

Application of clinical decision support tools for predicting outcomes with vedolizumab therapy in patients with inflammatory bowel disease: A KASID multicentre study

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Summary

Background/Aim: We aimed to validate clinical decision support tools (CDSTs) to predict real-life effectiveness of vedolizumab (VDZ) in patients with inflammatory bowel disease.

Methods: We retrospectively enrolled patients with Crohn's disease (CD) or ulcerative colitis (UC) treated with VDZ at 10 tertiary referral centres in Korea between January 2017 and November 2021. We assessed clinical remission (CREM) and response (CRES), corticosteroid-free clinical remission (CSF-CREM) and response (CSF-CRES), biochemical response based on C-reactive protein (BioRES[CRP]) and faecal calprotectin (BioRES[FC]), endoscopic healing (EH), and the need to optimise or switch drugs based on CDST-defined response groups. Additionally, the area under the receiver operating characteristics curve (AUC) for the CDSTs was calculated.

Kyuwon Kim and Jae Jun Park contributed equally to this work as first authors.

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Results: We included 143 patients with CD and 219 with UC. We observed incremental trends on CSF-CRES at week 14 (W14) ($p_{\text{trend}}=0.004$) and decreasing trends for the need to optimise or switch drugs ($p_{\text{trend}}=0.016$) in CD from the low to high probability groups. Except for CSF-CREM at W54, we noticed incremental trends for all clinical responses at W14, W26 and W54 ($p_{\text{trend}}<0.001$) in UC. W26 and W54 BioRES[CRP] and W14 EH also showed increasing trends ($p_{\text{trend}}<0.05$) in UC. With increasing probabilities of response, drug optimisation or switching was less frequently required in UC ($p_{\text{trend}}=0.013$). With 26 points cut-off, CDSTs effectively identified W14 CSF-CRES, W26 BioRES[CRP], BioRES[FC] and W54 BioRES[CRP] in UC, all with AUCs >0.600 , whereas CDSTs showed poor accuracy in CD.

Conclusions: CDSTs for VDZ had acceptable accuracy in predicting effectiveness outcomes including clinical and biochemical outcomes in UC. However, their utility in CD was limited.

1 | INTRODUCTION

Vedolizumab (VDZ) is a recombinant humanised monoclonal antibody that selectively binds to the $\alpha 4\beta 7$ integrin expressed on gut-specific lymphocytes.¹ With favourable efficacy and safety proven in the pivotal GEMINI trials, VDZ was approved for patients with moderately-to-severely active Crohn's disease (CD) and ulcerative colitis (UC) intolerant or refractory to conventional therapies or biologics, including tumour necrosis factor (TNF) inhibitors.²⁻⁴

Despite the introduction of VDZ, the widespread use of VDZ for patients with inflammatory bowel disease (IBD) is yet unavailable due to the limited availability of biologics and small molecular agents and the associated considerations of cost-effectiveness. In real-world settings, predicting therapeutic outcomes remains difficult, and a significant proportion of patients with IBD might experience primary or secondary loss of response to biologics.⁵⁻⁷ Additionally, the lack of optimal therapeutic sequencing strategies further complicates treatment decisions. Given these conditions, it is important to identify patients who are most likely to respond to biologics, including VDZ, before initiating therapy.

With the increasing need for personalised therapeutic approaches to identify patients who are most likely to benefit from VDZ, Dulai et al. utilised data from the GEMINI 1, 2 and VICTORY consortium cohort to develop and validate clinical decision support tools (CDSTs) for predicting the outcomes of VDZ treatment in patients with CD⁸ and UC,⁹ respectively. These CDSTs demonstrated a fair discriminant function, as indicated by the areas under the receiver operating characteristic curves (AUCs) exceeding 0.6. Specifically, the AUC for achieving corticosteroid-free remission in UC was 0.65, while in CD, the AUCs ranged from 0.66 for corticosteroid-free remission to 0.75 for corticosteroid-free deep remission at W26. Notably, these tools showed sensitivities exceeding 90%, suggesting their potential to identify patients with IBD who

are most likely to respond to VDZ therapy.^{8,9} Further validation of CDSTs for patients with CD demonstrated their clinical utility in predicting exposure-efficacy relationships and surgery risk over a 12-month period,¹⁰ as well as clinical outcomes at week 48.¹¹ Among patients with UC, CDST could predict the exposure-efficacy relationships and histoenoscopic mucosal improvement at week 52.¹² However, the usefulness of CDSTs for predicting biochemical outcomes is not yet established.

Several studies have reported the favourable efficacy and safety profiles of VDZ in Asian IBD populations¹³⁻¹⁷ and have identified a similar pharmacokinetic profile of VDZ between Asian and non-Asian patients with moderately-to-severely active CD and UC.¹⁸ Nonetheless, uncertainty remains regarding whether these CDSTs can be effectively utilised in Asian populations in real-world practice. Therefore, we aimed to validate each CDST for predicting effectiveness outcomes, including biochemical responses, and the need for drug optimisation or switching during maintenance therapy in Korean patients with IBD.

2 | MATERIALS AND METHODS

2.1 | Patients

We conducted a retrospective analysis of data from 365 patients with IBD (144 with CD and 221 with UC) who underwent VDZ treatment between January 2017 and November 2021 at 10 tertiary referral centres in Korea. Eligibility criteria included patients with IBD aged >18 years who received scheduled VDZ therapy during the study period. Patients with IBD unclassified or lacking essential baseline data for calculating CDST scores were excluded. All consecutive eligible patients were included without additional exclusion criteria, such as primary non-response or early adverse events.

2.2 | Calculation of CDST for VDZ (VDZ-CDST) for CD and UC

The VDZ-CDST for CD⁸ was calculated using the following five variables:

1. No prior bowel surgery (+2 points).
2. No prior TNF inhibitor therapy (+3 points).
3. No prior fistulising disease (+2 points).
4. Baseline albumin (+0.4 points per unit [g/L]).
5. Baseline C-reactive protein (CRP) (−0.5 points if 3.0–10.0 mg/L, −3.0 points if >10 mg/L).

Patients with VDZ-CDST scores for CD of ≤13, >13 to ≤19 and >19 points were classified as having low, intermediate or high probabilities of response to VDZ therapy, respectively.⁸

The VDZ-CDST for UC⁹ was calculated using the following four variables:

1. Disease duration ≥2 years (+3 points).
2. No prior TNF inhibitor therapy (+3 points).
3. Baseline endoscopy moderate activity (+2 points).
4. Baseline albumin concentration (+0.65 points per unit, g/L).

Patients with VDZ-CDST scores for UC of ≤26, >26 to ≤32 and >32 points were classified as having low, intermediate or high probabilities of response to VDZ therapy, respectively.⁹

2.3 | VDZ treatment

Patients with IBD received induction therapy with intravenous VDZ infusions of 300 mg at week (W)0, W2 and W6. Those who showed clinical response to VDZ induction therapy received intravenous infusions of VDZ (300 mg every 8 weeks) as maintenance therapy from W14. At the discretion of clinicians, patients with an inadequate response to VDZ could receive optimised treatment with a 300 mg dose every 4 weeks from W18.

2.4 | Data collection

Patient demographics, clinical characteristics and laboratory results, including serum albumin (g/dL), serum CRP (mg/dL) and faecal calprotectin (FC) (mg/kg), were collected from the electronic medical records of each centre. IBD-related data included date of initial IBD diagnosis, family history of IBD, previous and concomitant medication history, baseline disease activity (CD activity index [CDAI] for CD, partial Mayo score [pMS] for UC) and endoscopic disease activity. For patients with CD, disease location/behaviour (L1–L3/B1–B3, perianal disease modifier) based on the Montreal classification,¹⁹ CD-related bowel resection history and stoma presence were recorded. For patients with UC,

disease extent (E1–E3) based on the Montreal classification¹⁹ was documented.

This study was conducted in accordance with the Declaration of Helsinki and its later amendments. Ethical approval for the study and data acquisition was obtained from the institutional review board of each centre, including Asan Medical Center (IRB number: 2021-1244).

2.5 | Outcomes

Data collected from each institution were compiled at a single centre (Asan Medical Center), and the effectiveness outcomes were evaluated using the same response evaluation criteria by a single researcher (KK). We assessed clinical, biochemical and endoscopic outcomes in patients with CD and UC. Additionally, we investigated the need for drug optimisation or switching during maintenance therapy within W54.

Clinical activity at W14, W26 and W54 was assessed using CDAI and pMS for patients with CD and UC, respectively. For patients with CD, clinical remission (CREM) was defined as CDAI ≤150 points,²⁰ and clinical response (CRES) was defined as a reduction in CDAI of ≥100 points from baseline.²⁰ For patients with UC, CREM was defined as a pMS of ≤2 points with no individual subscore >1 point, and CRES was defined as a reduction from baseline in pMS of ≥3 points and ≥30% along with either a reduction in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of ≤1 point.²⁰

Corticosteroid-free CREM (CSF-CREM) and CRES (CSF-CRES) were evaluated only in patients with baseline concomitant use of corticosteroids and defined the same as CREM and CRES without concomitant corticosteroid use.

Biochemical response (BioRES) based on serum CRP (BioRES[CRP]) and FC (BioRES[FC]) was assessed at W26 and W54. BioRES was defined as CRP or FC decreases below the cut-offs in patients with elevated CRP (≥0.6 mg/dL) or FC (≥250 mg/kg) at baseline.

Endoscopic activity was assessed at W14 for UC patients, and W52 for both UC and CD patients. Endoscopic healing (EH) was defined as no visible ulcers for patients with CD,²¹ and Mayo endoscopic subscore ≤1 point for patients with UC.²²

Patients in remission for any effectiveness outcomes at baseline (W0) were excluded from each outcome assessment. In patients with a stoma, we assessed BioRES[CRP], EH and the need for drug optimisation or switching within a year. Patients who stopped VDZ because of primary or secondary loss of response, who received bowel resection, or who were lost to follow up were considered to have failed to achieve any outcomes. Cases with missing data were excluded from the evaluation of effectiveness outcomes.

2.6 | Statistical analyses

Categorical variables were expressed as numbers and percentages and analysed using Fisher's exact or chi-squared test. Continuous

variables were expressed as medians and interquartile ranges (IQRs). Changes in CDAI or pMS from baseline to W54 in each treatment group were analysed using the Kruskal-Wallis test. Associations between each outcome and VDZ-CDST-defined probability groups were tested using a chi-squared test for trends in each treatment group. The discriminant function of each VDZ-CDST was assessed through receiver operating characteristics curve analyses and estimated by AUC. The AUC score ranges from 0 to 1, with a higher value indicating better performance of the model in predicting the target variable. Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio of the VDZ-CDSTs with cut-offs (13 and 19 points for CD; 26 and 32 points for UC) in predicting each effectiveness outcome and the need for drug optimisation or switching during maintenance therapy were calculated. All P-values were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using R (version 3.6.3; R Core Team, Vienna, Austria).

3 | RESULTS

3.1 | Baseline characteristics

The study flowchart is presented in [Figure 1](#), showing the patients evaluated at each effectiveness outcome. Among 365 patients with IBD who received VDZ, one patient with CD was excluded because of missing baseline CRP level. Two patients with UC were excluded because of missing baseline endoscopic activity data. The remaining 362 patients with IBD (143 with CD and 219 with UC) were finally included and classified into low (44 with CD and 49 with UC), intermediate (73 with CD and 118 with UC) and high (26 with CD and 52 with UC) probability groups for VDZ treatment response, respectively.

[Table 1](#) displays the baseline patient demographic data. The median ages at the first VDZ infusion were 35.0 (IQR, 27.0–42.0) and 47.0 (IQR, 32.0–58.0) among patients with CD and UC, respectively. The median disease duration at the first VDZ infusion was 10.0 (IQR, 5.0–15.0) years in CD and 4.0 (IQR, 2.0–7.0) years in UC. The median duration of VDZ therapy was 14.0 months (IQR, 9.0–31.0) among patients with CD, and 13.0 months (IQR, 6.0–30.0) among patients with UC. Approximately 10% of the patients had a family history of IBD, and both CD and UC patients showed a male predominance. Among patients with CD, 98 (68.5%) had ileocolonic disease, 66 (46.2%) had penetrating disease, and 87 (60.8%) had perianal disease. In comparison, 112 (51.1%) of patients with UC had extensive colitis. Approximately 90% of patients with CD and 75.8% of patients with UC had been previously exposed to TNF inhibitors. At the start of VDZ induction, 97 (67.8%) patients with CD and 85 (38.8%) with UC received concomitant immunomodulator therapy.

When stratified by CDST-defined groups, disease duration, disease location, perianal disease, previous exposure to TNF inhibitors, baseline albumin and baseline CRP significantly differed among the

three groups with CD ([Table S1](#)). Among patients with UC, age, disease extent, previous exposure to TNF inhibitors, baseline albumin, baseline CRP and baseline FC level significantly differed among the three probability groups ([Table S2](#)).

3.2 | Effectiveness outcomes according to CDST-defined groups

3.2.1 | Clinical outcomes

In the assessment of clinical outcomes, 45 patients with CD who had a stoma or were in clinical remission at baseline were excluded from the assessment of clinical outcomes. Among patients with UC, seven patients in clinical remission at baseline and one patient with a missing baseline partial Mayo score were excluded. [Figure 2A](#) shows the rates of clinical outcome achievement at W14, W26 and W54 among patients with CD according to CDST-defined groups. There was an incremental trend in the response rate of W14 CSF-CRES, from 24.1% in the low probability group to 68.4% in the high probability group ($p_{\text{trend}} = 0.004$; [Table S3](#)). However, no such trends were observed in the other clinical outcomes according to CDST-defined probability groups through W14, W26 and W54.

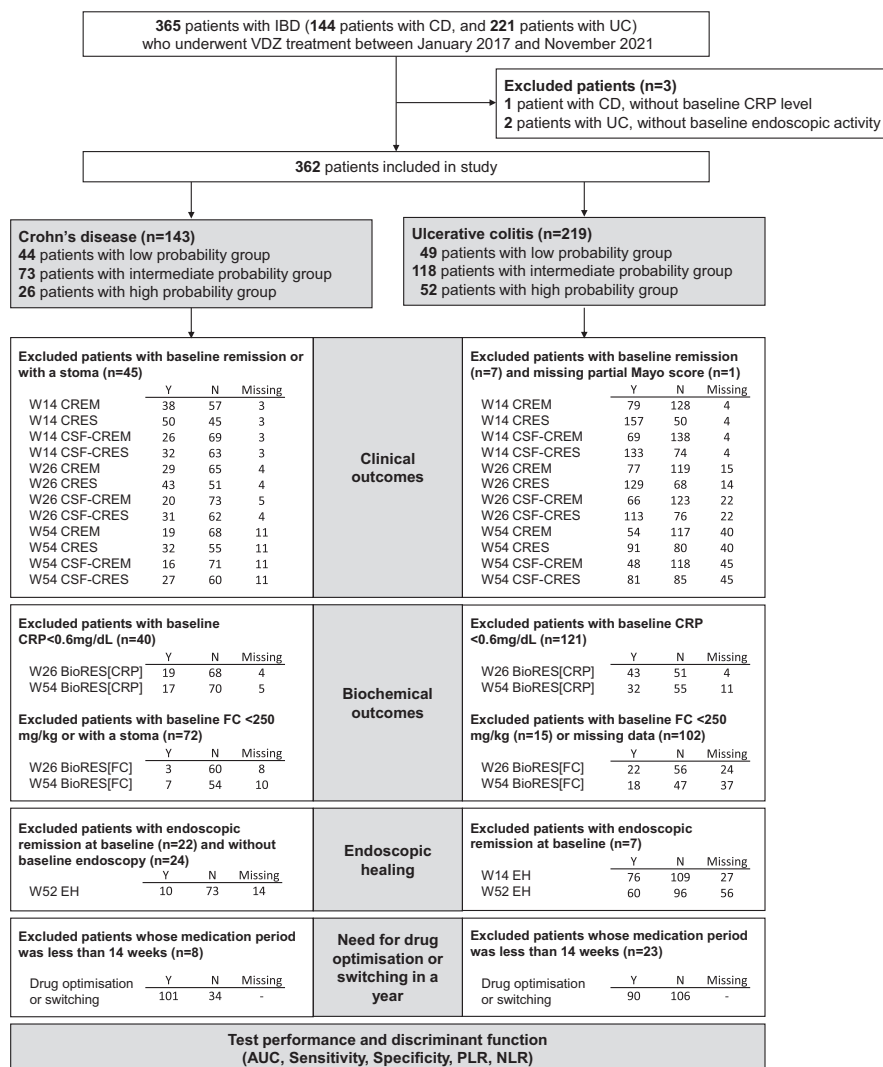
Conversely, among patients with UC, rates of CREM, CRES, CSF-CREM and CSF-CRES at W14 and W26 showed decreasing trends from the high probability group to the intermediate and then, to the low probability groups (W14 CREM, 57.1% vs. 38.2% vs. 18.8%, $p_{\text{trend}} < 0.001$; W14 CRES, 93.9% vs. 74.5% vs. 60.4%, $p_{\text{trend}} < 0.001$; W14 CSF-CREM, 55.1% vs. 30.0% vs. 18.8%, $p_{\text{trend}} < 0.001$; W14 CSF-CRES, 87.8% vs. 62.7% vs. 43.8%, $p_{\text{trend}} < 0.001$; W26 CREM, 65.1% vs. 34.9% vs. 25.5%, $p_{\text{trend}} < 0.001$; W26 CRES, 86.0% vs. 65.1% vs. 47.9%, $p_{\text{trend}} < 0.001$; W26 CSF-CREM, 61.0% vs. 30.1% vs. 22.2%, $p_{\text{trend}} < 0.001$; W26 CSF-CRES, 82.9% vs. 57.8% vs. 43.5%, $p_{\text{trend}} < 0.001$) ([Figure 3A](#), [Table S4](#)). At W54, the high probability group also showed higher rates of CREM, CRES and CSF-CRES compared with those in the intermediate and low probability groups (W54 CREM, 46.9% vs. 29.8% vs. 24.4%, $p_{\text{trend}} = 0.046$; W54 CRES, 78.1% vs. 52.1% vs. 37.8%, $p_{\text{trend}} < 0.001$; W54 CSF-CRES, 69.0% vs. 46.7% vs. 40.0%, $p_{\text{trend}} = 0.02$).

3.2.2 | Biochemical outcomes

In the assessment of BioRES[CRP], 40 patients with CD who had a baseline CRP < 0.6 mg/dL were excluded. Regarding BioRES[FC], 12 patients with a stoma and 83 patients with CD who had a baseline FC < 250 mg/kg were excluded from the assessment. BioRES[CRP] and BioRES[FC] rates showed no significant incremental trends through the three probability groups at W26 and W54 among patients with CD ([Figure 2B](#), [Table S3](#)).

Among patients with UC, 121 patients who had a baseline CRP < 0.6 mg/dL were excluded from the assessment of BioRES[CRP].

FIGURE 1 A study flowchart showing the patients at each effectiveness outcome. AUC, area under the receiver operating characteristics curve; BioRES, biochemical response; CD, Crohn's disease; CREM, clinical remission; CRES, clinical response; CSF-CREM, corticosteroid-free clinical remission; CSF-CRES, corticosteroid-free clinical response; CRP, C-reactive protein; EH, endoscopic healing; FC, faecal calprotectin; IBD, inflammatory bowel disease; NLR, negative likelihood ratio; PLR, positive likelihood ratio; UC, ulcerative colitis; VDZ, vedolizumab; W, week.



Similarly, for the assessment of BioRES[FC], 15 patients with a baseline FC <250mg/kg and 102 patients with missing data were excluded. The rates of BioRES[CRP] at W26 and W54 were higher in the high probability group compared with the intermediate and low probability groups (W26 BioRES[CRP], 75.0% vs. 49.0% vs. 30.3%, $p_{\text{trend}}=0.007$ and W54 BioRES[CRP], 70.0% vs. 40.0% vs. 21.9%, $p_{\text{trend}}=0.005$; Figure 3B, Table S4). No such trend was observed in the rate of BioRES[FC].

3.2.3 | Endoscopic healing

Regarding EH, 22 patients with endoscopic remission at baseline and 24 patients without baseline endoscopy were excluded among CD patients. Similarly, seven patients with endoscopic remission at baseline were excluded among UC patients. Although the rates of EH at W14 (in UC) and W52 (in CD and UC) appeared to be numerically higher in the high probability groups, a significant incremental trend in EH rate was observed only in W14 among patients with UC (65.8% vs. 37.3% vs. 28.9%, $p_{\text{trend}} < 0.001$; Figures 2C and 3C, Tables S3 and S4).

3.2.4 | Need for drug optimisation or switching

During maintenance therapy, the rates of drug optimisation or switching to other classes of drugs were investigated among 135 patients with CD and 196 patients with UC, excluding 8 patients with CD and 23 patients with UC whose medication period was less than 14 weeks. The rates were 50.0%, 80.0% and 80.5% in the high, intermediate and low probability groups of patients with CD ($p_{\text{trend}}=0.016$; Figure 2D, Table S3). Among patients with UC, this trend was also observed, with rates of 31.3%, 48.1% and 57.1%, respectively ($p_{\text{trend}}=0.013$; Figure 3D, Table S4).

3.2.5 | Test performance and discriminant function of each CDST

The VDZ-CDST for CD with a cut-off of 13 points could not discriminate any outcomes with an AUC of >0.600 (Table 2). However, with a cut-off of 19 points, the VDZ-CDST for CD discriminated W14 CRES with an AUC of 0.606 (95% CI, 0.500–0.704), W14 CSF-CREM with an AUC of 0.601 (95% CI, 0.495–0.700), W14

TABLE 1 Baseline patient demographic data.

	Crohn's disease (n = 143)	Ulcerative colitis (n = 219)
Age at VDZ initiation, median (IQR), years	35.0 (27.0–42.0)	47.0 (32.0–58.0)
Disease duration at VDZ administration, median (IQR), years	10.0 (5.0–15.0)	4.0 (2.0–7.0)
Duration of VDZ therapy, median (IQR), months	14.0 (9.0–31.0)	13.0 (6.0–30.0)
Male, n (%)	95 (66.4)	133 (60.7)
Family history of IBD, n (%)	14 (9.8)	20 (9.1)
Patient with ostomy, n (%)	25 (17.5)	0 (0)
IBD phenotype, n (%)		
Disease location ^a		
Ileal (L1)	30 (21.0)	
Colonic (L2)	15 (10.5)	
Ileocolonic (L3)	98 (68.5)	
Disease behaviour ^a		
Non-stricturing/non-penetrating (B1)	33 (23.1)	
Stricturing (B2)	44 (30.8)	
Penetrating (B3)	66 (46.2)	
Disease extent ^a		
Proctitis (E1)		18 (8.2)
Left-sided colitis (E2)		89 (40.6)
Extensive colitis (E3)		112 (51.1)
P (perianal disease), n (%)	87 (60.8)	
Previous exposure to TNF inhibitors, n (%)	129 (90.2)	166 (75.8)
Concomitant corticosteroids, n (%)	29 (20.3)	84 (38.4)
Concomitant IMMs, n (%)	97 (67.8)	85 (38.8)
Disease activity at initiation		
Crohn's disease activity index ^b , mean ± SD	256.4 ± 97.3	
Partial Mayo score ^c , mean ± SD		6.2 ± 1.8
Baseline albumin, mean ± SD, g/dL	3.6 ± 0.6	3.9 ± 0.6
Baseline C-reactive protein ^d , mean ± SD (mg/dL)	1.8 ± 1.9	1.3 ± 2.5
Baseline faecal calprotectin ^e , mean ± SD (mg/kg)	1476.4 ± 2985.9	2397.7 ± 4365.1

Abbreviations: IBD, inflammatory bowel disease; IMM, immunomodulator; IQR, interquartile range; TNF, tumour necrosis factor; VDZ, vedolizumab; W, week.

^aDisease location, behaviour and extent were based on the Montreal classification.

^bBaseline Crohn's disease activity index was available in 116 patients with Crohn's disease without ostomy and missing data.

^cBaseline partial Mayo score was available in 218 patients with ulcerative colitis.

^dBaseline C-reactive protein values from one patient with Crohn's disease and one patient with ulcerative colitis were missing.

^eBaseline faecal calprotectin values were available among 88 patients with Crohn's disease and 97 patients with ulcerative colitis.

CSF-CRES with an AUC of 0.656 (95% CI, 0.551–0.750) and W26 BioRES[FC] with an AUC of 0.640 (95% CI, 0.509–0.757), although all with a low sensitivity under 40% and a relatively high specificity over 80% (Table S5). Additionally, with a cut-off of 19 points, the VDZ-CDST for CD identified the need for drug optimisation or switching, with an AUC of 0.617 (95% CI, 0.530–0.699), a sensitivity of 35.3% (95% CI, 19.7–53.5) and a specificity of 88.1% (95% CI, 80.1–93.7).

As for the VDZ-CDST for UC with a cut-off of 26 points, it discriminated W14 CSF-CRES with an AUC of 0.603 (95% CI, 0.533–0.671), a sensitivity of 84.2% (95% CI, 76.9–90.0) and a specificity of 36.5%

(95% CI, 25.6–48.5; Table 3). Furthermore, the VDZ-CDST discriminated the rates of W26 BioRES[CRP] and BioRES[FC] with AUCs of 0.609 (95% CI, 0.503–0.708) and 0.619 (95% CI, 0.502–0.727), respectively, as well as W54 BioRES[CRP] with an AUC of 0.618 (95% CI, 0.507–0.720). When applying a cut-off of 32 points, the VDZ-CDST for UC discriminated additional effectiveness outcomes, including W14 CRES, W26 CREM, W14 CSF-CREM, W14 CSF-CRES, W26 CSF-CREM, W26 CSF-CRES and W14 EH with AUCs of >0.600, although with a poor sensitivity (Table S6). However, the other effectiveness outcomes were poorly discriminated, with AUCs of <0.600.

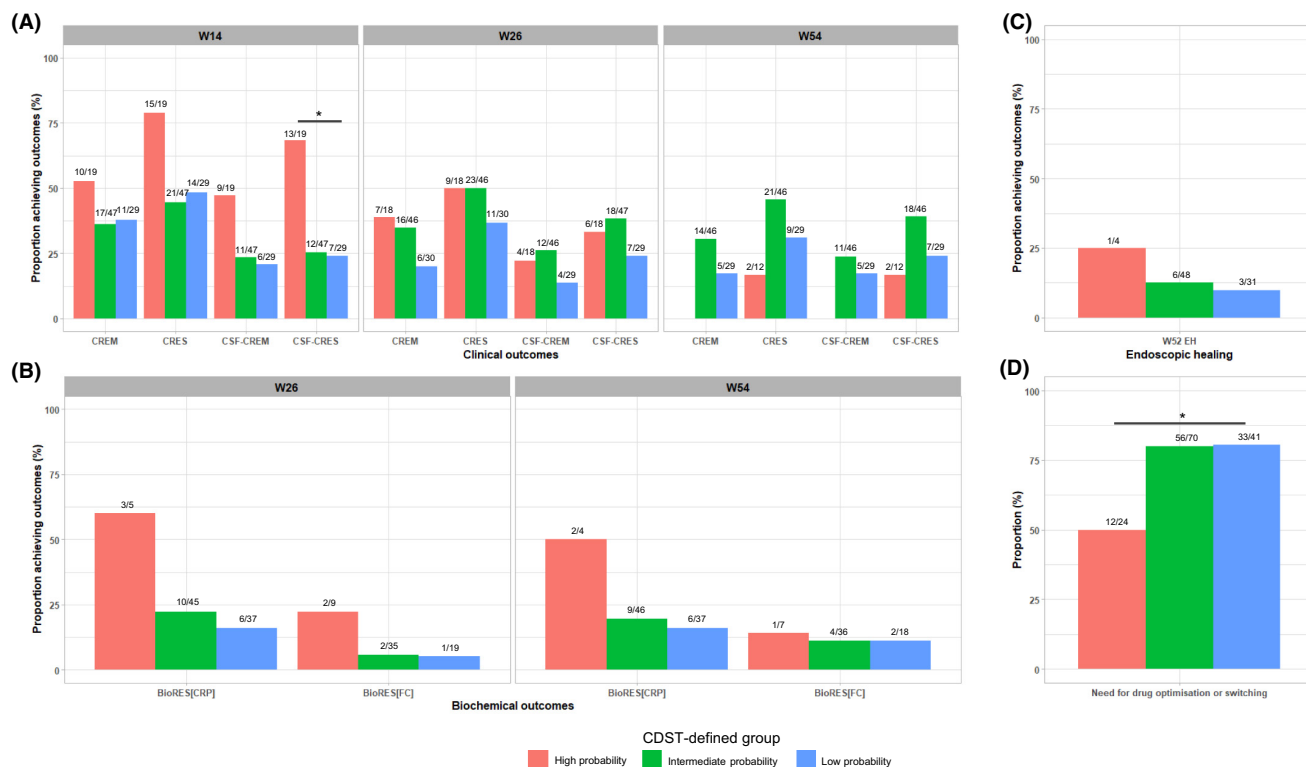


FIGURE 2 Achievement of effectiveness outcomes and need for drug optimisation or switching according to clinical decision support tool (CDST)-defined groups among patients with Crohn's disease. The bar plots represent the proportion of patients achieving (A) clinical outcomes, (B) biochemical outcomes, (C) endoscopic healing, and (D) the proportion of patients requiring drug optimisation or switching according to CDST-defined groups. The numbers displayed above each bar represent the number of patients who achieved outcomes. The red, green and blue bars indicate high, intermediate and low probability groups, respectively. * $p < 0.05$. BioRES, biochemical response; CRP, C-reactive protein; CREM, clinical remission; CRES, clinical response; CSF-CREM, corticosteroid-free clinical remission; CSF-CRES, corticosteroid-free clinical response; FC, faecal calprotectin; High, high probability group; Intermediate, intermediate probability group; Low, low probability group.

3.2.6 | Comparison of VDZ-CDST and UST-CDST for patients with CD

Considering that the majority of patients with CD included in this study had previously been exposed to TNF inhibitors, which could impact the effectiveness of treatments and the function of CDSTs, we employed ustekinumab (UST)-CDST²³ in the CD cohort for comparison with VDZ-CDST. The clinical outcomes were then assessed at W14, 26 and 54. As illustrated in Figure S1A, no discernible trend was observed in any clinical outcomes, as all p -values for trends were insignificant across UST-CDST-defined groups. Furthermore, when comparing the ROC curves and their AUC values for VDZ-CDST and UST-CDST, as presented in Figure S1B, all AUC values for UST-CDST ranged between 0.4 and 0.5, indicating no significant disadvantage in choosing VDZ over UST.

4 | DISCUSSION

In this study, we aimed to validate and expand the utility of VDZ-CDSTs in Korean populations by applying those developed by Dulai et al.^{8,9} to over 100 patients with CD and UC each from 10 tertiary

referral centres using real-world data. The overall rate of achieving clinical outcomes in this study was approximately 30% in both CD and UC, which aligns with the results of previous validation studies in clinical trial cohorts¹² and real-world data.^{10,11} When stratified according to CDST-defined groups, more patients in the intermediate to high probability groups appeared to achieve various effectiveness outcomes at W14, W26 and W54, compared with those in the low probability group. Conversely, more patients in the low probability group experienced drug optimisation or switching within 1 year. However, the VDZ-CDST generally could not effectively distinguish effectiveness outcomes among patients with CD, as most AUCs were < 0.600 , indicating that its application in clinical practice was less satisfactory. However, among patients with UC, the VDZ-CDST showed an acceptable discriminant function, especially for BioRES, suggesting its potential utility in predicting objective outcomes in real-world settings.

Among patients with CD in this study, 22.2% of the high probability group achieved W26 CSF-CREM. This proportion was slightly lower than the 30% reported by the VICTORY consortium where the original CDST was validated.⁸ Additionally, a French real-world study reported that 80% of the high probability group achieved W48 CSF-CREM.¹¹ In the present study, none of high probability

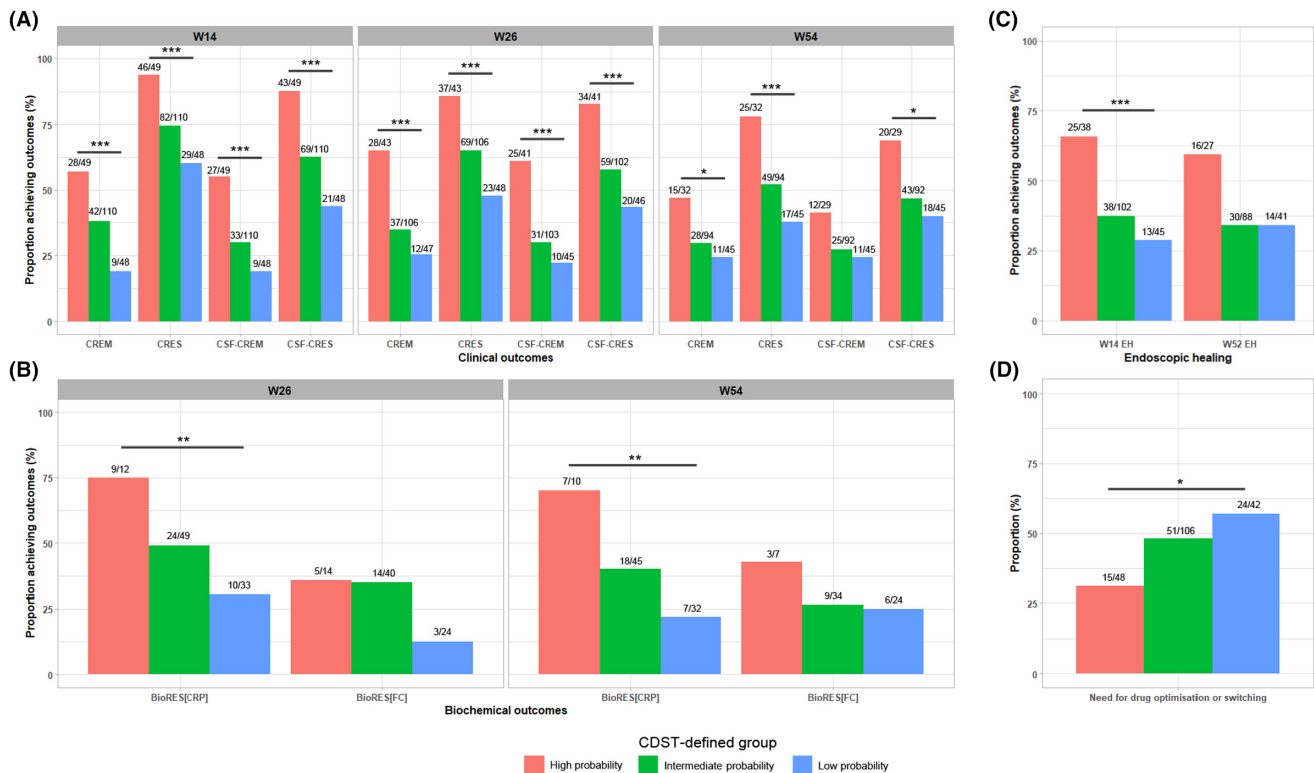


FIGURE 3 Achievement of effectiveness outcomes and need for drug optimisation or switching according to clinical decision support tool (CDST)-defined groups among patients with ulcerative colitis. The bar plots represent the proportion of patients achieving (A) clinical outcomes, (B) biochemical outcomes, (C) endoscopic healing, and (D) the proportion of patients requiring drug optimisation or switching according to CDST-defined groups. The numbers displayed above each bar represent the number of patients who achieved outcomes. The red, green and blue bars indicate high, intermediate and low probability groups, respectively. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$. BioRES, biochemical response; CREM, clinical remission; CRES, clinical response; CSF-CREM, corticosteroid-free clinical remission; CSF-CRES, corticosteroid-free clinical response; CRP, C-reactive protein; FC, faecal calprotectin; High, high probability group; Intermediate, intermediate probability group; Low, low probability group.

patients with CD showed W54 CSF-CREM, which poorly correlated with the CDST-defined groups. However, among patients with UC, incremental response rates from the low to high probability groups were demonstrated in all clinical outcomes except for W54 CSF-CREM, and several clinical outcomes such as W26 CSF-CREM and W54 CREM showed higher rates compared with those observed in the clinical trials.^{9,12} In particular, among patients with UC, >60% of the high probability group achieved W26 CSF-CREM, compared with 32% of the high probability group achieving W26 CSF-CREM in the VICTORY consortium.⁹ Additionally, a validation study¹² using VARSITY trial cohort data reported that 39.7% of the high probability group achieved W52 CREM, whereas 46.9% of the high probability group in the present study achieved W54 CREM. These different trends in clinical outcome achievement rates among CD and UC patients can be more comprehensively identified in Figure S2A,B, which presents changes in CDAI or pMS according to CDST-defined groups for VDZ treatment periods up to W54. Patients with CD and UC in the high probability group showed considerable decreases in CDAI and pMS at W14, respectively. However, all three probability groups in patients with CD showed increasing trends of CDAI from W14 to W26, which was steeper in the high probability group. In contrast, among patients with UC, the high probability group showed

a larger reduction of pMS, sustained through a year, whereas pMS showed an increasing trend from W14 to W26 and then from W26 to W54 in the intermediate and low probability groups.

One possible reason for the differences in response rates in our study population with previous studies, as well as the relatively lower efficacy of VDZ-CDSTs in the present study, could be the higher proportion of patients with TNF inhibitor exposure (90.2% in patients with CD and 75.8% in patients with UC). Previous exposure to TNF inhibitors is associated with a poor response and treatment failure to VDZ, regardless of the reason for TNF inhibitor discontinuation.^{2,3,24-27} Under the national health insurance reimbursement policies in Korea, VDZ could only be reimbursed after TNF inhibitor failure until it was approved as a first-line therapy in August 2020. With the study period spanning from January 2017 to November 2021, the majority of our patients have inevitably been exposed to TNF inhibitors. Although this may have contributed to reducing the heterogeneity of medication exposure among participating centres, our results should be interpreted with caution in TNF inhibitor-naïve individuals.

Furthermore, the phenotypic characteristics of our study population, particularly in terms of prior IBD-related intestinal surgery, prior fistulising disease and disease location in CD, might also have

TABLE 2 CDST test performance and discriminant function for patients with Crohn's disease (13 points cut-off).

	AUC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PLR (95% CI)	NLR (95% CI)
W14 CREM	0.513 (0.408–0.617)	71.1 (54.1–84.6)	31.6 (19.9–45.2)	1.04 (0.79–1.36)	0.92 (0.49–1.72)
W14 CRES	0.527 (0.422–0.630)	72.0 (57.6–83.8)	33.3 (20.0–49.0)	1.08 (0.83–1.41)	0.84 (0.46–1.54)
W26 CREM	0.581 (0.475–0.682)	79.3 (60.3–92.0)	36.9 (25.3–49.8)	1.26 (0.97–1.64)	0.56 (0.26–1.22)
W26 CRES	0.558 (0.452–0.661)	74.4 (58.8–86.5)	37.3 (24.1–51.9)	1.19 (0.90–1.56)	0.69 (0.37–1.28)
W54 CREM	0.545 (0.435–0.652)	73.7 (48.8–90.9)	35.3 (24.1–47.8)	1.14 (0.83–1.57)	0.75 (0.33–1.69)
W54 CRES	0.541 (0.431–0.649)	71.9 (53.3–86.3)	36.4 (23.8–50.4)	1.13 (0.84–1.52)	0.77 (0.40–1.49)
W14 CSF-CREM	0.551 (0.446–0.654)	76.9 (56.4–91.0)	33.3 (22.4–45.7)	1.15 (0.88–1.51)	0.69 (0.32–1.51)
W14 CSF-CRES	0.565 (0.460–0.667)	78.1 (60.0–90.7)	34.9 (23.3–48.0)	1.20 (0.93–1.55)	0.63 (0.30–1.31)
W26 CSF-CREM	0.571 (0.464–0.673)	80.0 (56.3–94.3)	34.2 (23.5–46.3)	1.22 (0.92–1.60)	0.58 (0.23–1.48)
W26 CSF-CRES	0.562 (0.456–0.664)	77.4 (58.9–90.4)	34.9 (23.3–48.0)	1.19 (0.92–1.55)	0.65 (0.31–1.35)
W54 CSF-CREM	0.513 (0.403–0.621)	68.8 (41.3–89.0)	33.8 (23.0–46.0)	1.04 (0.72–1.50)	0.92 (0.42–2.05)
W54 CSF-CRES	0.554 (0.443–0.660)	74.1 (53.7–88.9)	36.7 (24.6–50.1)	1.17 (0.87–1.57)	0.71 (0.34–1.45)
W26 BioRES[CRP]	0.570 (0.459–0.676)	68.4 (43.5–87.4)	45.6 (33.5–58.1)	1.26 (0.86–1.83)	0.69 (0.34–1.41)
W26 BioRES[FC]	0.555 (0.425–0.680)	80.0 (28.4–99.5)	31.0 (19.5–44.5)	1.16 (0.72–1.86)	0.64 (0.11–3.88)
W54 BioRES[CRP]	0.545 (0.435–0.652)	64.7 (38.3–85.8)	44.3 (32.4–56.7)	1.16 (0.77–1.75)	0.80 (0.40–1.60)
W54 BioRES[FC]	0.505 (0.374–0.636)	71.4 (29.0–96.3)	29.6 (18.0–43.6)	1.02 (0.62–1.67)	0.96 (0.28–3.34)
W52 EH	0.542 (0.429–0.652)	70.0 (34.8–93.3)	38.4 (27.2–50.5)	1.14 (0.73–1.77)	0.78 (0.29–2.11)
Drug optimisation or switching	0.546 (0.458–0.632)	76.5 (58.8–89.3)	32.7 (23.7–42.7)	1.14 (0.90–1.43)	0.72 (0.37–1.40)

Abbreviations: AUC, area under the receiver operating characteristic curve; BioRES, biochemical response; CDST, clinical decision supporting tool; CI, confidence interval; CREM, clinical remission; CRES, clinical response; CSF-CREM, corticosteroid-free clinical remission; CSF-CRES, corticosteroid-free clinical response; CRP, C-reactive protein; EH, endoscopic healing; FC, faecal calprotectin; NLR, negative likelihood ratio; PLR, positive likelihood ratio; W, week.

contributed to the different results. Whereas the prevalence of a history of IBD-related intestinal surgery and fistulising disease was 44% and 36% in the GEMINI 2 cohort utilised for CDST development,⁸ our CD cohort exhibited higher percentages at 51% and 46%, respectively. In terms of disease location, approximately 90% of cases involved the ileum (21.0% with ileal CD and 68.5% with ileocolonic CD), while colonic CD accounted for only 10.5%. The high prevalence of ileocolonic CD is considered a characteristic feature of Korean CD patients, as observed in population-based studies of Korean patients with CD.^{28,29} Theoretically, the distribution of integrin $\alpha 4\beta 7$ -expressing T lymphocytes, which is a therapeutic target of VDZ, is lowest in the ileum and more abundant in the descending colon.³⁰ Therefore, the impact of $\alpha 4\beta 7$ blockade may be limited in the ileal homing of effector T lymphocytes. A recent meta-analysis by Dulai et al.³¹ supports this by demonstrating that patients with isolated ileal CD were less likely to respond to VDZ compared with those with colonic CD. The inverse correlation between VDZ response rates and ileal involvement could also be inferred among CDST-defined groups, with only 6.8% of patients in the low probability group having colonic CD, whereas one-third of patients with colonic CD (5/15) in the high probability group.

The results of the present study demonstrated that a VDZ-CDST could predict BioRES in patients with UC, although its prediction ability was less satisfactory in patients with CD. As clinical activity scoring indices such as CDAI and pMS largely rely

on patient-reported symptoms, there may naturally exist a gap between the clinical activity scores and actual gut inflammation. In contrast, both CRP and FC are objective tools that can be obtained in a less invasive way; in particular, FC is highly correlated with clinical disease activity, endoscopic findings and histologic indices.^{32–35} Therefore, the expanded utility of VDZ-CDST to predict BioRES can more reliably facilitate the selection of optimal therapy. However, although the VDZ-CDST for CD originally included CRP as a variable, it could not predict even BioRES[CRP] among patients with CD. In the case of FC, we excluded CD patients with a stoma from the BioRES[FC] assessment, considering that the FC cut-off values might differ in such population.³⁶ Although still controversial, some studies^{32,37} also reported lower FC levels in patients with ileal CD compared with those in patients with colonic or ileocolonic CD. These findings suggest that FC can be influenced by disease location. The utility of the VDZ-CDST in predicting BioRES should be further explored in a larger number of patients with CD, using different FC cut-offs depending on disease location and stoma status.

The main strength of our study is that it is the first validation study on the usefulness of the VDZ-CDST for Asian patients with IBD, using real-life, multicentre clinical data during induction and maintenance periods up to 1 year. Despite the differences from the clinical trial setting, the overall response to VDZ appeared consistent with previous real-life data.¹¹ This is significant as real-life data can

TABLE 3 CDST test performance and discriminant function for patients with ulcerative colitis (26 points cut-off).

	AUC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PLR (95% CI)	NLR (95% CI)
W14 CREM	0.595 (0.525–0.663)	88.6 (79.5–94.7)	30.5 (22.6–39.2)	1.27 (1.11–1.47)	0.37 (0.19–0.73)
W14 CRES	0.598 (0.527–0.665)	81.5 (74.6–87.3)	38.0 (24.7–52.8)	1.32 (1.05–1.65)	0.49 (0.30–0.79)
W26 CREM	0.569 (0.497–0.639)	84.4 (74.4–91.7)	29.4 (21.4–38.5)	1.20 (1.03–1.39)	0.53 (0.29–0.96)
W26 CRES	0.595 (0.523–0.664)	82.2 (74.5–88.3)	36.8 (25.4–49.3)	1.30 (1.07–1.58)	0.49 (0.30–0.79)
W54 CREM	0.543 (0.466–0.620)	79.6 (66.5–89.4)	29.1 (21.0–38.2)	1.12 (0.94–1.34)	0.70 (0.39–1.28)
W54 CRES	0.582 (0.504–0.656)	81.3 (71.8–88.7)	35.0 (24.7–46.5)	1.25 (1.04–1.51)	0.53 (0.32–0.90)
W14 CSF-CREM	0.576 (0.506–0.644)	87.0 (76.7–93.9)	28.3 (20.9–36.6)	1.21 (1.06–1.39)	0.46 (0.24–0.90)
W14 CSF-CRES	0.603 (0.533–0.671)	84.2 (76.9–90.0)	36.5 (25.6–48.5)	1.33 (1.10–1.60)	0.43 (0.26–0.71)
W26 CSF-CREM	0.567 (0.493–0.638)	84.8 (73.9–92.5)	28.5 (20.7–37.3)	1.19 (1.02–1.38)	0.53 (0.28–1.01)
W26 CSF-CRES	0.583 (0.509–0.654)	82.3 (74.0–88.8)	34.2 (23.7–46.0)	1.25 (1.04–1.50)	0.52 (0.31–0.86)
W54 CSF-CREM	0.529 (0.451–0.607)	77.1 (62.7–88.0)	28.8 (20.9–37.9)	1.08 (0.89–1.31)	0.80 (0.44–1.44)
W54 CSF-CRES	0.548 (0.469–0.625)	77.8 (67.2–86.3)	31.8 (22.1–42.8)	1.14 (0.95–1.37)	0.70 (0.42–1.17)
W26 BioRES[CRP]	0.609 (0.503–0.708)	76.7 (61.4–88.2)	45.1 (31.1–59.7)	1.40 (1.04–1.88)	0.52 (0.28–0.96)
W26 BioRES[FC]	0.619 (0.502–0.727)	86.4 (65.1–97.1)	37.5 (24.9–51.5)	1.38 (1.06–1.80)	0.36 (0.12–1.10)
W54 BioRES[CRP]	0.618 (0.507–0.720)	78.1 (60.0–90.7)	45.5 (32.0–59.4)	1.43 (1.06–1.94)	0.48 (0.24–0.99)
W54 BioRES[FC]	0.525 (0.397–0.650)	66.7 (41.0–86.7)	38.3 (24.5–53.6)	1.08 (0.73–1.61)	0.87 (0.41–1.84)
W14 EH	0.561 (0.487–0.634)	82.9 (72.5–90.6)	29.4 (21.0–38.8)	1.17 (1.00–1.38)	0.58 (0.33–1.04)
W52 EH	0.524 (0.443–0.604)	76.7 (64.0–86.6)	28.1 (19.4–38.2)	1.07 (0.88–1.29)	0.83 (0.47–1.45)
Drug optimisation or switching	0.548 (0.476–0.619)	83.0 (74.5–89.6)	26.7 (17.9–37.0)	1.13 (0.97–1.32)	0.64 (0.37–1.10)

Abbreviations: AUC, area under the receiver operating characteristic curve; BioRES, biochemical response; CDST, clinical decision supporting tool; CI, confidence interval; CREM, clinical remission; CRES, clinical response; CSF-CREM, corticosteroid-free clinical remission; CSF-CRES, corticosteroid-free clinical response; CRP, C-reactive protein; EH, endoscopic healing; FC, faecal calprotectin; NLR, negative likelihood ratio; PLR, positive likelihood ratio; W, week.

reflect a situation closer to reality by including patient populations that are often excluded from clinical trials. Moreover, we evaluated the utility of VDZ-CDSTs across various effectiveness outcomes, including clinical, biochemical and endoscopic responses, as well as the need for drug optimisation or switching during 1 year of VDZ therapy, among a relatively large number of patients enrolled from multiple centres. This approach enhanced the generalizability of our findings, which highlighted the potential of VDZ-CDST in predicting BioRES among patients with IBD, especially among those with UC. However, caution is warranted when interpreting the results of BioRES and EH owing to the small sample size effect on the measured outcomes among the high probability group, resulting from both missing data and the decreased number of patients who continued with VDZ during the maintenance period. Overall, this study offers profound insights into the potential usefulness of VDZ-CDSTs among individuals with IBD and provides a promising direction for future research.

However, this study has several limitations. Due to its retrospective nature and the high proportion of patients previously exposed to TNF inhibitors, the applicability of the CDST in bio-naïve patients with IBD considering VDZ therapy is limited. Additionally, it is still difficult to determine whether VDZ or UST is more beneficial for CD patients who have previously been treated with TNF inhibitors.

Nevertheless, our comparison of the ROC curves and AUC values of VDZ-CDST and UST-CDST²³ suggests that choosing VDZ over UST likely did not significantly disadvantage the CD cohort in this study, as all the AUC values for UST-CDST were between 0.4 and 0.5. However, as these methods provide only indirect insights, there is a need for well-designed, prospective head-to-head trials comparing VDZ and UST in these populations. Furthermore, the inclusion of patients from tertiary referral centres may result in referral bias. Yet, considering that most patients starting biologics in Korea tend to be followed-up at the same referral centres rather than returning to primary or secondary institutions,³⁸ patients included in the present study may still be representative of the general population with IBD receiving VDZ in Korea. It is also important to note that despite the use of unified assessment tools such as CDAI, pMS and MES, there remains some inconsistency in management strategies across different centres.¹⁵ Nonetheless, for VDZ therapy, implementing the reimbursement criteria provided by the unified public medical insurance system in Korea could have reduced this heterogeneity. In this study, we analysed data from individuals receiving VDZ at both 4- and 8-week infusion intervals after W14, taking into consideration the small sample size when subdivided. As the serum VDZ trough level was not measured during the study, we could not confirm the exposure–effectiveness relationship previously established

in other studies.^{10,12} However, this omission might have affected the response rates and the function of VDZ-CDST. In addition, 11 patients with CD (7.7%) and 20 patients with UC (9.1%) discontinued VDZ therapy without dose intensification. This poses a risk of overestimating VDZ treatment failure in our study. Future well-designed, prospective studies that measure VDZ concentration and separately analyse effectiveness outcomes according to VDZ infusion intervals would provide deeper insights into the exposure–effectiveness relationship, thereby enhancing the effectiveness of VDZ-CDSTs.

In conclusion, our results suggest that VDZ-CDST may help guide the selection of the optimal biologic therapy for patients with UC, rather than patients with CD in the Korean population. Specifically, our findings highlighted the extended utility of VDZ-CDSTs in predicting BioRES. Future well-designed, multinational studies in the Asian population are necessary to optimise the function of VDZ-CDSTs and, ultimately, develop well-fitted, Asian-specific CDSTs.

AUTHOR CONTRIBUTIONS

Kyuwon Kim: Conceptualization; data curation; formal analysis; investigation; writing – original draft; writing – review and editing. **Jae Jun Park:** Formal analysis; investigation; writing – original draft; writing – review and editing. **Hyuk Yoon:** Investigation; writing – original draft; writing – review and editing. **Jun Lee:** Investigation; writing – original draft; writing – review and editing. **Kyeong Ok Kim:** Investigation; writing – original draft; writing – review and editing. **Eun Sun Kim:** Investigation; writing – original draft; writing – review and editing. **Su Young Kim:** Investigation; writing – original draft; writing – review and editing. **Sun-Jin Boo:** Investigation; writing – original draft; writing – review and editing. **Yunho Jung:** Investigation; writing – original draft; writing – review and editing. **Jun Hwan Yoo:** Investigation; writing – original draft; writing – review and editing. **Sung Wook Hwang:** Investigation; writing – original draft; writing – review and editing. **Sang Hyoung Park:** Investigation; writing – original draft; writing – review and editing. **Suk-Kyun Yang:** Investigation; writing – original draft; writing – review and editing. **Byong Duk Ye:** Conceptualization; funding acquisition; investigation; project administration; supervision; writing – original draft; writing – review and editing.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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