the contribution of ward pharmacists were published after 2013,[40-43] the change in contributions over time needs to be verified.

5 CONCLUSION

The present study demonstrated that concomitant ramelteon use, ward pharmacy service, duration of VCM <7 days, and average trough concentrations 10–15 mg/L reduce the risk of VIN. In addition, concomitant PIPC use is a risk factor for VIN as well as PIPC-TAZ. DT analysis identified the factor combination associated with the highest VIN risk, namely, VCM trough concentrations ≥20 mg/L and concomitant PIPC-TAZ use. We believe that our novel approach comprising the use of large EMR database and machine learning methods may help identify the risk factors for adverse reactions associated with other antibiotic therapies.

6 NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[49]

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Tables

Table 1. Univariate analysis of patient characteristics affecting vancomycin-induced nephrotoxicity

Description	With VIN (n=1,035)	Without VIN (n=6,271)	OR (95%CI)	*P*-value
Demographics				
Age (years), median (IQR)	75 (67–83)	75 (65–83)	1.005† (1.000–1.009)	0.038*
≥18 and <40 years, n (%)	27 (2.61)	274 (4.37)	0.586 (0.393–0.875)	0.008*
≥40 and <60 years, n (%)	120 (11.6)	761 (12.1)	0.950 (0.774–1.165)	0.620
≥60 and <80 years, n (%)	509 (49.2)	2,958 (47.2)	1.084 (0.950–1.236)	0.230
≥80 years, n (%)	379 (36.6)	2,278 (36.3)	1.013 (0.883–1.161)	0.856
Sex (male), n (%)	616 (59.5)	3,975 (63.4)	0.849 (0.742–0.971)	0.017*
Sex (female), n (%)	419 (40.5)	2,296 (36.6)	1.178 (1.030–1.348)	
BW (kg), median (IQR)	52.8 (45.5–62.6)	53.1 (45.0–62.7)	0.999† (0.994–1.004)	0.732
BW ≥100 kg, n (%)	3 (0.29)	43 (0.69)	0.421 (0.130–1.360)	0.136
Comorbidity				
CHF, n (%)	403 (38.9)	2,050 (32.7)	1.313 (1.146–1.503)	<0.001*
Cirrhosis, n (%)	27 (2.61)	128 (2.04)	1.286 (0.844–1.957)	0.240
CKD, n (%)	150 (14.5)	460 (7.34)	2.141 (1.758–2.608)	<0.001*
COPD, n (%)	54 (5.22)	306 (4.88)	1.073 (0.797–1.444)	0.642
Type 1 DM, n (%)	2 (0.19)	14 (0.22)	0.865 (0.196–3.813)	0.848
Type 2 DM, n (%)	155 (15.0)	762 (12.2)	1.273 (1.056–1.535)	0.011*
Cancer, n (%)	446 (43.1)	2,528 (40.3)	1.121 (0.982–1.281)	0.092
BMT, n (%)	26 (2.51)	106 (1.69)	1.499 (0.971–2.313)	0.066
Thyroid disease, n (%)	108 (10.4)	578 (9.22)	1.148 (0.924–1.425)	0.213
Infection type				
CRBSI, n (%)	22 (2.13)	108 (1.72)	1.239 (0.780–1.970)	0.363
BSI, n (%)	82 (7.92)	471 (7.51)	1.060 (0.830–1.353)	0.643

Sepsis, n (%)	361 (34.9)	1,958 (31.2)	1.180 (1.027–1.355)	0.019*
Pneumonia, n (%)	197 (19.0)	1,159 (18.5)	1.037 (0.877–1.226)	0.672
Osteomyelitis, n (%)	14 (1.35)	99 (1.58)	0.855 (0.487–1.502)	0.585
SSTI, n (%)	115 (11.1)	739 (11.8)	0.936 (0.760–1.153)	0.532
IE, n (%)	42 (4.06)	132 (2.10)	1.967 (1.381–2.802)	<0.001*
UTI or pyelonephritis, n (%)	163 (15.7)	1,084 (17.3)	0.894 (0.747–1.070)	0.223
PJI, n (%)	1 (0.10)	8 (0.13)	0.757 (0.095–6.060)	1.000
Peritonitis, n (%)	93 (8.99)	410 (6.54)	1.411 (1.115–1.786)	0.004*
Spinal cord abscess, n (%)	0 (0)	8 (0.13)	0.000 (N/A)	0.611
SSI, n (%)	57 (5.51)	353 (5.63)	0.977 (0.733–1.303)	0.875
Unknown, n (%)	322 (31.1)	2,116 (33.7)	0.887 (0.770–1.022)	0.096
Laboratory data				
Scr concentration (mg/dL), median (IQR)	0.70 (0.49–1.05)	0.73 (0.55–1.02)	1.133† (1.082–1.186)	<0.001*
CrCl (mL/min), median (IQR)	63.7 (39.7–93.2)	62.6 (40.3–91.8)	1.000† (0.999–1.002)	0.536
<30 mL/min, n (%)	187 (18.1)	909 (14.5)	1.301 (1.094–1.547)	0.003*
≥30 and <60 mL/min, n (%)	292 (28.2)	2,058 (32.8)	0.805 (0.696–0.930)	0.003*
≥60 and <90 mL/min, n (%)	272 (26.3)	1,663 (26.5)	0.988 (0.851–1.147)	0.872
≥90 mL/min, n (%)	284 (27.4)	1,641 (26.2)	1.067 (0.920–1.237)	0.390
WBC (mg/dL), median (IQR)	9,100 (5,800–14,000)	8,800 (5,600 − 12,900)	1.000† (1.000–1.000)	0.872
BUN (mg/dL), median (IQR)	18.0 (12.0–30.0)	17.8 (12.1–27.0)	1.005† (1.002–1.009)	0.005*
T-bil (mg/dL), median (IQR)	0.60 (0.40–1.09)	0.60 (0.40–0.90)	1.077† (1.040–1.115)	<0.001*
Alanine aminotransferase (U/L), median (IQR)	23.0 (12.0–44.0)	23.0 (13.0–44.0)	1.000† (0.999–1.001)	0.736
Aspartate aminotransferase (U/L), median (IQR)	28.0 (18.0–49.0)	27.0 (18.0–44.0)	1.000† (1.000–1.000)	0.724
CRP (mg/L), median (IQR)	9.43 (4.53–16.1)	8.29 (3.87–15.0)	1.010† (1.003–1.018)	0.008*
VCM data				

Daily dose (mg), median (IQR)	1,000 (1.000–1,500)	1,000 (1.000–1,750)	1.000† (1.000–1.000)	0.629
Daily dose/kg (mg/kg), median (IQR)	21.3 (15.4–29.8)	21.1 (15.6–29.5)	1.000† (1.000–1.000)	0.083
Duration (days), median (IQR)	11 (7–15)	9 (6–14)	1.029† (1.021–1.036)	<0.001*
<7 days, n (%)	214 (20.7)	1,795 (28.6)	0.650 (0.554–0.763)	<0.001*
≥7 and <14 days, n (%)	458 (44.3)	2,793 (44.5)	0.988 (0.866–1.128)	0.863
≥14 and <21 days, n (%)	230 (22.2)	1,217 (19.4)	1.187 (1.012–1.391)	0.035*
≥21 and <28 days, n (%)	69 (6.67)	269 (4.29)	1.594 (1.213–2.094)	<0.001*
≥28 days, n (%)	64 (6.18)	197 (3.14)	2.032 (1.521–2.716)	<0.001*
Average trough concentrations (mg/L), median (IQR)	17.0 (12.6–21.1)	13.7 (10.2–17.2)	1.075† (1.065–1.085)	<0.001*
<10 mg/L, n (%)	131 (12.7)	1,486 (23.7)	0.467 (0.385–0.566)	<0.001*
≥10 and <15 mg/L, n (%)	255 (24.6)	2,258 (36.0)	0.581 (0.500–0.675)	<0.001*
≥15 and <10 mg/L, n (%)	314 (30.3)	1,716 (27.4)	1.156 (1.001–1.335)	0.048*
≥20 mg/L, n (%)	335 (32.4)	811 (12.9)	3.222 (2.774–3.742)	<0.001*
Initial trough concentrations (mg/L), median (IQR)	14.0 (9.90–18.6)	11.9 (8.30–15.7)	1.055† (1.045–1.064)	<0.001*
<10 mg/L, n (%)	262 (25.3)	2,288 (36.5)	0.590 (0.508–0.685)	<0.001*
≥10 and <15 mg/L, n (%)	324 (31.3)	2,188 (34.9)	0.850 (0.738–0.979)	0.024*
≥15 and <10 mg/L, n (%)	236 (22.8)	1,225 (19.5)	1.217 (1.039–1.425)	0.015*
≥20 mg/L, n (%)	213 (20.6)	570 (9.09)	2.592 (2.179–3.083)	<0.001*
Maximum trough concentrations (mg/L), median (IQR)	19.3 (13.7–25.4)	15.1 (11.1–19.6)	1.064† (1.056–1.072)	<0.001*
<10 mg/L, n (%)	108 (10.4)	1,250 (19.9)	0.468 (0.380–0.577)	<0.001*
≥10 and <15 mg/L, n (%)	206 (19.9)	1,840 (29.3)	0.598 (0.509–0.704)	<0.001*
≥15 and <10 mg/L, n (%)	225 (21.7)	1,699 (27.1)	0.747 (0.638–0.875)	<0.001*
≥20 mg/L, n (%)	496 (47.9)	1,482 (23.6)	2.974 (2.598–3.404)	<0.001*

Concomitant medications				
Loop diuretic, n (%)	416 (40.2)	1,868 (29.8)	1.584 (1.383–1.814)	<0.001*
Ramelteon, n (%)	53 (5.12)	380 (6.06)	0.837 (0.623–1.124)	0.236
Aminoglycosides, n (%)	52 (5.02)	194 (3.09)	1.657 (1.211–2.267)	0.001*
AMPH-B, n (%)	33 (3.19)	65 (1.04)	3.144 (2.057–4.806)	<0.001*
PIPC-TAZ, n (%)	309 (29.9)	1,147 (18.3)	1.901 (1.640–2.204)	<0.001*
PIPC, n (%)	11 (1.06)	22 (0.35)	3.051 (1.475–6.311)	0.002*
Vasopressor drugs, n (%)	168 (16.2)	685 (10.9)	1.580 (1.316–1.898)	<0.001*
Nitric acid-based medicines, n (%)	70 (6.76)	328 (5.23)	1.314 (1.006–1.716)	0.044*
ACE-I, n (%)	55 (5.31)	341 (5.44)	0.976 (0.728–1.308)	0.871
ARB, n (%)	180 (17.4)	997 (15.9)	1.113 (0.935–1.326)	0.226
Acyclovir, n (%)	38 (3.67)	205 (3.27)	1.128 (0.793–1.605)	0.503
Foscarnet, n (%)	8 (0.77)	18 (0.29)	2.706 (1.174–6.240)	0.023*
NSAIDs, n (%)	329 (31.8)	1,711 (27.3)	1.242 (1.077–1.432)	0.003*
Intravenous radiocontrast dye, n (%)	11 (1.06)	116 (1.85)	0.570 (0.306–1.062)	0.073
CNI, n (%)	39 (3.77)	110 (1.75)	2.193 (1.513–3.179)	<0.001*
With ward pharmacy service, n (%)	339 (32.8)	2,535 (40.4)	0.718 (0.625–0.825)	<0.001*
Number of hospital beds				
≥20 and <100 beds, n (%)	10 (0.97)	43 (0.69)	1.413 (0.708–2.821)	0.325
≥100 and <300 beds, n (%)	67 (6.47)	520 (8.29)	0.765 (0.588–0.996)	0.046*
≥300 and <500 beds, n (%)	445 (43.0)	2,453 (39.1)	1.174 (1.028–1.341)	0.018*
≥500 beds, n (%)	513 (49.6)	3,255 (51.9)	0.911 (0.798–1.039)	0.163

ACE-I: angiotensin-converting-enzyme inhibitor; AMPH-B: amphotericin B; ARB: angiotensin II receptor blocker; BMT: bone marrow transplant; BSI: bloodstream infection; BUN: blood urea nitrogen; BW: body weight; CHF: chronic heart failure; CI: confidence interval; CKD: chronic kidney disease; CNI: calcineurin inhibitor; COPD: chronic obstructive pulmonary disease; CRBSI: catheter-related blood stream infection; CrCl: creatinine clearance;

CRP: C-reactive protein; DM: diabetes mellitus; IE: infectious endocarditis; IQR: interquartile range; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; PIPC: piperacillin; PIPC-TAZ: piperacillin-tazobactam; PJI: prosthetic joint infection; Scr: serum creatinine; SSI: surgical site infection; SSTI: skin and soft-tissue infection; T-bil: total-bilirubin; TDM: therapeutic drug monitoring; UTI: urinary tract infection; VCM: vancomycin; VIN: vancomycin-induced nephrotoxicity; WBC: white blood cell.

Peritonitis includes intra-abdominal abscess. *Significantly different (P-value < 0.05); †Odds ratio indicates odds per single unit increase.

Table 2. Independent factors affecting vancomycin-induced nephrotoxicity determined by multiple logistic regression analysis

Description	OR (95%CI)	*P*-value
Demographics		
Age (years)		
≥18 and <40 years	0.689‡ (0.434–1.093)	0.114
≥40 and <60 years (reference)	1.000	
≥60 and <80 years	1.206‡ (0.946–1.538)	0.131
≥80 years	1.303‡ (0.993–1.710)	0.057
Sex (male)	0.824 (0.711–0.955)	0.010*
BW ≥100 kg	0.518 (0.151–1.773)	0.295
Comorbidity		
CHF	1.120 (0.956–1.311)	0.161
COPD	1.020 (0.741–1.403)	0.905
Type 1 DM	0.667 (0.134–3.308)	0.620
Type 2 DM	1.236 (1.011–1.511)	0.039*
Cancer	1.111 (0.958–1.288)	0.164
BMT	1.127 (0.561–2.265)	0.736
Thyroid disease	0.984 (0.779–1.242)	0.891
Laboratory data		
CrCl (mL/min)		
<30 mL/min	0.953‡ (0.730–1.245)	0.725
≥30 and <60 mL/min	0.737‡ (0.607–0.896)	0.002*
≥60 and <90 mL/min (reference)	1.000	
≥90 mL/min	1.502‡ (1.225–1.841)	<0.001*
WBC (mg/dL)	1.000† (1.000–1.000)	0.822
BUN (mg/dL)	1.002† (0.997–1.007)	0.484
T-bil (mg/dL)	1.075† (1.035–1.116)	<0.001*
Alanine aminotransferase (U/L)	0.999† (0.998–1.0004)	0.183
Aspartate aminotransferase (U/L)	1.000† (0.999–1.001)	0.217
CRP (mg/L)	1.008† (0.9996–1.016)	0.064
VCM data		
Daily dose (mg)	1.000† (1.000–1.000)	0.171
Duration (days)		
<7 days	0.748‡ (0.623–0.899)	0.002*
≥7 and <14 days (reference)	1.000	
≥14 and <21 days	1.124‡ (0.937–1.348)	0.208
≥21 and <28 days	1.375‡ (1.018–1.858)	0.038*

≥28 days	2.079‡ (1.516–2.852)	<0.001*
Average trough concentrations (mg/L)		
<10 mg/L	0.539‡ (0.427–0.680)	<0.001*
≥10 and <15 mg/L	0.668‡ (0.556–0.802)	<0.001*
≥15 and <20 mg/L (reference)	1.000	
≥20 mg/L	2.587‡ (2.149–3.114)	<0.001*
Concomitant medications		
Loop diuretic	1.229 (1.048–1.441)	0.011*
Ramelteon	0.701 (0.512–0.959)	0.027*
Aminoglycosides	1.569 (1.124–2.190)	0.008*
AMPH-B	2.653 (1.669–4.217)	<0.001*
PIPC-TAZ	2.056 (1.754–2.409)	<0.001*
PIPC	2.868 (1.298–6.338)	0.009*
Vasopressor drugs	1.485 (1.205–1.831)	<0.001*
Nitric acid-based medicines	1.081 (0.809–1.446)	0.597
ACE-I	0.795 (0.578–1.092)	0.156
ARB	1.088 (0.902–1.312)	0.379
Acyclovir	1.110 (0.684–1.802)	0.672
Foscarnet	1.370 (0.461–4.072)	0.571
NSAIDs	1.328 (1.137–1.553)	<0.001*
Intravenous radiocontrast dye	0.505 (0.261–0.977)	0.042*
CNI	2.137 (1.323–3.452)	0.002*
With ward pharmacy service	0.741 (0.638–0.861)	<0.001*
Number of hospital beds		
≥20 and <100 beds	1.947‡ (0.921–4.117)	0.081
≥100 and <300 beds	0.838‡ (0.617–1.136)	0.255
≥300 and <500 beds	1.158‡ (0.997–1.345)	0.055
≥500 beds (reference)	1.000	

ACE-I: angiotensin-converting-enzyme inhibitor; AMPH-B: amphotericin B; ARB: angiotensin II receptor blocker; BMT: bone marrow transplant; BUN: blood urea nitrogen; BW: body weight; CHF: chronic heart failure; CI: confidence interval; CNI: calcineurin inhibitor; COPD: chronic obstructive pulmonary disease; CrCl: creatinine clearance; CRP: C-reactive protein; DM: diabetes mellitus; NSAID: non-steroidal anti-inflammatory drug; OR: odds ratio; PIPC: piperacillin; PIPC-TAZ: piperacillin-tazobactam; T-bil: total-bilirubin; VCM: vancomycin; WBC: white blood cell. *Significantly different (P-value < 0.05), †Odds ratio indicates odds per single unit increase. ‡Odds ratio is for comparison with reference value.

Table 3. Comparison of vancomycin trough concentrations between patients with ward pharmacy service and those without before and after propensity score matching

Description	Before propensity score matching			After propensity score matching		
	With ward pharmacy service (n=2,874)	Without ward pharmacy service (n=4,432)	*P*-value	With ward pharmacy service (n=2,770)	Without ward pharmacy service (n=2,770)	*P*-value
Average trough concentrations (mg/L), median (IQR)	13.7 (10.1–17.2)	14.3 (10.7–18.2)	<0.001* a)	13.8 (10.2–17.2)	14.3 (10.7–18.4)	<0.001* a)
<10 mg/L, n (%)	687 (23.9)	930 (21.0)	0.003* b)	646 (23.3)	577 (20.8)	0.025* b)
>=10 and <15 mg/L, n (%)	1,018 (35.4)	1,495 (33.7)	0.138 b)	992 (35.8)	920 (33.2)	0.042* b)
>=15 and <20 mg/L, n (%)	784 (27.3)	1,246 (28.1)	0.437 b)	757 (27.3)	787 (28.4)	0.369 b)
>=20 mg/L, n (%)	385 (13.4)	761 (17.2)	<0.001* b)	375 (13.5)	486 (17.5)	<0.001* b)
Initial trough concentrations (mg/L), median (IQR)	11.8 (8.30–15.6)	12.3 (8.60–16.3)	<0.001* a)	11.8 (8.38–15.6)	12.4 (8.60–16.4)	<0.001* a)
<10 mg/L, n (%)	1,069 (37.2)	1,481 (33.4)	<0.001* b)	1,017 (36.7)	933 (33.7)	0.018* b)
>=10 and <15 mg/L, n (%)	984 (34.2)	1,528 (34.5)	0.834 b)	957 (34.5)	938 (33.9)	0.591 b)
>=15 and <20 mg/L, n (%)	565 (19.7)	896 (20.2)	0.561 b)	546 (19.7)	558 (20.1)	0.687 b)
>=20 mg/L, n (%)	256 (8.91)	527 (11.9)	<0.001* b)	250 (9.03)	341 (12.3)	<0.001* b)
Maximum trough concentrations (mg/L), median (IQR)	15.2 (11.1–19.9)	15.9 (11.6–20.8)	<0.001* a)	15.2 (11.2–19.9)	16.0 (11.7–20.9)	<0.001* a)
<10 mg/L, n (%)	583 (20.3)	775 (17.5)	0.003* b)	546 (19.7)	485 (17.5)	0.035* b)

>=10 and <15 mg/L, n (%)	817 (28.4)	1,229 (27.7)	0.517 b)	798 (28.8)	750 (27.1)	0.151 b)
>=15 and <20 mg/L, n (%)	762 (26.5)	1,162 (26.2)	0.780 b)	734 (26.5)	735 (26.5)	0.976 b)
>=20 mg/L, n (%)	712 (24.8)	1,266 (28.6)	<0.001* b)	692 (25.0)	800 (28.9)	0.001* b)

IQR: interquartile range. *Significantly different (P-value<0.05). a: Mann–Whitney U test. b: Pearson's χ^2 test.

Figure legends

Figure 1. Patient selection flowchart.
Scr: serum creatinine; VCM: vancomycin; VIN: vancomycin-induced nephrotoxicity.

Figure 2. Decision tree model estimating combinations of factors modulating the risk of vancomycin-induced nephrotoxicity.
CrCl: creatinine clearance; PIPC-TAZ: piperacillin-tazobactam; VCM: vancomycin; VIN: vancomycin-induced nephrotoxicity.

Figure 3. Comparison of proportions of vancomycin-induced nephrotoxicity between patients 'with ramelteon and those without', 'piperacillin-tazobactam and piperacillin' and 'with ward pharmacy service and those without'.
a and d: with ramelteon vs. those without before and after propensity score matching; b: piperacillin-tazobactam vs. piperacillin. c and e: with ward pharmacy service vs. those without before and after propensity score matching. PIPC: piperacillin. PIPC-TAZ: piperacillin-tazobactam. VIN: vancomycin-induced nephrotoxicity. N.S.: not significant by Pearson's χ^2 test (for (a)) and Fisher's exact test (for (b)). *Significantly different by Pearson's χ^2 test ($P < 0.05$).

Fig.1

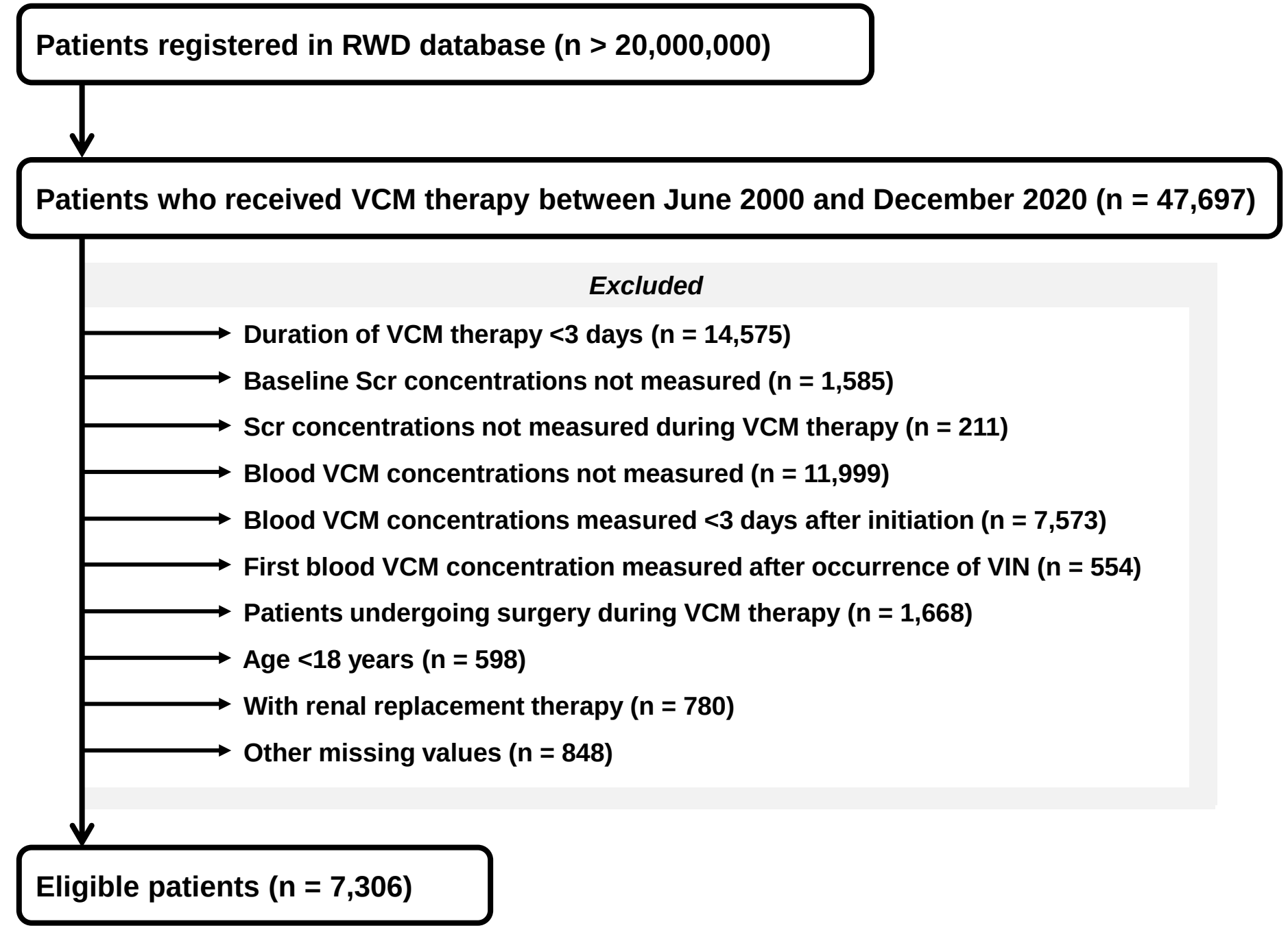
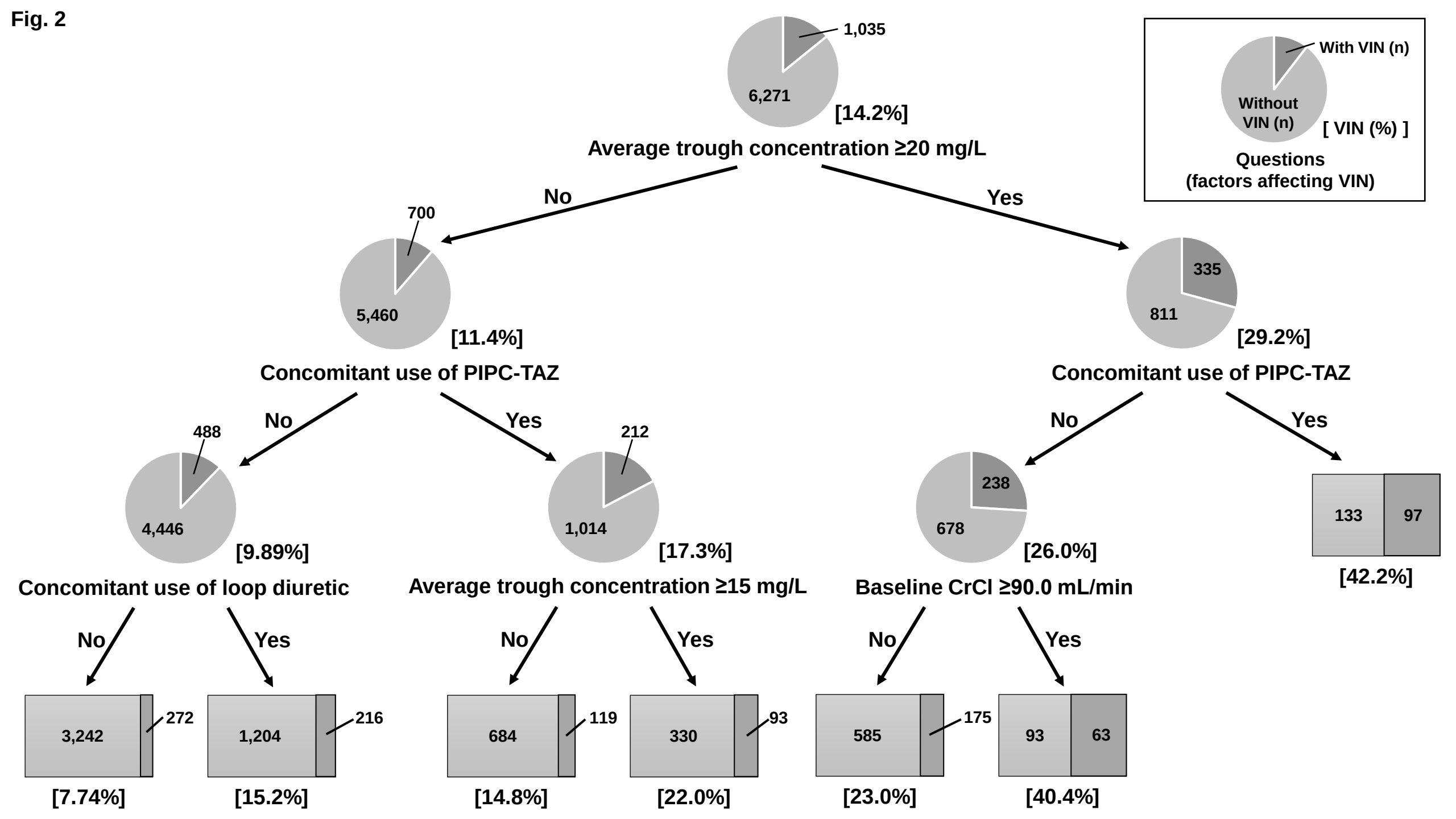
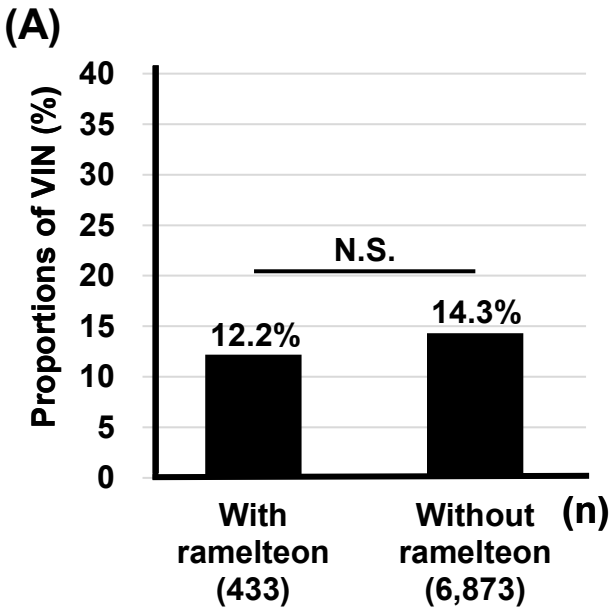
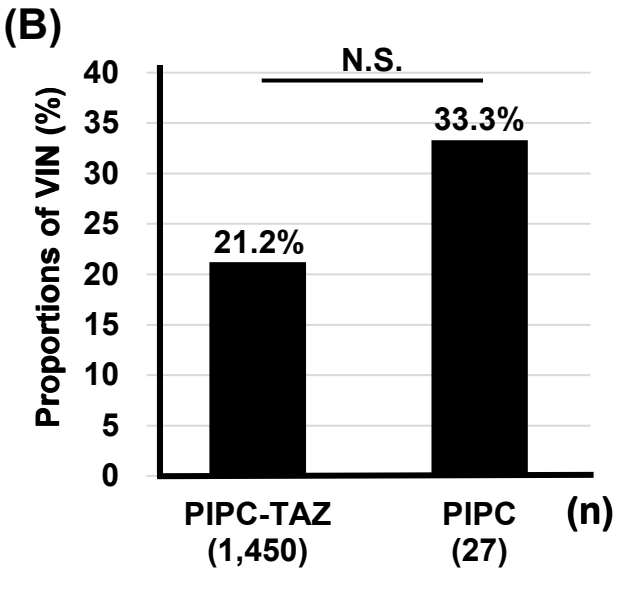

Patients registered in RWD database (n > 20,000,000)
Patients who received VCM therapy between June 2000 and December 2020 (n = 47,697)
Excluded
Duration of VCM therapy <3 days (n = 14,575)
Baseline Scr concentrations not measured (n = 1,585)
Scr concentrations not measured during VCM therapy (n = 211)
Blood VCM concentrations not measured (n = 11,999)
Blood VCM concentrations measured <3 days after initiation (n = 7,573)
First blood VCM concentration measured after occurrence of VIN (n = 554)
Patients undergoing surgery during VCM therapy (n = 1,668)
Age <18 years (n = 598)
With renal replacement therapy (n = 780)
Other missing values (n = 848)
Eligible patients (n = 7,306)

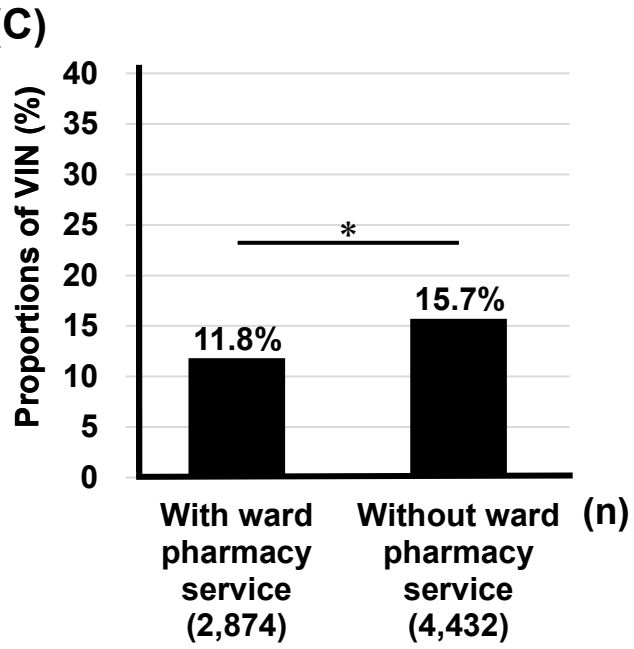
Fig. 2


1,035
6,271
[14.2%]
Average trough concentration ≥20 mg/L
With VIN (n)
Without VIN (n)
[VIN (%)]
Questions (factors affecting VIN)
No
Yes
700
5,460
[11.4%]
335
811
[29.2%]
Concomitant use of PIPC-TAZ
Concomitant use of PIPC-TAZ
No
Yes
No
Yes
488
4,446
[9.89%]
212
1,014
[17.3%]
238
678
[26.0%]
133
97
[42.2%]
Concomitant use of loop diuretic
Average trough concentration ≥15 mg/L
Baseline CrCl ≥90.0 mL/min
No
Yes
No
Yes
No
Yes
3,242
272
[7.74%]
1,204
216
[15.2%]
684
119
[14.8%]
330
93
[22.0%]
585
175
[23.0%]
93
63
[40.4%]

Before propensity score matching







After propensity score matching