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Research Article

Clinical and Biochemical Determinants of the Systemic Inflammation Response Index During Vancomycin Therapy

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Abstract

Background: Vancomycin (VAN) is the standard of care for Gram-positive infections. The systemic inflammation response index (SIRI) has been associated with infections and sepsis across various clinical settings; however, the correlates and determinants of the SIRI during VAN therapy remain unexplored. This retrospective cross-sectional study aimed to identify the determinants of the SIRI among adults treated with VAN. **Methods:** Medical records of 299 patients who received VAN were analyzed consecutively. Prevalence rates were calculated; Spearman's correlation and regression models were employed to evaluate associations; risk assessment was conducted using prevalence ratios and odds ratios; diagnostic potential was assessed using receiver operating characteristic curves. **Results:** The SIRI was significantly higher in intensive care unit (ICU) patients than in non-ICU patients receiving VAN therapy ($p < 0.0001$). Age, blood pressure, creatinine, Na^+, CO_2, albumin, aspartate transaminase (AST), gamma-glutamyl transferase (GGT), bilirubin, coefficient of variation in red cell distribution width (RDW-CV), and platelet count were significantly and differentially correlated with the SIRI. In the adjusted analysis, ICU requirement emerged as the strongest independent predictor of SIRI, with ICU patients showing a 2.13-fold higher SIRI($p < 0.0001$). Moreover, the prevalence of ICU requirement was 1.61 times higher in individuals with increased SIRI ($p = 0.0018$), whose odds of ICU requirement were 2.16 times higher ($p = 0.0016$). The SIRI also demonstrated moderate discriminatory ability, with the highest performance observed in patients younger than 50 years (area under the curve [AUC] = 0.731, $p = 0.0001$). **Conclusions:** The SIRI is a novel and cost-effective marker that is correlated with distinct demographic and clinical variables and independently associated with ICU requirement in VAN-treated patients and may aid in the risk stratification and management of this vulnerable patient cohort.

Keywords: biomarker; vancomycin; critical care; inflammation; infection

1. Introduction

Vancomycin (VAN) is a tricyclic glycopeptide antibiotic isolated from *Streptococcus orientalis*. The bactericidal effect of VAN is mediated through the inhibition of glucosyltransferase activity that catalyzes peptidoglycan polymerization in the bacterial cell wall [1]; therefore, it is indicated for infections caused by Gram-positive bacteria, including staphylococci, streptococci, and enterococci. Because of its poor oral absorption, VAN is administered by IV infusion and mainly excreted through the kidneys. Therapeutic drug monitoring (TDM) is required for VAN due to its narrow therapeutic index, high toxicity in overdose, and variability in pharmacokinetics [2]. Moreover, subtherapeutic levels precipitate the emergence of VAN-resistant strains [3], and a strict correlation between serum levels and adverse effects does not exist with many of the toxic effects observed within the therapeutic range.

According to the clinical guidelines published by the Saudi Ministry of Health (MOH) [4], the loading dose of VAN is intravenously administered at 25 to 30 mg/kg, with a maximum of 3 g in obese adults, while the maintenance dose ranges from 15 to 20 mg/kg every eight to 12 hours. The half-life of VAN ranges from four to 12 hours, and a steady-state circulating level is reached after four to five half-lives, which is typically achieved within one to two days of regular dosing. Due to the long distribution phase of VAN, only trough levels, determined 30 minutes before the fourth dose onward, are monitored to ensure that the serum concentration is within the therapeutic range. The target trough range is 10–15 mg/L and 15–20 mg/L for uncomplicated and complicated infections, respectively. Peak levels are not monitored since they do not correlate with toxicity or efficacy.

The toxic effects of VAN include red man syndrome (non-IgE hypersensitivity due to rapid infusion), nephrotoxicity, ototoxicity, neutropenia, and thrombocytopenia [5,6]. In particular, impaired renal function significantly prolongs the half-life of VAN and the treatment duration required to achieve a steady-state serum level. VAN-induced nephrotoxicity occurs due to proximal tubule injury with an increase in serum creatinine of ≥0.3 mg/dL or ≥50% from baseline within two to seven days of initiating therapy. Risk factors of renal injury due to VAN include high trough levels, prolonged therapy, exposure to nephrotoxic medications, sepsis, intensive care unit (ICU) admission, and volume depletion [7].

The Saudi MOH mandates periodic complete blood count (CBC) measurements to monitor neutropenia and

thrombocytopenia, which are often encountered in VAN-treated patients, mainly due to myelosuppression. Recently, CBC-derived ratios and indices have gained widespread interest in various clinical settings. The systemic inflammation response index (SIRI) is a composite biomarker that reflects innate immune activation and adaptive immune suppression in the systemic circulation [8].

$$\text{SIRI} = \frac{\text{absolute neutrophil count} \times \text{absolute monocyte count}}{\text{absolute lymphocyte count}}$$

In particular, elevated neutrophils and monocytes indicate enhanced inflammatory burden and phagocytic activity, while lymphopenia suggests immune dysregulation and worsening outcomes. As such, SIRI has emerged as a promising marker of systemic inflammation in a wide spectrum of conditions. SIRI was reported to be associated with sepsis and mortality in patients with various conditions, including stroke [9], cardiovascular disease [10], pancreatic adenocarcinomas [8], breast cancer [11], and gastric cancer [12]. Furthermore, elevated SIRI was detected in psoriasis [13], renal disease [14], lupus nephritis [15], catheter-related bloodstream infection [16], stroke-associated pneumonia [17], necrotizing pneumonia [18], and infections in subjects with anti-synthetase syndrome [19].

Critically ill patients in the ICU receiving VAN require adjusted dosing and continuous infusion [20] and exhibit significant individual variation in pharmacokinetics and pharmacodynamics [21]. Moreover, renal function tests can detect VAN-induced nephrotoxicity only when 50% of function is lost [5], highlighting the need for more sensitive markers of kidney function, especially in vulnerable patients. Accordingly, this study was designed to identify the clinical and biochemical determinants of SIRI in adult patients receiving VAN therapy.

2. Experimental Design

2.1 Study Design and Patients

This retrospective cross-sectional study took place at King Khalid University Hospital, a tertiary care academic center located in Riyadh, Saudi Arabia. The study was approved by King Saud University Ethics Committee (approval number: E-25-9553; approval date: February 12, 2025). Due to the retrospective, cross-sectional design of the study, no *a priori* sample size calculation was performed. Instead, to minimize selection bias and maximize statistical power, data were consecutively extracted from the hospital registry for adult patients (≥18 years) who received VAN between January 2024 and February 2025. Patients who were younger than 18 years old, did not receive VAN, or had missing SIRI parameters were excluded. The same cohort has previously been used for related biomarker analyses [22] as part of a broader project exploring the clinical utility of emerging inflammatory, organ-specific, and composite scores during VAN therapy. Each biomarker was separately analyzed to permit focused and detailed identification of specific associated factors and correlates.

The dataset included age, gender, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), VAN dosage and trough levels, ICU status, comorbidities, and laboratory parameters—including liver and renal function tests (Cobas 8100, Roche Diagnostics, Indianapolis, IN, USA) and CBC (XN-2000, Sysmex Corporation, Kobe, Hyogo, Japan). Isolated organisms and sensitivity profiles can be found in our previous publication [22]. All data were recorded at the time of VAN trough level determination as mandated by the Saudi MOH. Patients were primarily stratified according to ICU status whereas secondary stratification was based on gender; age distribution into three groups, namely, <50 years (100 subjects), 50–65 years (79 subjects), and >65 years (120 subjects) [23]; and VAN trough levels.

2.2 Statistical Analysis

All analyses were performed using Prism 9.0 (GraphPad Software, Inc., San Diego, CA, USA) and Excel 2019 (Microsoft Corporation, Redmond, WA, USA). The difference in prevalence was examined using a Chi-square test, followed by the calculation of residuals. Data did not pass normality as assessed by D'Agostino-Pearson, Anderson-Darling, and Kolmogorov-Smirnov tests. Thus, the Mann–Whitney *U* test was used to compare medians between the ICU and non-ICU groups with interquartile range. . Spearman's correlation was computed, and regression models were constructed to evaluate associations. In multivariable regression models, multicollinearity among variables was tested using variance inflation factor (VIF) analysis. Principal component analysis (PCA) was performed to probe data variance. To minimize scale-dependent bias across parameters, variables were standardized to a mean of 0 and a standard deviation of 1 prior to PCA. Principal components (PC) were selected using parallel analysis with Monte Carlo simulation (1000 iterations, 95th percentile threshold). Prevalence ratio (PR), odds ratio (OR), prevalence difference (PD), and area under the curve (AUC) in receiver operating characteristic (ROC) curve analysis, along with the positive predictive value (PPV) and negative predictive value (NPV), were computed using Koopman asymptotic score, Newcombe/Wilson, Baptista-Pike, and Wilson-Brown methods, respectively. For overall risk analysis, a pooled median cutoff was used, whereas for subgroup ROC optimization, cutoff values were determined by calculation of Youden index.

3. Results

Table 1 shows the demographic and clinical characteristics of ICU and non-ICU patients. Weight, BMI, blood pressure (BP), creatinine, phosphate, calcium, magnesium, albumin, aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, red blood cells (RBCs), hematocrit,

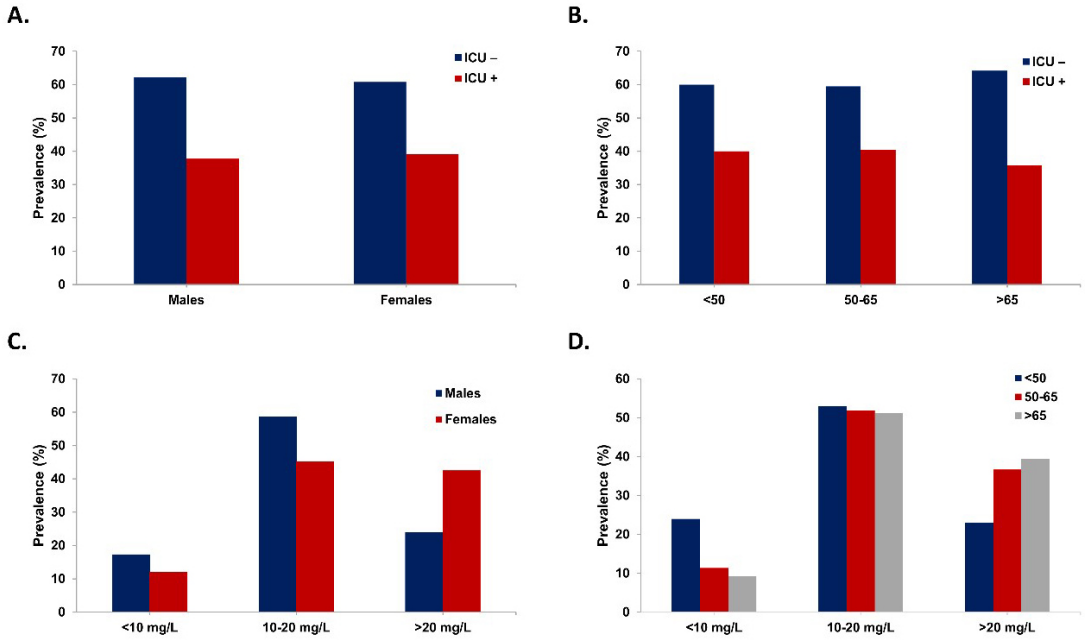

Fig. 1. Distribution of patients based on ICU status and VAN trough levels. Prevalence (%) of ICU requirement based on (A) gender and (B) age group. Prevalence (%) of VAN trough levels based on (C) gender and (D) age group. VAN, vancomycin.

hemoglobin, white blood cells (WBCs), platelets, and mean platelet volume were significantly different between the two groups as determined by the Mann–Whitney *U* test.

The Chi-square test revealed no significant association between gender (Fig. 1A) or age (Fig. 1B) and ICU admission ($p = 0.7979$ and 0.9853, respectively). Only about half of the patients (52.01%) had trough levels within the therapeutic range, while 33.22% had supratherapeutic levels, and therapeutic failure was observed in 14.77%. Gender-wise comparisons (Fig. 1C) reveal a significant Chi-square test, $\chi^2(2) = 11.65$, $p = 0.003$, indicating an appreciable association between gender and trough levels. Specifically, males had a higher proportion of therapeutic levels (58.67%) compared to females (45.3%). Furthermore, therapeutic failure was slightly more common in males (17.3% vs. 12.2%), while more females had supratherapeutic levels (42.6% vs. 24.0%).

Age was also a significant factor influencing trough levels, $\chi^2(4) = 13.72$, $p = 0.0083$. In particular, as seen in Fig. 1D, patients aged <50 years were the most affected by therapeutic failure, constituting 24.0% of all cases. Conversely, supratherapeutic levels were most common (39.50%) in older patients (>65 years). In the 50–65 age group, 51.90% had a therapeutic level, and 36.71% had a supratherapeutic level. However, the association between ICU admission and trough levels was not significant ($p = 0.716$).

Based on the observed variability in ICU distribution and VAN trough levels across demographic subgroups, we next examined whether SIRI differed according to ICU status. SIRI was significantly higher in ICU patients of both genders and when analyzed in isolation (Fig. 2A–C). When stratified by age (Fig. 2D–F), the difference remained significant in younger (<50 years) and older (>65 years) patients but not in the 50–65 age group.

Spearman's correlation (Table 2) identified multiple variables that are significantly associated with SIRI, including age, DBP, serum creatinine, CO_2, albumin, AST, gamma-glutamyl transferase (GGT), total bilirubin, conjugated bilirubin, and unconjugated bilirubin. In non-ICU patients, all correlations persisted along with platelets, except DBP and AST. In ICU patients, only liver markers and coefficient of variation in red cell distribution width (RDW-CV) were negatively associated with SIRI.

Table 3 shows a linear regression model formulated to determine factors independently associated with SIRI. No evidence of multicollinearity was observed since all VIF values were <1.1. It was found that each one-year increase in age elevated SIRI by 1.5% ($p = 0.0005$). Notably, ICU patients had a 2.13-fold increase in SIRI compared to non-ICU patients ($p < 0.0001$), indicating that ICU requirement was the strongest predictor of increased SIRI. Moreover, a one-unit elevation in serum creatinine or unconjugated bilirubin is associated with increases in SIRI of 0.1% ($p < 0.0001$) and 2.2% ($p < 0.0001$), respectively. In contrast, SIRI decreased by a small magnitude for every one-unit increase in AST activity ($p = 0.0013$). It should be emphasized that these variables represent associations rather than causative factors.

Further inspection of the data by PCA revealed highly negative loadings for SIRI (–0.78), age (–0.56), and creatinine (–0.53) on PC1, and positive loadings for uncon-

Table 1. Characteristics of study subjects.

Parameter	Non-ICU (n = 184)	ICU (n = 115)	p-value
Age (years)	59.50 (54.99–60.78)	61.0 (53.44–59.86)	0.4449
Gender (male/female %)	51.09/48.91	49.57/50.43	0.7979
SBP (mmHg)	121.0 (118.7–124.9)	111.0 (108.5–115.4)	<0.0001
DBP (mmHg)	64.50 (57.0–73.0)	58.0 (52.0–68.0)	0.0002
Weight (kg)	68.0 (65.90–71.92)	70.0 (71.15–78.98)	0.0416
BMI (kg/m^2)	25.32 (25.70–27.96)	27.53 (27.21–29.93)	0.0316
Vancomycin dose (mg)	1000 (1016–1131)	1000 (1066–1180)	0.2170
Vancomycin trough (mg/L)	22.10 (16.44–18.70)	21.60 (16.21–19.29)	0.8651
Creatinine (µmol/L)	81.0 (121–175.70)	110.0 (130.8–182.7)	0.0223
Na^+ (mmol/L)	138.1 (134.1–140.7)	138.2 (134.9–144.4)	0.0911
K^+ (mmol/L)	4.11 (3.64–5.68)	4.06 (4.027–4.31)	0.9064
Cl^- (mmol/L)	101.9 (97.89–102.6)	103.6 (98.37–104.6)	0.3015
PO_4^{3-} (mmol/L)	1.05 (1.05–1.16)	1.22 (1.16–1.34)	0.0063
Ca^{2+} (mmol/L)	2.08 (2.04–2.10)	2.02 (2.0–2.09)	0.0573
Mg^{2+} (mmol/L)	0.81 (0.79–0.85)	0.89 (0.86–0.93)	0.0005
CO_2 (mmol/L)	23.10 (22.39–23.84)	22.0 (21.57–23.39)	0.2774
Albumin (g/L)	29.60 (29.01–30.70)	28.0 (26.80–28.85)	0.0067
ALT (U/L)	18.60 (21.64–30.89)	27.50 (55.64–183.9)	0.0002
AST (U/L)	23.30 (15.50–37.80)	36.0 (20.80–95.90)	<0.0001
ALP (U/L)	112.5 (126.3–159.1)	102.0 (143.5–204.4)	0.8619
GGT (U/L)	50.0 (71.49–109.7)	52.0 (70.55–153.5)	0.6501
Total bilirubin (µmol/L)	6.40 (10.41–27.19)	10.30 (21.60–56.11)	<0.0001
Conj. bilirubin (µmol/L)	3.40 (6.16–20.61)	6.80 (15.26–43.49)	<0.0001
Unconj. bilirubin (µmol/L)	2.90 (3.73–6.77)	3.40 (5.89–13.06)	0.0137
RBCs (×10^9/L)	3.50 (3.47–3.71)	3.20 (3.18–3.44)	0.0018
HCT (%)	30.0 (30.08–31.86)	27.15 (26.99–28.78)	<0.0001
Hemoglobin (g/dL)	9.60 (8.50–11.18)	8.70 (8.10–10.0)	0.0002
MCH (pg)	28.10 (27.41–28.21)	28.20 (27.30–28.22)	0.9342
MCHC (g/L)	319.0 (300.2–317.0)	324.0 (285.4–314.9)	0.2043
MCV (fL)	86.90 (85.62–88.05)	85.90 (84.20–86.95)	0.2422
RDW-CV (%)	16.20 (16.22–17.21)	16.50 (16.57–17.72)	0.1133
WBCs (×10^9/L)	9.38 (9.30–11.12)	11.37 (11.60–15.63)	0.0042
Platelets (×10^9/L)	271.0 (265.50–312.0)	182.0 (179.2–238.20)	<0.0001
MPV (fL)	10.40 (10.32–10.68)	10.70 (10.56–10.99)	0.0408

Results are shown as medians (95% CI). SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; RBCs, red blood cells; HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RDW-CV, coefficient of variation in red cell distribution width; WBCs, white blood cells; MPV, mean platelet volume; ICU, intensive care unit; Conj., conjugated; Unconj., unconjugated.

jugated bilirubin (0.74) and AST (0.70) on PC2, as depicted in Fig. 3A. The distribution of patients relative to PC1 and PC2 is shown in Fig. 3B,C, respectively, and loadings are superimposed on these distributions in Fig. 3D. Furthermore, eigenvalues (Fig. 3E) suggest that PC1 (1.37, 27.36% variance) and PC2 (1.17, 23.38%) together accounted for 50.74% of the variance with loading patterns suggesting contributions from inflammatory, renal, and hepatic variables. PC3 (19.8%), PC4 (17.05%), and PC5 (12.41%) all had eigenvalues of <1.0 and, therefore, contributed less to variance than PC1 and PC2 (Fig. 3F).

Table 4 indicates the likelihood of ICU admission based on SIRI using a pooled median cutoff of 4.0. The PR value indicates that the prevalence of ICU admission in patients with high SIRI (≥4.0) is 1.61 times higher than that of their non-ICU counterparts (p = 0.0018). The PD between high and low SIRI was 0.18, reflecting a significantly higher prevalence of ICU admission in patients with

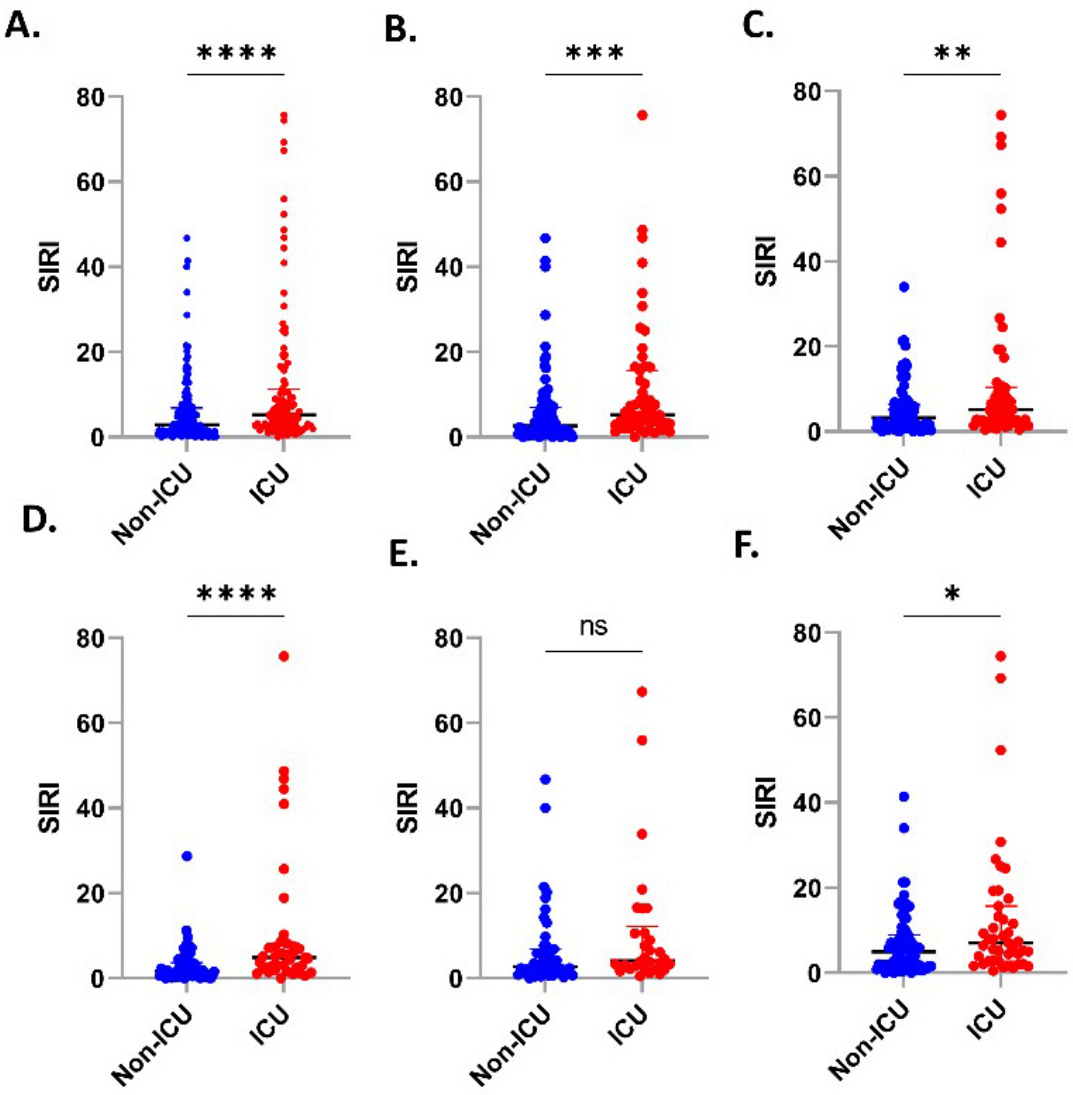

Fig. 2. SIRI is significantly increased in ICU patients. SIRI in (A) all patients, (B) males, (C) females, and (D) patients aged <50 years, (E) 50–65 years, and (F) >65 years. Results are shown as medians (IQR). No significance is indicated by ns, whereas significance is shown as *(<0.05), **(<0.01), ***(<0.001), and ****(<0.0001). SIRI, systemic inflammation response index.

high SIRI (p = 0.0015). The OR indicates that the odds of ICU admission are 2.16 times higher if SIRI is increased (p = 0.0016). An analysis of the PPV revealed that 70.8% of patients with increased SIRI required an ICU stay, but a low SIRI does not necessarily rule out the need for ICU admission based on a NPV of 47.2%.

Finally, we constructed ROC curves to explore the discriminatory power of SIRI for ICU admission. When all patients were considered (Fig. 4A), the AUC was 0.654 (p < 0.0001), which persisted when males (Fig. 4B) and females (Fig. 4C) were analyzed alone. When the participants were stratified by age, SIRI had the highest diagnostic accuracy in younger patients (Fig. 4D), with an AUC of 0.731 (p = 0.0001), while it lacked significance in the 50–65 age group (Fig. 4E) and regained it in older patients (AUC = 0.623, p = 0.0254, Fig. 4F).

Diagnostic metrics for optimal cutoff values are presented in Table 5, which varied across demographic subgroups. The highest cutoff was found in subjects >65 years of age (>8.0) who also demonstrated the lowest Youden index (0.20). Conversely, the strongest diagnostic performance was observed in individuals younger than 50 years of age who had the highest Youden index (0.35). Altogether, SIRI shows a modest-to-fair discriminatory ability based on ICU requirement.

4. Discussion

This is the first study to explore the clinical and biochemical determinants of SIRI in VAN-treated patients. Our results indicate that ICU requirement is the strongest predictor of increased SIRI, which underscores its potential clinical utility in identifying patients at risk for needing

Table 2. Spearman's correlation (ρ) of SIRI with clinical parameters.

Parameter	Total (n = 299)	p-value	Non-ICU (n = 184)	p-value	ICU (n = 115)	p-value
Age	0.2172	0.0002	0.2939	<0.0001	0.01956	0.8364
DBP	–0.1642	0.0046	–0.0434	0.5592	0.1441	0.1261
Creatinine	0.2464	<0.0001	0.2104	0.0042	0.0001	0.9989
Na^+	–0.1142	0.0501	–0.1745	0.0181	–0.0003	0.9972
CO_2	–0.1576	0.0067	–0.1686	0.0225	–0.1468	0.1192
Albumin	–0.1260	0.0305	–0.1705	0.0210	–0.2382	0.0107
AST	0.1168	0.0454	0.0633	0.3948	–0.1639	0.0813
GGT	0.1168	0.0455	0.1467	0.0481	–0.1929	0.0397
Total bilirubin	0.2572	<0.0001	0.2247	0.0023	–0.2322	0.0129
Conj. bilirubin	0.2735	<0.0001	0.2330	0.0015	–0.2388	0.0105
Unconj. bilirubin	0.1884	0.0012	0.1834	0.0132	–0.1218	0.1966
RDW-CV	0.0808	0.1664	0.0823	0.2680	–0.2173	0.0202
Platelets	0.0041	0.9438	0.1795	0.0151	0.0281	0.7663

ALT, alanine transaminase; DBP, diastolic blood pressure; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; RDW-CV, coefficient of variation in red cell distribution width.

Table 3. Multivariable regression analysis of SIRI.

Predictor	B	SE	95% CI	t value	p-value
Age	0.006515	0.001851	0.002871 to 0.01016	3.519	0.0005
ICU	0.3288	0.06858	0.1938 to 0.4638	4.794	<0.0001
Creatinine	0.0004272	0.0001943	4.480×10^{-5} to 0.0008096	2.199	0.0287
Unconj. bilirubin	0.009519	0.002332	0.004929 to 0.01411	4.082	<0.0001
AST	-8.901×10^{-5}	2.732×10^{-5}	-0.0001428 to -3.523×10^{-5}	3.258	0.0013

The model is adjusted for gender, vancomycin trough level, hypertension, diabetes mellitus, renal disease, and cancer.

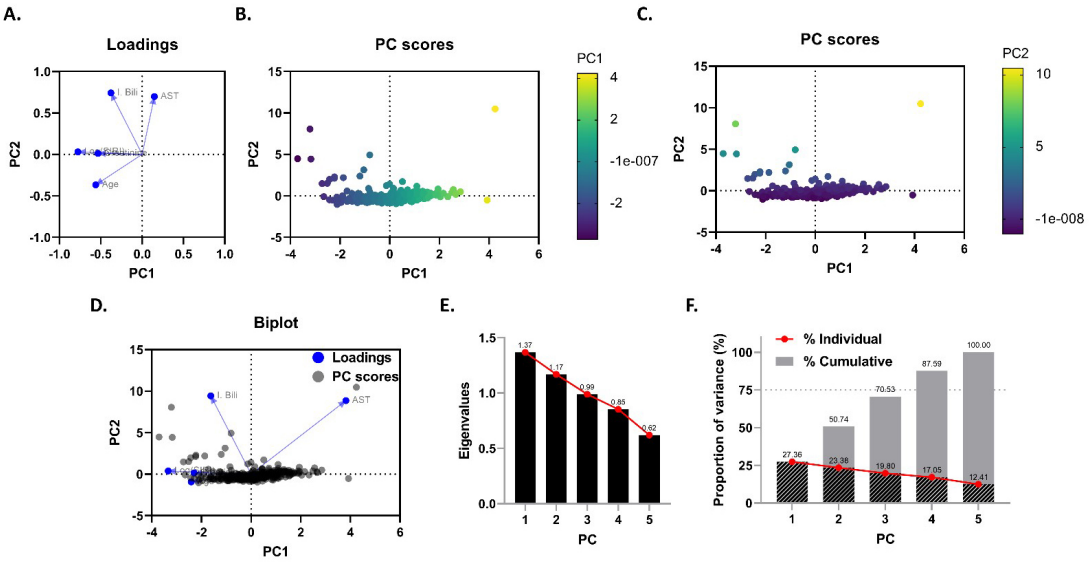

Fig. 3. PCA of data variance. (A) Loadings, (B) PC scores relative to PC1, (C) PC scores relative to PC2, (D) biplot showing loadings and PC scores, (E) a scree plot showing eigenvalues of each PC, and (F) individual and cumulative proportion of variance explained by each PC. PCA, principal component analysis.

critical care. Since SIRI is inexpensive and readily available from routine CBC results, the clinical prospects of this marker may hold significant promise for screening, diagnostic, therapeutic, and prognostic applications.

TDM for VAN is the cornerstone of patient management, as it reduces sepsis-related mortality [24]. We found that therapeutic failure was more prevalent in young patients (Fig. 1), which corroborates a previous study by Ishii

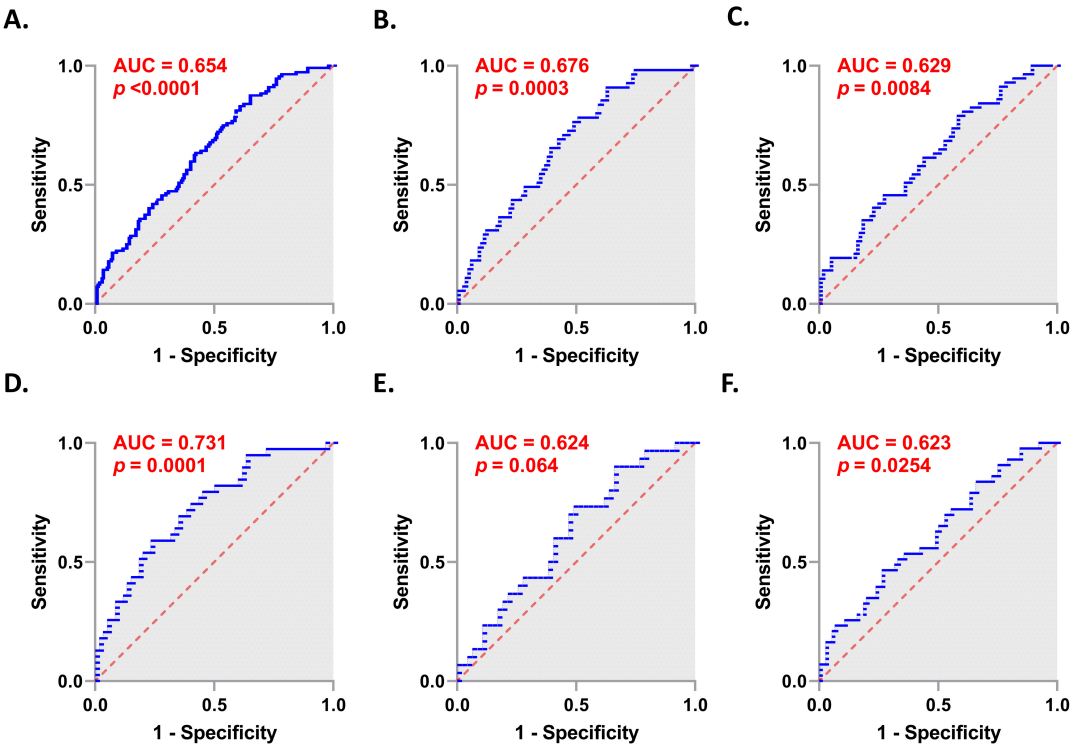

Fig. 4. Diagnostic power of SIRI for ICU admission. ROC curves for (A) all patients, (B) males, (C) females, and (D) patients aged <50 years, (E) 50–65 years, and (F) >65 years. ROC, receiver operating characteristic.

Table 4. Risk assessment of SIRI for ICU requirement.

Parameter	Score	95% CI	*p*-value	*z* statistic
PR	1.61	1.1948–2.1822	0.0018	3.118
PD	0.18	0.0641–0.2893	0.0015	3.183
OR	2.16	1.3407–3.4925	0.0016	3.160
PPV	0.71	0.6316–0.7739	–	–
NPV	0.47	0.3916–0.5536	–	–

PR, prevalence ratio; PD, prevalence difference; OR, odds ratio; PPV, positive predictive value; NPV, negative predictive value.

et al. [23] showing that patients aged <50 years were at increased risk for subtherapeutic levels. Interestingly, this did not correspond to increased risk of ICU admission (Fig. 1), which, in contrast to the findings of Altowayan et al. [25], is also confirmed by the lack of significant association between trough levels and ICU admission. This observation points to the contribution of other factors and the heterogeneous nature of patient cohorts. Overall, the observed age disparity may indicate that young patients have higher VAN clearance due to better kidney function, a larger volume of distribution for hydrophilic drugs than their older counterparts, or more severe infections.

Older patients and females exhibited a higher risk for supratherapeutic levels than younger patients and males, which may be explained by reduced clearance, a lower volume of distribution, comorbidities, or polypharmacy [25,26]. Females, in particular, have significantly less muscle mass than males, which influences their drug metabolism. Furthermore, the effect of sex hormones on renal function cannot be overlooked [27]. It has recently been reported that female patients had significantly higher trough levels than males [28], which is in agreement with multiple previous studies [29,30], further arguing for individualized dosing regimens. It should be mentioned, however, that males were found to be somewhat more prone to bloodstream infections caused by VAN-resistant enterococci [31], highlighting the complexity of gender disparity in antimicrobial therapy.

Our analysis of SIRI based on ICU status (Fig. 2) revealed that gender does not seem to be a major factor driving the inflammatory response in this patient cohort. The robust immune response may account for the elevated SIRI in the young age group, while the increased disease burden may be a contributing factor in older patients. The lack of a significant SIRI increase in patients aged 50–65 years suggests that inflammation is comparatively less pronounced in this group and may reflect subgroup heterogeneity or relatively inferior diagnostic performance as further supported by ROC findings (Fig. 4).

Our correlation analysis indicates that SIRI behaves differently in adults receiving VAN based on their ICU status, which supports its potential use in risk stratification. In our regression model, creatinine was a significant predictor of SIRI, which indicates that patients with renal impair-

Table 5. ROC-derived diagnostic thresholds for ICU requirement.

Group	SIRI	Sensitivity	95% CI	Specificity	95% CI	LR	Youden
Both genders	>1.637	0.8750	0.8011–0.9241	0.3552	0.2895–0.4269	1.357	0.2302
Males	>1.645	0.9091	0.8042–0.9605	0.3763	0.2846–0.4779	1.458	0.2854
Females	>2.056	0.7895	0.6671–0.8753	0.4222	0.3254–0.5254	1.366	0.2117
<50 years	>3.732	0.5897	0.4342–0.7292	0.7667	0.6456–0.8556	2.527	0.3564
50–65 years	>2.818	0.7333	0.5555–0.8582	0.5106	0.3724–0.6472	1.499	0.2439
>65 years	>8.005	0.4651	0.3251–0.6108	0.7368	0.6282–0.8227	1.767	0.2019

LR, likelihood ratio.

ment experience increased inflammation that could be exacerbated by VAN treatment. Regarding age, SIRI showed a significant increase in stable patients, reflecting aging-related chronic inflammation, which was likely masked in the ICU group by comorbidities. This was also true in the case of acid-base status, where Na^+ and CO_2 were inversely related to SIRI in non-ICU patients, whereas fluid replacement in critical illness likely abrogated such a relationship [32].

Importantly, the strongest negative association between SIRI and albumin was found in ICU patients, while other liver markers showed a shift toward negative correlation compared to their non-ICU counterparts. Albumin is a negative acute phase protein and has a half-life of approximately 21 days, which makes it a good index of chronic disease [33]. The negative correlation with SIRI independently of ICU status suggests systemic inflammation, malnutrition, liver disease, or capillary leakage [34]. Of note, the positive correlations of AST, GGT, and bilirubin with SIRI strongly support hepatic dysfunction and metabolic stress.

Overall, SIRI may be useful in the assessment of infection severity and nutritional status during VAN therapy, as it significantly correlates with hepatic involvement [35]. This aligns with previous reports highlighting the central role of neutrophils and monocytes in liver disease. Resident Kupffer cells in the liver stimulate neutrophil migration, accumulation, and trap formation, which, in turn, recruit monocyte-derived macrophages through cytokines, chemokines, and adhesion molecules that exacerbate tissue injury and inflammatory damage. Simultaneously, once instigated by free radicals released from neutrophils, monocytes switch phenotypes to initiate hepatic cellular repair and promote tissue remodeling [36]. Collectively, the association of SIRI with renal and liver markers seems to indicate a possible interplay between systemic inflammation and VAN-associated renal or hepatic dysfunction which could be further explored in longitudinal studies using serial SIRI measurements.

We also identified RDW-CV as an exclusive marker in the ICU group, whose negative correlation possibly indicates myelosuppression caused by VAN [37]. In contrast, platelets were only correlated with SIRI in non-ICU patients, probably due to a higher risk of antibody-mediated cytotoxicity in critically ill patients [38]. Thus, elevated SIRI may predict inflammatory thrombocytopenia, which is often complicated by life-threatening gastrointestinal bleeding.

Risk assessment measures (Table 4) and ROC curves (Fig. 4) suggest that SIRI is a robust predictor of ICU admission, with significant PR, PD, OR, and AUC values. Whether this association is due to sepsis severity, multiorgan dysfunction, or both remains to be determined. Nonetheless, SIRI was not sufficiently reliable to rule out the need for ICU, given the moderate NPV, which necessitates close patient monitoring irrespective of diminished SIRI values. In any case, increased neutrophils and monocytes with or without lymphopenia are a typical immune response against bacterial infections, and, therefore, SIRI may serve as an early marker of severe bacterial sepsis.

Limitations

This study has several strengths. First, the exclusion of pediatric patients mitigates potential confounding stemming from variable immune responses. Second, the large sample size ensures sufficient statistical power to allow for the generalizability of the findings to diverse patient populations. Third, the heterogeneity of the analyzed cohort represents general hospital populations which enhances the applicability of the findings to routine clinical practice. Fourth, the use of a hospital registry and the simultaneous collection of clinical and laboratory data minimizes temporal bias. However, some limitations also deserve consideration. The cross-sectional nature of the study precludes causal inference, the single-center design may compromise external validity, and residual confounding may have potentially been introduced due to the lack of data on physical activity, dietary habits, and medication intake. Furthermore, detailed documentation of infection type, duration of VAN therapy, and compliance with trough monitoring were not consistently available in the hospital registry. Additionally, the absence of a non-VAN comparator group may undermine the potential contribution of VAN exposure in the observed associations.

5. Conclusions

In conclusion, this report characterized the clinical profiles of adult patients receiving VAN and demonstrated

the first evidence of the association between SIRI and key demographic and clinical variables including ICU requirement. Since it is readily available from routine clinical lab measurements, SIRI represents a cost-effective marker that may be used alongside other established tests to assess the need for close monitoring and to identify patients at risk for deteriorating kidney and liver function during VAN exposure. These findings support the need for prospective longitudinal studies investigating the clinical prospects of SIRI in addition to other novel ratios and indices that could be used for risk stratification in antimicrobial therapy.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author, M.A.A., upon reasonable request. The dataset is not publicly available as it would contravene ethical standards, compromise participant confidentiality, and breach legal requirement.

Author Contributions

MAAand JA designed the research study. MAA, JA and SAA performed the research. MAA, JA, and SAA analyzed the data. MAA, JA, and SAA wrote the original draft and contributed to manuscript revision. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by King Saud University Ethics Committee (approval number: E-25-9553; approval date: February 12, 2025). The study was carried out in accordance with the guidelines of the Declaration of Helsinki. Informed consent was waived due to the retrospective design of the study.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/Pharmazie51565.

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