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Gut Microbiota Perturbation Are Linked to Endoscopic Severity of Diverticular Disease

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ABSTRACT

Background & Aims: It is not known whether the gut microbiota (GM) may vary according to the endoscopic severity of diverticular disease (DD). We aimed to profile the GM in DD patients according to the severity of the diverticular inflammation and complication assessment (DICA) classification (DICA 1 vs. DICA 2 vs. DICA 3).
Methods: We retrospectively assessed the GM in a population of patients with DD. We analyzed stool samples collected by fecal swab for microbiological studies. Among them, we identified DD patients in whom DD was scored according to DICA classification. The severity of the abdominal pain was measured using a 10-point visual analogue scale (VAS).
Results: The GM of 71 DD patients [49 (69.0%) were scored as DICA1, 18 (25.4%) as DICA2, and 4 (5.6%) as DICA3 was analysed. The three groups did not differ in alpha diversity, but significantly separated in the PCoA of beta diversity (p=0.018). Taxonomically, DICA1 group was characterized by higher relative abundances of the phylum *Actinobacteriota*, the families Erysipelatoclostridiaceae and *Bacteroidaceae*, and the *genera Lachnospiraceae ND3007 group* and *Bacteroides* (p≤0.1); DICA2 group was mainly discriminated by higher proportions of *Streptococcaceae* (p=0.018); DICA3 group was mainly discriminated by the phylum *Bacteroidota*, the families *Prevotellaceae* and *Succinivibrionaceae*, and the genera *Prevotella, Alloprevotella* and *Dialister* (p≤0.045). Stratifiyng patients by abdominal pain severity, only for the DICA2 group the PCoA of beta diversity showed a significant separation between the moderate and severe groups (p=0.024), with the latter also showing higher alpha diversity (p=0.05). Taxonomically, the severe group was enriched in the families *Enterobacteriaceae* and *Erysipelotrichaceae*, and the genera *Megasphaera* and *Veillonella*, while depleted in *Sutterellaceae* and *Blautia* compared to the moderate group (p≤0.08).
Conclusions: GM in DD may vary according to endoscopic disease severity and clinical characteristics. Such associations may improve patient stratification and clinical management.

Key words: DICA classification – diverticulosis – diverticular disease – gut microbiota – abdominal pain severity – Bristol stool form scale.

Abbreviations: AD: acute diverticulitis; DD: diverticular disease; DICA: diverticular inflammation and complication assessment; GM: gut microbiota; PCoA: Principal Coordinates Analysis; SUDD: symptomatic uncomplicated diverticular disease; VAS: visual analogue scale.

INTRODUCTION

Despite the large number of colonoscopies routinely performed worldwide, with diverticulosis of the colon being the most common anatomical alteration detected [1], the first endoscopic classification of diverticulosis/diverticular disease (DD), called "Diverticular Inflammation and Complication Assessment" (DICA), was developed only in 2015 [2]. This classification has been validated through a continuous process [3, 4], and a recent large, prospective, and international study confirmed its role in predicting disease outcomes [5]. To date, the DICA classification has shown a significant relationship with several factors, both laboratory (erithro-sedimentation rate, C-reactive protein, and fecal calprotectin expression) [2, 6] and clinical (severity of diarrhoea and constipation) [7].

The gut microbiota (GM) is increasingly recognized as an important player in the pathogenesis of several intestinal diseases, including diverticular disease [8]. In particular, GM perturbations have been found in both symptomatic

uncomplicated diverticular disease (SUDD) [9-12] and acute diverticulitis (AD) [13]. However, we do not know whether GM abnormalities may also link to the endoscopic severity of DD. Here, we retrospectively evaluated DD patients for whom GM data are publicly available [11], and assessed potential differences in GM between patients with different disease scores, DICA 1, DICA 2 and DICA 3.

METHODS

We retrospectively assessed the GM in a population of patients with DD managed in primary care by general practitioners and territorial gastroenterologists. We analyzed stool samples collected by fecal swab for microbiological studies and stored at the Unit of Microbiome Science and Biotechnology, Department of Pharmacy and Biotechnology, University of Bologna (Bologna, Italy). Among them, we identified DD patients in whom DD was scored according to DICA classification [2], and whose fecal samples were collected between 1 March 2022 and 1 March 2023. The severity of the abdominal pain was measured using a 10-point visual analogue scale (VAS).

The study was conducted in accordance with clinical practice guidelines and the principles of the Declaration of Helsinki. All patients gave written informed consent before undergoing endoscopy and/or computed tomography scan and/or fecal sampling. Ethic Committee approval for this retrospective study was obtained from the Azienda Ospedaliero-Universitaria Ospedali Riuniti, Foggia, Italy (PROT. 164/CE/2023, October 23, 2023).

Inclusion criteria were: males and females >18 years; colonic DD diagnosed by colonoscopy and scored according to DICA classification [2] during the 6 months prior to enrolment; possibility of retrospectively reconstructing the symptoms (in particular the severity of abdominal pain by using a 10-point visual analogue scale, VAS, and bowel habits according to the Bristol stool form scale; fecal microbiota assessment performed at the Unit of Microbiome Science and Biotechnology, Department of Pharmacy and Biotechnology, University of Bologna (Bologna, Italy).

Exclusion criteria were: current or previous diagnosis (by abdominal computed tomography and/or ultrasonography) of AD (defined as inflammation of the colonic wall harboring diverticula with fat stranding, with or without complications such as abscesses, stenosis or fistulas, namely uncomplicated or complicated diverticulitis) [1]; inflammatory bowel diseases; ischemic colitis; prior colonic resection; patients with severe liver failure (Child-Pugh C); patients with severe kidney failure; pregnant women; women of childbearing potential not using a highly effective method of contraception; patients currently using or who have received any laxative agents <4 weeks prior to enrolment; patients currently using or who have received any mesalamine compounds <4 weeks prior to enrolment; patients currently using or who have received any probiotic agents <4 weeks prior to enrolment; use of non-steroidal anti-inflammatory drugs (NSAIDs) (except for acetyl-salicylic acid ≤100 mg/day) <4 weeks prior to enrolment; patients treated with antibiotics (including those not absorbed) <4 weeks prior to enrolment; patients with a history of cancer, of any origin, at the time of stool collection, and/or under treatment with chemotherapy and/or radiotherapy; a history of alcohol, drug, or chemical abuse; patients with a current or recent (≤3 months) episode of COVID-19 [14] at the time of the stool collection.

The primary endpoint was to profile the GM in SUDD patients according to the severity of the DICA classification (DICA 1 vs. DICA 2 vs. DICA 3). The secondary endpoint was to investigate correlations among GM, DICA classification and other patient metadata, namely abdominal pain severity (the main symptom characterizing DD) according to VAS score, and bowel habits according to the Bristol stool form scale.

Bioinformatics and Statistical Analysis

Raw sequences, obtained by 16S rRNA amplicon sequencing on an Illumina MiSeq platform, were deposited in the National Center for Biotechnology Information Sequence Read Archive (BioProject ID: PRJNA1216941). They were processed using a pipeline combining PANDASeq [15] and QIIME 2 [16]. After filtering for length and quality, reads were grouped into amplicon sequence variants (ASVs) using DADA2 [17]. Taxonomic assignment was performed using the VSEARCH algorithm [18] against the SILVA database (August 2020 release) [19], with chimeras systematically discarded during analysis. Alpha diversity was assessed using several metrics, such as the Shannon index, the number of observed ASVs and Faith's phylogenetic diversity. Beta diversity was assessed using weighted UniFrac distances, which were then used for Principal Coordinates Analysis (PCoA) plots.

All statistical analyses were performed using R software. PCoA plots were generated using the "vegan" (https://cran.r-project.org/package=vegan) and "Made4" [20] packages, and data separation was tested using PERMANOVA (function "Adonis" in "vegan"). Group differences in alpha diversity and relative taxon abundance were assessed using the Kruskal-Wallis test followed by post-hoc Wilcoxon tests. P-values were adjusted using the Benjamini-Hochberg method. A false discovery rate (FDR) ≤0.05 was considered statistically significant, and FDR ≤0.1 was considered a trend.

RESULTS

Of 71 SUDD patients, 49 (69.0%) were scored as DICA 1, 18 (25.4%) as DICA 2, and 4 (5.6%) as DICA 3. The three groups did not differ in demographic and clinical characteristics, except for the VAS score (Kruskal-Wallis test, $p=1.78\times10^{-5}$) (Table I).

The three groups also did not differ in alpha diversity (Wilcoxon test, p>0.05), but significantly separated in the PCoA of beta diversity (PERMANOVA, p=0.018) (Fig. 1A). Taxonomically (Figs. 1B-D), the DICA 1 group was characterized by higher relative abundances of the phylum *Actinobacteriota*, the families *Erysipelatoclostridiaceae* and *Bacteroidaceae*, and the genera *Lachnospiraceae ND3007 group* and *Bacteroides* (Wilcoxon test, p≤0.1). The DICA 2 group was mainly discriminated by higher proportions of *Streptococcaceae* (p=0.018). Finally, the phylum *Bacteroidota*, the families *Prevotellaceae* and *Succinivibrionaceae*, and the genera *Prevotella*, *Alloprevotella* and *Dialister* were the main discriminating taxa of the DICA 3 group (p≤0.045).

Table I. Demographic and clinical characteristics of SUDD patients with different DICA classification

	DICA1 (n=49)	DICA2 (n=18)	DICA3 (n=4)	p[a]
Male gender, n (%)	28 (57.1)	10 (55.6)	2 (50.0)	1
Median (IQR) age, years	61.9 (30-81)	67.5 (71-81)	68.5 (63-76)	0.137[b]
Presence of comorbidities, n (%)	35 (71.4)	13 (72.2)	4 (100)	0.721
Previous appendectomy, n (%)	6 (12.2)	6 (33.3)	1 (25.0)	0.09
Diagnostic tool, n (%)				0.912[c]
Colonoscopy	44 (89.8)	18 (100)	4 (100)	0.490
Computed tomography	5 (10.2)	2 (7.1)	1 (25.0)	0.507
Ultrasonography	1 (2.0)	/	/	1
Diet, n (%)				0[c]
Mediterranean	22 (44.9)	8 (44.4)	3 (75.0)	0.602
Prevalence of meat	5 (10.2)	/	/	0.49
Prevalence of fish	1 (2.0)	/	/	1
Vegetarian	9 (18.4)	5 (27.8)	/	0.5
Vegan	/	/	/	1
Abdominal pain, median (IQR) VAS score	3.0 (4)	4.0 (1)	9.5 (1.25)	1.78×10^{-5}[b]
Bristol stool form scale, median (IQR)	4.0 (2)	3.5 (2)	2.0 (1)	0.09[b]

DICA: diverticular inflammation and complication assessment; IQR: interquartile range; SUDD: symptomatic uncomplicated diverticular disease; VAS: visual analogue scale; [a]Fisher's exact test; [b]Kruskal–Wallis test; [c]χ^2 test.

For each DICA group, patients were further stratified by abdominal pain severity [estimated by VAS: mild (VAS score 1–3) vs. moderate (VAS score 4–7) vs. severe (VAS score 8–10)], and the above analyses were repeated. Only for the DICA 2 group, the PCoA of beta diversity showed a significant separation between the moderate and severe groups (PERMANOVA, p=0.024), with the latter also showing higher alpha diversity (Wilcoxon test, p=0.05) (Figs. 2A-B). Taxonomically (Figs. 2C-D), the severe group was enriched in the families *Enterobacteriaceae* and *Erysipelotrichaceae*, and the genera *Megasphaera* and *Veillonella*, while depleted in *Sutterellaceae* and *Blautia* compared to the moderate group (p≤0.08). Analyses were not possible for the DICA 3 group due to limited sample size.

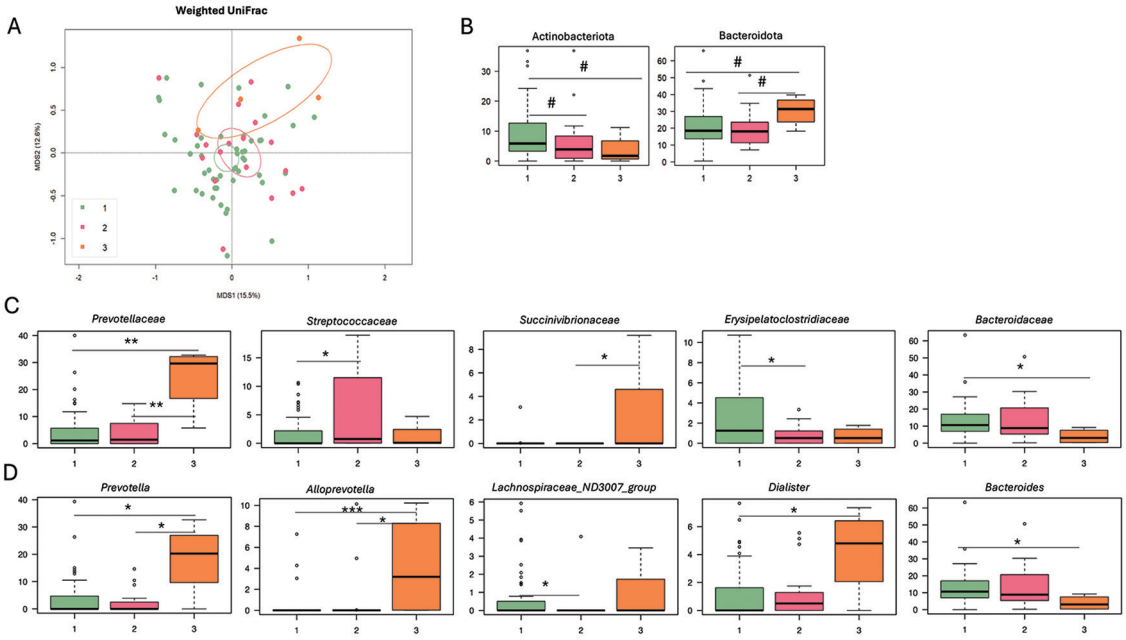

Fig. 1. Gut microbiota profile of SUDD patients stratified by DICA classification. (A) Principal Coordinates Analysis (PCoA) based on weighted UniFrac distances between gut microbiota profiles of SUDD patients stratified into DICA1, DICA2 and DICA3 groups. Ellipses include 95% confidence area based on the standard error of the weighted average of sample coordinates. A significant separation was found (PERMANOVA, p=0.018). Boxplots showing the relative abundance distribution of phyla (B), families (C) and genera (D) differentially represented between groups. Wilcoxon test; # 0.05<p≤0.1, * p≤0.05, ** p≤0.01, *** p≤0.001.

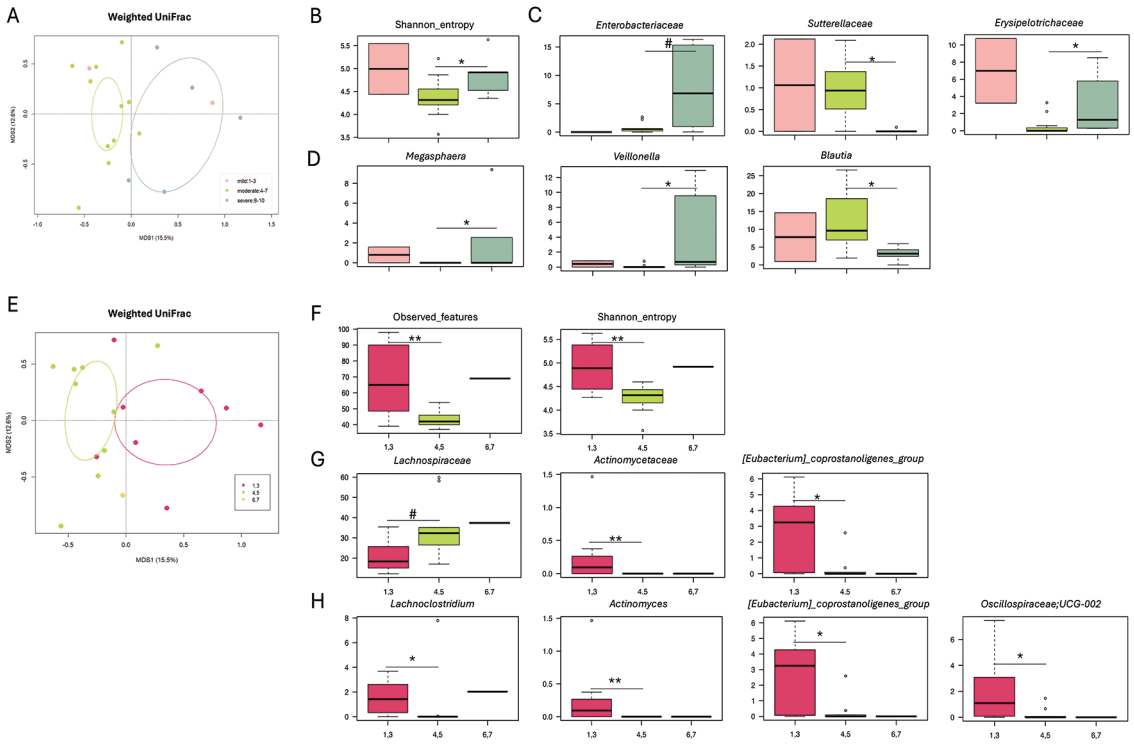

Fig. 2. Gut microbiota profile of SUDD patients with DICA2 classification stratified by abdominal pain severity and bowel habits. Principal Coordinates Analysis (PCoA) based on weighted UniFrac distances between gut microbiota profiles of SUDD patients with DICA2 classification stratified by abdominal pain severity, estimated by visual analog scale (VAS), into mild (VAS score 1–3) vs. moderate (VAS score 4–7) vs. severe (VAS score 8–10) (A), or bowel habits, estimated by Bristol stool form scale, into 1-3 vs. 4-5 vs. 6-7 (E). Ellipses include 95% confidence area based on the standard error of the weighted average of sample coordinates. A significant separation between groups was found in both cases (PERMANOVA, p≤0.024). Boxplots showing the distribution of alpha diversity, computed according to the Shannon index and the number of observed ASVs (B and F), and the relative abundance of families (C and G) and genera (D and H) differentially represented between groups. Wilcoxon test; # 0.05<p≤0.1, * p≤0.05, ** p≤0.01.

Likewise, for each DICA group, patients were stratified by bowel habits (estimated by Bristol stool form scale: 1-3 vs. 4-5 vs. 6-7), and all analyses were repeated. Again, analyses were not possible for the DICA 3 group due to limited sample size. Only for the DICA 2 group, the PCoA of beta diversity showed a significant separation between the 1-3 and 4-5 groups (PERMANOVA, p=0.039), with the latter also showing lower alpha diversity (Wilcoxon test, p=0.014) (Figs 2E-F). Taxonomically (Figs. 2G-H), the 1-3 group was enriched in *Actinomycetaceae* (and its genus *Actinomyces*), *[Eubacterium] coprostanoligenes* group, *Lachnoclostridium*, and *Oscillospiraceae UCG-002*, while depleted in *Lachnospiraceae* compared to the 4-5 group (p≤0.07).

DISCUSSION

Gut microbiota is becoming one of the most important players in the pathogenesis of the gastrointestinal disease, and DD is one of the disease curently under active investigation [8]. In the last years researchers have found that there was a lower abundance of commensal bacterial families and genera such as *Lachnospiraceae*, *Ruminococcus* and *Faecalibacterium* in AD patients compared with controls, and there was an increase in several genera with known pathogenic roles including *Fusobacteria*, *Prevotella* and *Paraprevotella* [21]. Moreover, and increased abundance of sulfur-reducing and sulfur-oxidizing bacteria (*Bacterioidetes, Cloacibacillus evryensis, Synergistia*) was found in surgical specimens of AD compared to nondiseased, adjacent normal regions [22]. Finally, women experiencing AD compared to controls, had increasing levels of pro-inflammatory taxa (*Ruminococcus gnavus*, and *Bilophila wadsworthia*) [13]. All these data showed that AD has GM perturbation characterized by overexpression of pro-inflammatory taxa. Similar data have recently detected also in SUDD patients. We found recently that SUDD patients with moderate-to-severe abdominal pain has overexpression of pro-inflammatory taxa, such as *Proteobacteria*, *Veillonellaceae*, *Blautia*, *Prevotellaceae*, and *Megasphaera* [11], and that medical treatment with sodium butyrte may restore this imbalance [12].

In this study, we demonstrated for the first time that GM perturbations in DD are closely associated with the endoscopic severity of the disease as measured by the DICA classification. In particular, DICA 2 patients showed a unique enrichment in *Streptococcaceae*, while DICA 3 patients showed an enrichment in *Prevotellaceae* (and its genera *Prevotella* and *Alloprevotella*), as well as in *Succinivibrionaceae* and *Dialister*. Most of these taxa, especially *Streptococcaceae*, *Prevotellaceae* and *Dialister*, have already been found to be enriched in SUDD patients and/or hypothesized to play a role in pain sensation [11]. Interestingly,

in the DICA 2 group, a worsening of dysbiosis was observed in patients with severe VAS, with enrichment in potentially harmful bacteria, including *Enterobacteriaceae*, *Erysipelotrichaceae*, and the *Veillonellaceae* genera *Veillonella* and *Megasphaera*. In particular, the overrepresentation of *Veillonellaceae* taxa, known lactate utilizers, suggests an increased availability of lactate and/or its metabolites (e.g., propionate) in the gut, which could contribute to intestinal discomfort and visceral hypersensitivity [23, 24]. Finally, the DICA 2 group also showed a GM variation according to Bristol stool form scale, with a depletion of health-associated taxa (e.g., *Lachnospira*) and an enrichment in opportunistic pathogens (e.g., *Actinomyces* and *Lachnoclostridium*) [25] in constipated patients.

These finding are interesting not only for the enrichment in the knowledge of the potential pathogenesis role of the GM in the severity of DD, but also because they open the way to potential treatment modulating GM. We know that probiotics may be useful not only in managing symptoms in SUDD patients, but also in obtaining quicker recovery in AD patients [26]. The data currently available on the role of probiotics in DD patients according to DICA classification showed that they may work better in less severe DICA score [27]. Looking at the results of this study, we could therefore stratify the patients according to DICA score and to try to use some probiotics strain already recognized as potential candidate for the management of these patients [28], alone or in combination with other drugs [27]. Also rifaximin could be a potential drug in a selecting population according to this study. Rifaximin is a non-systemic antibiotic that is able to decrease significantly pro-inflammatory taxa with contemporary increasing of anti-inflammatory taxa [29]. Thus, also this drug, alone or in combination with other drugs [27], could positively influence the gut microbiota expression in patients with DD. And that is why we excluded in this study patients taking rifaximin from less than four weeks at the time of fecal sampling.

Of course, this study has also some limitations. The first is the use of 16S rRNA amplicon sequencing, which is still the gold standard for microbiota profiling but does not allow high-resolution taxonomic profiling down to species level and functional insights, the lack of mechanistic information, the retrospective design. The second is that the DICA 3 group contains only four persons. This small group could limit the results obtained in this subgroup of patients. We know that only a small population of patients have DICA 3 score [5, 27], and it is not easy to enrol a robust sample size of patients with DICA 3 in real life. Moreover, the retrospective design of the study and the strict inclusion and exclusion criteria could have reduced further the DICA 3 patients available for this study. Further studies with larger DICA 3 sample size have therefore to confirm the results reported in this study. Despite these limitations, we think that the results reported in this study are useful to understand both pathogenesis and to plan a better management of these patients.

CONCLUSIONS

The associations between GM taxa and DD vary according to the endoscopic severity of the disease according to DICA score and, within each DICA group, according to the severity of abdominal pain and bowel habits. If confirmed in larger cohorts, such associations may improve patient stratification and their clinical management.

Conflicts of interest: A.T. served as speaker and/or consultant for AbbVie, Bayer, Fenix Pharma, Galápagos, Janssen, Nalkein, Omega Pharma, Sila. The rest of the authors declare no competing interests.

Authors' contribution: A.T. and G. P. conceived and designed the study. A.T. G.P., F.D'A., R.D.B and S.T. collected and analyzed the data and interpreted the results. A.T., G.P. and S.T. drafted the manscript. All the authors read and corrected the manuscript. A.T., G.P. and S.T. revised the manuscript criticaly for important intellectual content. A.T. is the guarantor of this article. All the authors approved the final version of the manuscript.

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