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Serum IL-10 and IL-12p40 levels and *IL28B* Gene Polymorphisms: Pretreatment Prediction of Treatment Failure in Chronic Hepatitis C

Takeji Umemura, [1] Satoru Joshita, [1] Suguru Yoneda, [1] Yoshihiko Katsuyama, [2] Tetsuya Ichijo, [1] Akihiro Matsumoto, [1] Kaname Yoshizawa, [1] Masao Ota, [3] Eiji Tanaka [1]

1: Department of Medicine, Division of Hepatology and Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan
2: Department of Pharmacy, Shinshu University Hospital, Matsumoto, Japan
3: Department of Legal Medicine, Shinshu University School of Medicine, Matsumoto, Japan

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Corresponding author: Takeji Umemura, MD, PhD, Department of Medicine,
Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan
E-mail: tumemura@shinshu-u.ac.jp
Telephone: +81-263-37-2634; Fax: +81-263-32-9412

Abbreviations: HCV, hepatitis C virus; NVR, null virological response; SVR, sustained virological response; PEG-IFN, pegylated interferon; ISDR, interferon sensitivity determining region; SNPs, single nucleotide polymorphisms; ROC, receiver-operating characteristic

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Abstract

Background: Both *IL28B* gene polymorphisms and serum levels of IL-10, IL-12p40, and IL-18 have been reported to affect the outcome of natural and pegylated interferon and ribavirin-treated hepatitis C virus (HCV) infection. **Methods:** To clarify their association and predictive value in treatment outcome of genotype 1 HCV-infected patients, we measured pretreatment serum IL-10, IL-12p40, and IL-18 levels using multiplex assays and determined *IL28B* gene polymorphisms (rs 8099917) in 52 cases with chronic hepatitis C. **Results:** High baseline levels of IL-10 ($P < 0.001$) and low levels of IL-12p40 ($P < 0.001$) were significantly associated with a null virological response (NVR) in our cohort. The *IL28B* polymorphism was tested and TT, TG, or GG genotypes were found in 60%, 38%, and 2% of patients, respectively, with corresponding NVR rates of 10%, 60%, and 100% ($P < 0.001$). Serum cytokine levels were significantly correlated with *IL28B* gene polymorphisms. When serum IL-10 levels were stratified at 5.0 pg/mL, NVR rates were 50% vs., 0% ($P = 0.004$) for the TT genotype and 87% vs. 0% ($P = 0.001$) for the TG or GG genotypes. Similarly, low IL-12p40 levels were associated with a NVR in patients with TG or GG genotypes ($P = 0.006$). In multivariate analysis, high IL-10, low IL-12p40, and *IL28B* TG or GG genotypes were independently associated with a NVR. **Conclusions:** Serum IL-10 and IL-12p40 levels in combination with *IL28B* genotype, especially G-allele carriage, are strong predictive markers of a NVR to HCV treatment with pegylated interferon and ribavirin.

Introduction

Chronic hepatitis C virus (HCV) infection often develops into chronic hepatitis leading to liver cirrhosis and/or hepatocellular carcinoma [1-3]. The successful eradication of HCV, defined as a sustained virological response (SVR), is therefore considered important. Despite recent advances, however, approximately 50% of patients with genotype 1 HCV infection do not achieve a SVR by conventional pegylated interferon (PEG-IFN) and ribavirin therapy [4-5].

It is considered beneficial to predict the response of patients with genotype 1 HCV and high viral load to PEG-IFN and ribavirin therapy before commencement of treatment because therapy can be long, costly, and have many side effects. To date, many predictive factors have been reported for treatment response. Regarding viral factors, substitutions at core amino acids 70 and 91 [6] or the interferon sensitivity determining region (ISDR) have been reported [7]. Concerning host factors, Ge et al. [8] recently identified single nucleotide polymorphisms (SNPs) located 5' to the IL28B gene that affect response to combination therapy using a genome-wide association study. Similarly, three other groups independently reported that these SNPs are associated with the effectiveness of combination treatment [9-11]. Thomas et al. also reported that the same SNPs are associated with spontaneous clearance of HCV [12].

IL-28A, IL-28B, and IL-29 gene products belong to the IFN lambda family. These cytokines are functionally considered to be interferons, but have been reported to be structurally related to the IL-10 family, which include IL-10, IL-22, IL-26, and the IFN lambda family. The ligand-binding chains for IL-22, IL-26, and IFN lambda are distinct from that used by IL-10. However, all of these cytokines use a common second chain, IL-10 receptor-2, to assemble their active receptor complexes. Thus, IL-10 receptor-2 is a shared component in at least four distinct class II cytokine-receptor complexes [13]. Although IL-10 was originally described as a cytokine synthesis inhibitory factor [14-15], recent studies have demonstrated that IL-10 produced by Th17 cells restrains the pathologic effects of Th17 [16-17]. Furthermore, elevated IL-10 levels are associated with a high risk of inefficient HCV clearance and resistance to IFN treatment [18-21]. Our recent study showed that low serum IL-10 levels as well as high IL-12p40 and IL-18 levels at baseline were independent predictive factors for a SVR to combination therapy

[22]. Therefore, in the present study, we investigated the association between treatment outcome and the influence of *IL28B* genotype and serum cytokine levels in combination therapy.

Patients and Methods

Subjects.

Fifty-two consecutively treated naïve patients with genotype 1 chronic hepatitis C were included in this study. Diagnosis of chronic hepatitis C was based on the following criteria as reported previously [23]: 1) presence of serum HCV antibodies and detectable viral RNA; 2) absence of detectable hepatitis B surface antigen and antibody to the human immunodeficiency virus; and 3) exclusion of other causes of chronic liver disease. No patients had a history of or developed decompensated cirrhosis or hepatocellular carcinoma. The baseline characteristics of the patients are shown in Table 1.

Laboratory Testing.

Antibodies to HCV were measured in serum samples via third-generation enzyme-linked immunosorbent assays (EIA-3; Abbott Laboratories, North Chicago, IL). Serum levels of HCV RNA were determined using the Cobas Amplicor assays (sensitivity 50 IU/mL: Roche Diagnostic Systems, Tokyo, Japan). HCV genotypes were determined using INNO-LiPA HCV II (Innogenetics, Gent, Belgium). All patients in our test cohort were infected with genotype 1b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and other relevant biochemical tests were performed using standard methods [24].

Anti-viral therapy and definition of treatment outcome.

All patients received body weight-adjusted PEG-IFNα-2b (PegIntron, Schering-Plough K.K., Tokyo, Japan; 45 kg or less, 60 μg/dose; 46 to 60 kg, 80 μg/dose; 61 to 75 kg, 100 μg/dose; 76 to 90 kg, 120 μg/dose; 91 kg or more, 150 μg/dose), and ribavirin (Rebetol, Schering-Plough K.K.; 60 kg or less, 600 mg/day; 61 kg to 80 kg, 800 mg/day; 81 kg or more, 1,000 mg/day) for 48 weeks.

The response to therapy categories were defined as follows: a SVR was defined

as undetectable serum HCV RNA 24 weeks after completing therapy. Relapse was defined as a reappearance of serum HCV RNA after treatment in patients whose HCV RNA level was undetectable during or at the completion of therapy. A null virological response (NVR) was defined as a decrease in HCV RNA of <2 log copies/mL at week 12 and detectable HCV RNA during the treatment course.

Detection of amino acid substitutions in the core and NS5A regions.

Core region and ISDR were determined by direct sequencing after amplification by reverse-transcription and polymerase chain reaction as reported previously [22]. Amino acids at positions 70 and 91 of the core region identical to the reference sequence HCV-J D90208 [25] were considered wild type [6]. The number of amino acid substitutions in the ISDR was defined as in Enomoto et al [7].

Detection of serum IL-10, IL-12p40, and IL-18.

Serum IL-10, IL-12p40, and IL-18 were quantified using Luminex® Multiplex Cytokine Kits (Procarta Cytokine assay kit) for serum samples obtained before the start of treatment as reported previously [22]. All collected samples were immediately stored at -70°C prior to testing.

Genotyping of IL28B.

Genomic DNA was isolated from the whole blood of patients using QuickGene-800 (Fujifilm, Tokyo, Japan). The concentration of genomic DNA was adjusted to 10-15 ng/μL for the TaqMan SNP genotyping assay. Genotyping of *IL28B* SNP (rs8099917) was performed with a TaqMan 5' exonuclease assay using primers supplied by Applied Biosystems. Probe fluorescence signals were detected with a TaqMan assay for Real-Time PCR (7500 Real Time PCR System, Applied Biosystems) according to the manufacturer's instructions.

The protocol of this study was approved by the ethics committee of Shinshu University School of Medicine and all patients provided written informed consent.

Statistical Analysis.

The Mann-Whitney *U* test was used to analyze continuous variables. The chi-square test with Yate's correction was used for the analysis of categorical data. In cases where the number of subjects was less than 5, Fisher's exact test was used. A *P* value of ≤ 0.05 was considered statistically significant. To predict treatment outcome, we analyzed receiver-operating characteristic (ROC) curves for serum levels of IL-10, IL-12p40, and IL-18. Optimal cutoff values were chosen as serum cytokine levels with the highest diagnostic accuracy, i.e., when the sum of the false-negative and false-positive rates was minimized. The respective overall diagnostic values were expressed using the area under the curve (AUC). Multivariate analysis was performed using a logistic regression model with stepwise method. Statistical analyses were performed using PASW Statistics 18.0J (IBM, Tokyo, Japan).

Results

Treatment outcome in patients with chronic hepatitis C.

Of the 52 patients receiving PEG-IFN and ribavirin therapy, 22 (42%) achieved a SVR. Among the 30 remaining patients, 14 had a relapse and 16 had a NVR. Before treatment, the median white blood cell count in the virological response group was significantly higher than that in the NVR group (Table 1). Hemoglobin value (15.4 vs. 14.1 g/dL; *P* = 0.021) was significantly higher in the SVR group compared to the NVR group as well. Substitutions in the ISDR and of aa70 and aa91 in the core region were not associated with treatment outcome.

Effects of anti-viral therapy on serum cytokine levels.

Serum samples obtained prior to antiviral therapy were examined for the presence of IL-10, IL-12p40, and IL-18 by multiplex assays. NVR patients showed significantly higher baseline IL-10 concentrations (8.1 pg/mL) than virological responders (4.1 pg/mL; *P* < 0.001) (Figure 1). The median baseline serum levels of IL-12p40 (22.1 vs. 11.7; *P* < 0.001) and IL-18 (24.8 vs. 16.0; *P* = 0.054) were higher in patients who achieved a virological response than in those with a NVR (Figure 1). Furthermore, serum IL-10 level (4.0 vs. 8.1 pg/mL; *P* <0.001) was significantly lower and serum IL-12p40 (25.0 vs. 11.7; *P* < 0.001) and IL-18 (31.6 vs. 16.0; *P* = 0.010) levels were significantly

higher in the SVR group compared with the NVR group. We also analyzed whether pretreatment serum cytokines were correlated with time to clearance of HCV RNA. Serum baseline IL-10 level was significantly lower in patients who eradicated HCV RNA 12 weeks after the start of treatment (P = 0.002).

IL28B genotype and treatment outcome.

Among the 52 patients studied for rs8099917, 31 had the TT genotype (60%), 20 had the TG genotype (38%), and 1 had the GG genotype (2%). Responses to combination therapy for rs8099917 are shown in Table 1. Overall SVR rates in patients with the TT genotype (16/31, 53%) and with the TG or GG genotypes (6/21, 29%) were not significantly different (P = 0.09). However, NVR rates in patients with either TG or GG (13/21 62%) were significantly higher than in those with TT only (3/31, 10%) (P < 0.001).

Association of IL28B genotype and serum cytokine levels.

Median serum IL-10 levels were significantly higher in patients with the TG or GG genotypes (7.7 pg/mL) compared to those with TT (4.1 pg/mL; P = 0.010) (Figure 2A). Conversely, patients with TT had significantly higher median IL-12p40 (20.6 vs. 14.5 pg/mL; P = 0.006) and IL-18 (27.9 vs. 16.6 pg/mL; P = 0.005) levels than patients with TG or GG (Figure 2A).

ROC curve analyses were performed to determine the optimal threshold values of serum cytokines for predicting treatment outcome among the 16 NVR patients and 36 cases with a virological response in our cohort (Figure 3). The optimal threshold value of IL-10 was identical to the 5.0 pg/mL that we had reported in a prior study [22]. The cut-off values for IL-12p40 and IL-18 were 12.1 pg/mL and 6.4 pg/mL, respectively. The calculated AUC for IL-10, IL-12p40, and IL-18 was 0.89 (95% confidence interval 0.77-0.96), 0.81 (0.67-0.90), 0.67 (0.52-0.79), respectively, as shown in Figure 3.

The presence of high IL-10 levels (≥5.0 pg/mL) was significantly greater among patients with TG or GG genotypes (71%; 15 of 21) than among those with TT (19%; 6 of 31, P < 0.001) (Figure 2B). High IL-12p40 levels (≥12.1 pg/mL) were significantly less prevalent (P = 0.018) among patients with TG or GG (62%; 13 of 21) than among those with TT (90%; 28 of 31). High IL-18 levels (≥6.5 pg/mL) were found in 100% (31/31) of

patients with TT but only 76% (16/21) patients with TG or GG (*P* = 0.008).

Predicting treatment outcome by serum cytokine levels in combination with IL28 genotype.

The NVR prediction rate by serum IL-10 in combination with rs8099917 genotype is shown in Figure 4. In patients with TT, a significantly higher proportion of patients with high serum IL-10 levels (50%; 3 of 6) showed a NVR than patients with low IL-10 (0%; 0 of 25) (*P* = 0.004). Similarly, a NVR was significantly more likely in high versus low IL-10 levels (87%; 13 of 15 vs. 0%; 0 of 6) (*P* = 0.001) in patients with TG or GG (Figure 4A).

NVR rates by serum IL-12p40 levels and IL-18 levels in combination with rs8099917 genotype are shown in Figures 4B and C. Among patients with the TT genotype, the NVR rate did not differ between low and high IL-12p40 levels (0% vs. 11%) (*P* = 0.729) or IL-18 levels (0% vs. 10%). In cases with TG or GG genotypes, the NVR rate was significantly higher for low IL-12p40 levels compared with high IL-12p40 levels (100% vs. 38%; P = 0.006). Patients with low serum IL-18 had a higher NVR rate, but this difference was not statistically significant (100% vs. 50%; *P* = 0.063).

Factors associated with a NVR to PEG-IFN and ribavirin therapy.

All factors found to be associated with a NVR were evaluated for independence in multivariate analysis. Genotype TG or GG (odds ratio 10.43 [95% confidence interval 1.73-62.96], *P* = 0.011), serum IL-10 levels ≥ 5.0 pg/mL (odds ratio 1.21 [95% confidence interval 1.03-1.41], *P* = 0.018), and IL-12p40 levels ≥ 17.4 mg/dL (odds ratio 0.84 [95% confidence interval 0.72-0.97], *P* = 0.020) were all independent predictive factors of a NVR.

Discussion

This study examined the *IL28B* (rs8099917) genotype and serum levels of IL-10, IL-12p40, and IL-18 in patients with chronic hepatitis C to assess their predictive value in treatment outcome with PEG-IFN and ribavirin. The key findings were: (1) *IL28B* G-allele carriers were associated with a NVR to PEG-IFN and ribavirin therapy in patients

infected with HCV genotype 1, consistent with recent findings; (2) *IL28B* genotype was associated with baseline serum IL-10, IL-12p40, and IL-18 levels; (3) in carriers of an *IL28B* G-allele, NVR rates were high (80-100%) and associated with elevated IL-10 and decreased IL-12p40 and IL-18 levels, thus providing new predictive markers of a NVR in PEG-IFN and ribavirin therapy; and (4) *IL-28B* genotype, high serum IL-10 levels, and low serum IL-12p40 levels were all independent factors related to a NVR in multivariate analyses.

IL28B gene polymorphisms have recently been linked to the outcome of HCV infection during spontaneous and treatment-induced elimination of HCV [8-10, 12]. In particular, carriage of a G-allele at the *IL28B* gene SNP (rs8099917) is associated with a NVR to PEG-IFN and ribavirin therapy in Japanese patients infected with HCV genotype 1 [10]. This finding was confirmed in our cohort with NVR rates of 62% with GT or GG genotypes versus 10% with TT genotypes ($P < 0.001$). Therefore, detection of the *IL28B* genotype is a useful marker to predict the outcome of PEG-IFN and ribavirin therapy in patients with chronic hepatitis C. Data for *IL28B* SNP in healthy subjects were not available for this study.

IFN lambda produces an antiviral state by triggering a cascade through the JAK-STAT pathway that up-regulates IFN-stimulated genes. IL28B binds to a distinct receptor that may up-regulate a different set of IFN-stimulated genes [26-27]; the precise role of IFN lambda in controlling multiple viral infections, including HCV, is currently under way. Further studies are also needed on how SNPs affect IL28B and other cytokine function.

A strong association between high IL-10, low IL-12p40, and low IL-18 levels and a NVR to PEG-IFN and ribavirin therapy was found in this study, which is consistent with previous studies [22, 28-30]. In ROC curve analyses, AUCs were high, especially for IL-10 (0.89) and IL-12p40 (0.81), confirming that these cytokines are strong predictive markers for a NVR. This study showed a strong correlation between the *IL28B* genotype and serum IL-10, IL-12p40, and IL-18 levels at baseline. Most strikingly, all patients who had low pretreatment IL-10 levels achieved a virological response regardless of *IL28B* genotype. In contrast, among patients with high IL-10 levels (≥5.0 pg/mL), NVR rates were 87% in *IL28B* G-allele carriers and 50% for the *IL28B* TT genotype. Additionally, all

IL28B G-allele carriers showed a NVR when pretreatment serum IL-12p40 and IL-18 levels were <12.1 pg/mL and <6.5 pg/m, respectively. It is unclear how serum IL-10, IL-12p40, and IL-18 are associated with a NVR to antiviral therapy in patients with chronic hepatitis C. Although IL-10 was originally described as a cytokine synthesis inhibitory factor, but recent studies have demonstrated that IL-10 produced by Th17 cells restrains the pathologic effects of Th17 [31]. Production of IL-12p40 is directed towards the elimination of intracellular pathogens and viruses because IL-12p40 is a proinflammatory cytokine that promotes the differentiation of Th1 cells, suppresses Th2 function, and amplifies the cytotoxicity of cytotoxic T lymphocytes and natural killer cells [32]. Megjugorac *et al.* [33] reported that IL-29-treated plasmacytoid dendritic cells inhibiting production of IL-13, IFN-γ, and IL-10 by allogeneic T cells were consistent with a role for this cytokine in plasmacytoid dendritic cell maturation and activation. Very recently, another report has been published demonstrating that IL-29 enhances IL-12p40 by macrophages and that IL-29 pretreatment primes the activation of macrophages induced by IFN-γ [34]. However, the association between IL-28B and such cytokines has not been studied. To explain this relationship, further studies are needed to clarify whether a direct or indirect interaction exists between pretreatment levels of these cytokines and *IL28B* genotype.

Although other predictive factors of PEG-IFN and ribavirin therapy have been reported, including core amino acid 70 and 91 and ISDR mutations [6-7], no such significant associations were found here, possibly because of our study population size, which indicates that other factors may be more significant in predicting treatment outcome. However, multivariate analysis confirmed that *IL28B* G-allele, high IL-10, and low IL-12p40 levels were significant predictors of a NVR in patients with PEG-IFN and ribavirin therapy in this study. Hence, *IL28B* G-allele carriers combined with high IL-10 and/or low IL-12 may require alteration of treatment dose, duration, or regimen with a new antiviral drug.

In conclusion, serum IL-10, IL-12p40, and IL-18 levels are associated with *IL28B* genotype in patients with genotype 1 chronic hepatitis C. Pretreatment serum IL-10 and IL-12p40 levels with *IL28B* GT or GG genotypes are particularly useful for predicting a NVR to PEG-IFN and ribavirin therapy. The clinical significance of *IL28B* genotyping

combined with baseline serum IL-10 and IL-12p40 levels to predict a NVR warrants further prospective validation.

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Table 1. Demographic and Clinical Characteristics of Patients with Chronic Hepatitis C

Characteristics	All (n = 52)	VR (n = 36)	NVR (n = 16)	*P* Value
Age (years) *	58 (17-74)	57 (17-72)	60 (45-74)	0.781
Male, n (%)	24 (46)	18 (50)	6 (38)	0.404
Body mass index (kg/m^2) *	23 (18-30)	24 (18-30)	22 (19-29)	0.115
White blood cell count (/μL) *	4470 (1980-7890)	4810 (1980-7890)	3700 (2270-5180)	0.007
Hemoglobin (g/dL) *	14.7 (12-18)	15.0 (13-18)	14.1 (12-16)	0.094
Platelets (10^4/μL) *	17.5 (8-30)	17.9 (8-30)	16.7 (9-27)	0.420
ALT (IU/L) *	75 (22-389)	68 (24-389)	91 (22-357)	0.663
AST (IU/L) *	58 (20-288)	49 (20-218)	78 (25-288)	0.092
HCV RNA (10^5 IU/mL) *	21 (1.1->50)	20 (1.1->50)	18 (2.9->50)	0.469
Core aa 70 (Arg70/Gln70/ND)	30/21/1	23/12/1	7/9/0	0.139
Core aa 91 (Leu91/Met91/ND)	37/14/1	26/9/1	11/5/0	0.463
ISDR of NS5A (wild/mutant)	44/8	29/7	15/1	0.218
rs8099917 allele (TT/TG/GG)	31/20/1	28/8/0	3/12/1	<0.001

* Mean (range)

Abbreviations: HCV, hepatitis C virus; VR, virological response; NVR, null virological response; AST, aspartate aminotransferase; ALT, alanine aminotransferase; aa, amino acid; ISDR, interferon-sensitivity determining region

Figure Legends

Figure 1. Detection of serum cytokines related to treatment outcome.

Boxes represent the interquartile range of the data. The lines across the boxes indicate the median values. The hash marks above and below the boxes indicate the 90th and 10th percentiles for each group, respectively. Open circles indicate outliers. Serum IL-10, IL-12p40, and IL-18 levels were detected in 36 patients with a virological response and 16 patients without.

Figure 2. Serum cytokines related to *IL28B* gene polymorphisms.

(A) Boxes represent the interquartile range of the data. The lines across the boxes indicate the median values. The hash marks above and below the boxes indicate the 90th and 10th percentiles for each group, respectively. Serum IL-10, IL-12p40, and IL-18 were detected in 31 patients with the TT *IL28B* genotype and 16 patients with the TG or GG genotypes.

(B) The prevalence of high serum IL-10, IL-12p40, and IL-18 levels in 31 patients with the TT *IL28B* genotype and in 16 patients with the TG or GG genotypes.

Figure 3. Receiver-operating characteristic curves for serum cytokine levels on treatment outcome.

The areas under the curve for IL-10, IL-12p40, and IL-18 were 0.89, 0.81, 0.67, respectively. All areas under the curve values were significantly higher than a 0.50 nonpredictive value ($P < 0.01$ for all comparisons). IL-10 is predictive of a nonresponse. IL-12p40 and IL-18 are predictive of a virological response.

Figure 4. Null virological response rate determined by serum cytokine levels and *IL28B* gene genotype.

The prevalence of a NVR in patients with high or low serum IL-10 (A), IL-12p40 (B), and IL-18 (C) levels according to IL28B genotype.

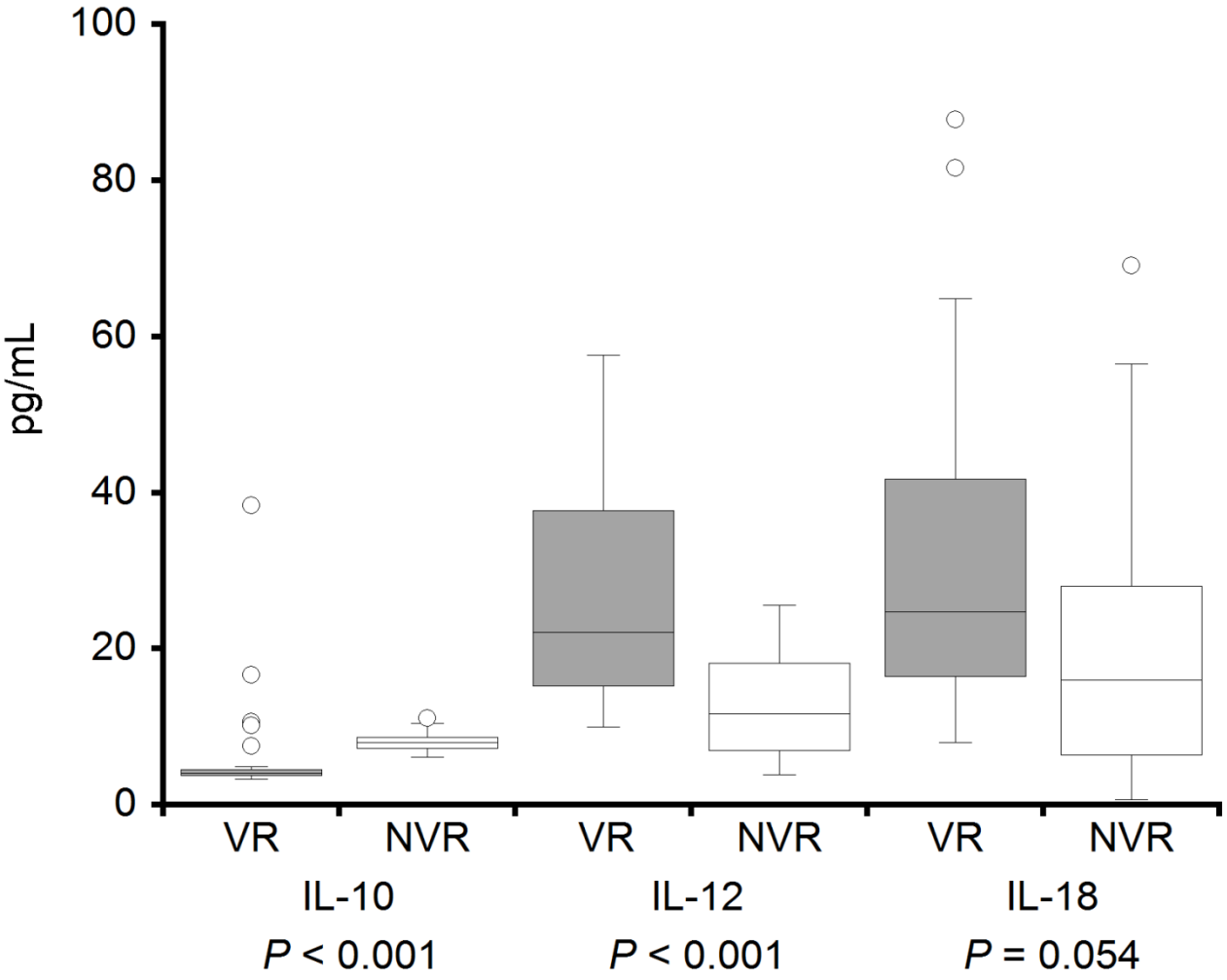

100
80
60
40
20
0
pg/mL
VR
NVR
VR
NVR
VR
NVR
IL-10
P < 0.001
IL-12
P < 0.001
IL-18
P = 0.054

Figure 1

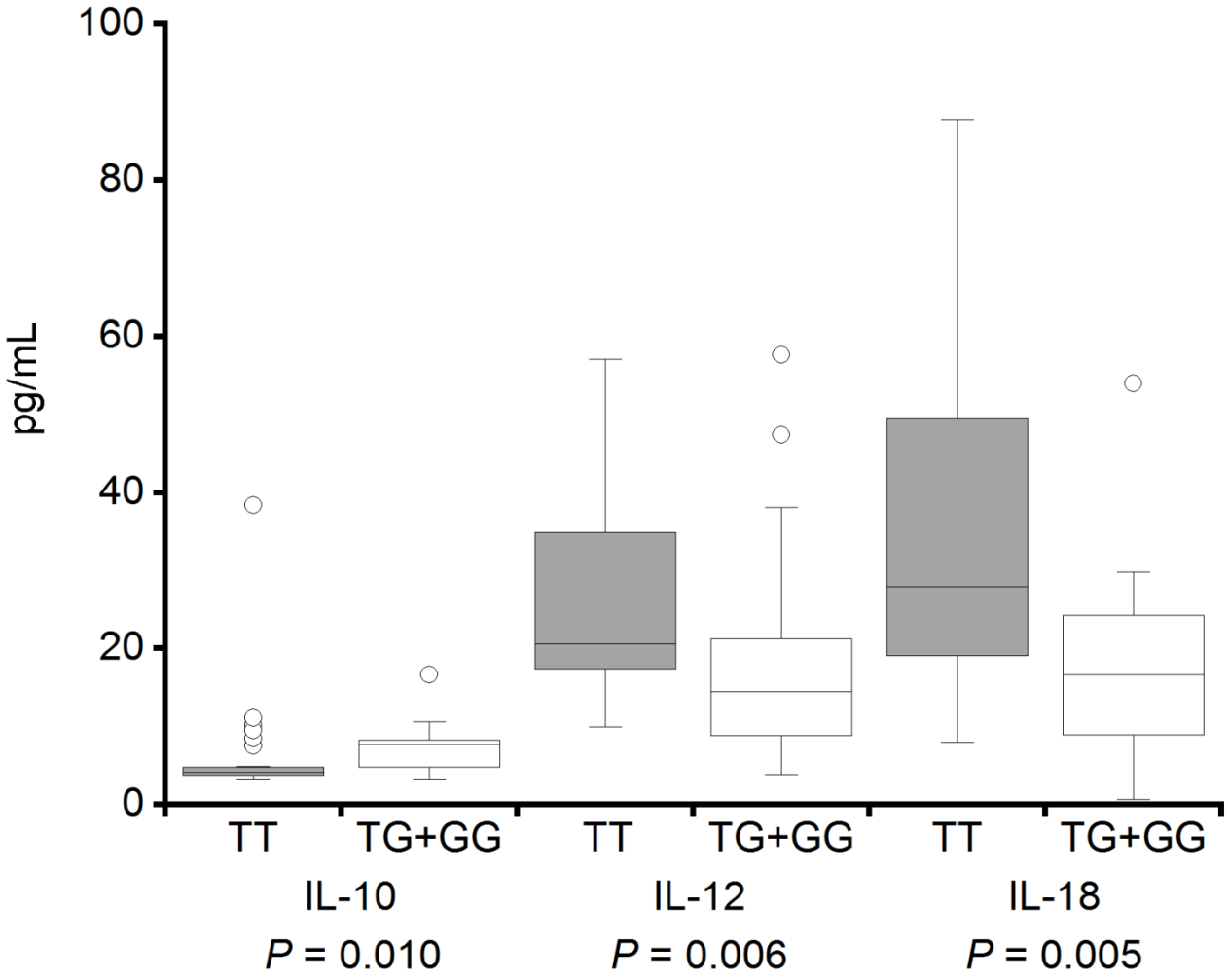

100
80
60
40
20
0
pg/mL
TT
TG+GG
TT
TG+GG
TT
TG+GG
IL-10
P = 0.010
IL-12
P = 0.006
IL-18
P = 0.005

Figure 2A

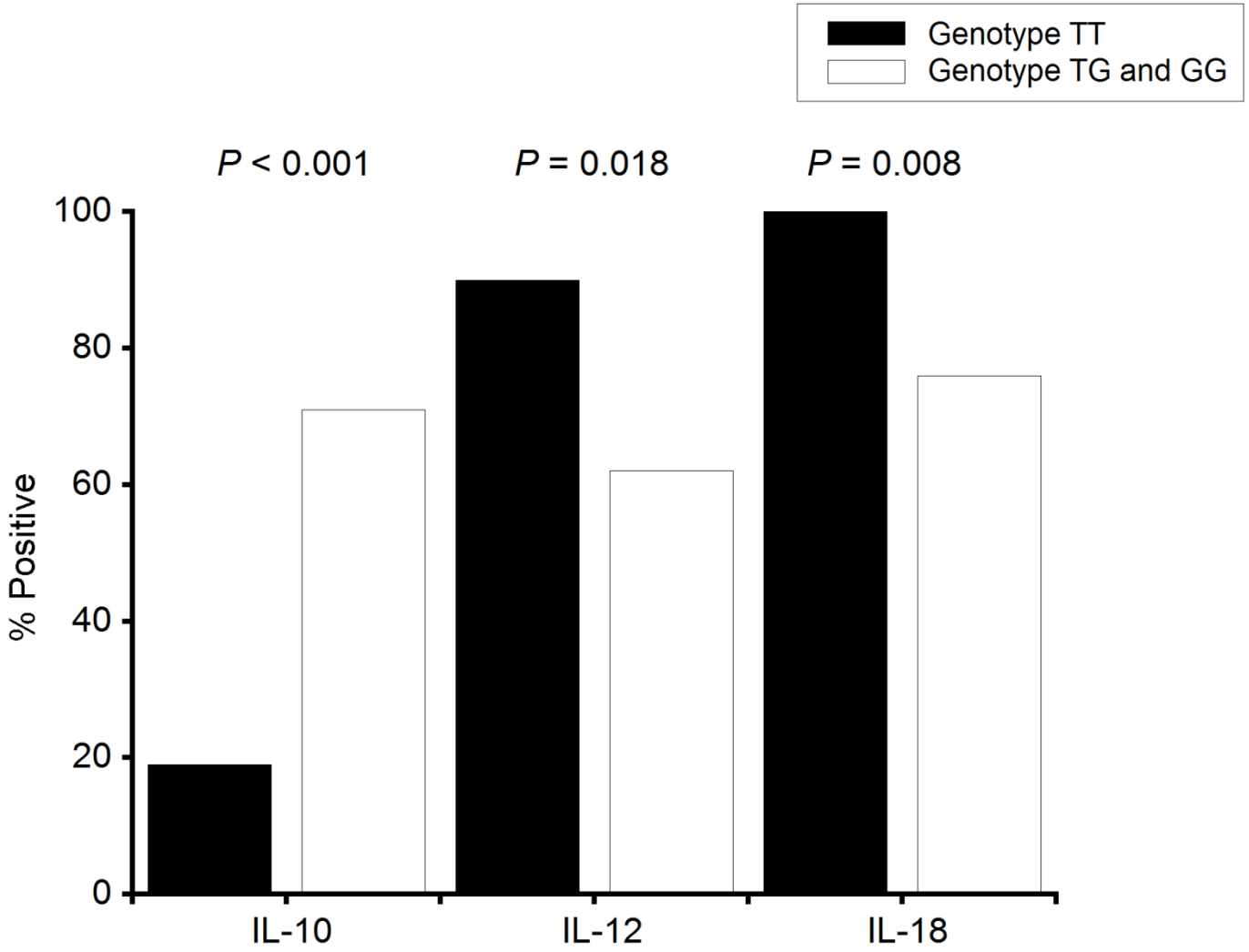
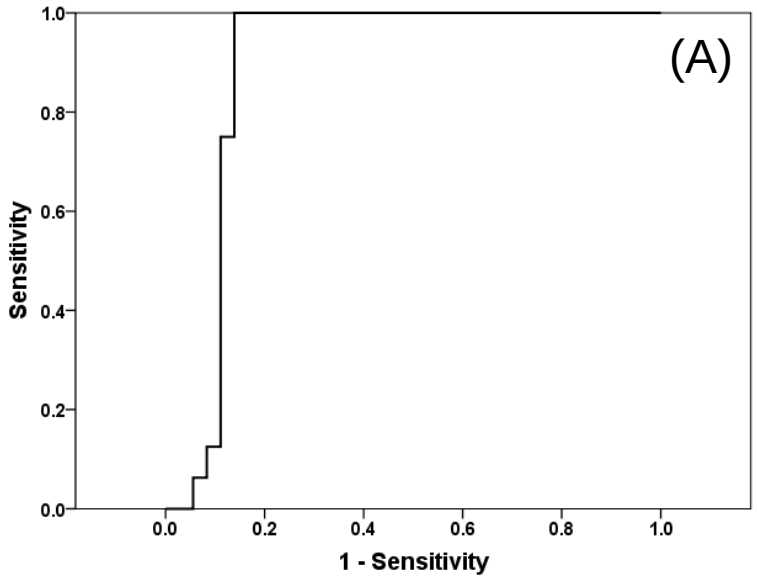
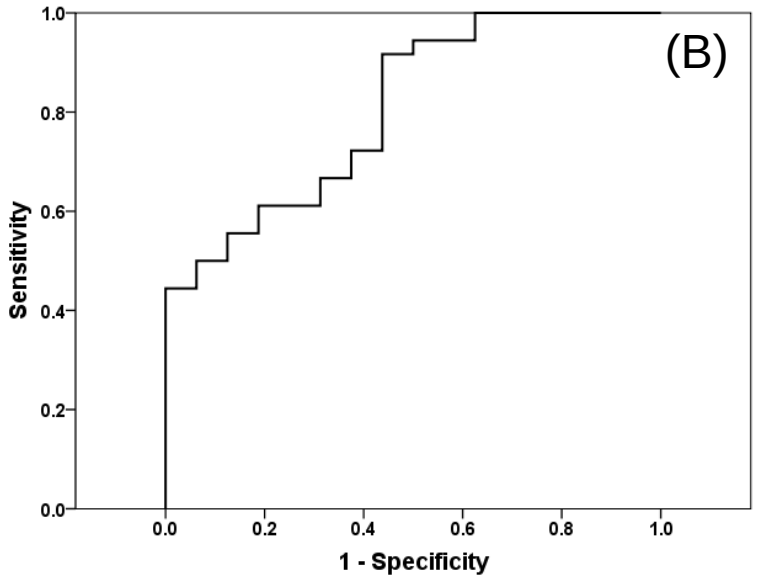

Genotype TT
Genotype TG and GG
P < 0.001
P = 0.018
P = 0.008
100
80
60
40
20
0
% Positive
IL-10
IL-12
IL-18

Figure 2B

Figure 3


(A)
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1 - Sensitivity


(B)
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity

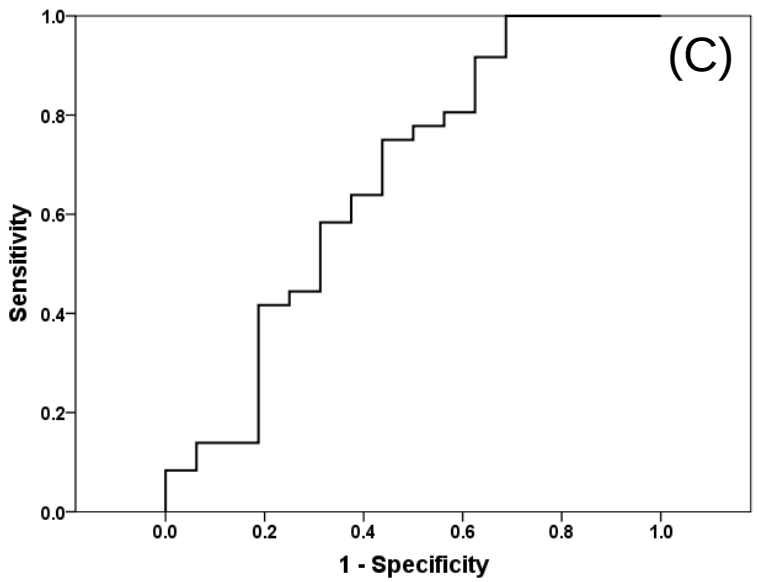

(C)
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specificity

Figure 4A

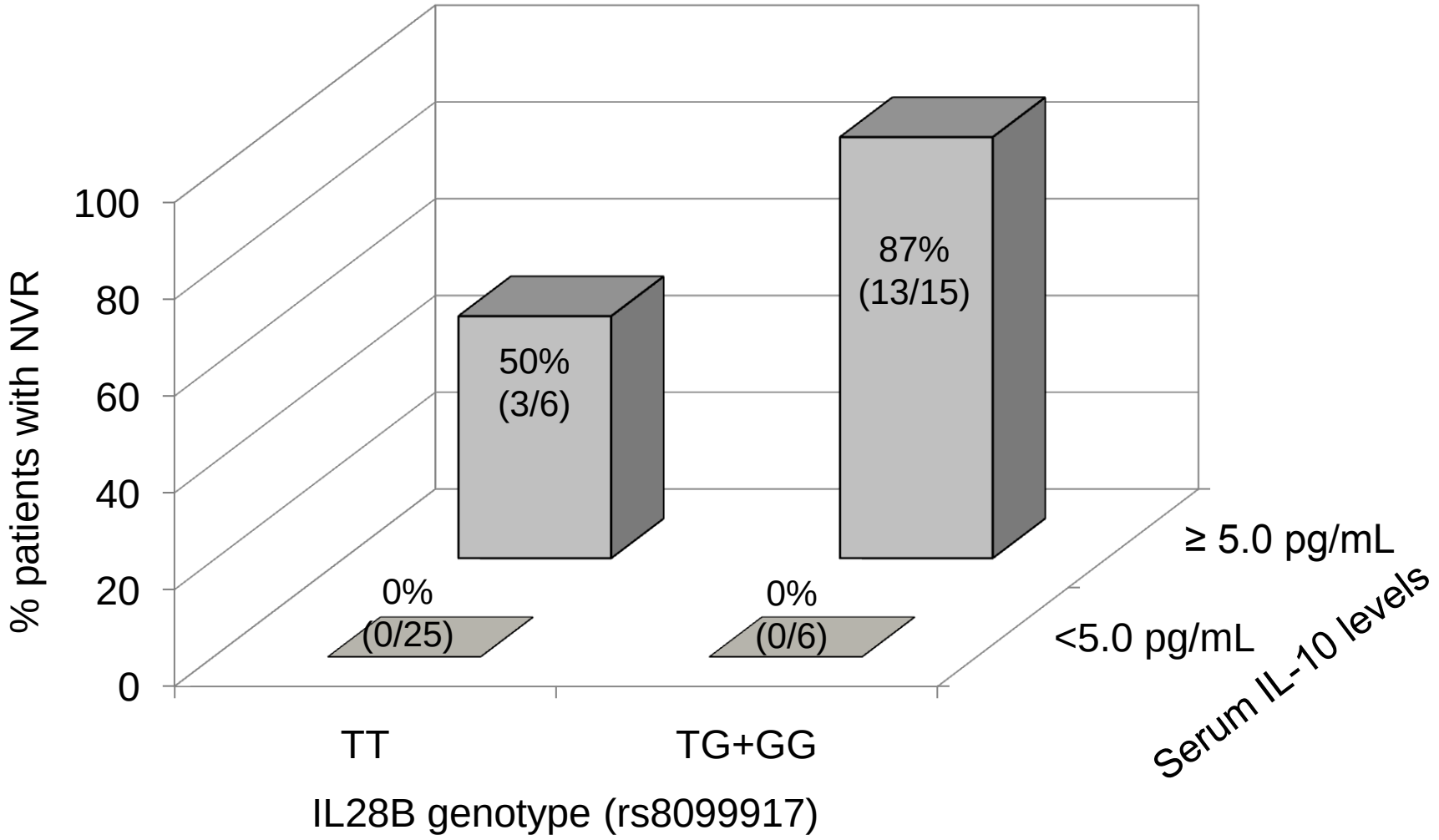

100
80
60
40
20
0
% patients with NVR
50%
(3/6)
87%
(13/15)
0%
(0/25)
0%
(0/6)
TT
TG+GG
IL28B genotype (rs8099917)
≥ 5.0 pg/mL
<5.0 pg/mL
Serum IL-10 levels

Figure 4B

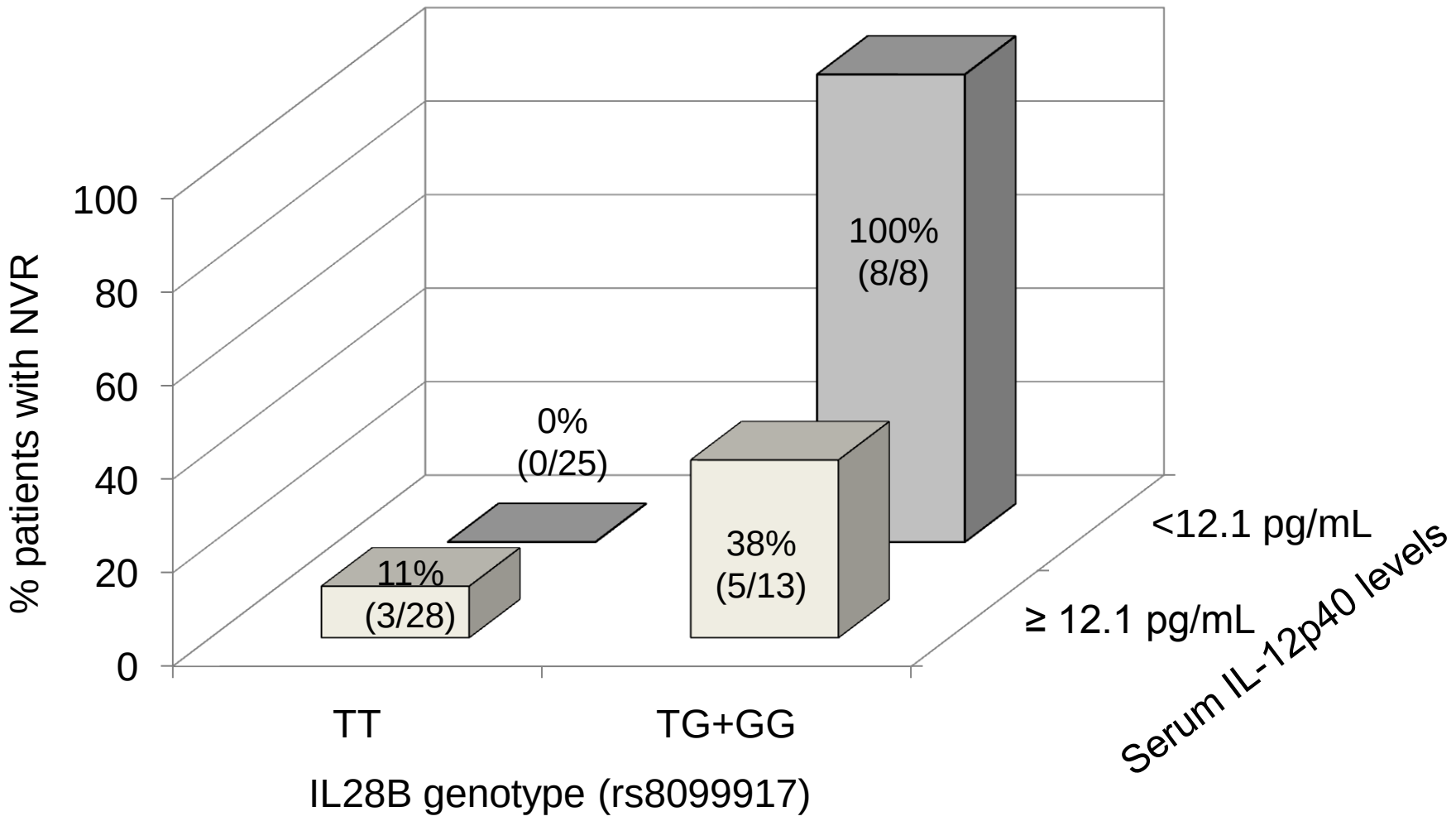
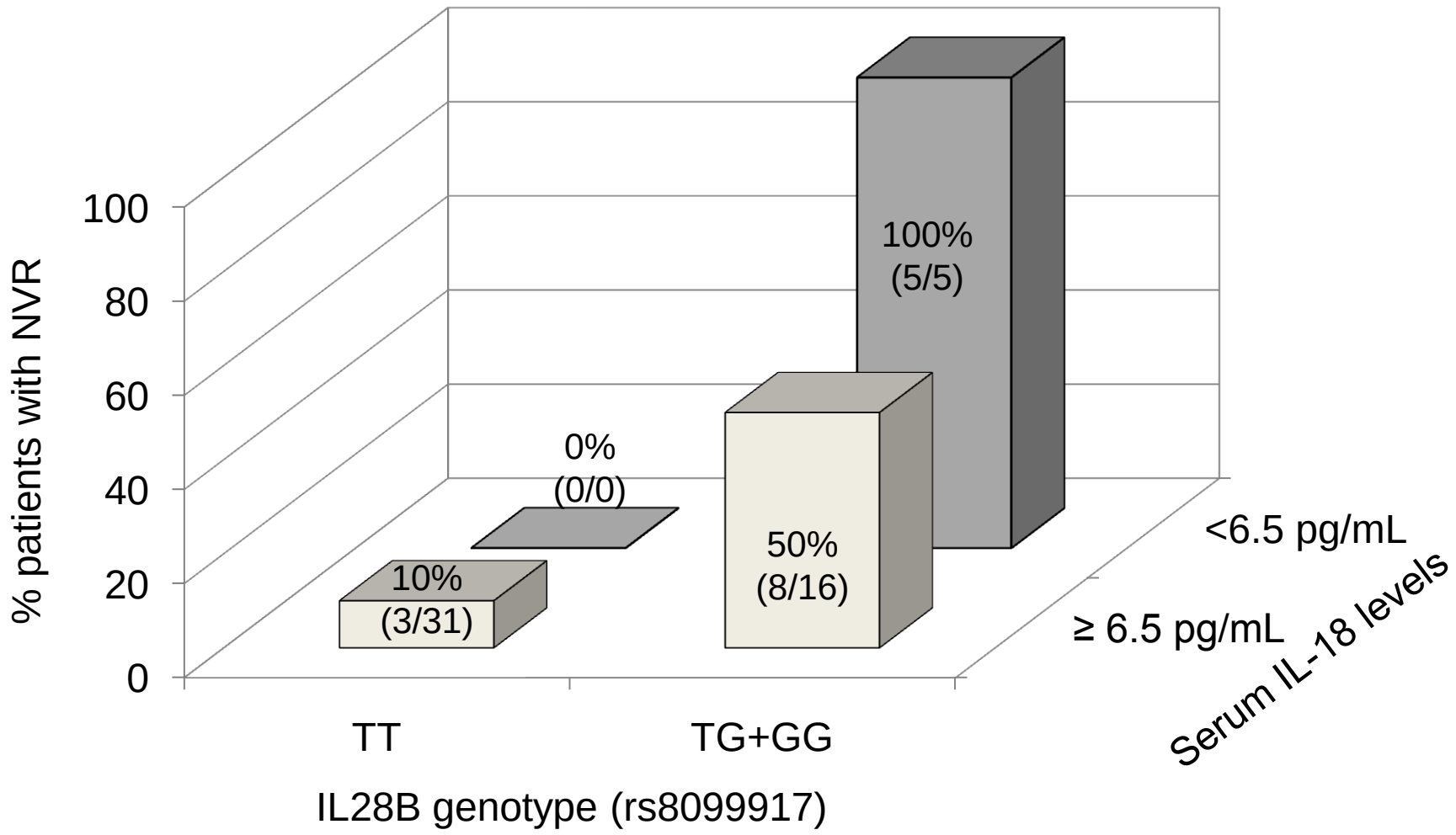

% patients with NVR
100
80
60
40
20
0
11%
(3/28)
0%
(0/25)
38%
(5/13)
100%
(8/8)
TT
TG+GG
IL28B genotype (rs8099917)
<12.1 pg/mL
≥ 12.1 pg/mL
Serum IL-12p40 levels

Figure 4C


% patients with NVR
100
80
60
40
20
0
10%
(3/31)
0%
(0/0)
50%
(8/16)
100%
(5/5)
TT
TG+GG
IL28B genotype (rs8099917)
<6.5 pg/mL
≥ 6.5 pg/mL
Serum IL-18 levels