

Time-to-event modelling and simulation of the risk of relapse after infusion interval extension of infliximab in patients with inflammatory bowel diseases

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BACKGROUND

- Extending the dosing interval between infliximab infusions has been attempted in patients with Crohn's disease (CD) and ulcerative colitis (UC) who sustained treatment response following an earlier interval shortening.
- We aimed to identify predictors of sustained remission and an optimal trough concentration (TC) target for sustained remission after infliximab interval extension.

METHODS

Data

- Data from 30 adult patients (17 CD, 13 UC) who underwent infliximab interval extension following earlier interval shortening, were collected from a single-centre database search.
- All patients were in steroid-free clinical remission (two-item patient-reported outcome [PRO2] ≤ 1 [UC] and ≤ 8 [CD]) and biological remission (C-reactive protein [CRP] < 5 mg/L or faecal calprotectin [FC] < 250 mg/kg) at the start of interval extension.

Model

- parametric time-to-event (TTE) model;
- event defined as loss of steroid-free combined clinical and biological remission (i.e. relapse);
- NONMEM 7.5
- various hazard functions were tested.
- time-varying covariates: infliximab TC, the presence of anti-infliximab antibodies, infliximab clearance, the infliximab dose amount, the infliximab dosing interval, average infliximab daily dose per interval, serum albumin, CRP, haemoglobin, white blood cell count, and body weight;
- baseline covariates: disease type, sex

- Clearance was calculated using weighted averaging of the Bayesian forecasted estimates of 18 popPK models of infliximab [1].
- The TTE model was used to simulate (n=2000) model-informed infliximab interval extension aimed at infliximab TCs ranging from 5 to 15 mg/L.

RESULTS

- Overall, 37% (n=11) of patients remained relapse-free until one year after infliximab interval extension (5 CD, 6 UC) (**Figure 1**).

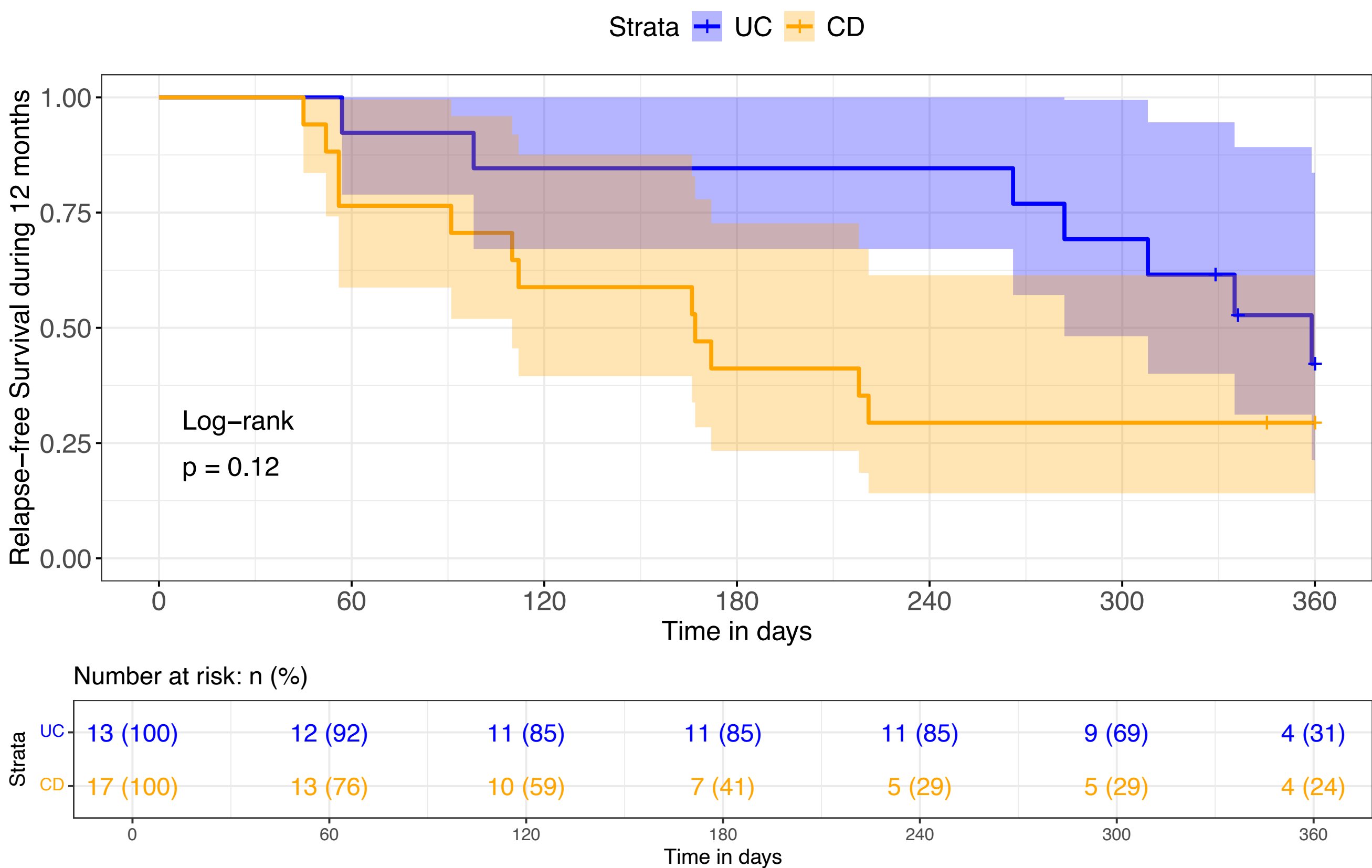


Figure 1. Kaplan–Meier plot of the sustained steroid-free clinical and biological remission stratified based on IBD type (CD in blue, UC in orange) including censoring (plus symbol). Shaded area represent 95% confidence intervals. Survival curves were compared using the log-rank test. CD, Crohn's disease; IBD, inflammatory bowel diseases; UC, ulcerative colitis.

- The proportion of patients with a TC above 5 mg/L – the widely accepted target concentration [2] – was 66% (19/29; one missing) at baseline and 48% (12/25; five missing) at one year.
- The median TC at one year after infliximab interval extension was 4.7 [range 1.6–10.8] mg/L in patients with CD and 4.9 [range 2.6–6.8] mg/L in patients with UC. TCs were not significantly different between relapsed and relapse-free patients during one year.
- A time-constant (exponential) hazard model best described the relapse data of patients with CD (**Table 1**, **Figure 2**).
- A Gompertz hazard model best described the data of patients with UC, with the relapse hazard risk increasing over time (**Table 1**, **Figure 2**).

Table 1. Parameter estimates of repeated time-to-event model.

Model parameter	Estimate (%RSE)
Baseline hazard (λ)	0.0035 (31%)
• Covariate effect of disease type UC on λ	-2.48 (66%)
Shape parameter (γ) [UC only]	0.0198 (40%)
• EC ₅₀ of infliximab on γ (mg/L)	3.14 (77%)

Abbreviations: EC50, infliximab TC of 50% inhibitory effect.

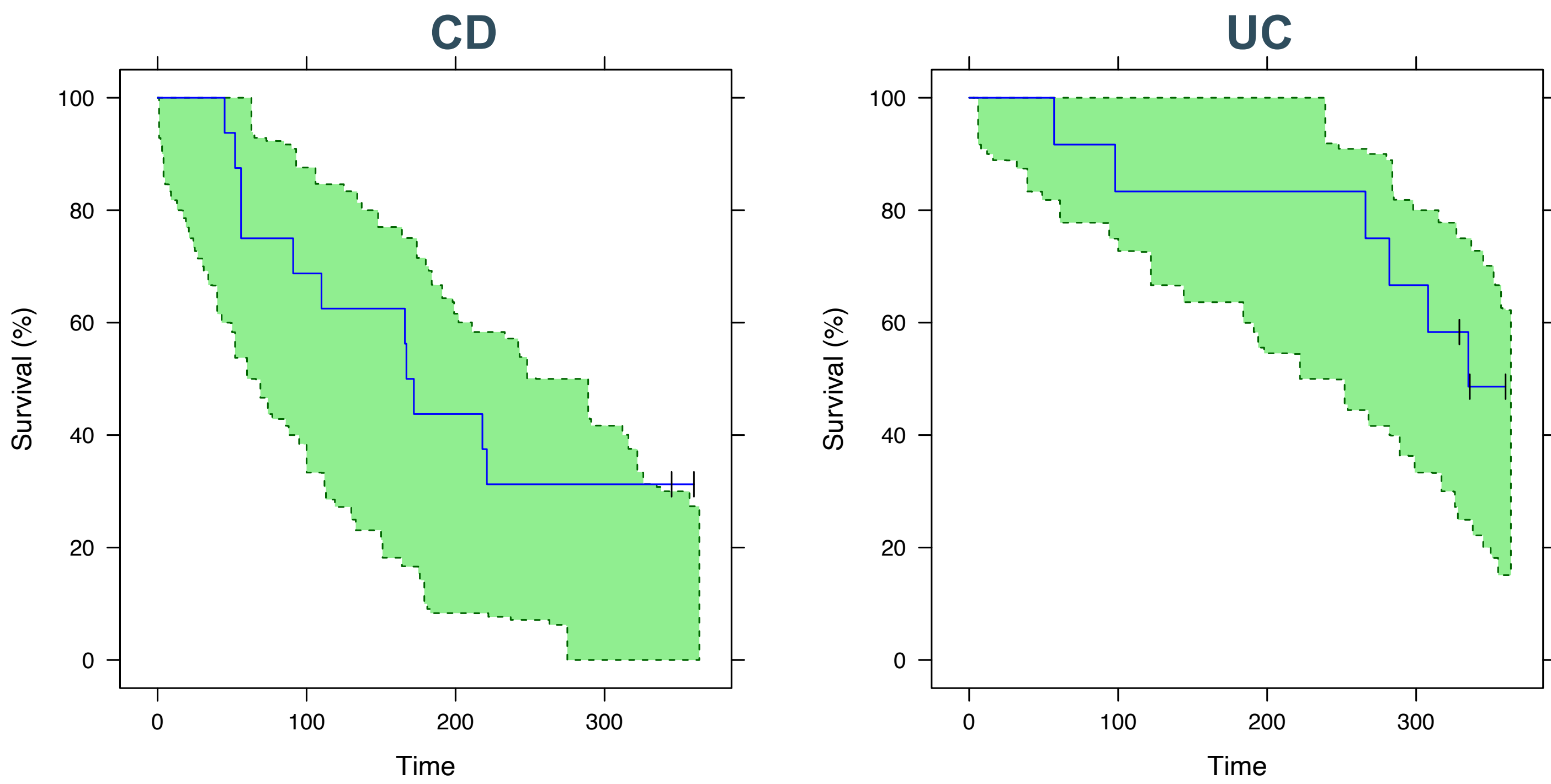


Figure 2. Kaplan–Meier curves and hazard functions of patients with CD and UC with sustained steroid-free clinical and biological remission at baseline.

- Patients with CD had an overall 12-fold higher baseline hazard of relapse than patients with UC.
- For patients with UC, the infliximab TC was inversely related to the relapse hazard risk and was included in the model using an inhibitory Emax function.
- The proportion of UC patients with sustained remission one year after interval extension was predicted to increase from 57% [95% prediction interval 54–60%] to 81% [95% PI 79–84%] with the targeted TC increasing from 5.0 to 15.0 mg/L.

CONCLUSION

- An exposure-response relationship was observed for infliximab in patients with UC but not CD.
- In patients with UC, the hazard risk increased with time, but this risk was lower when the infliximab TC increased, which supports a role for model-informed infliximab interval extension in patients with UC.

REFERENCES

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