Author/s:
Xie, KK;Braue, A;Martyres, R;Varigos, G

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Baseline demographics as predictors for therapeutic survival and response in psoriasis patients on biologic treatments

Running head: Psoriasis therapeutic outcome predictors

Authors: Dr. Kenneth Kun Xie, Dr. Anna Braue, Dr. Raymond Martyres, Prof. George Varigos

Affiliation: Department of Dermatology, Royal Melbourne Hospital, Department of Medicine, The University of Melbourne.

Author Contacts:

Dr. Anna Braue: anna@braue.com
Ph: 03 9342 4531
Address: Dept of Dermatology, Royal Melbourne Hospital, Po Box 2129, Grattan Street, Parkville VIC 3050

Dr. Raymond Martyres: raymond.martyres@bigpond.com
Ph: 03 9342 4531
Dept of Dermatology, Royal Melbourne Hospital, Po Box 2129, Grattan Street, Parkville VIC 3050

Prof. George Varigos: george.varigos@mh.org.au
Ph: 03 9342 4531
Dept of Dermatology, Royal Melbourne Hospital, Po Box 2129, Grattan Street, Parkville VIC 3050

Corresponding Author: Dr. Kenneth Kun Xie
kennethkxie@gmail.com
Ph: 0401939988

Address: 306/1 Grosvenor Street, Doncaster VIC 3018

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DR. KENNETH KUN XIE (Orcid ID : 0000-0003-4275-7565)

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Baseline demographics as predictors for therapeutic survival and response in psoriasis patients on biologic treatments

Abstract

Background/Objectives: Biologic agents provide a relatively safe and promising long-term therapeutic option for patients with moderate to severe psoriasis who have failed conventional treatment. However, these agents are not effective in all patients. We aimed to examine the association of baseline patient characteristics with short-term efficacy and the long-term survival of biological therapies in moderate to severe psoriasis.

Methods: We performed a retrospective observational study of all patients that received biologic treatment for psoriasis at the [Anonymous Institution] (N=146). We extracted data on patient demographics and medical history. The outcomes we measured included a 75% Reduction in Psoriasis Area and Severity Index (PASI) score at 12 and 24 weeks, total duration of drug survival, and Dermatology Life Quality Index (DLQI) scores. We used regression modeling to assess the association between each baseline patient characteristic and outcome measures.

Results: Increase in baseline BMI was associated with reduced likelihood of achieving PASI75 at 12 and 24 weeks (P = 0.014). Increased BMI also correlated with reduced long-term therapeutic survival (P = 0.03). Higher rates of treatment termination were noted in patients with greater baseline DLQI (P = 0.038).

Conclusions: Greater BMI at initiation of biologic treatment for psoriasis may contribute to decreased short-term efficacy. Similarly, a higher BMI or DLQI at baseline was associated with shorter duration of biologic treatment retention.

Key Words:

- Psoriasis
- Biologic therapy
- Drug survival
- BMI
- Efficacy

Learning Point:

- The optimization of patient weight and well-being may help improve the efficacy and retention of biologic therapy in individuals with moderate to severe psoriasis.

Abbreviations

APR: Australian Psoriasis Registry

BMI: Body Mass Index

DLQI: Dermatology Life Quality Index

HREC: Human Research Ethics Committee

IL: Interleukin

PASI75: 75% Reduction in Psoriasis Area and Severity Index

PBS: Pharmaceutical Benefit Scheme

QoL: Quality of Life

RCT: Randomized Control Trial

TNF: Tumor Necrosis Factor

Introduction

Psoriasis is a chronic, immune-mediated inflammatory disease, affecting 2-3% of the general population (1). The condition is characterized by distinct cutaneous manifestations with associated risks of systemic complications and psychological sequalae (2). Currently, no definitive cure exists and patients with moderate-to-severe psoriasis often require life-long suppressive therapy (1). Traditionally, medical treatment options have included topical agents, phototherapy, and non-biologic systemic therapies (3). The development of novel biologic agents, such as anti-TNF alpha and anti-IL12/23 antibodies, targeting immune modulation, offers a potentially safer and long-term option for patients with severe psoriasis (4).

The results from recent studies report substantial heterogeneity in therapeutic response and drug survival with biological agents (5, 6). However the reasons underlying this heterogeneity remain

unclear. A range of factors, such as patient demographics, genetics, disease related factors, presence of comorbidities, psychological and behavioral features may all contribute to the observed response variation (7). The identification of factors associated with positive or negative treatment outcomes, will improve therapeutic decision-making (8). In particular, patient baseline demographic characteristics before the initiation of biologics, may be an important predictor of treatment outcomes (7).

The objective of this study was to assess the association of baseline patient demographics with short-term efficacy of and long-term adherence to biological agents in individuals with moderate-to-severe psoriasis.

Methods

Study Design and Sample

We performed a retrospective observational analysis of patients with psoriasis attending the [Anonymous Institution]. These patient data were recorded in the Australasian Psoriasis Registry (APR). The APR is an online Australian and New Zealand registry established in 2008 for psoriasis patients on systemic and biologic therapies. Patient information stored in the registry includes: general health status, state of their psoriasis, quality of life (QoL), and treatments that they are receiving, or have received previously. These data are updated after each patient review (9).

In Australia, patients are able to qualify for biologic therapy subsidized by the Pharmaceutical Benefit Scheme (PBS), if they are: 18 years of age or older, have had psoriasis for more than 6 months, have failed to achieve an adequate response to three types of standard treatment for a minimum of 6 weeks, and have a PASI score of ≥ 15 (10). We included all patients in the APR that are currently or have previously received biologic treatments at the [Anonymous Institution]. Only biologic-naïve patients were included in this study, and treatment data from the first biologic treatment episode was included for each patient. All patients qualified under PBS criteria, and consent was obtained before data was entered into the registry. Ethics for this study was approved by the [Anonymous Institution] Human Research Ethics Committee (HREC).

Data Extraction

We extracted data from the APR database in March 2015. Baseline data for each patient was extracted based on the date closest to the induction of biologic treatment. These included Age, BMI, Gender, Ethnicity, Alcohol and Smoking status, and Dermatology Life Quality Index (DLQI) scores. BMI was further stratified into normal weight (BMI: 18.5 - 24.9), overweight (BMI: 25.0 - 29.9), obese (BMI: 30.0 - 39.9) and morbidly obese (BMI >40). Smoking and alcohol consumption were recorded as current smokers vs non-smokers and current drinkers vs non-drinkers. Concordant with the United States Census Bureau, we defined patients originating from Europe, the Middle East or North Africa as 'White', and patients with other ethnicities as 'Non-white' (11). DLQI was also further stratified into DLQI < 10, and those with DLQI ≥ 10, representing mild, and moderate to severe impairment of QoL respectively.

Improvements in PASI scores at 12 and 24 weeks following the initiation of biologic therapy was recorded for anti-TNF and anti-IL12/23 agents respectively. A ≥ 75% decrease in psoriasis area and severity index (PASI75) compared to baseline was recorded as a marker of short-term efficacy. Total duration of drug use in days, as well as reason for treatment termination was documented to assess the therapeutic survival. Temporary treatment interruptions of < 90 days was not considered treatment discontinuations as patients often cease their treatment for short intervals due to elective surgery or infections (12).

We defined short-term efficacy as the achievement of PASI75 at 12 weeks for anti-TNF therapy (Adalimumab, Etanercept, Infliximab), and at 24 weeks for anti-IL 12/23 treatments (Ustekinumab), as per the Australian PBS guidelines (10). We defined treatment survival on the number of consecutive days a patient stayed on a biologic agent.

Statistical Analysis

Descriptive statistics were used to appraise and compare the ditribution of the baseline variables, changes in PASI and total length of drug retention. For predictors of short-term efficacy, logistic regression analysis was employed to assess the correlation between each baseline patient characteristic and the likelihood of achieving PASI75 at 12 and 24 weeks for anti-TNF and anti-IL 12/23 agents respectively. Cox regression analysis together with Kaplan-Meier curves were performed for each baseline characteristic to determine the association with long-term therapeutic survival. Log rank test was used to assess differences in survival between subgroups. Ongoing treatment at the time of data extraction, withdrawals from registry, and patient death was excluded in

the survival analysis. In our study, patients with missing data were excluded , and a p-value of < 0.05 was considered statistically significant.

Results

Patient Characteristics

Table 1 summarieses the baseline characteristics, of the 146 patients who received biologics for the treatment of psoriasis. The mean age was 44.7 years (Standard deviation (SD) =14.2). A total of 80 patients were male (54.8%), and the mean BMI at the start of biologic treatment was 30.8 (SD 6.9). A total of 114 received anti- TNF alpha treatment (Adalimumab = 44, Etanercept = 48, and Infliximab = 22), and 32 received anti IL-12/23 therapy (Ustekinumab). Before commencing a biologic agent, the median baseline DLQI and PASI was 4 (Interquartile range (IQR) 0-23) and 25 (IQR 0-100) respectively. 52 patients (38.8%) smoked amd 86 patients (64.2%) used alcohol. Baseline patient characteristics were similar between the anti TNF-alpha and anti IL-12/23 treatment groups according to the parameters listed (Table 1).

Predictors of Therapeutic Response

A total of 75.6% of patients achieved PASI75 after 12 weeks of anti-TNF alpha and 24 weeks of anti-IL 12/23 treatments. The univariable associations between each baseline predictor and initial treatment response are presented in Table 2. Higher BMI was associated with lower initial treatment response in the whole group (odds ratio (OR)=0.91, 95% CI = 0.85 - 0.98, p=0.01). There was no association between any of the other potential predictors and initial treatment response. When stratified by treatment group, there was no association between any of the predictors and initial treatment response in those who received anti IL-12/23 treatment (n=25). However in those who received anti TNF-alpha treatment (n=98), higher BMI was also associated with less treatment response (OR = 0.89, 95% CI 0.82 - 0.97,p=0.007).

Predictors of Treatment Survival

A total of 130 patients were assessed for drug survival time, with a mean of 1258.8 (95% CI = 1069.0 - 1448.7) days. The effect of each baseline characteristic towards treatment cessation is summarized in Table 2. In all biologics combined, increased baseline BMI (p = 0.003) and DLQI (p = 0.038) was found to be associated with increased likelihood of treatment cessation, with a hazards ratio of 1.044 (95% CI = 1.015 - 1.074) and 1.039 (95% CI = 1.002 - 1.077) respectively.

After stratification of BMI groups, the medium survival time in days were 1846.6 (95% CI = 1387.4 - 2325.7) for normal, 1450.4 (95% CI = 1166.5 - 1734.2) for overweight, 996.2 (95% CI = 670.4 - 1321.9) for obese, and 1116.5 (95% CI = 554.7 - 1678.3) for morbidly obese. These are demonstrated as Kaplan-Meier survival curves in Figure 1. There was a significant ($p = 0.008$) difference in treatment survival between the BMI groups.

The mean survival time for patients with DLQI < 10 was 1369.7 days (95% CI = 1141.2 - 1598.1), compared to 924.9 days (95% CI = 625.4 - 1224.3) in patients with a baseline DLQI ≥ 10. The difference in survival is demonstrated in the Kaplan-Meier survival curves presented in Figure 2. There was a significant ($p = 0.05$) difference in survival between the two DLQI groups.

Additional cox regression analysis was performed on patients receiving anti IL-12/23 (N = 25) and anti TNF-alpha (N = 101) agents respectively. A mean survival time of 1109.8 days (95% CI = 829.5 - 1390.0) was found in the anti IL-12/23 treatment group, with no statistically significant baseline predictors. The mean treatment survival time in the anti TNF-alpha group was 1194.4 days (95% CI = 993.4 - 1395.4). BMI was found to be significantly ($p = 0.002$) associated with increased treatment cessation, with a hazards ratio of 1.046 (95% CI = 1.016 - 1.077). Stratification of BMI also demonstrated significant ($p = 0.012$) difference between each BMI group. The mean treatment survival time in days, for each group were 1676.1 (95% CI = 1139.5 - 2212.6), 1464.5 (95% CI = 1156.8 - 1772.2), 895.2 (95% CI = 554.7 - 1678.3), and 1116.5 (95% CI = 554.7 - 1678.3) respectively for normal, overweight, obese and morbidly obese groups. Increased baseline DLQI on the other hand, did not demonstrate a statistically significant effect towards treatment cessation ($p = 0.075$), in patients treated with anti TNF-alpha.

Discussion

We report that in psoriasis patients commencing biologic immunotherapy, a higher BMI is associated with lower short-term therapeutic response, whilst both greater BMI and DLQI are associated with a shorter treatment survival. These findings suggest that pre-treatment patient characteristics may be used to predict the chance of treatment response and could potentially guide clinical decision-making and pre-treatment optimization of BMI.

Currently, significant consensus in the literature highlights obesity as an independent risk factor for the development of psoriasis. The effect of BMI on short-term treatment response for psoriasis has

been investigated with mixed results (6, 13-15). In two large randomized control trials, Menter et al. (N = 1212) and Papp et al. (N = 1230), the negative predictive effects of increased BMI towards short-term therapeutic response in Adalimumab ($P < 0.001$) and Ustekinumab ($P<0.001$) treatments respectively were elicited. Our study was also able to demonstrate a similar trend in patients receiving anti-TNF alpha treatment in an Australia specific cohort, and further substantiates higher baseline BMI as a predictor of poor treatment response from biological immunomodulation.

Although the exact mechanism responsible for the effect of BMI on biologics therapeutic response in psoriasis patients is unknown, a number of explanations exist. Several studies have postulated the possible influence of increased baseline inflammation and altered pharmacokinetics in obese patients (15). With higher levels of inflammatory cytokines, conventional dosing regimens are often inadequate in achieving satisfactory suppression of the disease, resulting in reduced therapeutic response (16). Additionally, increased adiposity can dramatically expand the volume of distribution, limiting the bioavailability of biologic agents (16). These mechanisms also help to explain the association of weight loss towards more favourable therapeutic response found in several studies (17, 18), which applies to both anti TNF-alpha and IL-12/23 inhibitors. Therefore, it was surprising that no significant trend was found in patients receiving Ustekinumab in our study. This could be partially explained by the small sample size in this group (n = 25).

The effect of high BMI on reduced retention of biologic treatment in psoriasis patients has also been established in several studies (5). The main concern stems from the increased rates of drug related and obesity related comorbidities associated with increased BMI (19). According to Gniadecki et al., obese patients receiving Infliximab, will have higher dosages, leading to increased occurrence of drug related adverse events (5). Additionally, Van der Reek et al. also demonstrated in their retrospective survival analysis of Etanercept, exacerbations of obesity related cardiovascular and metabolic complications could lead to treatment discontinuation. In our cohort, a high baseline BMI was associated with reduced treatment survival in patients receiving anti-TNF alpha.

Our study assessed the stratified effect of BMI on treatment survival of biologics. Patients who were morbidly obese had the worse treatment retention compared to normal and overweight groups. Yet, compared to patients who were obese, they demonstrated a better treatment survival time when the biologics were assessed together. The improved treatment survival in the morbidly obese group could be due to insufficient power as a consequence of a small sample size (n = 12). This small sample size and more pronounced comorbidities could also explain why the morbidly obese was the

only group that had no treatment retention after 2400 days (Figure 1). Additionally, a potential confounder could be that both Infliximab and Ustekinumab doses are increased in patients who are morbidly obese, and these patients are more likely to receive a satisfactory therapeutic dose (17, 20). Since improved satisfaction with treatment response is a crucial factor towards favourable treatment survival, a stepped dosing regime for biologics may be utilized in overweight and obese psoriasis patients.

Patient satisfaction and quality of life is another predictor towards long-term treatment retention. Currently, studies examining the effect of DLQI on treatment survival are lacking. In our cohort, reduced QoL as a consequence of psoriasis, represented by an increased baseline DLQI, was found to be associated with shorter biologic treatment duration. Similarly, in a recent observational study, Van den Reek et al. introduced the concept of 'Happy' drug survival, where increasing proportions of patients continuing on biologics therapy were 'happy' patients with DLQI < 5 (21). This suggests the possibility of employing pre-treatment counseling to improve drug retention in patients with higher DLQI. Furthermore, greater disease severity has been linked to a larger impact on patient QoL, making partial response from biologics much more likely in patients with higher baseline DLQI (22). As a consequence, these patients may experience impaired therapeutic satisfaction, leading to premature treatment cessation. Interestingly, when we assessed the effect of increased baseline DLQI on drug survival in patients receiving anti-TNF-alpha and anti-IL12/23 agents separately, a trend ($P = 0.075$) towards reduced drug survival was found in patients receiving anti-TNF-alpha. The lack of statistical significance was likely due to insufficient power in our sample.

Several inherent limitations were present in our study. This study was based on registry data collected from daily practice, where other factors could contribute to overall treatment survival and response. Important factors are treatment of choice by physicians and disease related features such as age of onset, diseases duration, family history, complications, previous treatments and comorbidities. Additionally, a retrospective database can result in small sample sizes due to the availability of patient data in the registry. Insufficient statistical power was noted in several of our analyses, especially in patients receiving Ustekinumab and also after stratifying patients into different weight groups. While the combined analysis of anti-TNF alpha agents in our study improved statistical power, it compromised the differentiation between their individual effectiveness, and variable impact on treatment longevity. Further follow up studies that examine the effect of weight modulation and psychological support on the survival of each individual biologic agent are warranted.

In conclusion, the association between a higher BMI and reduced treatment response can be partially explained by greater baseline inflammation and expanded volume of drug distribution associated with obesity. Increased rates of obesity related comorbidities provide an explanation for reduced survival in patients with higher BMI. These findings denote the significance of optimizing patient weight and it's associated comorbidities before and during biologic treatment to improve response and retention. Similarly, reduced biologics survival in patients of poorer baseline quality of life can be explained by greater baseline disease and increased likelihood of partial response, leading to treatment dissatisfaction and consequent cessation. Therefore, the importance of monitoring and improving patient well-being should also be employed by clinicians to improve biologic survival.

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Figure Legends

Figure 1: Biologics survival in patients of different BMI groups.

Kaplan-Meier survival curves for stratified BMI groups. Log Rank Test demonstrated significant (P = 0.008) differences in treatment survival between the BMI groups. Mean survival times: normal (1846.6, 95%CI = 1387.4 - 2325.7), overweight (1450.4, 95%CI = 1166.5 - 1734.2), obese (996.2, 95%CI = 670.4 - 1321.9) and morbidly obese (1116.5, 95%CI = 554.7 - 1678.3).

Figure 2: Biologics survival in patients with different levels of DLQI.

Log rank test demonstrated a significant (P=0.05) difference in treatment survival in patients with DLQI <10 compared to patients with baseline DLQI ≥ 10. The mean survival time for each is 1369.65 (1141.2 - 1598.1) and 924.9 (625.4 - 1224.3)

Tables

Table 1: General Patient Characteristics

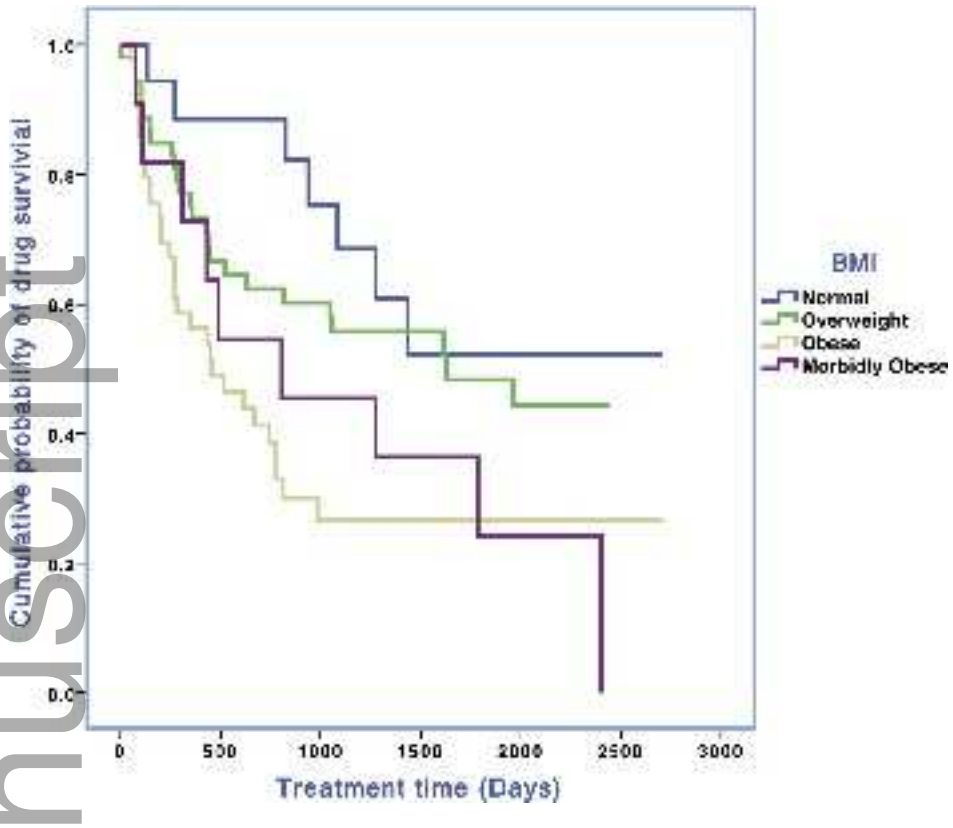
	Total	Anti TNF-Alpha	Anti IL-12/23
Treatment Size	**146**	**114**	**32**
Age (Years), Mean ± SD	**44.7 ± 14.2**	**45.1 ± 14.2**	**43.0 ± 14.4**
BMI, Mean ± SD	**30.8 ± 6.9**	**31.5 ± 7.4**	**28.6 ± 4.6**
Gender, Male/Female*	**80/66**	**63/51**	**17/15**
Ethnicity, White/Non-White*	**123/20**	**97/15**	**26/5**
Smoking, Smoker/Non-Smoker*	**52/82**	**43/60**	**9/22**
Alcohol, Drinker/Non-Drinker*	**86/48**	**64/39**	**22/9**
DLQI, Medium (Range)	**4 (0 - 23)**	**4 (0 - 23)**	**4 (0 - 21)**
Baseline PASI, Medium (Range)	**25 (0 - 100)**	**25 (0 - 100)**	**30.2 (16 - 100)**

*Chi-square tests were employed to compare categorical variables between each treatment group, with no statistical significant difference.

Table 2: Baseline predictors of therapeutic response and treatment survival.

Baseline Characteristic	Effect on therapeutic response	Effect on treatment survival (Event = treatment cessation)
Age	**0.995 (0.962 - 1.029)**	**1.005 (0.987 - 1.023)**
BMI	**0.913 (0.849 - 0.982)***	**1.044 (1.015 - 1.074)***
Male Sex	**2.097 (0.878 - 5.054)**	**0.772 (0.477 - 1.247)**
White Ethnicity	**1.188 (0.240 - 5.876)**	**0.841 (0.354 - 1.997)**
Current Smoker	**0.730 (0.287 - 1.854)**	**1.096 (0.663 - 1.813)**
Current Drinker	**1.024 (0.389 - 2.694)**	**1.109 (0.640 - 1.922)**
DLQI	**1.012 (0.941 - 1.088)**	**1.039 (1.002 - 1.077)***

Therapeutic response (n=123) is presented as odds ratios (95% Confidence Interval) for achieving PASI75 after 12 weeks. Treatment survival (n=130) is presented as hazards ratios (95% Confidence Interval) for the likelihood of treatment cessation. * indicate a P-value of < 0.05.



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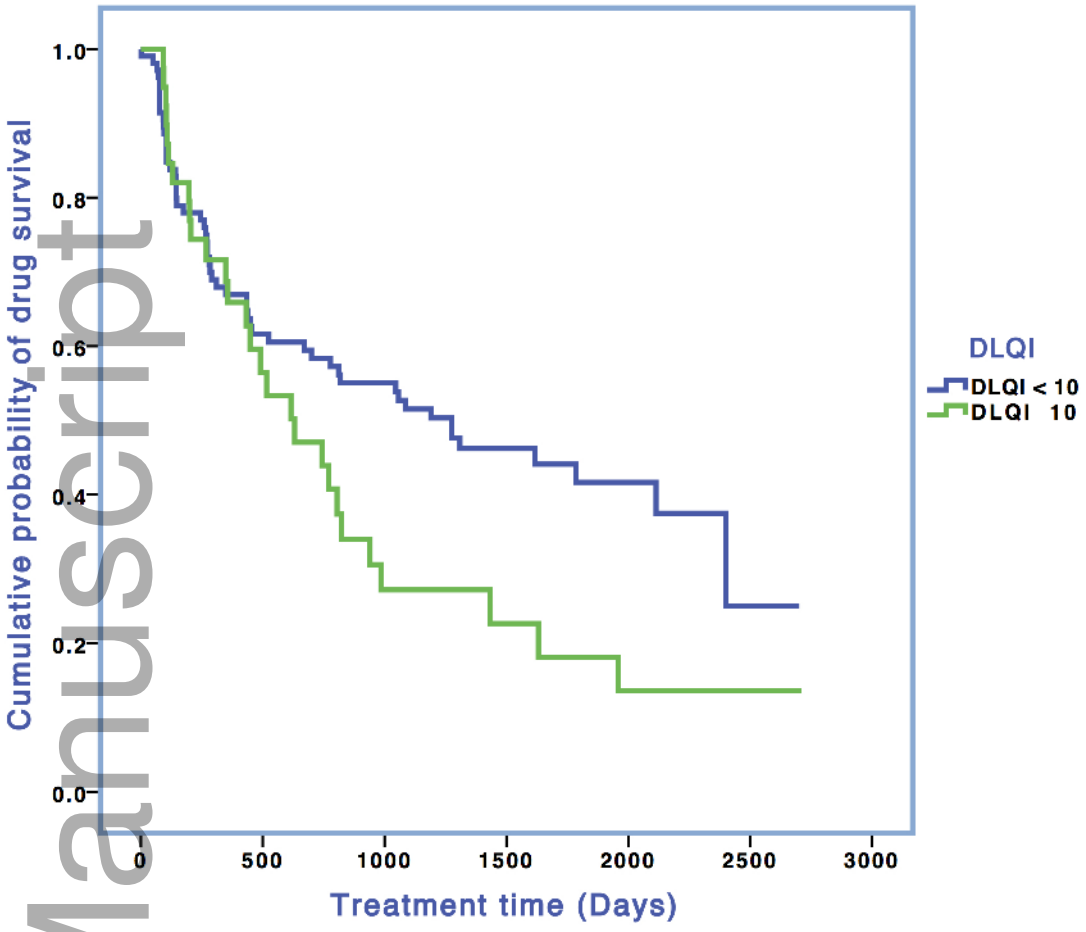

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