*Journal of Crohn's and Colitis*, 2026, **20**(**3**), jjag029
https://doi.org/10.1093/ecco-jcc/jjag029
**Original Article**

# Personalized infliximab rescue therapy to maximize colectomy-free survival in patients with acute severe ulcerative colitis

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## Abstract

**Background & Aims:** Infliximab is an established rescue therapy for patients with steroid-refractory acute severe ulcerative colitis (ASUC), yet optimal dosing strategies minimizing colectomy risk remain unclear. We aimed to develop a model-informed risk stratification algorithm to identify patients at high risk of colectomy within 90 days of initiating infliximab to support personalized dosing.

**Methods:** We conducted a multicenter, retrospective population pharmacokinetics (popPK) and exposure–response study using data from patients with ASUC. A parametric time-to-event model was developed to characterize the 90-day colectomy risk. Patient characteristics and pharmacokinetic projections were evaluated as predictors. These modelling results informed the development of an algorithm for risk stratification and personalized infliximab rescue dosing.

**Results:** Seven medical centers contributed data from 72 patients with ASUC, yielding a total of 152 infliximab serum concentrations. Eleven patients underwent colectomy within 90 days. The strongest predictor of colectomy was the clearance-normalized exposure between weeks 2 and 4 (area under the concentration–time curve, $AUC_{w2\text{-}4}$ to Bayesian-forecasted infliximab clearance, CL), with an area under the receiver operating characteristic curve of 0.79 (95% confidence interval [CI], 0.52-1.00). The $AUC_{w2\text{-}4}$/CL ratio was calculated by individualizing the popPK model using the patient's body weight, baseline C-reactive protein, and infliximab concentrations. Patients with a log-transformed $AUC_{w2\text{-}4}$/CL ratio < 5.79 were classified as high risk for colectomy (sensitivity 83%, specificity 85%). Overall classification accuracy was 85% (95% CI, 74-92).

**Conclusions:** We developed a model-based dose–exposure–response framework to predict colectomy risk in ASUC. We integrated the algorithm into an interactive tool to enable individualized infliximab rescue therapy.

**Key words:** colectomy; infliximab; personalized rescue therapy.

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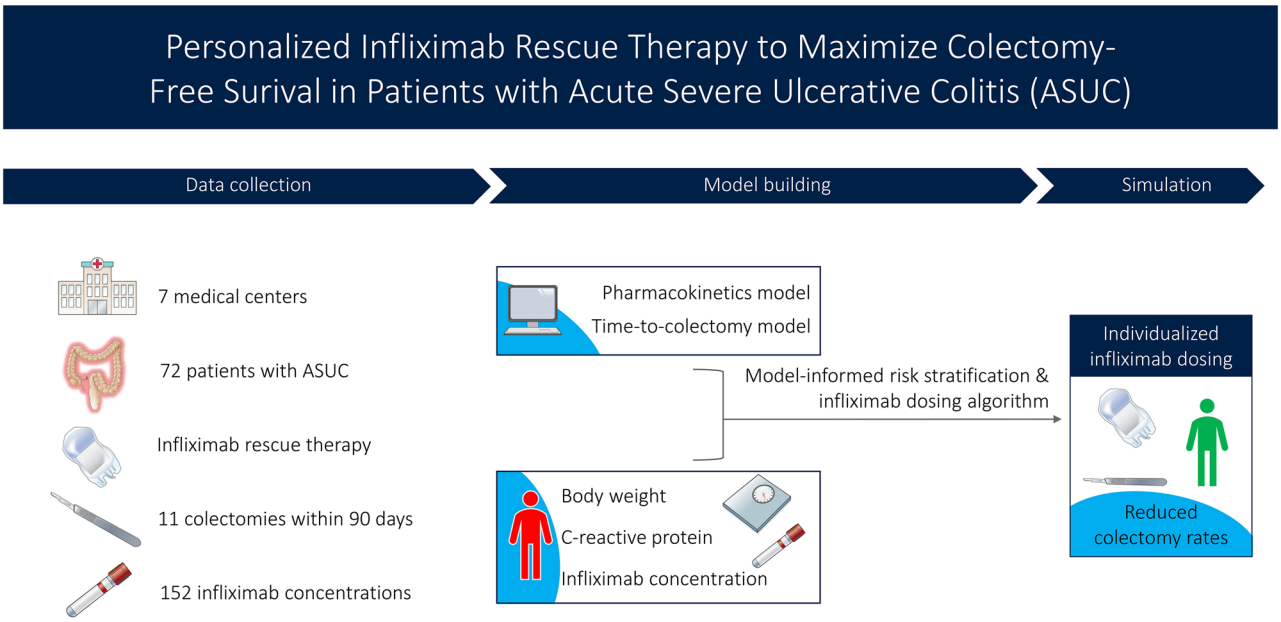
**Graphical abstract**




## 1. Introduction

Acute severe ulcerative colitis (ASUC) affects approximately one-quarter of patients with ulcerative colitis, either at initial presentation or later in the disease course.[1] ASUC represents a medical emergency with substantial morbidity. Despite advances in treatment, up to 36% of patients experience multiple episodes and around 40% ultimately require colectomy.[1] Corticosteroids are the primary treatment for ASUC, yet one in three patients fail to respond.[2,3] In such cases, infliximab emerged as the second-line treatment option.

Following the well-established general principles of the dose–exposure–response paradigm, achieving rapid and adequate infliximab exposure is essential for treatment success.[4,5] However, point-of-care therapeutic drug monitoring (TDM) of infliximab is particularly challenging in the ASUC setting. Disease-related factors such as target-mediated infliximab clearance and protein-losing enteropathy ("leaky gut") significantly alter the pharmacokinetics (PK) of infliximab.[6,7] Increased infliximab clearance results in a shorter half-life and lower trough concentrations compared to patients with less active disease.[6,7] These disease-driven changes are associated with more severe symptoms and higher colectomy rates.[8] Consequently, treating patients with ASUC with infliximab requires a specific dosing strategy that accounts for disease activity.

About 25 years ago, the first infliximab dose-finding study in steroid-refractory ASUC was conducted by Sands et al.[9] The study was terminated prematurely due to slow patient enrolment.[9] Despite the pressing medical need, the optimal dosing strategy has remained uncertain, causing the adoption of various clinical practices using intensified dosing regimens (higher doses and/or shorter intervals) to compensate for increased infliximab clearance.[10,11] Nevertheless, recent evidence from the PREDICT-UC trial suggests that intensified and accelerated infliximab rescue therapy does not improve remission or colectomy-free survival, compared to standard dosing.[12] Yes, results from the PREDICT-UC PK analysis trial show that day 3 infliximab exposure and day 7 infliximab clearance predict 3-month colectomy.[13] However, there is currently a lack of supportive evidence and a clinically actionable personalized dosing algorithm for risk stratification to address increased clearance at the point of care.

In this multicenter study, we pooled real-world clinical data from patients with steroid-refractory ASUC to develop and validate a model-informed dose–exposure–response framework. We used this model to construct a risk stratification algorithm that informs personalized infliximab rescue therapy. The algorithm has been implemented in an interactive software tool designed to support future clinical validation and maximize the success of infliximab rescue therapy in ASUC.

## 2. Materials and methods

### 2.1. Patients

We performed a multicenter, retrospective study using pooled data from patients 18 years and older hospitalized with corticosteroid-refractory ASUC diagnosed according to Truelove and Witts criteria.[14] Fifteen medical centers participating in the spECTRUM consortium—an international collaboration of TDM specialists in inflammatory bowel diseases, rheumatology, and dermatology spanning 23 countries across 5 continents—were contacted to query whether they agreed to participate and share individual-level data of patients who received infliximab as a rescue therapy as from January 1, 2013 and prior to March 1, 2023. Patients were eligible if they had not received anti-tumor necrosis factor therapy before and had at least 1 infliximab serum concentration measured within the first 14 weeks after the start of the infliximab rescue therapy.

The study was approved by the Ethics Committee Research UZ/KU Leuven (S64627), and written informed consent for the secondary use of data was obtained from participants of the original studies. We performed the study in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements including individual data protection.

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Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

### 2.2. Infliximab PK model development and evaluation

We characterized the infliximab dose–exposure relationship using population PK (popPK) modelling. Infliximab serum concentrations below the lower limit of quantification (LLOQ) and above the upper limit of quantification (ULOQ) were handled using the M3 method.[15] To address data heterogeneity across centers, we tested inter-center variability and various residual error models during model development. Stepwise covariate modelling (SCM) was performed to evaluate baseline covariate effects of body weight, body mass index (BMI), C-reactive protein (CRP), and serum albumin. Calibration of the final model was evaluated using prediction-corrected visual predictive check (pcVPC) plots ($n = 1000$ simulated replicates of the original dataset). Parameter uncertainty of the final model was evaluated using a nonparametric bootstrap ($n = 2000$ bootstrap runs). Missing covariates were handled using median imputation.

### 2.3. Time-to-colectomy model development and evaluation

We developed a parametric time-to-event model to describe time to colectomy. Exponential, Gompertz, Surge, and Weibull models have been tested as baseline hazard models. Predictors of hazard risk parameters were evaluated using SCM, in which baseline factors (body weight, BMI, CRP, and serum albumin) and infliximab exposure metrics were tested. The infliximab exposure metrics include empirical Bayes estimate (EBE)-based PK parameters—TDM-based individual clearance—and cumulative infliximab exposure across various time intervals (area under the concentration–time curve; AUC). AUC-to-clearance ratios (AUC/CL) were also considered in the covariate search. Calibration and uncertainty of the final model were evaluated using pcVPC plots and a nonparametric bootstrap. Receiver operating characteristics (ROC) curves were used to evaluate the discriminatory ability of the covariates tested in the time-to-event model.

### 2.4. Risk stratification and precision dosing algorithm

The maximum Youden *J* statistic was used to classify patients into low-risk and high-risk groups. The popPK and time-to-event models were used to calculate the optimal infliximab dosing regimen for each individual, required to reach a specified target probability of colectomy corresponding to the Youden *J* statistic.

### 2.5. Interactive risk stratification and precision dosing tool

An interactive risk stratification and precision dosing tool based on the final popPK and time-to-event model for colectomy was developed. The *Shiny* package (version 1.7.4) in R was used for developing the web application, which we published as an open-source application. In compliance with Regulation (EU) 2017/745, free access to the web application is provided under a license agreement for non-commercial research purposes.

## 3. Results

### 3.1. Patient characteristics

Data from 72 patients with ASUC were contributed by seven medical centers, providing a total of 152 infliximab concentrations. The step-by-step inclusion process that yielded this final cohort is depicted in Figure S1. The median [IQR] infliximab serum concentration was 6.7 [3.9-10.9] mg/L. Eleven patients (15%) underwent colectomy within the first 90 days (median time to colectomy 32 [range 11-84] days). At baseline, disease activity assessed by the Mayo endoscopic subscore was predominantly severe (81%), with the remainder classified as moderate (19%). The median first infliximab dose was 9.9 mg/kg (range 3.8-15.0), and patients received a median of 3 infusions (range 1-7) over a dosing period spanning a median of 7 days (IQR 0-42 days). Anti-infliximab antibodies were detected in 6 of 152 samples (4%). A detailed overview of the baseline characteristics, on-treatment characteristics, and outcomes is provided in Table 1.

### 3.2. Infliximab PK

The infliximab popPK was best described using a one-compartmental model with first-order elimination (Table 2, Supplementary Code). A higher body weight was associated with an increased infliximab clearance and volume of distribution (allometric scaling). A lower CRP at baseline was associated with a decreased clearance. The median [IQR] estimated a posteriori (ie, TDM-based) infliximab clearance in the population was 0.51 [0.32-0.73] L/day. The median [IQR] estimated infliximab half-life was 18.1 [12.9-28.7] days. Calibration of the final popPK model was adequate (Figure S2). Comprehensive goodness-of-fit diagnostics—encompassing observed versus predicted concentrations, residual plots, and individual concentration–time profiles—are provided in Figures S3 and S4.

### 3.3. Time-to-colectomy model

Information on colectomy was available for 71 patients. The hazard risk for colectomy was best described with a Weibull hazard function. Calibration of the final predictive model was adequate (Figure S5). The hazard risk for colectomy decreased as the week 2-4 AUC-to-infliximab clearance ratio ($AUC_{w2\text{-}4}$/CL) increased (Table 2).

Because the ratio of $AUC_{w2\text{-}4}$/CL predicted colectomy after week 4, 5 patients who experienced colectomy before week 4 have been excluded when internally evaluating the predictive performance of $AUC_{w2\text{-}4}$/CL. As compared to $AUC_{w2\text{-}4}$ and CL alone, $AUC_{w2\text{-}4}$/CL improved discrimination with an increase in area under the ROC curve (AUROC) from 0.76 (95% CI, 0.46-1.00) ($AUC_{w2\text{-}4}$) and 0.71 (95% CI, 0.44-0.97) (CL) to 0.79 (95% CI, 0.52-1.00).

### 3.4. Colectomy risk stratification algorithm

The logarithmic ratio of $AUC_{w2\text{-}4}$/CL of 5.79 was used to discriminate between patients at low and high risk for colectomy (sensitivity 83%, specificity 85%) (Figure 1, Figure S6). Patients with a logarithmic ratio of $AUC_{w2\text{-}4}$/CL below 5.79 were classified as high-risk, with ratio values ranging from 1.11 to 5.79 (14/66 patients; 21%). Patients with a logarithmic ratio of $AUC_{w2\text{-}4}$/CL of 5.79 and higher were classified as low-risk, with ratio values ranging from 5.79 to 8.84 (52/66 patients; 79%). The colectomy rate was 36% (5/14 patients) and 2% (1/52 patients) in the high- and low-risk group, respectively.

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**Table 1.** Summary of baseline, treatment, and outcome characteristics of studied patients ($N = 72$).

| Characteristic | Value |
|---|---|
| **Baseline demographics and phenotype** | |
| Age, years, median [IQR] | 34 [22-48] |
| Sex, female, n (%) | 18 (35) |
| Body weight[a], kg, median [IQR] | 63 [56-75] |
| Body mass index[b], kg/m$^2$, median [IQR] | 22 [19-26] |
| Active smoker:previous smoker:non-smoker, n (%) | 1 (3):9 (23):29 (74) |
| **Disease phenotype at baseline** | |
| Disease duration, years, median [IQR] | 3 [1-7] |
| Bowel movements, day, median [IQR] | 10 [8-15] |
| Disease extension, extensive:left sided, *n* (%) | 23 (70):10 (30) |
| Mayo endoscopic subscore, 3 (severe disease):2 (moderate disease), *n* (%) | 30 (81):7 (19) |
| **Serology at baseline** | |
| C-reactive protein[c], mg/L, median [IQR] | 30 [7-82] |
| Serum albumin[d], g/L, median [IQR] | 31 [27-38] |
| Hemoglobin, g/dL, median [IQR] | 12.5 [10.4-13.0] |
| White blood cell count, G/L, median [IQR] | 11 [8-14] |
| **Previous medication** | |
| Previous exposure to aminosalicylates, *n* (%) | 32 (74) |
| Previous exposure to immunomodulators, *n* (%) | 14 (33) |
| **Rescue therapy** | |
| Number of infliximab infusions per patient[e], *n*, median [range] | 3 [1-7] |
| Follow-up of the dosing period, days, median [IQR] | 7 [0-42] |
| First infliximab dose, mg/kg, median [range] | 9.9 [3.8-15.0] |
| Sampling time since the most recent infusion, days, median [IQR] | 26 [11-42] |
| Number of infliximab concentration measurements per patient[f], *n*, median [range] | 2 [1-5] |
| Number of patients with 1:2:3:4:5 infliximab concentrations, *n* (%) | 33 (46):18 (25):7 (10):8 (11):6 (8) |
| Exposure to thiopurine[g], *n* (%) | 14 (47) |
| Concomitant methotrexate[h], *n* (%) | 0 (0) |
| Concomitant aminosalicylates[i], *n* (%) | 3 (30) |
| Concomitant steroids, despite steroid refractoriness[j], *n* (%) | 13 (87) |
| Anti-infliximab antibodies, *n* (%) | 6 (4) |
| **Treatment outcome** | |
| Number of patients with colectomy performed within 90 days, *n* (%) | 11 (15) |
| Time to colectomy, days, median [range] | 32 [11-84] |

All percentages are based only on non-missing data.
[a]Body weight was missing for two patients.
[b]Body mass index was missing for 29 patients.
[c]C-reactive protein was missing for three patients.
[d]Serum albumin was missing for four patients.
[e]Schedules did not necessarily follow classical induction (eg, 0-2-6 weeks); timing was adapted by each center based on local expertise and patient response.
[f]Including 11 below and 56 above the limit of quantification (44% censored).
[g]One patient received thiopurines solely prior to the start of infliximab therapy, without concurrent administration.
[h]Methotrexate was missing for 42 patients.
[i]Aminosalicylates was missing for 62 patients.
[j]Concomitant steroids was missing for 57 patients.
Abbreviation: IQR, interquartile range.

Classification accuracy was 85% (95% CI, 74-92), and the associated Fisher's exact test *P*-value was 0.001. The effectiveness of the risk stratification algorithm is presented in Figure 2. The model-simulated proportion of patients without colectomy (%) aligns well with the observed proportion in the low-risk phenotype (Figure 2A) and the high-risk phenotype (Figure 2B).

### 3.5. Interactive precision dosing tool

We developed an evidence-based, interactive risk stratification and precision dosing tool to guide individualized infliximab rescue therapy for patients with ASUC. Input variables include baseline body weight and CRP, and infliximab serum concentration(s). By combining infliximab TDM and Bayesian forecasting, our tool performs individual patients' dosing simulations, targeting a user-defined 90-day colectomy risk (default 20%, corresponding to a logarithmic ratio of $AUC_{w2\text{-}4}$/CL of 5.79) (Figure 3). Additional details and user instructions are provided in the Supplementary Results. A snapshot of the tool is shown in Figure 4. Free access to the web application is provided at https://gitlab.kuleuven.be/pharmacometrics.

## 4. Discussion

The present work introduces a model-based algorithm to inform infliximab dosing in patients with ASUC. We demonstrated that clearance-normalized infliximab exposure best predicts time-to-colectomy. This is the first dose–exposure–response study of infliximab in patients with ASUC. Our findings pave the way towards personalized infliximab treatment in a highly vulnerable group of patients.

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**Table 2.** Population pharmacokinetics and time-to-event model parameter estimates.

| | Final model estimates (%RSE) [%shrinkage] | Bootstrap median [95% CI] |
|---|---|---|
| **Population pharmacokinetics model** | | |
| **Typical values** | | |
| **CL (L/d)** | 0.49 (13) | 0.49 [0.33-0.63] |
| **V (L)** | 13.2 (16.8) | 12.9 [9.0-18.1] |
| **Covariate effects** | | |
| **Baseline body weight on CL** | 0.75 (fixed) | 0.75 (fixed) |
| **Baseline body weight on V** | 1 (fixed) | 1 (fixed) |
| **Baseline C-reactive protein on CL** | 0.56 (32) | 0.64 [0.21-1.56] |
| **Interindividual variability** | | |
| **On CL (%CV)** | 72.1 (19) [32] | 68.6 [28.5-108.0] |
| **On V (%CV)** | 87.8 (37) [41] | 90.0 [3.9-207.7] |
| **Residual variability** | | |
| **Proportional error (%)** | 44 (10) | 43.5 [31.7-52.8] |
| **Time-to-event model** | | |
| **Typical values** | | |
| **Baseline hazard** | 0.001 (135)[a] | 0.001 [0.000-0.006] |
| **Shape parameter** | 1.08 (26) | 1.10 [0.70-2.29] |
| **Covariate effects** | | |
| **$AUC_{w2-4}$/CL on baseline hazard** | −0.56 (22) | −0.56 [−1.00 to −0.13] |

The number of successful bootstrap runs is 2000 out of 2000 attempts.
[a]RSE was back-calculated via the delta method with baseline hazard = $10^{\theta}$ where $\theta = -2.95$ (19.8%).
Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation calculated as CV = $\sqrt{e^{\omega^2}-1}$ with $\omega^2$ being the interindividual variability; RSE, relative standard error (for random effects and residual variability reported on the approximate standard deviation scale; standard error/variance estimate/2).

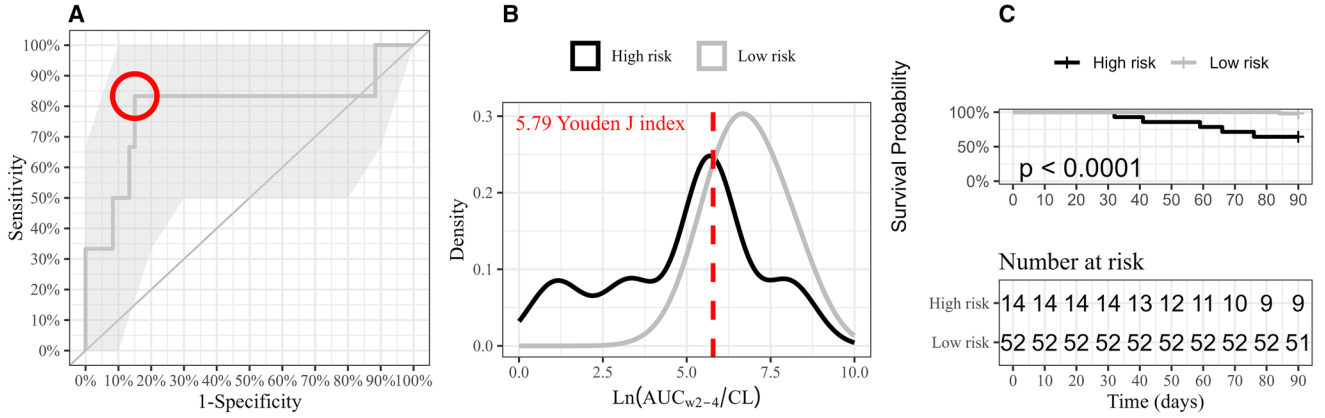


**Figure 1.** Discriminatory performance of the colectomy risk stratification algorithm. (A) Receiver operating characteristic curve representing the ability of clearance-normalized infliximab exposure to discriminate between patients with a high and a low colectomy risk. The 95% nonparametric confidence interval is represented by the grey shaded area. (B) Density plot representing the distributions of clearance-normalized infliximab exposure for patients with a high colectomy risk (black line) and a low colectomy risk (grey line). The optimal threshold derived from the youden *J* index is represented by a red circle and a red dashed line in panels A and B, respectively. (C) Kaplan–Meier estimates of the time to colectomy for patients with a high colectomy risk (black line) and a low colectomy risk (gray line). The *P*-value is calculated using the log-rank test.

ASUC is a severe medical condition of low incidence, and PK data are scarce. Through an international collaborative effort, we were able to pool PK data of 72 patients with ASUC, allowing us to build a popPK model, describing the relation between infliximab dosing and infliximab exposure. We identified CRP as a statistically significant covariate in the popPK model. Serum albumin is a more commonly withheld covariate in popPK models of monoclonal antibodies, possibly explained by its non-competitive shared FcRn-mediated recycling pathway. However, high correlation between CRP and serum albumin and a lack of standardization of serum albumin quantification across medical centers may explain why CRP outperformed serum albumin in our study. Moreover, we log-transformed CRP data, which is not commonly done, yet strongly advised, to account for its well-described non-normal distribution.[16] This resulted in a better model fit and more precise parameter estimates compared to models based on the untransformed CRP distribution and serum albumin (Table S1).

We combined infliximab exposure ($AUC_{w2-4}$) and infliximab PK (clearance) to predict colectomy within 90 days from the start of infliximab rescue therapy. The $AUC_{w2-4}$/CL ratio best predicted time-to-colectomy and was the sole covariate retained in our time-to-event model. Two patients may have equally high overall exposure, resulting in the same $AUC_{w2-4}$, yet one may have a higher clearance—due to higher target-mediated drug disposition and protein-losing enteropathy—and thus an increased risk of colectomy. Similarly, 2 patients may have the same infliximab clearance, yet 1 may have a lower infliximab

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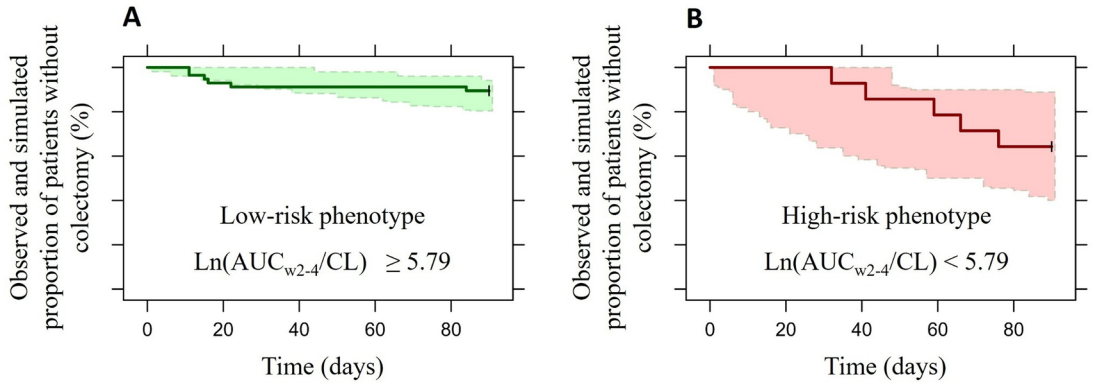


**Figure 2.** Predictive performance of the colectomy risk stratification algorithm. Kaplan–Meier visual predictive checks for the final time-to-colectomy model for patients with a low-risk phenotype (A) and a high-risk phenotype (B). The solid line represents the study data using Kaplan–Meier estimators, and the shaded area represents the 95% prediction interval of the final time-to-colectomy model. Risk stratification is based on the clearance-normalized infliximab exposure (ln($AUC_{w2-4}$/CL) threshold of 5.79 (youden *J* index).

exposure—due to insufficient dosing—and consequently will be at a higher risk of colectomy. Unlike for small molecules, drug clearance of monoclonal antibodies serves as a biomarker for disease severity in inflammatory bowel disease.[6–8] The $AUC_{w2-4}$/CL ratio combines both exposure (modifiable risk factor; exposure drives disease activity) and PK (unmodifiable risk factor; disease activity drives exposure), thereby accounting for the bidirectional relation between infliximab PK and pharmacodynamics.[17] Moreover, the $AUC_{w2-4}$/CL ratio may also remind us of the pharmacokinetic—pharmacodynamic (PKPD) index used to guide dosing of antimicrobials. Yet, not all patients will benefit from higher exposure, especially those who are inherently non-responsive to anti-TNF therapy. Future studies should focus on identifying patients with early therapy failure and developing alternative treatment strategies.

Unlike Battat et al., we did not identify baseline infliximab clearance as a predictor for colectomy. Battat et al. worked with the a priori estimated clearance, solely relying on baseline serum albumin and patient sex. Consequently, their clearance estimates are highly correlated with baseline serum albumin (Figure S7A). Li Wai Suen et al. identified day 7 infliximab clearance as a predictor for 3-month colectomy, estimating individual patient clearance using a previously published popPK model for ulcerative colitis, while keeping other PK parameters fixed. Incorporating observed data to refine an a priori popPK model is a valuable approach to better estimate a patient's true drug clearance. However, based on general PK principles, infliximab concentrations measured as early as days 5 and 7 may not provide sufficient information to reliably re-estimate true clearance, suggesting that further validation of this method is needed.

In contrast, our a posteriori (ie, TDM-based) clearance estimates are mainly informed by infliximab serum concentrations, alongside baseline CRP and body weight using a dedicated in-house developed popPK model in patients with ASUC (Figure S7C). In our study, a posteriori clearance, as such, did not have sufficient statistical power to predict colectomy alone. However, the clearance-normalized overall exposure between weeks 2 to 4 ($AUC_{w2-4}$/CL), was the strongest predictor of colectomy in our study (Table S2). By estimating CL *a posteriori*, we achieve a more accurate characterization than an a priori estimate could provide; however, this advantage comes with the limitation that it requires observed data and therefore cannot be obtained at baseline. Consequently, our workflow only applies to patients with a TDM sample available before experiencing colectomy. Our findings reinforce the observations from the PREDICT-UC trial, suggesting a combined exposure–clearance parameter. This further supports the reliability of clearance as a predictive biomarker in patients with ASUC. For a detailed comparison between Battat et al., Li Wai Suen et al., and the present study, we kindly refer to Table S3.

Personalized medicine approaches are increasingly being employed throughout clinical drug development. Lately, increasing focus has been given to model-informed dose optimization strategies such as model-informed precision dosing (MIPD) of infliximab.[18,19] Identifying and establishing early predictors of treatment outcome is an important asset to support dose optimization and early decision-making. Dedicated MIPD trials in patients with ASUC, such as the TITRATE trial,[20] did not meet statistical significance. However, their pioneering work paves the way for the design and execution of new studies. Historically, infliximab exposure has been used to guide dose selection, and the introduction of rapid assays has tremendously improved the traditional monitoring. In recent years, their availability has increased while costs have decreased, making them more accessible. Measuring drug exposure in combination with our developed popPK model enables Bayesian forecasting and the estimation of an individual patient's clearance and subsequent calculation of an individual patient's AUC. Our developed software tool streamlines this process, providing an easy and efficient approach for risk stratification by relying on available TDM data.

The present work has some limitations. First, the secondary use of multicenter, real-world data from a low-prevalence disease prevented control over the sampling design, resulting in sparse and unbalanced sampling. Consequently, we were unable to capture the biphasic terminal elimination of infliximab or account for clearance changes over time (due to disease progression or recovery) using inter-occasion variability and/or time-varying covariates. Additionally, a popPK approach presumes that pharmacokinetic parameters remain constant over time, which may not always hold true in the setting of ASUC. Despite heterogeneity in sampling schedules and assay methods, the gold standard nonlinear mixed effects modelling approach showed to be fit-for-purpose. Between-center variability was explicitly tested and found negligible. Model

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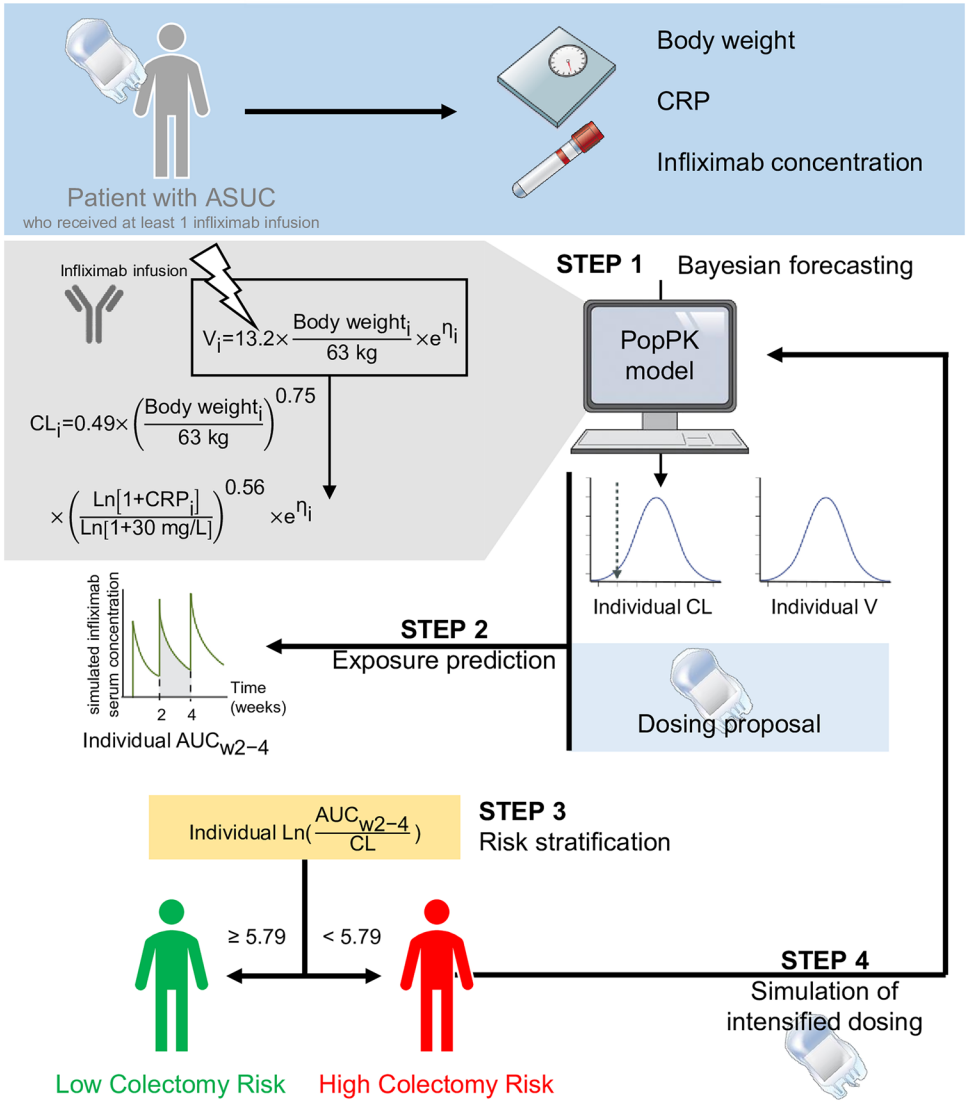


**Figure 3.** Schematic representation of the colectomy risk stratification algorithm. (Step 1) The infliximab clearance (CL) and volume of distribution (V) are estimated using Bayesian forecasting by leveraging the population pharmacokinetics (popPK) model and three patient-specific characteristics: (1) body weight, (2) C-reactive protein (CRP) at the start of infliximab rescue therapy, and (3) an infliximab concentration obtained in the first 2 weeks of infliximab rescue therapy. (Step 2) The overall infliximab exposure between weeks 2 and 4 (ie, area under the infliximab concentration–time curve between weeks 2 and 4, $AUC_{w2-4}$) is calculated for a proposal dosing regimen by leveraging the popPK model. (Step 3) The clearance-normalized infliximab exposure is calculated as the natural logarithm of the $AUC_{w2-4}$-to-clearance ratio ($\ln[AUC_{w2-4}/CL]$). A threshold of 5.79 distinguishes between patients at low risk for colectomy (≥5.79), who have relatively high infliximab exposure considering their infliximab clearance, and patients at high risk for colectomy (<5.79), who have relatively low infliximab exposure considering their infliximab clearance. (Step 4) If a patient is at high risk for colectomy in Step 3, intensified infliximab dosing schedules can be simulated in Step 2, thereby enabling personalized infliximab dosing at week 2 and potentially reducing the patient's colectomy risk.

robustness was confirmed through bootstrap validation and pcVPC diagnostics, supporting reproducibility despite heterogeneity. Future studies should aim to collect more samples, along with time-varying covariate measurements, to better characterize disease dynamics. Additionally, no histologic data were available, limiting our ability to correlate mucosal pathology with PK and outcome data. We relied on Mayo endoscopic subscores as a surrogate for disease severity. In this regard, results from dedicated infliximab PK studies in patients with ASUC, such as the IGNITE trial (EU CT 2023–503509-12-00), are awaited to provide further insights and address these limitations. Second, the time-to-colectomy model includes uncertainty regarding the (clinically indicated) time point of colectomy. The day of a colectomy is not purely driven by disease activity but also depends on clinical workflows and preferences of the patient. However, shifts of a few days only have a minor influence, considering the 90-day follow-up period. Additional uncertainty stems from the low number of events, bearing the risk of overfitting and issues with model stability. As additional data accrue, model performance should be reassessed and, if warranted, the model updated and recalibrated to refine parameter estimates. The low number of events was also reflected in the wide confidence intervals around the AUROC using the identified predictor (Figure 1). Although the threshold reflects the optimal mathematical solution, its clinical applicability must be weighed carefully before it is used for

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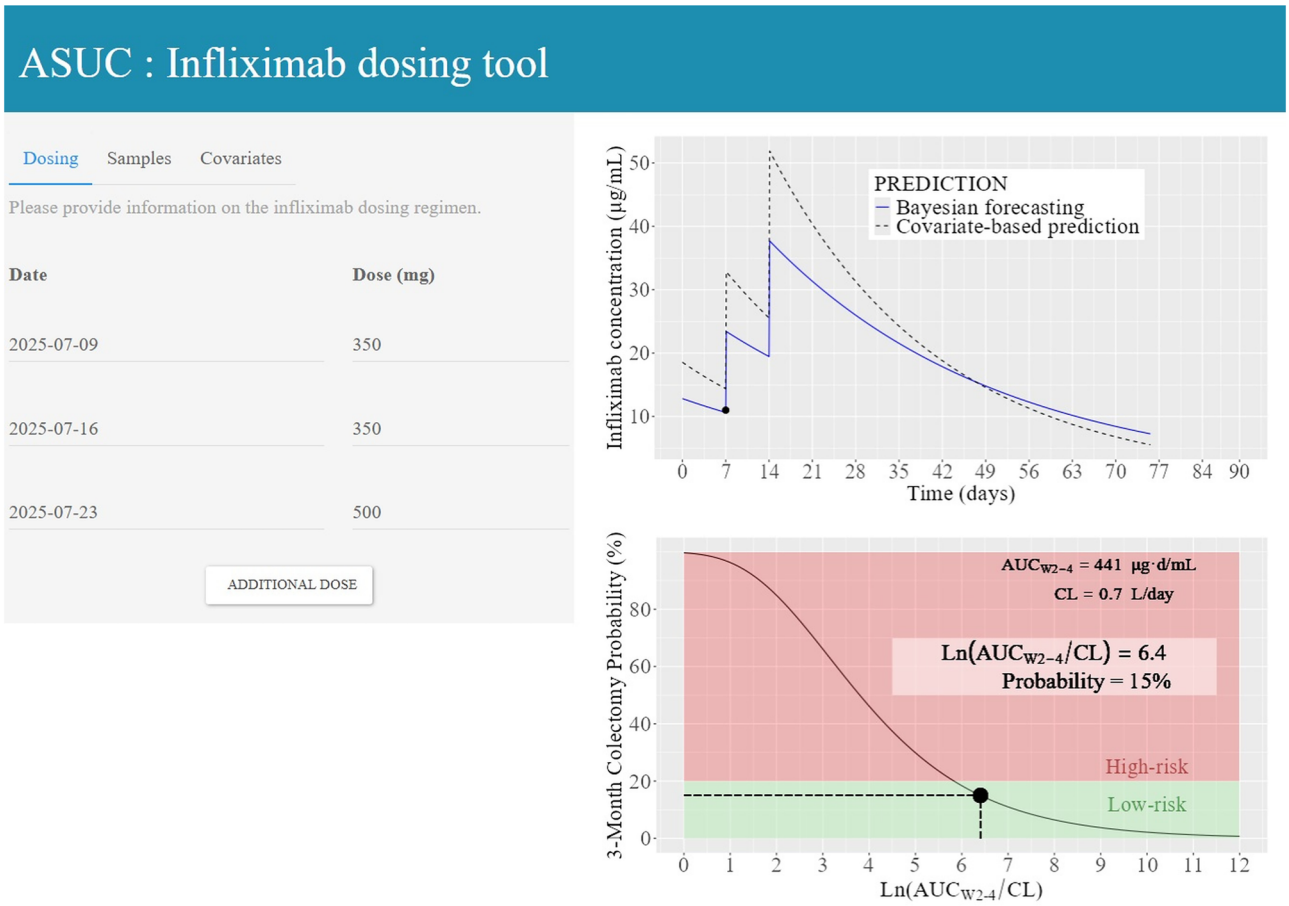


**Figure 4.** Interactive risk stratification and infliximab dosing tool. The tool consists of three tab panels that allow the user to provide patient-specific information: the infliximab dosing regimen ("dosing" tab), the infliximab concentration(s) measured in serum samples ("samples" tab), and the patient's body weight and C-reactive protein (CRP) at the start of infliximab rescue therapy ("covariates" tab). This information is used in combination with the infliximab population pharmacokinetics model to predict the patient's infliximab pharmacokinetic parameters (*a posteriori* Bayesian forecasting, solid line; a priori covariate-based prediction; dashed line), visualize the predicted infliximab concentration–time course under the provided dosing regimen, and the probability of colectomy within 90 days after start of infliximab rescue therapy.

decision-making. Third, we did not externally validate our risk stratification and dosing algorithm. We invite the scientific community to make use of our proposed workflow for external validation. Therefore, we provide access to model code and supporting resources. The developed software tool facilitates accessibility and clinical validation.

To conclude, we performed the first model-based dose–exposure–response analysis of infliximab in patients with ASUC. We provide supportive evidence for clearance monitoring of infliximab in patients with ASUC. We demonstrated methodological advances in predictive modelling that enable truly personalized infliximab dosing. This novel approach to precision medicine holds the potential to pave the way for more effective, personalized infliximab dosing.

## Acknowledgments

Parts of this work were presented at American College of Gastroenterology (ACG) 2024 in Philadelphia, International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) 2025 in Singapore, Digestive Disease Week (DDW) 2025 in San Diego, European Crohn's and Colitis Organisation (ECCO) 2025 in Berlin, Population Approach Group Europe (PAGE) 2025 in Thessaloniki.

## Author contributions

E. Niyigena and Y. Hoffert shared first co-authorship.
E. Dreesen is considered guarantor of the article.

Conceptualization: Emmanuel Niyigena, Yannick Hoffert, Erwin Dreesen. Data curation: Emmanuel Niyigena, Zhigang Wang. Formal analysis: Emmanuel Niyigena. Funding acquisition: Yannick Hoffert, Zhigang Wang, Erwin Dreesen. Investigation: Emmanuel Niyigena. Methodology: Emmanuel Niyigena, Yannick Hoffert. Project administration: Erwin Dreesen. Resources: Waqqas Afif, Alessandro Pedicelli, Xavier Roblin, Jurij Hanžel, Konstantinos Papamichael, Taku Kobayashi, Laure Elens, Marc Ferrante, Bram Verstockt, Séverine Vermeire, Niels Vande Casteele, Robert Battat, Erwin Dreesen. Software: Emmanuel Niyigena, Yannick Hoffert. Supervision: Erwin Dreesen. Validation: Yannick Hoffert. Visualization: Emmanuel Niyigena, Yannick Hoffert. Writing–original draft: Emmanuel Niyigena, Yannick Hoffert. Writing–review and editing: All authors. All authors approved the final version of the article, including the authorship list.

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## Supplementary material

Supplementary material is available at *ECCO-JCC* online.

## Funding

Y.H. is supported by a doctoral research grant from the Research Foundation—Flanders, Belgium (grant number 1SHAA24N). Z.W. is supported by a doctoral research grant from the Research Foundation—Flanders, Belgium (grant number 1SF2924N). M.F. is a senior clinical investigator of the Research Foundation Flanders (FWO). B.V. is supported by the Clinical Research Fund (KOOR) at the University Hospitals Leuven and the Research Council at KU Leuven.

## Conflicts of interest

W.A. received speakers fees, served as an advisory board member, and a clinical investigator for Abbvie, Amgen, BMS, Eli-Lilly, Janssen, Merck, Novartis, Pfizer, Sandoz, Sanofi, Takeda. X.R. received speakers, consultancy and moderator fees from Mayoli-spindler, Janssen, AbbVie, Takeda, Ferring, Celltrion, Pfizer; Advisory boards: Celltrion, AbbVie, Lilly, Janssen, Takeda. J.H. received speaker's fees from AbbVie, Eli Lilly, Janssen, Takeda, and consulting fees from Alimentiv Inc. K.P. received lecture/speaker fees from Physicians Education Resource LLC, Grifols and Prometheus Laboratories Inc; scientific advisory board fees from Procise Dx Inc, Scipher Medicine Corporation and Celltrion Inc.; and consultancy fees from Prometheus Laboratories Inc. T.K. served as an advisory board member, consultant, or speaker for AbbVie, Alfresa Pharma, Alimentiv, Bristol Myers Squibb, Celltrion, Covidien, EA Pharma, Eli Lilly, Ferring Pharmaceuticals, Galapagos, Gilead Sciences, Janssen Pharmaceuticals, JIMRO, Kissei Pharmaceutical, Kyorin Pharmaceutical, Mitsubishi Tanabe Pharma, MSD, Mochida Pharmaceutical, Nippon Kayaku, Pfizer, Takeda, and Zeria Pharmaceutical, and has received research funding from AbbVie, Alfresa Pharma, Bristol Myers Squibb, EA Pharma, Gilead Sciences, Kyorin Pharmaceutical, Mochida Pharmaceutical, Nippon Kayaku, Otsuka Holdings, Pfizer, Sekisui Medical, Samsung, Takeda, and Zeria Pharmaceutical. M.F. reports to have received research grants from AbbVie, EG Pharma, Janssen, Pfizer, Takeda and Viatris; consultancy fees from AbbVie, AgomAb Therapeutics, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Janssen-Cilag, MRM Health, Merck Sharp and Dohme, Pfizer, Takeda and ThermoFisher; and speakers' fees from AbbVie, Biogen, Boehringer Ingelheim, Dr Falk Pharma, Ferring, Janssen-Cilag, Merck Sharp and Dohme, Pfizer, Takeda, Truvion Healthcare and Viatris. B.V. received research support from AbbVie, Biora Therapeutics, Landos, Pfizer, Sossei Heptares, and Takeda; speaker fees from Abbvie, Biogen, Bristol Myers Squibb, Celltrion, Chiesi, Eli Lily, Falk, Ferring, Galapagos, Johnson and Johnson, MSD, Pfizer, R-Biopharm, Sandoz, Takeda, Tillots Pharma, Truvion, and Viatris; consultancy fees from Abbvie, Alfasigma, Alimentiv, Applied Strategic, AstraZeneca, Atheneum, BenevolentAI, Biora Therapeutics, Boxer Capital, Bristol Myers Squibb, Eli Lily, Galapagos, Guidepont, Landos, Merck, Mylan, Nxera, Inotrem, Ipsos, Johnson and Johnson, Pfizer, Progenity, Sandoz, Sanofi, Santa Ana Bio, Sapphire Therapeutics, Sosei Heptares, Takeda, Tillots Pharma, and Viatris; and holds stock options from Vagustim. S.V. received grants from AbbVie, J&J, Pfizer, Galapagos, and Takeda; consulting and/or speaking fees from AbbVie, Abivax, AbolerIS Pharma, AgomAb, Alimentiv, Arena Pharmaceuticals, AstraZeneca, Avaxia, BMS, Boehringer Ingelheim, Celgene, CVasThera, Dr Falk Pharma, Ferring, Galapagos, Genentech-Roche, Gilead, GSK, Hospira, Imidomics, Janssen, J&J, Lilly, Materia Prima, MiroBio, Morphic, MRM Health, Mundipharma, MSD, Pfizer, Prodigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Surrozen, Takeda, Theravance, Tillots Pharma AG and Zealand Pharma. N.V.C. received research grants from R-Biopharm and personal fees from AcelaBio, Alimentiv, Pfizer, ProciseDX, Prometheus Biosciences, Spyre Therapeutics, and is an employee of Mirador Therapeutics. R.B. received speaker/consulting/moderator fees from Bristol Myers Squibb, Janssen, AbbVie, Takeda, Ferring, Celltrion, Pfizer; Advisory boards: Celltrion, AbbVie, Pfizer, Lilly, Janssen, Bristol Myers Squibb, Takeda. E.D. received consultancy fees from Alimentiv and argenx, lecture fees from Celltrion and Galapagos, and financial support from Celltrion, Janssen, Pfizer, Prometheus, R-Biopharm, and Sandoz, outside the submitted work, with all honoraria/fees being paid to KU Leuven and not to any personal account of Erwin Dreesen. The remaining authors declare no conflicts of interest.

## Ethics statement

The Ethics Committee Research (EC Research) of University Hospitals Leuven (UZ Leuven) approved the study (S64627). Written informed consent for the secondary use of data of prospectively collected data was obtained from participants of the original studies in compliance with the approval of the (local) Ethics Committees.

## Data availability statement

The individual participant data underlying the reported results were provided by collaborating researchers and are not publicly available due to privacy or institutional restrictions. Access to the data may be granted upon reasonable request and with permission from the original data custodians. NONMEM model code that supports the findings of this study is included within this paper and its Supplemental Material files.

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