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Genetic Markers Predict Primary Non-response and Durable Response to Anti-Tumor Necrosis Factor Therapy in Ulcerative Colitis

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Abstract

Background: Despite a high non-response rate, predictors of response to anti-tumor necrosis factor (TNF) therapy in ulcerative colitis (UC) remain limited. We aim to determine clinical and genetic predictors of primary non-response (PNR) and durable response (DR) to anti-TNF therapy in a large prospective UC cohort.

Methods: Using the Illumina ImmunoChip, candidate polymorphisms associated with clinical outcomes of PNR and DR were separately evaluated and combined into weighted genetic risk scores. Combined genetic and clinical multivariable models for PNR and DR were compared to clinical predictive models using area under the receiver operating characteristics (AUROC) curves. Models were internally (DR) or externally (PNR) validated. Multivariable logistic regression was utilized to assess the association of genetic risk scores with infliximab levels and antibodies.

Results: Of 231 patients, 28 (12%) experienced PNR and 120 (52%) experienced DR. There was no significant difference in clinical features between primary non-responders and responders. Eight alleles were associated with PNR. A combined clinical-genetic model (AUROC 0.87) more

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accurately predicted PNR compared to a clinical only model (AUROC 0.57; $p < 0.0001$). In an external cohort of 131 patients, increasing tertiles of PNR genetic risk score correlated with increased risk of PNR ($p = 0.052$). Twelve candidate loci were associated with DR. Genetic risk score quartiles for DR demonstrated a strong dose-response relationship in predicting treatment duration. Genetic risk scores for PNR and DR were not associated with infliximab levels or antibody formation.

Conclusion: Genetic polymorphisms enhance prediction of PNR and DR to anti-TNF therapy in patients with UC.

Keywords

Inflammatory Bowel Disease; Ulcerative Colitis; Biologics (IBD); Genomics; Epidemiology

Introduction

Anti-tumor necrosis factor (TNF) therapies have revolutionized our ability to achieve clinical remission and endoscopic healing in patients with moderate-to-severe ulcerative colitis.^{1–3} However, up to 30% of patients are primary non-responders to these medications.^{4, 5} Primary non-response to anti-TNF therapy has serious implications on disease course, including predicting low likelihood of response to other treatments within the same therapy class and a greater need for surgery.⁵ In addition, approximately 15% of patients who do initially respond to therapy subsequently lose response annually such that just over half of the patients initiated on therapy remain on drug at the end of 2 years.⁶

To date, there are few tools to accurately predict primary non-response and durable response to anti-TNF therapy, primarily as the mechanisms remain incompletely understood. Clinical risk factors that have been associated with primary non-response include severe disease,^{4, 7} age,^{8, 9} duration of colitis, disease extent,¹⁰ elevated c-reactive protein levels,^{7, 11, 12} and lower baseline albumin levels.^{5, 13} However, the predictive value of clinical risk factors remains poorly replicated and inadequate, thereby limiting utility in current practice. A few prior studies have attempted to use genetic markers to predict response to anti-TNF therapy in ulcerative colitis premised on the hypothesis that single nucleotide polymorphisms (SNPs) related to the pathogenesis of disease or mechanisms of action of anti-TNFs determine likelihood of response. Limited, small prior studies examining individual candidate SNPs have examined the association with IL-13 receptor (*IL13Ra2*), IL-23 receptor (*IL23R*), TNF-receptor I (*TNFR1*), IgG Fc receptor IIIa (*FcYRIIIa*), neonatal Fc receptor (*VNTR2/VNTR3*), apoptosis related genes (*Fas ligands*, *caspase 9*), and MAP kinases.^{14–23}^{16–19, 21–25} These candidate gene studies have not been widely replicated, and a targeted approach may miss other relevant polymorphisms. In addition, many prior studies failed to differentiate between primary and secondary non-responders, two events with recognized distinct biologic basis.

Understanding predictors of primary non-response and durable response to anti-TNF therapy is a key unmet need and gains urgency with availability of therapies with distinct mechanisms of action that have broadly similar efficacy as anti-TNF therapies. A priori prediction of outcomes will help clinicians guide a personalized therapeutic approach to

inflammatory bowel disease in choosing amongst multiple therapeutic classes with distinct mechanisms of action and avoiding unnecessary exposure to therapies that are unlikely to be of benefit. In a large prospective cohort of patients with ulcerative colitis, we aimed to identify clinical parameters and genetic markers that predict primary non-response and durable response to anti-TNF therapy among both IBD-risk alleles and non-risk alleles implicated in immune response, and validate our findings.

Materials and Methods

Population:

The Prospective Registry in IBD Study at MGH (PRISM) is an ongoing prospective registry of adult patients with Crohn's Disease (CD) and UC who receive care at the MGH Crohn's and Colitis Center for inflammatory bowel disease.^{26, 27} All patients age 18 with inflammatory bowel disease are offered voluntary enrollment without exclusion. However, this study included only Caucasian patients. From this population, for this study, we included all patients meeting the following criteria: (1) confirmed diagnosis of UC according to standard criteria; (2) initiation of first anti-TNF agent with full clinical documentation within our healthcare system; (3) follow-up duration of at least 12 weeks to identify whether the patient experiences primary non-response and 24 months to determine if a patient experiences durable response; and (4) genotyping with the Illumina ImmunoChip.

Genotyping:

Patients included in the study were genotyped using the Illumina ImmunoChip-v1 on the Illumina Bead Express platform at the Broad Institute (Cambridge, MA). The ImmunoChip is an Illumina genotyping platform containing 196,524 polymorphisms (718 small insertion deletions, 195,806 SNPs), with dense coverage of known major immune and inflammatory diseases loci.

Outcome and covariates:

Patients were characterized into clinical outcomes of primary non-response, non-durable response, and durable response through detailed chart review of gastroenterologist documentation from clinical office visits or hospitalizations, colonoscopy and/or sigmoidoscopy reports, radiologic imaging, and operative notes. Patients were categorized as primary non-responders if no clinical response was noted within 12 weeks of initiating an anti-TNF therapy or if the patient required alteration in therapeutic approach for ongoing clinical activity within this time (addition of a corticosteroid or another class of medication, UC-related hospitalization, or surgery). Patients that discontinued anti-TNF therapy within 12 weeks of initiation due to adverse drug effect or intolerance were not included as primary non-responders. Patients were categorized as durable responders by maintenance of response to anti-TNF therapy for at least 24 months after initiation. Patients who required anti-TNF dose escalation/optimization to maintain response were included in the durable response outcome if remission was maintained. Covariate clinical features, including duration of disease at anti-TNF initiation, age of diagnosis, gender, smoking status, and extent of disease were collected via medical record review. Laboratory parameters within 1 month prior to

initiation of anti-TNF therapy, including albumin, erythrocyte sedimentation rate, and C-reactive protein, were also collected for the subset of patients for which these were available.

As part of routine clinical care at our center, many patients who lost response to infliximab underwent testing for infliximab trough level and antibodies either at Prometheus laboratories or Mayo clinical laboratories. Where available, this information was retrieved from the medical record. If a patient had more than one set of antibodies and levels drawn, the first trough level was used for analysis. Infliximab trough levels were categorized as therapeutic ($\geq 5 \mu\text{g/ml}$) or subtherapeutic ($< 5 \mu\text{g/ml}$), based on current guidelines.²⁸ Antibodies were categorized as present or absent. Anti-TNF trough and antibody levels were only obtained for the subpopulation with infliximab exposure, as over 80% of patients in our cohort were treated with infliximab and, until recently, drug levels and antibodies were only commercially available for this anti-TNF drug.

Genetic and clinical risk score development:

Two separate genetic association analyses for PNR and DR were performed using Plink v1.07.²⁹ For each analysis, immuno-chip Single Nucleotide Polymorphisms (SNPs) that met Hardy-Weinberg equilibrium threshold of $p > 0.001$, genotyping call rate $> 99\%$, and genotyping success rate $> 80\%$ were included in analysis. For the 201 IBD-associated alleles, a genetic association for inclusion in PNR or DR genetic risk scores was set as significant if $p < 0.05$. For other Immuno-chip loci, in this hypothesis generating study, a threshold of $p < 1 \times 10^{-6}$ was used. Using significant alleles from each genetic association analysis, separate weighted genetic risk scores for PNR and DR were calculated as a cumulative sum of the product of log-odds ratio and allele burden for each of the risk SNPs. Genetic risk scores for PNR and DR were then entered into multivariable logistic regression models with relevant clinical covariates determined using a priori knowledge.

Discrimination of the genetic and combined models:

Calibration of the combined genetic/clinical models was tested using logistic regression with the Hosmer and Lemeshow goodness-of-fit test. To test discrimination, each combined genetic/clinical multivariable model was compared to the clinical predictive model and the genetic risk score using area under the receiver operating characteristics (AUROC) curves and likelihood ratio tests.

External validation of the primary non-response genetic risk score:

External validation of the primary non-response genetic risk score was then performed in an independent cohort of 131 Caucasian adult patients (age ≥ 18) with UC recruited at the IBD Center at Cedars-Sinai Medical Center who underwent genotyping with the same Illumina Immuno-chip-v1 platform.³⁰ Primary non-response was defined in this cohort as lack of response after 8 weeks of initiation of anti-TNF therapy. Logistic regression was utilized to determine the association of PNR genetic risk score tertile, derived in the primary cohort, with primary non-response in the validation cohort.

Internal validation of the durable response genetic risk score:

External validation of the durable response genetic risk score was not performed due to significant differences in the definition for durable response between the primary and external cohorts. Consequently, we performed internal validation by bootstrapping with 10,000-fold replications. We separately performed internal validation in our cohort through a Kaplan Meier analysis with time to cessation of anti-TNF therapy as a time-to-event analysis.

Assessment of the association between genetic risk score and infliximab trough levels and antibodies:

Amongst the 190 individuals that were exposed to infliximab, eighty-four (44%) underwent infliximab level and antibody testing, of which 79 were confirmed to have levels drawn at trough. We performed univariate and multivariable logistic regression to determine the association of genetic risk scores for PNR and DR with therapeutic trough level and antibodies.

All statistical analysis was performed using SAS Studio (Cary, NC).

Ethical Considerations

The study was approved by the Institutional Review Board of Partners Healthcare.

Results

Study Cohort

Five-hundred-thirty-nine patients with an enrollment diagnosis of ulcerative colitis underwent genotyping on the Illumina ImmunoChip at our center. After excluding those with no exposure to anti-TNF therapy (n=229), those with a diagnosis of CD or IBD-U (n=41), those that were post-colectomy at anti-TNF initiation (n=14), or those with insufficient follow-up documentation (n=24), we had a final cohort of 231 patients with UC included in this analysis. The mean age at diagnosis of UC of included patients was 29.5 years with a mean disease duration of 8.4 years at the time of anti-TNF initiation. Over 90% of patients had pancolitis (56.3%) or left-sided colitis (35.1%). Just over half (50.8%) of patients were women. Eighty-two percent of patients were initiated on infliximab as their first anti-TNF agent.

Of 231 patients, 28 (12%) experienced PNR, 120 (52%) experienced DR, and the remainder experienced non-durable response. There was no significant difference in baseline clinical features of primary non-responders as compared to responders (table 1). The mean disease duration of primary non-responders was 7.0 years, as compared to 8.6 years for responders (p=0.29). Pancolitis was observed in 57.1% of primary non-responders, as compared to 56.2% of responders. Amongst the subset of patients with laboratory parameters within 1 month prior to initiation of anti-TNF therapy, the mean serum albumin level was 4.2 g/dL (SD 0.4; n=13) amongst primary non-responders and 4.0 g/dL (SD 0.6; n=118) amongst responders (p=0.34). The median serum ESR was 12.0 mm/hr (IQR 2, 28; n=10) in primary non-responders, and was 18.0 mm/hr (IQR 12, 37; n=105) in responders (p= 0.16). The

median serum CRP was 2.2 mg/dL (IQR 0.2, 14.7; n=11) in primary non-responders, and was 7.4 mg/dL (IQR 1.2, 26.1; n=105) in responders (p=0.28).

Predictors of Primary Non-Response

On genetic association analysis, seven IBD-associated alleles, and one non-IBD-associated allele were found to be associated with PNR (table 2) and were incorporated into a weighted genetic risk score. Six of these alleles were associated with increased risk of PNR, while two were inversely associated. The alleles with the strongest effect sizes were rs6679677 (potential genes *PTPN22*, *PHTF1*; OR 2.26, p=0.041) and rs3851228 (potential genes *TRAF3IP2-AS1*; OR 2.33, p=0.027).

Multivariable analysis including clinical and genetic features revealed the genetic risk score as the only significant predictor of primary non-response (p = 3.87×10^{-8} ; table 3). Age at ulcerative colitis diagnosis, disease duration, gender, disease extent, and active smoking were not significantly associated with primary non-response. Using area under the receiver operating curves (AUROC), both a combined clinical-genetic model (AUROC 0.87) and genetic risk score alone (AUROC 0.86) more accurately predicted PNR compared to a clinical only model (AUROC 0.57; p < 0.0001; figure 1a). The combined clinical and genetic model was well-calibrated in our cohort (Hosmer and Lemeshow p=0.153). The genetic risk score was not independently associated with pancolonic disease extent (OR 1.08, 95% CI 0.91 – 1.29). However, it did predict colectomy (OR 1.56, 95% CI 1.20 – 2.04, p=0.001), when adjusted for gender, disease duration, age at diagnosis, smoking, and disease extent.

Within the subset of patients (n=104) that had laboratory markers of disease severity drawn within 1 month prior to starting anti-TNF therapy, 94 patients were responders and 10 patients were primary non-responders. Adjusting for serum albumin, C-reactive protein, and erythrocyte sedimentation rate slightly improved the discrimination of the model in the primary cohort (AUROC 0.90). However, genetic risk score remained the only independently significant predictor of primary non-response (p=0.0019).

External validation of the primary non-response genetic risk score

One-hundred-thirty-one patients were included in the validation cohort. Of these, 32 patients (24.4%) experienced primary non-response, and 99 patients (75.6%) were responders. Increasing tertiles of genetic risk score were associated with a trend to increased risk of PNR (p = 0.052). Compared to patients in the lowest genetic risk tertile, patients in the highest risk tertile had a trend to increased odds of primary non-response (OR 2.30; p = 0.088).

Predictors of Durable Response

A total of twelve candidate loci were associated with DR and were included in a weighted genetic risk score: 11 IBD-associated alleles, and 1 non-IBD associated allele (table 4). Six alleles had a positive association with DR, while the other 6 were associated with a decreased risk of DR. Multivariable analysis including clinical and genetic features revealed the genetic risk score as the only significant predictor of durable response (p= 4.74×10^{-11} ; table 5). AUROC curves demonstrated that both a combined genetic-clinical model

(AUROC 0.80) and genetic risk score alone (AUROC 0.79) more accurately predicted DR as compared to a clinical-only model (AUROC 0.57; $p < 0.0001$; figure 1b).

Within the subset of patients ($n=104$) that had laboratory markers of disease severity drawn within 1 month prior to starting anti-TNF therapy, 55 patients were durable responders and 49 patients were non-responders. Addition of serum albumin, C-reactive protein, and erythrocyte sedimentation rate to the combined clinical/genetic model did not substantially improve the discrimination of the model (AUROC 0.82). Genetic risk score remained the only independent predictor of durable response ($p=7.28 \times 10^{-6}$).

Internal validation of the durable response genetic risk score

For the genetic-clinical model, bootstrapping with 10,000 replications internally validated a mean c-statistic of 0.806 (95% CI 0.806 – 0.807) with potential optimism of 0.020 (95% CI 0.019 – 0.020). Genetic risk score quartiles for durable response demonstrated a strong dose-response relationship in predicting duration of treatment, with higher quartiles exhibiting the longest duration of therapy ($p_{\text{logrank}} < 0.0001$; figure 2).

Predictors of primary non-response and durable response are mutually exclusive

On univariate analysis, genetic risk score for durable response did not predict and was not protective against primary non-response (OR 1.01; 95% CI 0.83 – 1.24). Similarly, genetic risk score for primary non-response did not predict and was not protective against durable response (OR 0.92; 95% CI 0.78 – 1.08), emphasizing likely distinct biologic mechanisms for the two different outcomes.

There is no association between genetic risk score and infliximab levels or antibodies

Multivariable-adjusted logistic regression demonstrated no association between quartiles of genetic risk score for primary non-response and therapeutic infliximab trough level ≤ 5 $\mu\text{g/ml}$ (supplementary figure; $p=0.41$). Similarly, there was no association between genetic risk score for durable response and infliximab level ≤ 5 $\mu\text{g/ml}$ ($p=0.65$).

On multivariable-adjusted logistic regression, there was a no association between genetic risk score for primary non-response and presence of infliximab antibodies (supplementary figure; $p=0.97$). There was no association between genetic risk score for durable response and presence of antibodies ($p=0.47$).

Discussion

Personalizing therapy in ulcerative colitis and a priori prediction of response to a particular therapeutic class is attaining greater urgency with the availability of treatments with comparable efficacy targeting distinct therapeutic pathways. Thus far, clinical predictors and single gene candidate studies have yielded inconsistent results and inadequate predictive value. In this study of a large prospective registry of patients with ulcerative colitis, we identified SNPs associated with primary non-response and durable response, and demonstrated that a combined clinical and genetic risk model utilizing these SNPs more accurately predicted outcomes than clinical factors alone.

In prior studies, extensive disease¹⁰ and markers of severe disease^{4, 7} have been associated with anti-TNF non-response and subsequent colectomy. However, the results remain poorly replicated. For example, while Morita et al.¹³ demonstrated an inverse association between week-2 CRP level and week 8 response to anti-TNF therapy, Lee et al.¹¹ found that CRP > 10 mg/dl predicted colectomy, but not primary non-response to anti-TNF therapy. Ferrante et al.⁸ found no association between age at diagnosis, duration of disease, elevated CRP, or active smoking and 10-week response to infliximab. We similarly did not find an association between clinical risk factors and anti-TNF response in our cohort.

Nearly all prior studies of polymorphisms associated with response to anti-tumor necrosis factor therapies have been performed in Crohn's disease, or have assessed individual candidate genes with small sample sizes.^{16-19, 21-25} Several of the SNPs identified in our analysis are consistent with prior observations relating to the same pathway of effect. Jurgens et al.²² demonstrated that patients homozygous for IL-23 receptor SNPs that increased risk of inflammatory bowel disease were more likely to respond to anti-TNF therapy as compared to patients with IL-23 receptor SNPs that decreased risk. In our cohort, a polymorphism of *CCL2*, a chemokine part of the IL-23 pathway that decreases T-cell migration and impacts downstream TNF- α levels, decreased risk of durable response. It is possible that polymorphisms in this SNP decrease the effect of this protective chemokine.³¹⁻³⁵ *Suppressor Of Cytokine Signaling 1 (SOCS1)*, a component of the IL-12 pathway, was associated with higher likelihood of durable response in our cohort.³⁵ TNF- α mediates type 1 inflammatory response through the regulation of IL-12.^{36, 37} Polymorphisms in the IL-12 pathway may change the sensitivity of this pathway to TNF- α regulation, increasing the likelihood of durable response to anti-TNF therapy. *PTPN22* (rs6679677), associated with a 2.26-fold increased odds of primary non-response to anti-TNF therapy in our cohort, is a gene associated with several immune signaling pathways.³⁸ It has been associated with increased disease severity and extent in ulcerative colitis, and need for escalation of therapy to agents including azathioprine and anti-TNF medications.³⁹ However, it is associated with decreased serum TNF- α levels.^{34, 40, 41} Polymorphisms in this gene may impact TNF and other cytokine levels, placing patients at increased risk for more severe disease and non-response to anti-TNF therapy.

We did not identify an association between therapeutic infliximab trough levels or infliximab antibodies and primary non-response or durable response. While we acknowledge this may be due to lower statistical power, it may also imply that the associations of these SNPs may be mediated by mechanisms other than drug pharmacokinetics or antibody formation. This should be further addressed in larger studies to more robustly define the mechanistic relationship of these SNPs with non-response to anti-TNF therapy.

Our study has many strengths. Utilizing a prospective registry of patients newly initiated on anti-TNF therapy, we were able to accurately characterize outcomes of primary non-response and durable response, in addition to other clinical risk factors for these outcomes. While other studies of genetics and anti-TNF response in ulcerative colitis have focused on targeted SNPs, genotyping using the Illumina immunoChip allowed for an unbiased assessment of SNPs associated with anti-TNF response in ulcerative colitis. We also tested

our primary non-response genetic risk score in an external validation cohort of patients and demonstrated promising results, providing a basis for further validation in future studies.

Our findings should be interpreted within the limitations of our study design. Within our large prospective registry, a small proportion of patients initiated anti-TNF therapy while followed at our institution, limiting the power of our study. As genome-wide level of significance was not used in this hypothesis generating study, it is possible that some SNP associations are by chance. However, several SNPs did show a significant association with plausible mechanisms of action, providing a further basis for mechanistic exploration. Response to treatment was characterized based on global physician impression through careful review of subjective symptoms and objective testing. Due to retrospective study design, standardized disease activity scores, fecal calprotectin, and endoscopic severity indices were not routinely utilized as these were not obtained at each visit, leading to subjectivity in defining response. The entire population in this study was Caucasian, possibly limiting the generalizability of SNPs identified.

In summary, we present a large comprehensive study of both genetic and clinical risk factors for anti-TNF response in ulcerative colitis. Clinical factors alone do not predict response to anti-TNF therapy. However, we have demonstrated that a weighted genetic risk score significantly enhances prediction of response to anti-TNF therapy, and have shown the applicability of this score in an external validation cohort of primary non-response. By identifying loci implicated in anti-TNF non-response, this study provides new markers to further basic research in the pathogenesis of this disease. Larger prospective studies are required to confirm the predictive utility of these SNPs. As more data on genetic predictors become available for different classes, it is possible that it may be useful to select therapy in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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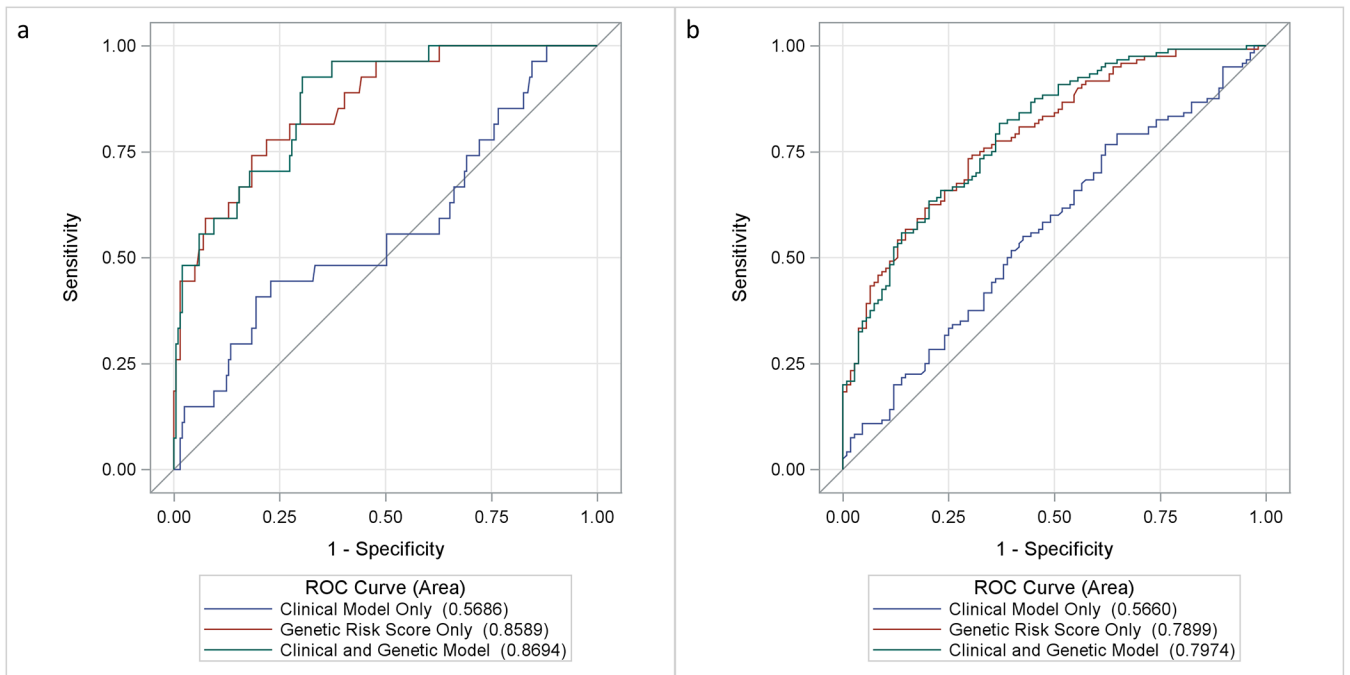


Figure 1: Receiver operating curves comparing a combined genetic and clinical model to genetic and clinical models alone for PNR (a) and DR (b)

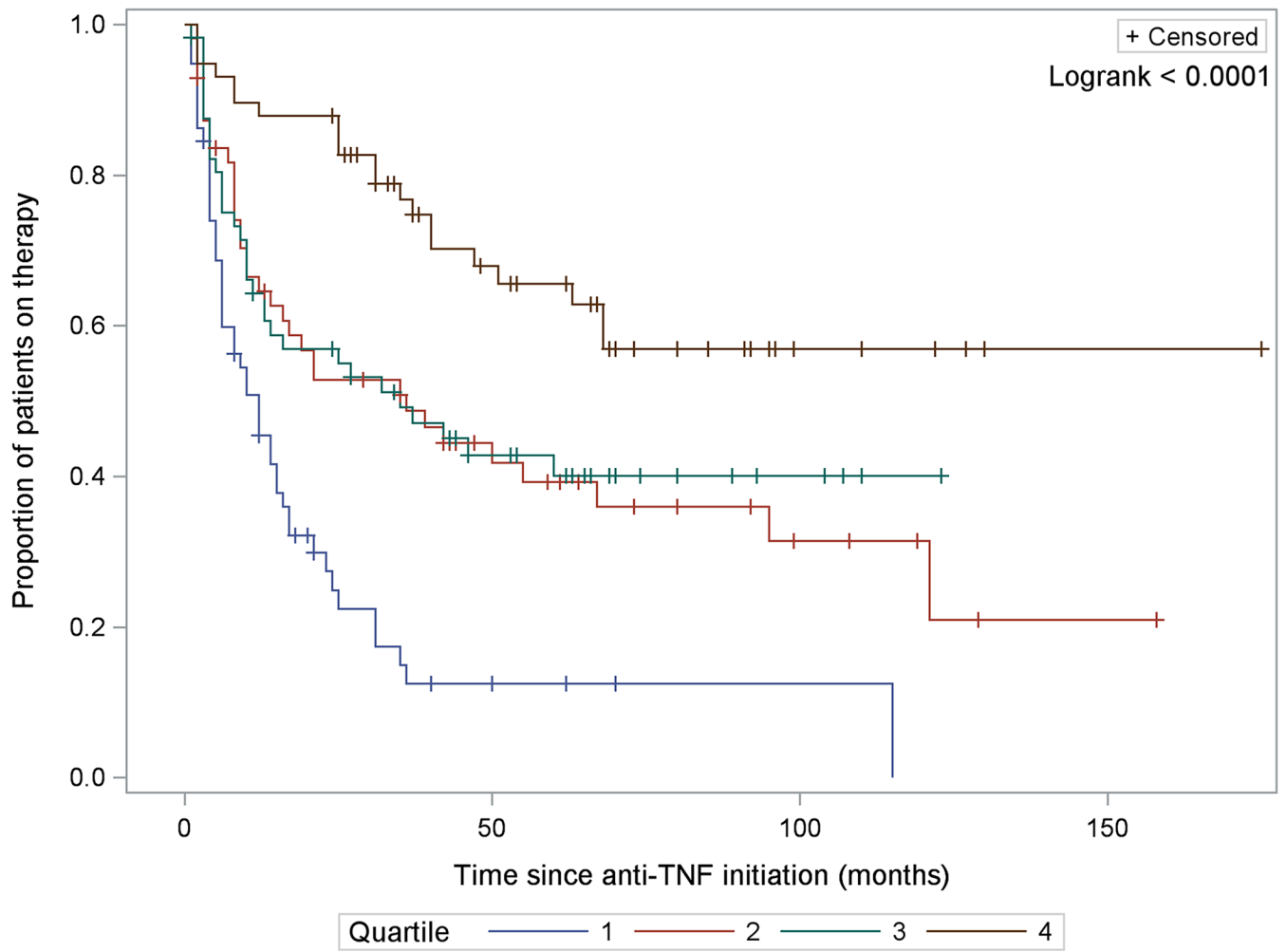


Figure 2: Time to cessation of anti-TNF biologic therapy, stratified by risk burden of 12 SNPs associated with durable response. Increasing quartile indicates increasing genetic burden for durable response

Table 1:

Comparison of characteristics of patients with Ulcerative Colitis initiating anti-tumor necrosis factor therapy (anti-TNF) with and without primary non-response

	Primary non-responders (n=28)	Responders (n= 203)	P-value
Age at diagnosis (SD) (in years)	29.6 (11.7)	29.5 (11.8)	0.99
Disease duration (SD) (in years)	7.0 (6.2)	8.6 (7.6)	0.29
Female (%)	14 (50.0)	103 (50.7)	0.94
Disease extent, n (%)			0.74
Proctitis	1 (3.6)	15 (7.4)	
Left-sided colitis	11 (39.3)	70 (34.5)	
Pancolitis	16 (57.1)	114 (56.2)	
Unknown	0 (0.0)	4 (2.0)	
First anti-TNF Therapy, n (%)			0.58
Infliximab	21 (75.0)	169 (83.3)	
Adalimumab	5 (17.9)	27 (13.3)	
Golimumab	1 (3.6)	2 (1.0)	
Certolizumab	1 (3.6)	5 (2.4)	
Tobacco Use, n (%)			0.66
Current smoker	1 (3.6)	12 (5.9)	
Former smoker	9 (32.1)	49 (24.1)	
Never-smoker	18 (64.3)	137 (67.5)	
Unknown	0 (0.0)	5 (2.5)	

Table 2:

Single nucleotide polymorphisms associated with primary non-response in ulcerative colitis

Chromosome	SNP	Risk Allele	Odds Ratio	P-value	Potential genes
1	rs6679677	A	2.26	0.041	<i>PTPN22, PHTF1</i>
6	rs3851228	T	2.33	0.027	<i>TRAF3IP2-AS1</i>
9	rs4743820	C	1.81	0.044	<i>NFIL3</i>
11	rs568617	T	0.39	0.042	<i>FIBP</i>
12	rs653178	C	1.78	0.049	<i>SH2B3, ATXN2</i>
13	rs3742130	A	1.98	0.023	<i>UBAC2, GPR18</i>
21	rs2284553	A	1.80	0.037	<i>IFNGR2, IFNAR1, IL10RB</i>
9	rs1330307	C	0.23	5.65E-06	

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Table 3:

Multivariable analysis of predictors of primary non-response to anti-TNF therapy in Ulcerative Colitis

	Odds ratio	95% confidence interval	P-value
Age at diagnosis	0.980	0.940, 1.019	0.319
Disease duration	0.959	0.887, 1.026	0.249
Gender	1.055	0.383, 2.888	0.916
Disease extent (pancolitis vs. not)	0.680	0.236, 1.935	0.467
Active Tobacco Use	0.135	0.002, 2.316	0.284
Genetic Risk Score (per 1 unit increase)	3.419	2.294, 5.562	3.87×10^{-8}

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Table 4:

Single nucleotide polymorphisms associated with durable response in ulcerative colitis

CHR	SNP	Risk Allele	Odds Ratio	P	Potential genes
1	rs670523	A	0.64	0.021	<i>UBQLN4, RIT1, MSTO1</i>
2	rs6716753	C	0.61	0.026	<i>SP140</i>
4	rs4692386	T	0.57	0.004	<i>RBP-J</i>
7	rs1077773	G	0.68	0.035	<i>AHR</i>
8	rs921720	A	0.67	0.042	<i>TRIB1</i>
10	rs2790216	A	1.56	0.048	<i>CISD1, IPMK</i>
11	rs907611	A	1.54	0.039	<i>TNNI2, LSP1</i>
16	rs529866	T	2.18	0.001	<i>SOCS1, LITAF, RMI2</i>
16	rs5743289	T	1.79	0.033	<i>NOD2</i>
17	rs3091315	G	0.63	0.024	<i>CCL2, CCL7</i>
18	rs9319943	C	1.66	0.037	
16	rs12051532	C	2.35	8.44E-06	

Table 5:

Multivariable analysis of predictors of durable response to anti-TNF therapy in Ulcerative Colitis

	Odds ratio	95% confidence interval	P-value
Age at diagnosis	0.978	0.952, 1.005	0.116
Disease duration	0.997	0.956, 1.039	0.873
Gender	1.132	0.603, 2.125	0.700
Disease extent	1.195	0.636, 2.244	0.580
Active Tobacco Use	1.817	0.428, 7.712	0.418
Genetic Risk Score (per 1 unit increase)	2.799	2.060, 3.803	4.74×10^{-11}

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