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Diverticular Inflammation and Complication Assessment classification, CODA score and fecal calprotectin in clinical assessment of patients with diverticular disease: A decision curve analysis

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Abstract

Background and Aims: The Diverticular Inflammation and Complication Assessment (DICA) classification and the Combined Overview on Diverticular Assessment (CODA) were found to be effective in predicting the outcomes of Diverticular Disease (DD). We ascertain whether fecal calprotectin (FC) can further aid in improving risk stratification.

Methods: A three-year international, multicentre, prospective cohort study was conducted involving 43 Gastroenterology and Endoscopy centres. Survival methods for censored observations were used to estimate the risk of acute diverticulitis (AD) in newly diagnosed DD patients according to basal FC, DICA, and CODA. The net benefit of management strategies based on DICA, CODA and FC in addition to

[†]The co-author Fabio Baldi is deceased.

CODA was assessed with decision curve analysis, which incorporates the harms and benefits of using a prognostic model for clinical decisions.

Results: At the first diagnosis of diverticulosis/DD, 871 participants underwent FC measurement. FC was associated with the risk of AD at 3 years (HR per each base 10 logarithm increase: 3.29; 95% confidence interval, 2.13–5.10) and showed moderate discrimination (c-statistic: 0.685; 0.614–0.756). DICA and CODA were more accurate predictors of AD than FC. However, FC showed high discrimination capacity to predict AD at 3 months, which was not maintained at longer follow-up times. The decision curve analysis comparing the combination of FC and CODA with CODA alone did not clearly indicate a larger net benefit of one strategy over the other.

Conclusions: FC measurement could be used as a complementary tool to assess the immediate risk of AD. In all other cases, treatment strategies based on the CODA score alone should be recommended.

KEYWORDS
acute diverticulitis, CODA score, DICA score, diverticular disease, diverticulosis, fecal calprotectin

INTRODUCTION

Although diverticulosis of the colon is the most frequently recognized anatomical alteration during colonoscopy,[1] for many years, an endoscopic classification has been absent, and only imaging-based[2–4] or clinically based[5–7] classifications have been available. Nonetheless, endoscopic diverticular inflammation is detected in up to 2% of patients undergoing colonoscopy.[8–10]

In 2015, the first endoscopic classification of diverticulosis/diverticular disease, called "Diverticular Inflammation and Complication Assessment" (DICA), was presented.[11] After its validation in two studies,[12,13] a recent large prospective study confirmed that this classification has a significant impact in predicting disease outcomes.[14] Its clinical evolution, a prognostic score named "Combined Overview on Diverticular Assessment" (CODA), enhanced the predicting value of this classification.[14]

Fecal calprotectin (FC) is a cytoplasmic antimicrobial protein mainly detected in granulocytes, monocytes, and macrophages. This protein, which is released during cell activation or death, is stable in feces for several days after excretion.[15] FC has shown to be a sensitive marker of activity in inflammatory bowel diseases[16] and in predicting disease relapses.[16]

Increased levels of FC may also be found in systemic diseases involving the gastrointestinal tract,[17] such as diverticular disease (DD). FC was found to increase in symptomatic uncomplicated diverticular diseases (SUDD).[18] It was able to discriminate SUDD from Irritable Bowel Syndrome,[18] and dropped significantly after treatment.[19–21] However, we do not know whether and when FC may be included in the decision-making process for DD.

In this study, we performed a prospective investigation and applied decision curve analysis to assess the role of FC in patients with DD according to the DICA classification and CODA score. We compared the net benefit of management strategies based on the DICA classification and CODA score with a strategy based on baseline FC

Key summary

Summarize the established knowledge on this subject

- The Diverticular Inflammation and Complication Assessment (DICA) classification and the Combined Overview on Diverticular Assessment (CODA) score are validated prognostic tools for diverticulitis.
- However, the role of Fecal Calprotectin (FC) in the decision-making process in Diverticular Disease (DD) in comparison with the available validated tools is unknown.

What are the significant and/or new findings of this study?

- This large (871 patients) prospective cohort study collected FC from DD patients inEurope and South America, who were prospectively followed up for three years.
- The CODA score provided the best predictive accuracy and net benefit in predicting acute diverticulitis (AD) in the long-term (3-year). FC showed a comparative short-term prognostic value with CODA (3 months) and enhanced the prognostic value of the DICA endoscopic classification.
- FC measurement, together with the DICA classification and CODA score, may be a possible tool to gauge the short-term risk of acute-diverticulitis.

alone or in combination with the CODA score. The results of the current study may improve and guide decision making in patients with DD.

METHODS

Study design and study aims

This is a post-hoc analysis of an international multicentre prospective cohort study that included 871 patients with DD in 43 centres located in Europe and South America. A centralized laboratory analysis of FC was not planned in our initial study protocol. To homogenize and increase the comparability across centres, we considered as valid FC measurements only those deriving from quantitative assays expressed in μg/g.

Our aims were (i) to evaluate the prognostic capacity of FC for predicting diverticulitis in patients with diverticulosis/DD, (ii) to compare the prognostic performance of FC with validated prognostic tools available (i.e., DICA classification and CODA score),[14] and (iii) to compare the clinical utility of management strategies based on the CODA classification, the DICA score, and the combination of CODA score with FC by comparing the net benefit of management strategies based on the three different prognostic approaches.

Only patients at the first diagnosis of diverticulosis/DD (i.e., newly diagnosed DD patients) were enrolled during a consecutive period of 6 months. A common database was built to collect demographic and clinical data. Symptoms were assessed using a 10-point visual scale, from 0 (absence) to 10 (worst).

Patients were clinically assessed at entry, after 3, 6, 9 and then every 6 months for 3 years. The duration of follow-up was estimated on the available data about AD occurrence/recurrence. AD occurrence is generally low in diverticulosis,[22] and generally occurs within 2 years in patients with SUDD.[23] Moreover, diverticulitis usually recurred within 18 months mainly.[10] As DICA 1 is a diverticulosis without a sign of inflammation but can be associated with symptoms, similar to the ones occurring in SUDD (1), and DICA 2 and 3 are diverticulosis with a sign of present (DICA 2) or present/past inflammation (DICA 3), we thought that a 3-year follow-up was the right follow-up time to observe the outcome of the diverticulosis/DD according to the DICA classification. Detailed eligibility criteria are reported in the extended method section.

Statistical analysis

Descriptive statistics included medians and interquartile ranges (IQR) for continuous variables and frequency analyses for categorical variables. The two-sample Wilcoxon rank-sum test or the Kruskal–Wallis test were used to compare continuous variables across groups.

We assessed the association between FC measured at baseline and diverticulitis by means of time-to-event (survival) methods for censored observations. Time to event was defined as the time from the baseline visit until the date of event or censoring. Kaplan–Meier estimates were employed to plot cumulative incidence curves, compared by log-rank tests and univariate Cox regression.

The value of any new candidate prognostic biomarker should be evaluated against the best available prognostic tools. We fit four Cox regression models considering as predictors: (i) the DICA classification; (ii) the CODA score (i.e., a multivariable model including component predictors DICA classification, age, and pain score, as appropriate)[24]; (iii) DICA classification and FC; (iv) CODA score (i.e., component predictors) and FC. To assess whether the model fit was significantly improved by adding FC to the validated prognostic tools available (i.e., the DICA classification and CODA score), we applied a likelihood ratio (LR) test. For all models, a linear combination of predictors and individual predicted probability was computed.

The base 10 logarithm of baseline FC treated as a continuous variable was used. To display the predictive potential of FC, we plotted Kaplan–Meier curves stratified by FC dichotomized at a threshold of 90 μg/g. This threshold was selected by maximally selected rank statistics (*R* package: *survminer*).

We assessed model discrimination using the Harrell's c-statistic.[24] We computed the Brier score for right censored data to gauge the predictive accuracy of these models, and calculated the Nagelkerke's *R*-squared (as a measure of overall model performance).[24] Regarding the univariable model including FC as the only predictor, we assessed model calibration by plotting the observed proportion versus predicted risk of diverticulitis and reporting a smoothed calibration curve with 95% confidence intervals across the risk spectrum.[24] We also reported a calibration plot for the model consisting of a combination of CODA score and FC.

To assess whether the discrimination capacity of FC varies over time (i.e., prediction in the short-term vs. long term), we used time-dependent receiver operating characteristic (ROC) curve analysis by means of inverse probability of censoring weighting (*R package*: timeROC).[25]

Decision curve analysis

When a new candidate biomarker is added to an existing validated score, changes in the discrimination capacity are usually minimal. For this reason, using discrimination measures to establish the usefulness of a new biomarker has been duly criticized. We compared the clinical utility of the existing prognostic tools (i.e., DICA classification and CODA score) with that of the addition of FC to the CODA score by quantifying the net benefit of these management strategies when different threshold probabilities for prognosis of diverticulitis were considered (i.e., decision-curve analysis; see eAppendices 1 and 2).[26,27]

Stata software (Stata Corp., College Station, TX, USA) and the R software were used for statistical analysis.

RESULTS

Table 1 reports the baseline demographic and clinical characteristics. Patients were predominantly men (50.4%) with a median age of

TABLE 1 Baseline demographic and clinical characteristics of the study population ($N = 871$).

	Median (IQR) or *N* (%)
Age, years	65 (56–72)
≥65	451 (51.8)
Gender, male	439 (50.4)
BMI, kg/m^2	26 (23.2–28.9)
≥30	166 (19.1)
Smoking	
Smokers	246 (28.2)
Non-smokers	513 (58.9)
Ex-smokers	112 (12.8)
Appendectomy	224 (25.7)
Presence of co-morbidities	
Charlson's score	3 (2–4)
Charlson's score >3	220 (25.2)
Presence of any symptom	682 (78.3)
Cumulative symptom score[a]	8 (2–13)
>7	441 (50.6)
Abdominal pain	2 (0–5)
>2	404 (46.4)
Meteorism	2 (0–4)
>2	371 (42.6)
Constipation	0 (0–2)
>2	208 (23.9)
Diarrhea	0 (0–2)
>2	199 (22.8)
DICA classification	
1	488 (56.0)
2	279 (32.1)
3	104 (11.9)
CODA score	10 (7–16)
Fecal calprotectin, μg/g	25 (12–70)
>90[b]	151 (17.3)

Note: Values are expressed as number (percentage) for categorical variables and as median (interquartile range) for continuous variables.

Abbreviations: BMI, body mass index; IQR, interquartile range.

[a]The cumulative symptom score ranges from 0 to 40 points. It is obtained by adding the points regarding abdominal pain, meteorism, constipation, and diarrhea as measured on a 10-points visual analog scale.

[b]This threshold was selected by the maximally selected rank statistic (see Methods section).

65 years (IQR, 56–72). They were slightly overweight (median BMI: 26; IQR 23.2–28.9), and 28.2% of them were smokers. Most patients (56.0%) had a DD corresponding to DICA 1 classification, 32.1% DICA 2, and 11.9% DICA 3, and a median CODA score of 10 (IQR, 7–16). Basal FC varied widely across patients and ranged from 8 to 1800 μg/g with a median of 25 μg/g (IQR, 12–70).

A total of 65 diverticulitis events and 19 surgeries due to complications occurred during an average follow-up of 2.8 years. The cumulative incidence of diverticulitis was 26.5 per 1000 person-years, corresponding to an estimated 3-year risk of 7.6% (95% CI, 6.0–9.6%). The cumulative incidence of surgery due to complications was 7.7 per 1000 person-years, corresponding to an estimated 3-year risk of 2.3% (95% CI, 1.4–3.5%).

Prognostic significance of fecal calprotectin

Higher baseline FC levels, expressed as the base 10 logarithms, were significantly associated with increased hazard of developing AD over the 3-year follow-up (HR, per each log unit increase: 3.29; 95% CI, 2.13–5.10; $p < 0.001$). The estimated 3-year cumulative probability of diverticulitis was 5.2% (95% CI, 3.8–7.1%) in patients with basal FC < 90 μg/g, and 18.9% (95% CI, 13.5–26.2%) in patients with basal FC ≥ 90 μg/g, which significantly differed across strata (log-rank test, $p < 0.001$; Figure 1). Baseline FC levels were significantly ($p < 0.001$) higher in patients who later developed AD (median: 77 μg/g; IQR, 30–178 μg/g) as compared to those who did not (median: 24 μg/g; IQR, 12–66 μg/g; Figure 2a). FC increased with increasing DICA classification (Kwallis test, $p < 0.001$; Figure 2b) and increasing CODA scores (Kwallis test, $p < 0.001$; Figure 2c). FC showed good apparent calibration (Appendix Figure 1), and moderate discrimination (c-statistic: 0.685; 95% CI, 0.614–0.756). Table 2 summarizes other measures of performance.

Comparison of fecal calprotectin with the DICA classification and CODA score

The DICA classification and the CODA score are validated prognostic tools for predicting the clinical outcomes of DD.[1] We confirmed that DICA classification and CODA score were significant predictors of the risk of diverticulitis in the study population as shown in Table 2, and Appendix Tables 1 and 2. The c-statistics of the DICA classification (0.779; 95% CI, 0.728–0.830) and CODA score (0.827; 95% CI, 0.786–0.868) were significantly higher compared with FC (p-values for the difference: 0.020 and 0.001, respectively). As apparent from the other measures of performance, both DICA classification and CODA score were better prognostic tools than FC alone.

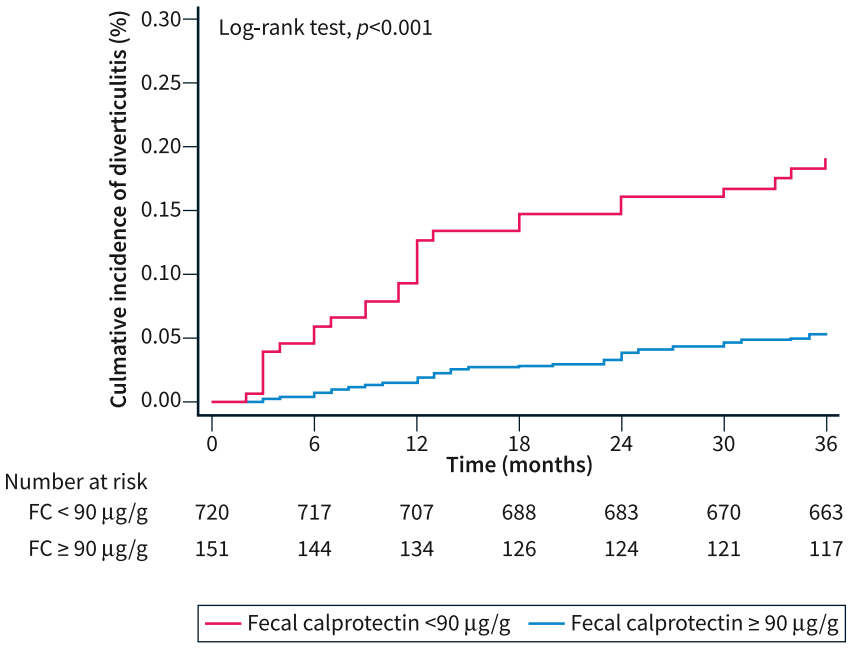

FIGURE 1 Kaplan–Meier curves of cumulative incidence of diverticulitis from patients categorized into high and low fecal calprotectin (FC) levels at baseline. The threshold (90 µg/g) was selected by maximally selected rank statistics. This threshold is used purely for illustrative reasons and should not be considered as the best threshold to adopt for long-term decision making.

Combination of fecal calprotectin with DICA classification and CODA score

FC and DICA classifications were both fitted in a multivariable Cox model (Appendix Table 3). An LR test indicated an improved model fit over a Cox model using DICA classification as the only predictor (LR test, $p = 0.003$). The combination of FC and DICA classification showed a slight but significant increase in discrimination capacity over DICA classification alone (c-statistic: 0.806 vs. 0.779, p-value for the difference = 0.022; Table 2).

The FC and CODA score (i.e., its predicting components)[24] were fitted in a multivariable Cox model (Appendix Table 4). The LR test indicated an improved model fit over a Cox model using the CODA score alone (LR test, $p = 0.010$). The discrimination capacity of the combination of FC and CODA score did not differ in comparison to that of CODA score alone (c-statistic: 0.832 vs. 0.827, p-value for the difference = 0.41; Table 2). The individual probability of developing diverticulitis for each of the 871 patients according to the linear combination of CODA score and FC is displayed in Appendix Figure 2, and its calibration is reported in Appendix Figure 3.

Clinical utility of management strategies based on DICA classification, CODA score, and the combination of CODA score and fecal calprotectin

To evaluate and compare the clinical utility of management strategies based on the CODA classification, the DICA score and the combination of the CODA score and FC, we used the decision curve analysis. Decision curve analysis inherently incorporates the consequences of clinical action that is the result of risk stratification after applying a prognostic score or rule. It is important to show that taking clinical actions on the basis of a certain prognostic score offers a larger net benefit over other existing strategies in a range of plausible thresholds. For extended guidance on how to interpret the decision curve analysis, please refer to eAppendix 2.

We examined the relationship between a range of threshold probabilities for predicting diverticulitis in patients with DD and the relative value of false-positive and false-negative results (i.e., the net benefit). The net benefit of the three management strategies was plotted and compared (Figure 3). Here, we compared strategies based on DICA classification (strategy 1), CODA score (strategy 2), and the linear combination of CODA score and FC (strategy 3). All three scores offered a better net benefit than a strategy of "treating all" and "treating none" over a large range of plausible threshold probabilities. Among the three management strategies, strategy 1 based on the DICA classification offered the lowest net benefit at most threshold probabilities. Between strategies 2 and 3, no score offered a clearly larger net benefit over the other in the entire spectrum of plausible threshold probabilities. More in detail, strategy 2 based on the CODA score offered the largest net benefit at decision thresholds from 16% to 22% and from 29% to 37%, whereas strategy 3 based on the CODA score and FC offered a larger benefit at other threshold probabilities except for those below 8%, where strategies 2 and 3 offered a similar net benefit. Under these circumstances, a simpler and less expensive strategy should be recommended (i.e., a treatment strategy based on the CODA score alone).

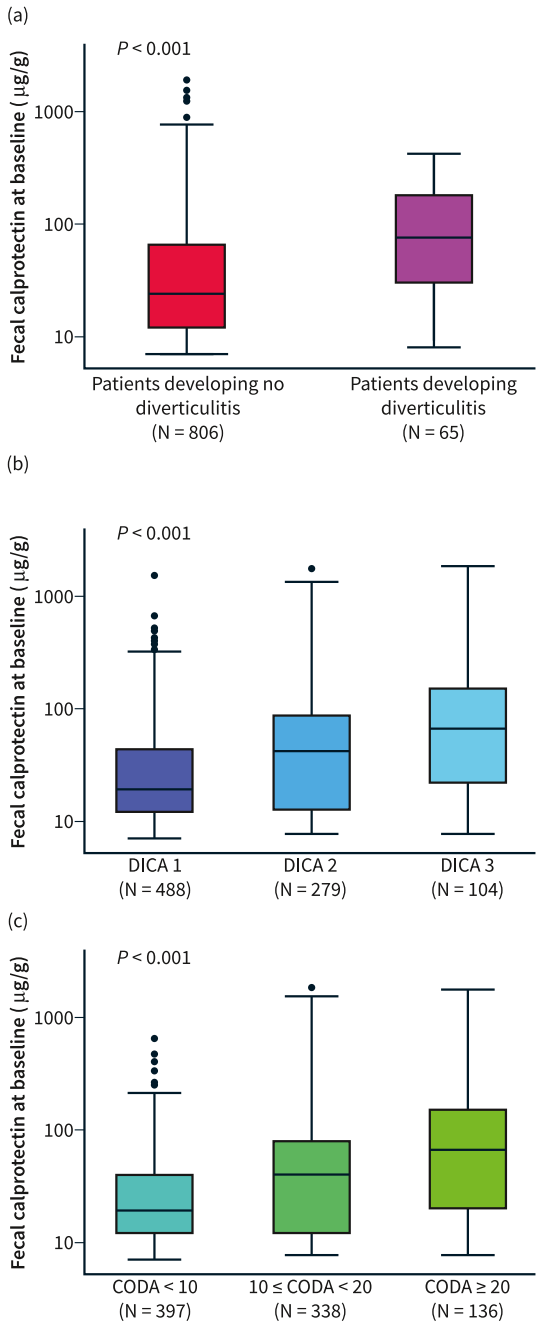

FIGURE 2 Box plots displaying (a) baseline fecal calprotectin (FC) in patients who developed diverticulitis versus those who did not; (b) by Diverticular Inflammation and Complication Assessment (DICA) endoscopic classification levels; (c) and by Combined Overview on Diverticular Assessment (CODA) score. The *p*-values reported correspond to a two-sample Wilcoxon rank-sum test (a) and the Kruskal–Wallis test (b and c).

Short-term prediction of clinical outcomes

FC is a non-invasive intervention that may be used for the short-term management of patients with DD. We investigated its prognostic value in a timeframe of 3 months instead of the previous analyses conducted at 3 years of follow-up.

The time-dependent area under receiving operator curves at 3 months showed very high discrimination capacity for FC (time-dependent $AUC_{3months}$ = 0.976, 95% CI: 0.966–0.986), CODA score ($AUC_{3months}$ = 0.962, 95% CI: 0.950–0.974), and DICA classification ($AUC_{3months}$ = 0.943, 95% CI: 0.933–0.954). The discrimination capacity of FC at 3 months was comparable to that of the CODA score (*p* for the difference = 0.10) and significantly higher than that of the DICA score ($p < 0.001$). The Brier score at this time-frame was virtually the same for the two scores and FC (0.009; 95% CI: 0.003–0.015).

The discrimination capacity of FC decreased quickly with longer follow-up times, while the discrimination by DICA and CODA was more stable and higher at longer follow-up times (Appendix Figure 4). FC demonstrated a significant short-term prognostic value, which, however, deteriorated quickly after 3 months. Accordingly, Figure 4 describes the possible short-term (3-month) risk stratification of patients with newly diagnosed colonic diverticulosis detected on endoscopy.

DISCUSSION

The field of gastroenterology moves forward in the evolving landscape of personalized medicine. Collecting biomarkers through non-invasive methods to predict the evolution of a disease has become increasingly common. FC is an easily collected biomarker that correlates with the severity of inflammatory bowel diseases (IBD) (mainly ulcerative colitis), may predict the course of these diseases, and harbours immune-regulatory functions.[28] These properties render it an interesting marker of inflammation in DD.

In this context, FC has been used mainly to differentiate DD from irritable bowel syndrome as well as non-invasive marker of inflammation in response to treatment or following an episode of AD.[1,29] However, the extent to which FC could predict the course of DD was rather uncertain before the current study. We recently found that the DICA endoscopic score, its clinical evolution, and the CODA score accurately predict the evolution of DD.[14] Both these prognostic tools have been developed and validated in a wide international prospective study, but the role of FC in comparison with DICA and CODA is unknown.

We found FC to be a moderately accurate predictor of the 3-year risk of diverticulitis. FC levels were strongly associated with the DICA classification and classes of CODA score. Despite this, DICA classification and CODA score were both more accurate predictors of AD in the long-term. This finding is not surprising. Although calprotectin is a useful marker of inflammation, both DICA and CODA rely on a structured endoscopic evaluation; thus, they can provide a more exhaustive picture of the risk of complications in patients with DD, which is characterized by extensive structural and functional changes of the bowel wall.[1]

In personalized medicine, it is important to use up-to-date methodology to guide decisions in clinical practice. As recently reported,[30,31] decision analytic methods are useful tools to determine

TABLE 2 Performance measures of fecal calprotectin, DICA classification, CODA score, and the combination of fecal calprotectin with these two prognostic tools in predicting subsequent acute diverticulitis.

	Harrel's c-statistic (95% CI)	Brier score (95% CI)	Nagerlkerke's R^2 (95% CI)
Fecal calprotectin[a]	0.685 (0.614–0.756)	0.0610 (0.0466–0.0754)	0.226 (0.091–0.409)
DICA classification	0.779 (0.728–0.830)	0.0525 (0.0396–0.0653)	0.571 (0.399–0.734)
DICA classification + fecal calprotectin[a]	0.806 (0.755–0.857)	0.0507 (0.0381–0.0633)	0.619 (0.448–0.778)
CODA score	0.827 (0.786–0.868)	0.0498 (0.0373–0.0623)	0.659 (0.525–0.798)
CODA score + fecal calprotectin[a]	0.832 (0.793–0.871)	0.0486 (0.0362–0.0609)	0.689 (0.568–0.834)

Abbreviations: CI, confidence interval; CODA, Combined Overview on Diverticular Assessment; DICA, Diverticular Inflammation and Complication Assessment; FC, fecal calprotectin.

[a]The base 10 logarithm of baseline FC as a continuous variable.

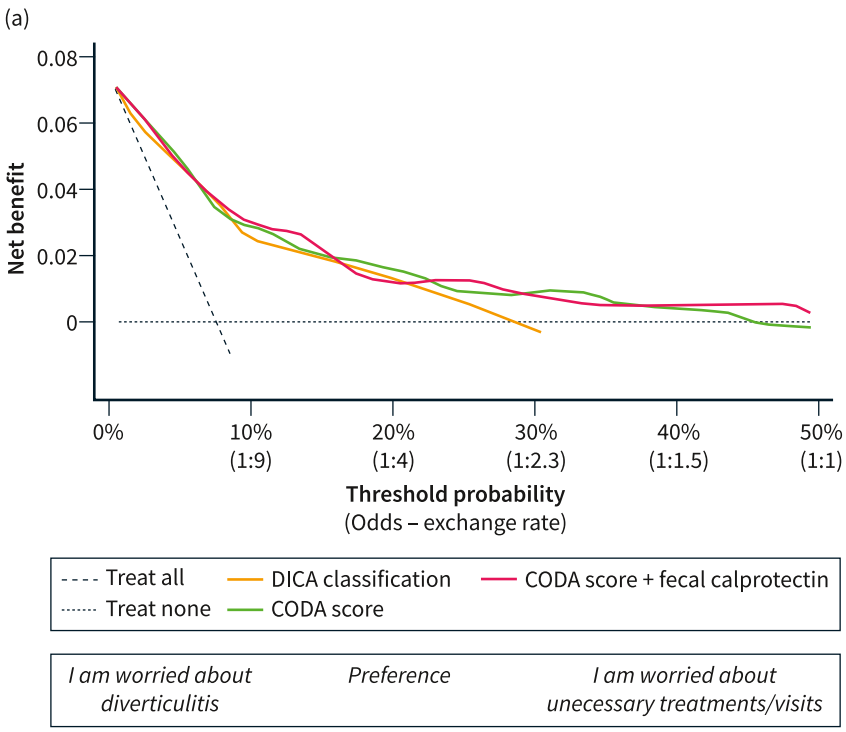

FIGURE 3 Decision curve analysis plotting the net benefit of management strategies adopted on the basis of three prognostic tools predicting the 3-year risk of diverticulitis in patients with Diverticular Disease (DD). The net benefit corresponding to using the Diverticular Inflammation and Complication Assessment (DICA) classification (in orange), the Combined Overview on Diverticular Assessment (CODA) score (in green) and the CODA score plus fecal calprotectin (FC) are compared to strategies to "treat all" (diagonal dashed line) and "treat none" (horizontal dashed line). The net benefit, plotted on the *y* axis, is a metric representing the benefit of a certain intervention minus its harms multiplied by an exchange rate (*x* axis). The unit of net benefit is true positive. A net benefit of 0.05, for instance, means to find "5 true positives for every 100 patients in the target population" with no harms (i.e., benefit is "net"). The net benefit is plotted over a range of possible decision thresholds/exchange rates (i.e., individual predicted probabilities derived by applying the prognostic tool). The net benefit also incorporates any consequence (i.e., clinical actions taken) of knowing the individual risk of a subsequent diverticulitis. The net benefit of five different strategies is compared. The two extreme—default—strategies are "treat all" (diagonal dashed line) and "treat none" (horizontal dashed line), meaning enacting clinical actions as if all patients with DD will develop diverticulitis (i.e., "treat all"), or as if nobody of them will develop diverticulitis (i.e., "treat none"). The *x* axis can also be renamed preference: clinicians more worried about the harms of a missed diverticulitis (i.e., true positive) will adopt thresholds closer to a predicted probability of zero (i.e., left side of the graph), while clinicians more worried about the harms/costs of unnecessary interventions/visits (i.e., on false positives) will adopt higher thresholds (i.e., right side of the graph). The *x* axis is also called "exchange rate", which is an odds ratio and represents how many false positives are worth one true positive (i.e., adopting a threshold probability of 20% means that a patient with a predicted probability over 20% will be considered likely to develop diverticulitis—and treated accordingly—and by adopting this classification rule/threshold, one accepts that one true positive is worth four false positives). Interventions associated with different harms/costs may need the adoption of different thresholds/exchange rates. The prognostic tool corresponding to the highest net benefit over the largest range of threshold probabilities should be adopted. When this is unclear, the simpler prognostic tool or the one corresponding to lower costs/harms/inconvenience should be used. For a comprehensive guidance regarding interpreting the decision curve analysis, please see eAppendix 2.

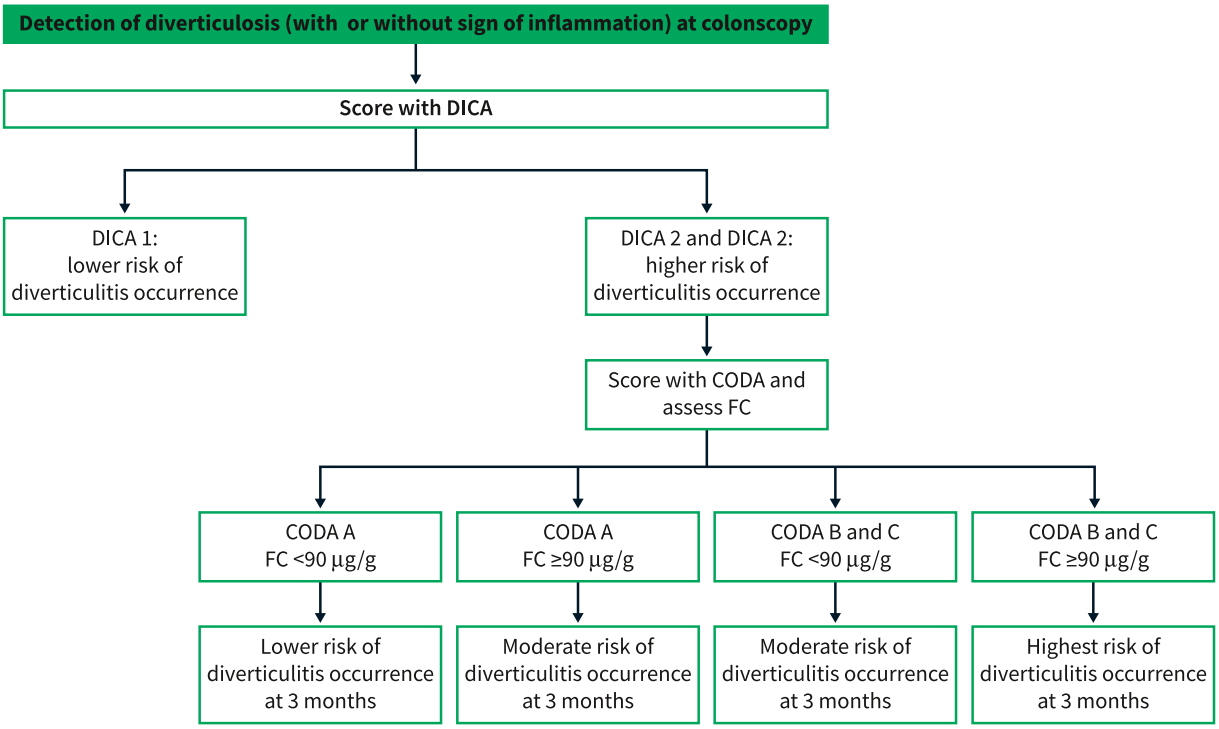

FIGURE 4 Flow-chart suggesting the possible short-term (3-month) risk stratification of patients with newly diagnosed colonic diverticulosis detected on endoscopy. CODA, Combined Overview on Diverticular Assessment; DICA, Inflammation and Complication Assessment; FC, fecal calprotectin.

under which circumstances prognostic scores and biomarkers provide the net benefit for a population of patients. In this study, we used the decision curve analysis to compare the net benefit of management strategies based on the DICA classification and CODA score (i.e., the two existing validated prognostic scores for predicting clinical outcomes of DD) with a strategy based on baseline FC alone or in combination with the CODA score.

FC enhanced the predictive value of DICA classification over the course of DD; however, this was not the same for the CODA score. When used in combination with CODA, there was no clear net benefit in comparison to CODA alone. In other words, adding two clinical parameters or adding FC to the DICA classification provided similar net benefits for patients with DD over the spectrum of plausible thresholds used for decision making. FC seems to be an important but not a mandatory tool in the decision making in patients suffering from DD, limiting its use in predicting the long-term evolution of the disease. Moreover, FC has some limitations regarding its use in real life: lack of standardized assessment,[32] no easy availability even in developed countries,[33] and high variability across well-known diseases.[34]

Irrespectively of the role of FC, the DICA classification has been confirmed as the keystone to build up a reliable predicting score for the outcome of DD. Adding clinical (CODA score) or laboratory (FC) findings enhances the prognostic value of DICA, but assessing the colon harboring diverticula with this classification is a necessary step to set up reliable decision-making in these patients. Of course, the DICA classification has some limitations. It is useful when the patient is diagnosed first with diverticulosis/DD, but we do not know whether it may be useful in the same way in patients with well-known diverticulosis/DD and, probably, already treated. Moreover, we do not know yet whether DICA-based risk stratification can improve treatment choices. Considering this, new therapeutic trials should be designed according to these classifications in order to identify patients with DD who need prophylactic treatment.

However, updating the DICA classification or the CODA score of a patient over time would require new colonoscopy; thus, it cannot be performed often, especially in fragile patients. FC may be a non-invasive tool providing useful short-term information when the DICA classification of a patient may be outdated (i.e., >3 years). The discrimination capacity of FC in predicting AD in the short term (i.e., 3 months) was very high with no significant differences as compared to CODA. This finding may support the complementary use of FC to gauge the short-term risk of acute-diverticulitis and perhaps as a surrogate marker to assess treatment effectiveness. This novel finding, however, should be considered in light of the study limitations. This study is a post-hoc analysis of an international multicentre prospective cohort study. A centralized laboratory analysis of FC was not planned in our initial study protocol, which is a weakness. Although we took steps to increase the comparability across centres, further studies using a standardized and centralized assessment of FC are warranted to confirm our findings on the use of FC to assess the short-term risk of AD.

In conclusion, we believe that the results of the current study can contribute to improving decision making in patients with DD. Our

data suggest that FC may predict clinical outcomes in the short-term. If adequately confirmed in further ad hoc studies, this biomarker could be used as a complementary tool to assess the immediate risk of diverticulitis in patients with longstanding DD in whom performing further colonoscopy is deemed inconvenient or unfeasible.

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CONFLICT OF INTEREST STATEMENT

Silvio Danese, MD, PhD, served as speaker, consultant, and/or advisory board member for Abbvie, Allergan, Alfa Wassermann, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Gilead, Hospira, Johnson and Johnson, Merck, MSD, Mundipharma, Pfizer Inc., Sandoz, Takeda, Tigenix, UCB Pharma, Vifor: Giovanni Maconi, MD, served as speaker and/or advisory board fees for AlfaSigma, Arena, Janssen, Gilead, Roche; Gerardo Nardone, MD, PhD, received funding for target projects from Apharm and Sofar; Anna Pietrzak, MD, served as lecturer for AlfaSigma and Polpharma; Jaroslaw Regula, MD, PhD, served as lecturer for AlfaSigma, Takeda, Ipsen and Servier; Franco Scaldaferri, MD, PhD, served as lecturer for Sanofi; The remaining authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL

The study was conducted according to the World Medical Association Declaration of Helsinki of 1975. It was approved by the Ethic Committee of the coordinator centre and all participating centres. The study was recorded at www.ClinicalTrials.gov (NCT02758860).

PATIENTS CONSENT STATEMENT

All study participants provided informed written consent prior to endoscopic investigation and to take part in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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