

Disease activity guided tapering of rituximab in clinical practice: a retrospective cohort study of rheumatoid arthritis patients.

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Background: We investigated the effect of disease activity-guided dose optimization (DAGDO) of rituximab on disease activity and rituximab dose in rheumatoid arthritis (RA) patients.

Methods: A retrospective cohort was conducted of RA patients who used rituximab between April 2012 and February 2022, were eligible for DAGDO and had ≥ 2 Disease Activity Score 28-joint count CRP (DAS28-CRP) measurements available during follow-up. We identified three treatment periods: 1) full dose rituximab continuation period, 2) rituximab DAGDO period, and 3) stable rituximab dose after DAGDO. Primary outcome was the difference in mean DAS28-CRP between the three treatment periods. This was analysed using a linear mixed-model with a random intercept, corrected for potential confounders. The mean percentage of the rituximab Daily Defined Dose (%DDD) was calculated as secondary outcome, with 1000mg/6months as 100% reference.

Results: 387 RA patients were included in the cohort. Median follow-up time was 46 months (IQR: 25-78) with a mean of 9 disease activity measurements (SD: 6) per patient. 299 patients attempted DAGDO during follow-up and therefore entered period 2 at least once, of whom 226 also entered period 3. The mean DAS28-CRP was 2.37 (95% CI: 2.29, 2.44) for period 1, 2.32 (95% CI: 2.24, 2.40) for period 2, and 2.27 (95% CI: 2.18, 2.36) for period 3, the latter significantly lower compared to period 1 ($p=0.022$). The mean %DDD for the three time periods was 111% for the continuation period, 64% in the DAGDO period and 71% in the period with stable rituximab dose after DAGDO.

Conclusion: This relatively large retrospective cohort study shows that DAGDO of rituximab has no negative effects on disease activity, and leads to relevant dose reduction in RA patients doing well on full dose rituximab.

Conflicts of interest to disclose: We declare no competing interests

Disentangling variation in quality of care: a systematic review

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Introduction: Much effort is being put in mitigating unwarranted variation in quality of care. Appropriately targeting these efforts requires information about the 'level' (e.g., patient, physician, hospital) to which observed variation can be attributed. This study aims to synthesize the results of quantitative studies analyzing variation in quality indicators at multiple levels, to determine at which level variation is most existing, and to identify which type of quality indicators show most variation.

Methods: Embase, Medline, Web of Science, Cochrane, and Google Scholar were systematically searched from January 2010-February 2022. We included studies that reported a measure of level-specific variation in quality relative to total variation, such as the intraclass correlation coefficient (ICC).

Results: Of 5360 studies reviewed, 28 studies met the inclusion criteria. Across included studies, case-mix adjusted variation was studied for multiple diseases using 88 indicators in total. Analyzed indicators pertained to intermediate clinical outcomes (N=49), final clinical outcomes (N=20), processes of care (N=6), patient-reported experiences (N=9) and patient-reported outcomes (N=3). All studies reported an estimate of between-hospital variation (N= 88 indicators), with 5 studies also analyzing variation at the physician-level (N=32 indicators). Variation that could be partitioned to hospitals (mean ICC=5.3%, range across indicators 0%-73%) was generally higher compared to variation partitioned to physicians (mean ICC=2.7%, range 0.1%-12.7%). Attributed level-specific variation was highest for process-indicators (mean ICC=25%; range 3%-73%), followed by intermediate clinical outcome indicators (mean ICC=4.9%; range 0.09%-39.7%).

Conclusion: Although some variation in quality indicators was attributed to the hospital or physician level to a significant degree, the proportion is often small relative to residual (patient-level) variation. Variation reduction strategies aimed at care providers only have potential impact if there is sufficient variation at that level, after adequate adjustment for patient characteristics. This is more often the case for indicators that can be influenced, i.e. process indicators.

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Prediction models for hospitalization and length of stay in patients with chronic kidney disease: a systematic review and external validation study

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Introduction: Chronic kidney disease (CKD) is a global cause of mortality and quality-of-life reduction. Prognostic prediction models (PPMs) in CKD mainly focus on disease progression and mortality, although CKD patients have reported to also wish for information on hospitalizations. Therefore, we aimed to identify and validate all currently available hospitalization/length-of-stay (LoS) PPMs in CKD patients and to develop a new PPM if valid PPMs were not identified.

Methods: We performed a systematic search in PubMed and per PPM collected detailed information on development, performance, and risk of bias (RoB) assessed by PROBAST. Where possible, we validated PPMs on discrimination (C-statistic) and calibration (calibration plots). Validation data sources were NECOSAD (2000 Dutch hemodialysis patients) and EQUAL (1700 European pre-dialysis patients). If no valid PPMs were identified, we intended to develop a new PPM for hospitalization within 1 year after hemodialysis start with a Fine-Gray model. Predictors were selected based on clinical relevance according to literature and clinical expertise. NECOSAD and EQUAL served as development and validation cohorts, respectively.

Results: We identified 6 studies developing 17 PPMs altogether. Three PPMs predicted 30-day hospital readmission, two predicted 6-month hospitalization rate, 10 predicted prolonged LoS, and ≥ 1 and ≥ 6 hospitalizations within one year were both predicted once. No full prediction formulas were reported, but six studies reported model coefficients. After contacting authors, no more information on prediction formulas was obtained. Many PPMs used variables only locally available. Thus, validation was strongly impeded, but preliminary results showed poor discrimination. RoB was high due to complete-case analyses and exclusion of individuals based on future information. The new PPM is being developed.

Conclusion: Hospitalization/LoS PPMs in CKD patients are scarce and at high RoB. Limited reporting and unavailability of variables impede validation. Therefore, we are now developing a PPM for hospitalization within 1 year after hemodialysis initiation.

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Developing and validating a clinical prediction model for stages of acute kidney injury in critically ill patients

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Introduction: Acute kidney injury (AKI) is a global concern with high incidence and poor prognosis among critically ill patients. AKI is frequently only detected well after its onset, at which stage the injury may be irreversible. Thus, early risk stratification is crucial in AKI management. We aimed to develop and validate the first clinical prediction model for different stages of AKI within seven days after ICU admission.

Methods: We used data from the Simple Intensive Care Studies II (SICS-II), a prospective cohort study including 1010 critically ill adults at University Medical Center Groningen, the Netherlands. The prognostic outcome was the highest KDIGO-based stage of AKI (0/1/2/3) within the first seven days of ICU stay. Least absolute shrinkage and selection operator (LASSO) and proportional odds logistic regression were used for variable selection and model estimation. Receiver operating characteristic (ROC) curve, calibration plot, and decision curve analysis were applied to evaluate model performance and clinical usefulness. We internally validated the model using bootstrapping or 10-fold cross-validation when appropriate.

Results: Of the SICS-II cohort, 976 patients were eligible for our analyses (median [IQR] 64 [52-72] years, 38% female). Among them, 283, 228, and 135 patients progressed to their highest severity of AKI at stages 1, 2, and 3, respectively, after seven days of ICU admission. We derived a 14-variable model for predicting the ordinal prognostic outcome with relatively good discrimination (area under the ROC curve of 0.765 in the internal validation) and good calibration. The model showed promising clinical usefulness, demonstrated by the net benefit gain compared to the default policies of “treat all” or “treat none” over a wide range of clinically plausible thresholds, especially for predicting AKI at a more severe stage (stage 2/3).

Conclusion: Using readily available predictors in the ICU setting, we could derive a prediction model for different stages of AKI with good performance and promising clinical usefulness.

Conflicts of interest to disclose: We declare no competing interests

Comparison of 6xR-CHOP21 versus 6xR-CHOP+2R for advanced-stage diffuse large B-cell lymphoma: a propensity score weighted population-based analysis

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Introduction: Standard first-line treatment for most patients with advanced-stage diffuse large B-cell lymphoma (DLBCL) is six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone administered every 21 days (6xR-CHOP21). Although, Dutch treatment guidelines allowed for additional rituximab administrations (6xR-CHOP21+2R). We aimed to assess the comparative effectiveness of these two treatment options in patients diagnosed with advanced-stage DLBCL in the Netherlands, since there is no randomized comparison.

Methods: From the nationwide, population-based Netherlands Cancer Registry, we identified adult (≥ 18 years) patients diagnosed with advanced-stage DLBCL (stages II-IV) in the Netherlands between 2014 and 2018 who completed 6xR-CHOP21 \pm 2R. Event-free survival (EFS) was measured from the end of treatment (EOT) until progression, relapse, the start of second-line treatment, or death. Overall survival (OS) was measured from EOT until death. We weighted patients using stabilized inverse propensity scores to balance the patient characteristics between the treatment groups. The difference in EFS and OS between the two treatment groups was calculated by Kaplan-Meier curves, Cox proportional hazards models, and restricted mean survival time. We performed a stratified analysis to assess EFS and OS between the two treatment options across the four International Prognostic Index (IPI) risk groups.

Results: Of the 1,626 included patients, most were male (55.9%), the median age was 70 years (interquartile range[IQR]; 63-76), and most were treated with 6xR-CHOP21+2R (54.7%). At a median follow-up of 4.5 years (IQR: 3.9-5.4 years), 6xR-CHOP21+2R was associated with better EFS (hazard ratio[HR]: 0.75; 95% confidence interval[CI]: 0.62-0.91) and OS (HR: 0.74; 95% CI: 0.60-0.92). Stratified analysis according to the IPI risk group revealed that this association was more pronounced with advancing IPI risk, particularly in patients with high-risk IPI (4-5).

Conclusion: This propensity-weighted analysis using nationwide observational data shows that 6xR-CHOP21+2R is associated with better EFS and OS than 6xR-CHOP21 in patients with advanced-stage DLBCL and a high-risk IPI score.

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Mapping the research field of prognostic models in nephrology: a scoping review

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Introduction: Prognostic models can strongly support individualized care and shared decision-making. However, their use in nephrological patient care seems to be limited. Therefore, we aimed to assess how many models are available, which outcomes they predict, and to evaluate their methodological rigour. To do so, we performed a scoping review of studies developing, validating or updating a prognostic model for patients with chronic kidney disease (CKD).

Methods: The PRISMA extension for Scoping Reviews was adhered to for transparent reporting. A systematic search in PubMed and Embase was performed to identify relevant studies. Studies were screened, and data was extracted on general characteristics of the included studies and their reporting and methodological quality. Furthermore, we extracted the predicted outcome definitions, and which models were validated and/or updated most often. Descriptive statistics were used to summarise all findings.

Results: In total, 596 studies were included. Many studies included less than 500 participants (41.4%). Furthermore, only 13.2% of studies published after publication of the TRIPOD statement referred to it. Although a measure of discrimination of the model was usually presented (79.5%), a measure of calibration was presented in 43.5% the studies. Of the 411 development studies, most performed only internal validation (57.9%) or no validation at all (27.7%). The majority of models predicted disease progression (n=78), mortality (n=79) and graft survival (n=59). If validated or updated at all (n=199), most models (n=123/199) were externally validated and/or updated only once. The remainder (n=76) was validated and/or updated more, with a median (IQR) of 2 (2-4).

Conclusion: More than 400 prognostic models have been developed to predict outcomes for patients with CKD, mainly regarding disease progression and patient or graft survival. Methodological rigour, external validation, updating and impact assessment deserve more attention to help bridge the gap between prediction research and nephrological patient care.

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