CORRESPONDENCE

Clusters of Differentiation 24 Polymorphism and Hepatocellular Carcinoma

To the Editor:

We read with great interest the recent report by Li et al.[1] analyzing the correlation between the clusters of differentiation 24 (CD24) polymorphism and risk of chronic hepatitis B virus (HBV) infection. In their study, the CD24 P170 T allele (thymidine at position 170) was correlated with a strong, statistically significant increased risk of developing chronic HBV infection. They also showed that CD24 polymorphism may associate with development of hepatocellular carcinoma (HCC). Chronic HBV infection is one of the most important risk factors for HCC. Many patients with chronic HBV infection are more prone to develop liver cirrhosis and HCC when the infection is rampant. In view of these theories, genetic variants underlying chronic HBV infection should be related to HCC susceptibility.

Results of a genome-wide association show the overlapping relation of the Corticotropin-releasing hormone receptor 2 (*CRHR2*) gene with HCC mediated largely through its association with HBV infection.[2] To analyze if CD24 polymorphisms are associated with host susceptibility to HCC, we described a case–control study of 235 cases with HCC and 268 healthy controls in a southeast Chinese population. All patients presented clear histopathological confirmation of HCC. Patients who had preoperative chemotherapy or preoperative chemoradiotherapy were excluded. Population controls were selected from a pool of cancer-free subjects living in the same region as the cases. The control subjects were frequency-matched to the cases on sex and age. The T/T homozygote in CD24 P170 was correlated with a strong, statistically significant increased risk of developing HCC (adjusted odds ratio = 2.96, 95% confidence interval = 1.54-5.79; Table 1). Hence, we proposed that genes underlying a susceptibility to chronic HBV infection may also be relevant to HCC. This result is analogous to the overlapping relation of gene polymorphism with lung cancer that is mediated largely through its association with chronic obstructive pulmonary disease.[3]

HCC is one of the most common malignant neoplasms in the world. HBV, hepatitis C virus, excessive alcohol intake, and exposure to aflatoxin B1 are major risk factors for the development of HCC. Approximately 80% of HCC incidence worldwide is etiologically associated with HBV. In view of these facts, HCC is the outcome of chronic inflammation. Genes regulated in local inflammation may be linked with HCC through inflammatory or immune-modulating pathways. Liver inflammation induced by hepatitis B is produced by the cellular immune response against viral antigens present in infected hepatocytes. In this local microenvironment, preneoplastic transformation of hepatocytes is believed to happen. This therefore shows that the CD24 P170 T/T genotype increases the risk of HCC. Genetic factors underlying HBV could be related to HCC risk. Future genome-wide association studies may consider this overlap phenomenon.

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Table 1. Association Between CD24 P170 Genotype and Risk of HCC

Genotype	Control n (%)	Case n (%)	Crude OR (95% CI)	*P*	*Adjusted OR (95% CI)	*P*
CC	136 (50.7)	109 (46.4)	1.0		1.0	
CT	117 (43.7)	90 (38.3)	0.96 (0.66-1.39)	0.829	0.95 (0.65-1.38)	0.788
TT	15 (5.6)	36 (15.3)	2.99 (1.56-5.75)	0.001	2.96 (1.54-5.79)	0.001

CI, confidence interval; OR, odds ratio.
*OR were adjusted by sex.

Reply:

We read with great interest the letter by Sheng and Shui. The data presented are consistent with our initial observation that the cluster of differentiation (CD)24 polymorphism associates with progression from chronic hepatitis B Virus infection to liver cirrhosis and hepatocellular carcinoma (HCC).[1] We also reported, in a transgenic model of HCC, that targeted mutation of the *CD24* gene reduces the size of HCC in the mice. The compelling data by Sheng and Shui raised an import issue on the role for CD24 in HCC pathogenesis. Although we have not observed CD24 expression in HCC samples, recent work by Lee et al.[2] suggests that CD24 is a marker for HCC stem cells and may play an important role in HCC stem cell function. It would be of great interest to determine whether the function of CD24 is to regulate adaptive[3] and innate immune responses[4] or HCC stem cell function[2] or both.

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Idiopathic Noncirrhotic Intrahepatic Portal Hypertension Is an Ongoing Problem in India

To the Editor:

Schouten et al. describe the need for histological confirmation of idiopathic noncirrhotic portal hypertension and its contrasting incidence between the West and India.[1] We prefer the term idiopathic noncirrhotic intrahepatic portal hypertension (NCIPH) to distinguish it from extrahepatic portal vein thrombosis—the most common cause of pediatric portal hypertension at our center.[2]

After the report from Chandigarh in 2002,[3] there is scarce literature on the incidence of biopsy-proven NCIPH in India. We herein report on our recent experience with NCIPH.

From 2005 to 2007, retrospective analysis of 227 portal hypertensive patients who underwent liver biopsy at our center showed that of 62 patients labeled as having "cryptogenic cirrhosis," 30 (48%) were diagnosed as having NCIPH after liver biopsy.[4]

We prospectively studied the prevalence of NCIPH among all new portal hypertensive patients in our unit from July 2009 to July 2010 (after institutional ethics committee approval). NCIPH was diagnosed as per the previously described criteria.[4] The need for liver biopsy in each patient was decided on a case-by-case basis, based on the clinical scenario.

Of 610 consecutive new portal hypertensive patients studied, cryptogenic cirrhosis (210 patients) was the most common cause of portal hypertension identified after noninvasive tests. Of 44 cryptogenic cirrhosis patients who underwent liver biopsy, 17 (39%) had NCIPH and 8 had "true cryptogenic cirrhosis." NCIPH and true cryptogenic cirrhosis patients were 27 (range, 14-59) and 42 (range, 25-67) years old, respectively; 10 and 4 patients, respectively, were males. Hepatic venous pressure gradient measured in 15 NCIPH and 4 true cryptogenic cirrhosis patients was 7 (range, 1-21) and 18 (range, 10-27) mmHg, respectively ($P = 0.012$).

Liver biopsies were performed percutaneously in 4 NCIPH patients and transjugularly in 13. Number of cores in percutaneous biopsies was 3 per patient and 3 (range, 1-6) in transjugular biopsies; length of the largest core was 13 (range,12-15) in percutaneous and 12 mm (range, 6-16) in transjugular biopsies. The number of portal tracts in liver biopsies was 10 (range, 5-20). Liver biopsies showed no significant fibrosis (6 patients), mild portal/periportal fibrosis (10), moderate fibrosis (1), mild perisinusoidal fibrosis (1), abnormal portal venous ectasia (6), and mild diffuse sinusoidal dilatation (8); no patient had cirrhosis or severe fibrosis.

In summary, in 2009-2010 and 2005-2007,[4] 39%-48% of patients with clinical diagnosis of cryptogenic cirrhosis who underwent liver biopsy at our center had NCIPH.

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Reply:

We would like to thank Goel et al. for their reply to our review of idiopathic noncirrhotic portal hypertension (INCPH).[1,2]

The authors studied the prevalence of INCPH among all new portal hypertension patients from July 2009 until July 2010. Eventually, 17 (39%) patients were diagnosed with INCPH. The authors described the morphological features observed in liver specimens from these 17 INCPH patients. Interestingly, neither

the presence of nodular regenerative hyperplasia nor obliteration of portal venules (phlebosclerosis)—both the most frequently observed morphological features in liver specimens of Western INCPH patients—were found.[3,4] The apparent absence of these features in Indian INCPH patients could imply differences in pathophysiological mechanisms between patients from different continents.

As reported by Goel et al., liver biopsy is mandatory in the diagnosis of INCPH. Its main role is the exclusion of liver cirrhosis, which may be very difficult to discern by radiological examinations only. In addition, the diagnosis of INCPH can be suggested or supported by the presence of morphological features such as nodular regenerative hyperplasia, phlebosclerosis, increased number of portal vascular channels, paraportal shunt vessels, and sinusoidal dilatation. However, one must take into account that these features can also be observed in patients without clinical signs of portal hypertension.

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I148M Variant of PNPLA3 Confer Increased Risk for Nonalcoholic Fatty Liver Disease Not Only in European Population, but Also in Chinese Population

To the Editor:

We read, with great interest, the article by Sookoian et al. reporting on when after having performed a systematic review by a meta-analysis, they found that the I148M variant of PNPLA3 can be used as a risk marker for predicting susceptibility and histological severity of nonalcoholic fatty liver disease (NAFLD).[1] Here, we would like to draw attention to our similar studies between rs738409 in PNPLA3 and NAFLD in the Chinese population and that we found significant associations between rs738409 and NAFLD.

Recent genome-wide association studies revealed that the genetic variation, rs738409 (I148M), in PNPLA3 influences NAFLD and plasma levels of liver enzymes.[2-4] However, the association of rs738409 with the development and severity of NAFLD in the Chinese population has not yet been reported. We tested the association of histologic NAFLD with the I148M variant of PNPLA3 in 112 patients of NAFLD and 120 matched controls in our department. Our results showed that in the Chinese population, individuals harboring the G allele of rs738409 were susceptible to NAFLD, and that rs738409 was associated with the histological fibrosis stage. PNPLA3 may be involved in the progression of fibrosis in NAFLD. Our results showed that the rs738409 G allele in PNPLA3 was significantly associated with increased odds of histologic NAFLD (odds ratio [OR] = 3.03; 95% confidence interval [CI] = 1.98-6.71). After analysis of the association between the G allele of rs738409 in PNPLA3 and the steatosis grade, we found that there was not an association ($P > 0.05$). Furthermore, we also did not observe any association of this variant with body mass index, triglyceride levels, high- and low-density lipoprotein levels, or diabetes ($P > 0.05$). Generally, our research results are very similar to Prof. Sookoian's previous report.

In summary, our data highlight three points. First, we show that genetic variation at PNPLA3 confers a markedly increased risk of increasingly severe histological features of NAFLD, not only limited to European populations. Second, our research sample size is small and only a single central research, and this did not allow us to get the better results, compared with Prof. Sookoian's report. Third, although the genotypes of different geographic and ethnic factors may have a significant effect on the above results, we still want to say that the I148M variant of PNPLA3 can be used as a risk marker for predicting the susceptibility and histological severity of NAFLD in the Chinese population.

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Potential conflict of interest: Nothing to report.

Noninvasive Assessment of Liver Fibrosis: the Clinical Context and Question are Important

To the Editor:

We read the recent article on noninvasive assessment of liver fibrosis, and we would like to make some comments.[1]

First, when using a noninvasive marker in a specific patient, both the clinical context and question are important. The sensitivity, specificity, and area under the receiver operating characteristic curve of a noninvasive test are not enough. In our recent meta-analysis of transient elastography (TE), we incorporated pretest probabilities as well as summary sensitivities and specificities to calculate post-test probabilities and, therefore, clinically translate the performance of such markers.[2] If we assume that TE is used as a screening tool to detect cirrhosis (pretest probability = 0.5), a measurement above the cirrhosis cut-off value would mean a 90% probability of cirrhosis, whereas a measurement below this value would suggest a cirrhosis risk of 16%. Obviously, by manipulating the cut-off, either sensitivity or specificity can be increased at the expense of the other, depending on the clinical question, but this has not been adequately addressed, to date. For instance, if noninvasive tests are to be used as population-screening tests for fibrosis, then the emphasis should be on enhancing sensitivity. In an individual patient, if the index of suspicion for fibrosis/cirrhosis is low, one would need enhanced specificity, whereas with a high suspicion index, an enhanced sensitivity is more useful.

Second, noninvasive markers do not provide unexpected additional or alternative diagnoses. In this specific case scenario, there would be no information on steatosis, which is associated with fibrosis severity and treatment outcome.

Third, because the evaluation of noninvasive markers is shifting to clinical outcomes, it is important to remember that histological staging is descriptive and categorical and not designed as a prognostic tool. Therefore, regarding clinical outcomes, noninvasive fibrosis markers should be compared to established prognostic models. If histology is to be used a comparator for prognostic studies, then a quantitative histological assessment, such as collagen proportionate area or other prognostically validated morphometric approach, should be used.[3]

Last, sensitivities and specificities of noninvasive fibrosis markers are probably overestimated, because failed measurements are not calculated in the estimation of these parameters. This needs to be addressed in future studies.

In conclusion, noninvasive markers should be used and interpreted in the specific context of individual patients, because, clearly, one size does not fit all. Regarding the patient in the case scenario, we would advocate the performance of liver biopsy, because noninvasive tests can only potentially diagnose, but not exclude, cirrhosis and cannot give any other reliable information apart from this.

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Targeting the Renin-Angiotensin System: Potential Beneficial Effects of the Angiotensin II Receptor Blockers in Patients with Nonalcoholic Steatohepatitis

To the Editor:

We read, with great interest, the article by Torres et al. about the efficacy of combination therapy with rosiglitazone and metformin or losartan on improving liver histology in patients with nonalcoholic fatty liver diseases; the investigators conclude that adjuvant therapies are ineffective.[1] It is certainly a very interesting study to find out some prospect ideas about the therapeutic potential of "combination effects" or "combination therapy," because we are still uncertain as to whether or not disregarding combination therapy is a good option for nonalcoholic steatohepatitis (NASH) patients. As discussed by the investigators, an interesting drug to consider is telmisartan, which also acts as a partial agonist of *peroxisome proliferator-activated receptor gamma*. In fact, in addition to the observed effects on fatty liver reversion, telmisartan is able to improve insulin resistance, but is less effective than losartan in preventing plasminogen-activator inhibitor-1 gene expression.[2] Therefore, combining both actions in one molecule may improve some aspects of NASH, but not all of them.

At any rate, there are other reasons to think about the importance of the blockade of the renin-angiotensin system (RAS) in the liver of NASH patients. Perhaps, in the study of Torres et al., improvement in body weight was not as expected, because treatment with thiazolidinediones may prevent an interesting, poorly explored effect of angiotensin receptor blockers (ARBs) on the regulation of body weight.[2] In addition, we recently observed a local upregulation of the angiotensin I–converting enzyme in the liver of patients with NASH, suggesting a putative role of the RAS in the progression of liver histology.[3]

Finally, the investigators speculated that both environmental and genetic influences are likely involved in the lack of universal improvement observed in the patients enrolled in this trial. Can we expect that all patients are equal responders to the therapy? Certainly, we cannot. We previously showed that a gene variant (A1166C) in the angiotensin II type 1 receptor predicts the

therapeutic response to losartan; we found a higher response to losartan among AA homozygous.[4] We wonder whether, before discharging ARBs, we might improve our ability to select patients who are able to respond better, tailoring the therapy, depending on their genetic background.

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Potential conflict of interest: Nothing to report.

Metabolic Syndrome is Also a Risk Factor for Primary Liver Cancer in Patients Younger than 65 Years of Age?

To the Editor:

We read with great interest the article by Welzel et al.[1] The study reported a positive association between metabolic syndrome and hepatocellular carcinoma (HCC), but the results were restricted to people aged ≥65 years of age. Although the incidence of obesity and/or metabolic syndrome is showing no sign of decline, the epidemic of hepatitis B (HBV) and C (HCV) viruses is at its peak, thus increasing the incidence of HCC.[2,3] To provide further insights on the association of HCC and metabolic syndrome on the interaction with HBV/HCV infection, we report data from an Italian case–control study on HCC. The study was conducted between 1999 and 2002 in the province of Pordenone, Northeastern Italy, and in Naples, Southern Italy.[4] Cases comprised 185 patients aged 43-84 years (50% below age 65 years) with incident HCC, who had not yet received any cancer treatment at study entry. The control group included 412 cancer-free patients from the same areas as the cases.[4]

Metabolic syndrome was associated with a four-fold higher risk of HCC. The association was confirmed among hepatitis B surface antigen (HBsAg)-negative and antibody to HCV (anti-HCV)-negative subjects (odds ratio [OR] = 4.00; 95% confidence interval [CI] = 1.30-12.27). According to the individual preexisting medical condition, only diabetes was significantly associated with HCC

Table 1. Multiple Logistic Regression Analysis Examining the Association Between HCC and Each Preexisting Medical Condition Contributing to Metabolic Syndrome

	HCC		Controls			
Preexisting Medical Conditions	**N**	**%**	**N**	**%**	**OR (95% CI)***	***P* Value**
All study subjects	**185**		**404**			
Diabetes	37	20.0	26	6.4	3.75 (1.66-8.44)	0.0001
Hypercholesterolemia	2	1.1	24	5.9	0.52 (0.08-3.39)	0.63
Hypertension	41	22.2	116	28.7	1.17 (0.63-2.17)	0.50
Obesity	114	61.6	258	63.9	1.26 (0.72-2.20)	0.42
Metabolic syndrome	10	5.4	16	4.0	4.00 (1.30-12.27)	0.015
HBsAg-negative and anti-HCV-negative	**38**		**360**			
Diabetes	9	23.7	23	6.4	3.52 (1.34-9.23)	0.011
Hypercholesterolemia	1	2.6	23	6.4	0.69 (0.08-5.81)	0.73
Hypertension	16	42.1	101	28.1	2.07 (0.92-4.65)	0.078
Obesity	29	76.3	232	64.4	1.95 (0.82-4.67)	0.13
Metabolic syndrome	6	15.8	15	4.2	4.19 (1.23-14.23)	0.022

*Adjusted for center, sex, age, education, drinking status, maximum lifetime alcohol intake, smoking status, cigarettes per day, hepatitis B surface antigen (HBsAg) and/or antibody to HCV (anti-HCV) positivity, when appropriate.

risk (OR = 3.75; 95% CI = 1.66-8.44; Table 1). This result was in agreement with a recent study.[5]

Our results are therefore in agreement with the study by Welzel et al.[1]; in particular, our study confirms that metabolic syndrome is also a risk factor for HCC in people younger than 65 years (50% of our study population).

Our results on metabolic syndrome, together with heavy drinking (in the North) and high HCV prevalence (in the South), contribute to explain the high incidence of and mortality rates from HCC in Italy.[3,6] In order to reduce the burden of liver cancer, actions to control the recent epidemic of metabolic syndrome should be promoted.

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Ribavirin Pharmacokinetics and Interleukin 28B Plus Cytochrome P450 27B1 Single-Nucleotide Polymorphisms as Predictors of Response to Pegylated Interferon/Ribavirin Treatment in Patients Infected with Hepatitis C Virus Genotype 1/4

To the Editor:

Bitetto et al. described how vitamin D serum level is complementary to the interleukin 28B (IL28B; rs12979860) polymorphism in predicting the achievement of sustained virological response (SVR) in treatment-naive patients receiving standard pegylated interferon (Peg-IFN) and ribavirin (RBV) for the treatment of genotype 1 chronic hepatitis C virus (HCV).[1]

It should be also noted how vitamin D serum levels may be influenced by polymorphisms in the gene coding for a related metabolic enzyme (cytochrome P450 27B1 [CYP27B1]).[2] The association between responsiveness to therapy for difficult-to-treat HCV infections and IL28B (rs12979860 and rs8099917) single-nucleotide polymorphisms (SNPs) were evaluated.[1,3]

Prior to the discovery of these new predictive factors, both dosage and pharmacokinetic exposure of RBV have been repeatedly found to be associated with the therapeutic outcome of chronic HCV hepatitis.[4,5] No data are, however, yet available on the interplay between RBV pharmacokinetics and these newly introduced predictive factors.

In the analysis of 91 patients with chronic genotype 1/4 HCV hepatitis who received standard Peg-IFN/RBV treatment, we found that further to IL28B (rs8099917) SNP (odds ratio [OR] = 2.83, 95% confidence interval [CI] = 1.08-7.39, $P = 0.034$) and CYP27B1 (rs4646536) SNP (OR = 3.90, 95% CI = 1.37-11.14, $P = 0.011$), the presence of RBV concentrations >2500 ng/mL (OR = 3.08, 95% CI = 1.21-7.85, $P = 0.019$) was an independent predictor of SVR.

It is worth noting (Fig. 1) how no patients with all three unfavorable factors had SVR, whereas a tendency to higher rates of SVR was seen according to the combination of favorable genetic and RBV pharmacokinetic factors. These results reveal that rs8099917 G allele, rs4646536 C allele (related to low 25-hydroxyvitamin D3 serum concentrations), and RBV plasma concentrations (<2500 ng/mL) could predict which patients are likely to experience treatment failure in this group of difficult-to-treat HCV-infected patients.

Based on these findings, we believe that in addition to these recently characterized human genetic factors, the individual pharmacokinetic exposure to RBV should not be neglected among the predictors of anti-HCV treatment outcome.

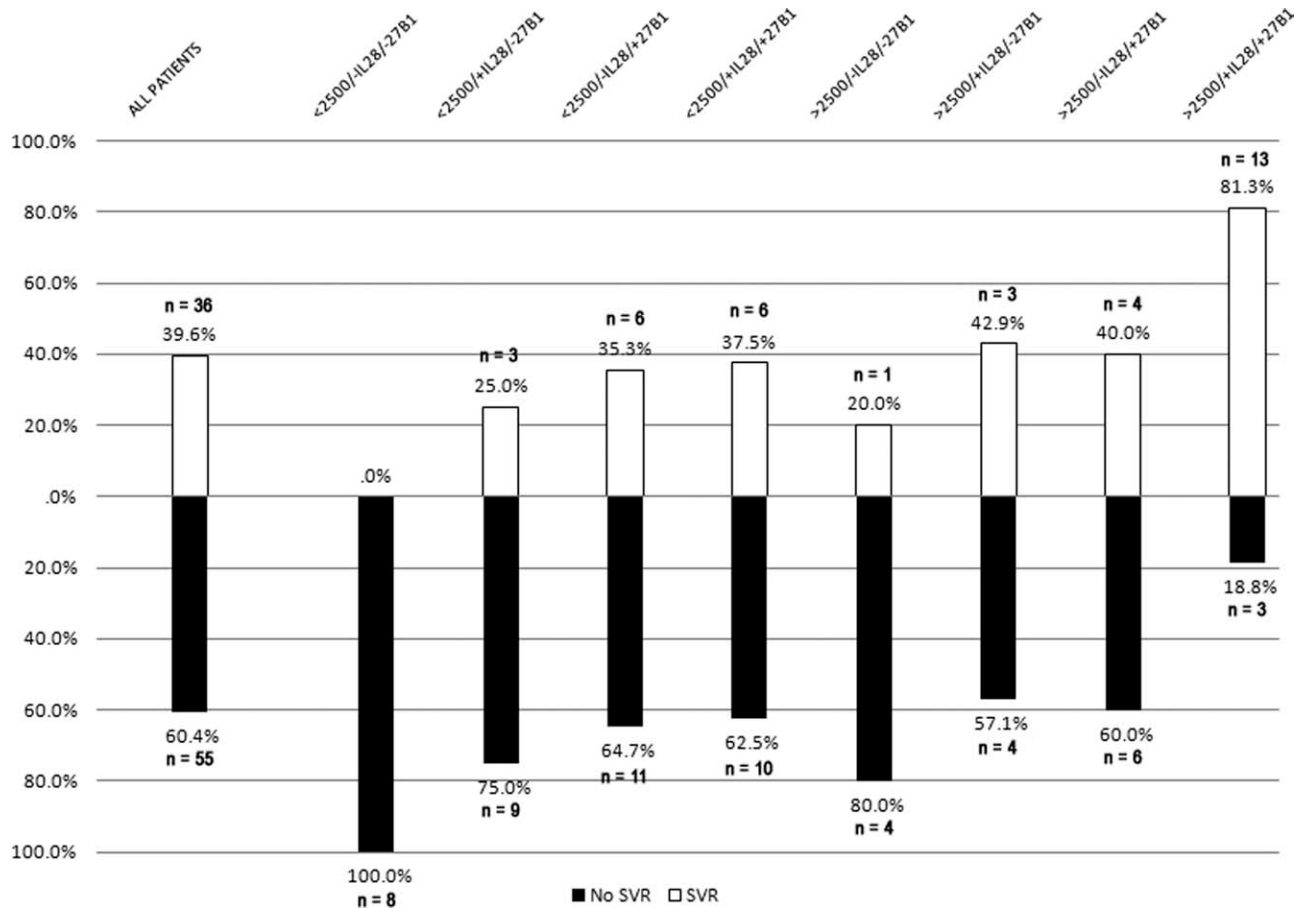

Fig. 1. Number and percentage of patients with SVR (white columns) and without SVR (black columns), stratified for each predictor factor combinations.

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