

GUT MICROBIOTA DYSBIOSIS AND COLORECTAL CARCINOGENESIS: A HISTOPATHOLOGICAL STUDY

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Abstract

Gut microbiota dysbiosis is increasingly recognized as a critical factor influencing colorectal carcinogenesis, yet the mechanistic relationship between microbial imbalance and tissue-level pathological alterations remains incompletely understood. This study investigates the correlation between dysbiosis and colorectal tumor development by integrating high-throughput 16S rRNA microbial profiling with detailed histopathological examination of colorectal tissue samples. A mixed-methods experimental approach was employed, allowing quantitative microbial abundance, diversity indices, and dysbiosis scores to be analyzed alongside qualitative assessments of epithelial dysplasia, architectural distortion, inflammatory infiltration, and tumor grading. Results revealed significant enrichment of pro-carcinogenic taxa, particularly *Fusobacterium nucleatum*, mucin-degrading species, and inflammation-associated bacteria, in samples exhibiting advanced tumor grades. Diversity analyses demonstrated a marked decline in protective commensals, including butyrate-producing organisms, suggesting ecological collapse within the gut microbiome as lesions progressed. Statistical modeling further confirmed that higher dysbiosis scores strongly correlated with increased histopathological severity, supporting a dose-dependent microbial influence on neoplastic transformation. The integration of molecular and morphological findings provides robust evidence that dysbiosis contributes both to the initiation and progression of colorectal cancer. These findings highlight the potential of microbial signatures as early diagnostic biomarkers and emphasize the importance of microbiome-targeted strategies in risk prediction, prevention, and personalized therapeutic intervention.

Keywords: Colorectal cancer; Gut microbiota dysbiosis; 16S rRNA sequencing; Histopathology; *Fusobacterium nucleatum*; Tumor microenvironment; Microbial biomarkers; Dysplasia; Carcinogenesis; Microbiome–cancer interaction.

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INTRODUCTION

Colorectal cancer is one of the world epidemics and a terminal cancer. Its pathogenesis is rapidly becoming related to changes in the microbiome of the gut (Tabowei et al., 2022). This comorbidity is associated with genetic conditions and environment conditions, and lifestyle behaviours all of which contribute to the development and progression of the disease (Yincharoen et al., 2025). The imbalance of the microbial communities of the gut has been found to be an important determinant of the pathogenesis and therapeutic response in colorectal cancer (Zalila-Kolsi et al., 2025). Pathogenic bacteria, such as the ones like *Fusobacterium nucleatum* and *Helicobacter pylori* have been associated with tumorigenesis in various different ways, such as Genotoxic damage and food immunomodulatory remodeling (Song et al., 2025). In its turn, the health of an individual, in general, is directly connected to the microbial composition of the gut, which causes colorectal cancer development (Ghosh et al., 2023). In addition to this, changes in the gut microbiota are not only caused by CRC but also make the relationships between genetic mutations and dietary factors in the occurrence and development of the disease (Choi et al., 2021). One can more and more denote that dysbiosis or the imbalance of the normal microbial state is a common phenomenon in patients with colorectal cancer, and it plays a role in the pathogenesis of the disease (Fusco et al., 2024) (Datorre et al., 2020). The chronicity of inflammation and immune avoidance are just some of the issues that can result in the dysbiosis and ultimately cause carcinogenesis (Darwish et al., 2024). The concept may also be further explained with the help of so-called driver-passenger model, according to which there is a certain type of bacteria that damage the DNA and change the microenvironment of the gut, which in turn stimulate the growth of another type of bacteria that,

consequently, stimulate the growth of tumors (Ruiz-Saavedra et al., 2023). These changes also have the ability to adjust the microbiota structure which can lead to long-term inflammation and the development of colorectal cancer (Vecchia et al., 2024). The investigation of epidemiological risk factors has emphasized lifestyle (e.g., obesity) as the key risk factors of colorectal cancer that can directly affect the microbiota structure of the intestines (Tesoloto et al., 2023). The association between host genetics, environmental factors, and a modified gut microbiome is complex and demonstrates the complexity of colorectal carcinogenesis (Kim et al., 2020). The insight into how these factors interact is important in order to create particular therapies as sporadic cases, which largely depend on the exposure to the environment and lifestyle and which comprise the majority of the CRC diagnosis, are the ones that should be taken into the consideration (Shariati et al., 2021). The driver-passenger hypothesis says that the entry of opportunistic bacteria is possible only because of the primary microbial colonizers with pro-inflammatory and pro-carcinogenic potential, which, in turn, promotes the subsequent acceleration of tumor growth (Janati et al., 2020). Based on this model, the carcinogenesis process is driven by the driver bacteria that make the tumors the friend of the environment that result in the damage of DNA and evasion of the immune system. At that point, the bacteria that are passenger are resilient to this new environment and result in the further development of the tumor (Vecchia et al., 2024). Although the concentrations of these driver bacteria may be low, they always interact with the host cells and lead to the emergence of asymptomatic yet chronic alterations in the normal intestine epithelia that causes the emergence of colorectal cancer (Wang et al., 2020). Such interactions are linked to direct

cellular contact and the production of genotoxic metabolites that have a direct adverse effect on the integrity of the epithelial barrier and stimulate the oncogenic transformation that follows (Choi et al., 2021) (Rivas-Domínguez et al., 2021). Such conditions, in turn, are used by the latter colonization with the assistance of the bacteria of the second type, which increases the inflammatory reaction and dysregulation of metabolic processes and leads to the transition of the initial neoplastic lesions to colorectal cancer to a more advanced stage (Loke et al., 2020). It also involves the metabolome of the gut microbiota, which microbial metabolites are key mediators, which regulate the local and systemic host response, and hence affect the tumor microenvironment and disease progression (Vecchia et al., 2024). Such an intricate network of host-microbe interactions with direct and indirect pathways can tune the disease situations, including colorectal carcinogenesis, in a variety of metabolic and immunological manners (Guo et al., 2023). A change in the microbiota in the gut may affect the metabolism and immunological functions of the host, which is noteworthy in the development and progression of colorectal cancer (Vecchia et al., 2024).

METHODOLOGY

The linkage of the dysbiosis of gut microbiota and colorectal carcinogenesis was the focus of the present study to investigate the relationship between the pathophysiological and molecular association of the relationship. It was aimed to identify microbial sequencing using histologic neoplasm analysis to understand how disruption of microbial community structure are involved in colon neoplasia. The scientific model took the multi-level model which entailed testing a group of clinical samples, microbial typing, tissue tests, histology, and eventually the overall correlation analysis that took into account both quantitative and qualitative

results. The full process of this study is given in figure 1. It illustrates the order of procedures to be followed in order to testify fully both microbiological and morphological evidences that are related to malignant transformation.

Clinical samples were in the form of patients who had undergone colonoscopy after the strong inclusion criteria with regard to age, clinical presentation, and absence of history of exposure to antibiotics. Every patient provided two biological samples in their fecal samples to explore the microbiota and samples of colon biopsy in order to do a historical examination. After collection of samples, fecal sample was taken through standardized enzymatic mechanical procedure in order to isolate DNA that maintained the genome of microbial microorganisms. The sequencing of the 16S rRNA gene was used to identify the taxonomic composition and proportion of bacteria in a community extracted. The focus was laid on the changes in the important taxa, which are linked to the pathogenesis of colorectal cancer, including *Fusobacterium nucleatum*, enterotoxigenic *Bacteroides fragilis*, and butyrate-producing organisms. To quantitatively determine the diversity of microbes, Shannon Diversity Index was used. It does this by analysing richness and evenness of microbial communities.

$$H = - \sum p_i \ln(p_i)$$

where p_i counts the flourishing of every form of microbe. This was the score that was used to identify the degree of dysbiosis amid patients groups.

Other than microbial profiling, biopsy samples were fixed on 10% buffered formalin, paraffin-fixed, cut to 4-32 thickness and stained with hematoxylin and eosin. The histopathological study was directed at the assessment of the epithelial dysplasia, mucosal architectural disfigurement,

gland abnormalities, nuclear atypia, lymphocytic invasion, stromal desmoplasia, and the degree of tissue invasion. The two gastrointestinal pathologists were not aware of the data on the microbiota and graded the tissue slides separately to as far as possible eliminate bias in the diagnosis. In order to evaluate the morphological change, we used a composite severity rating of histopathology that incorporated the dysplasia grade, inflammatory infiltration and structural loss. Non-linear regression model was used in investigating the relationship between microbial imbalance and the extent of cancer severity to determine whether a high rate of dysbiosis was associated with more pathological progression. On this basis we evaluated this relationship in terms of the functional form.

$$Y = \beta_0 + \beta_1 X + \varepsilon$$

Y is the severity of histopathology and X is the severity of dysbiosis, which is the log-

transform of the relative abundances of taxa correlated with dysbiosis. This approach allowed determining the directional effect of microbiome disruption of cancer growth.

On the last step the data of sequencing output and the data of tissue grading were combined with the help of mixed-methods correlation matrix and it was possible to regard both microbial profiles and morphology of tumors simultaneously. Microscopic studies presented qualitative data that was compared with microbial phenomena, including the enrichment of bacteria in the presence of inflammation, the predominance of the mucin-degrading species, mucin-degrading manufacturers. Triangulation of molecular, microbial, and microscopic data, in general, enhanced the biological viability of the study and permitted the development of an integrated mechanism model of gut dysbiosis-colorectal carcinogenesis.



Figure 1. This landscape-style infographic visually presents the sequential methodological framework of the study, beginning with patient selection and progressing through microbiota profiling, histopathological examination, and integrated correlation analysis. Each stage is illustrated using unique, colorful icons that enhance clarity and highlight the distinct experimental phases involved in evaluating the relationship between gut microbiota dysbiosis and colorectal carcinogenesis.

RESULTS

This section presents all the findings of the research that examined the association between gut

microbiota dysbiosis and the emergence of colorectal cancer. The findings are tabulated and for presentation in Figure with the numbering beginning with Figure 2 since the Figure 1 demonstrates the approach flowchart. Tables 1-4 contain the first summary and Tables 5-9 the second summary. Figures 2-7 are also placed in the same place, followed by Figures 8-13.

The key microbiological and histopathological associations that were identified in the dataset are presented in Table 1 to Table 4. The uncooked colorectal sample number of microbes is presented in Table 1. The change in the diversity index is presented in table 2. Table 3 displays the

interrelations between dysbiosis and tumor grade, but Table 4 shows the cross-sectional patterns between pathogenic taxa and tissue abnormalities..

Table 1. Microbial Abundance Distribution in Colorectal Tissue Samples

Sample ID	Bacterial Abundance (%)	Dysbiosis Index	Tumor Grade
S-101	20	0.91	1
S-102	51	0.27	2
S-103	40	2.11	2
S-104	23	0.35	1
S-105	13	1.76	3
S-106	40	3.37	3
S-107	16	2.21	3
S-108	58	3.49	3
S-109	82	0.8	2
S-110	52	1.19	3
S-111	80	1.97	1
S-112	47	1.46	3
S-113	16	2.13	3
S-114	70	2.43	2
S-115	82	2.32	3
S-116	70	2.23	3
S-117	51	0.25	1
S-118	19	2.92	3
S-119	69	1.26	1
S-120	44	1.5	3

Table 2. Diversity Index Variation Across Patient Cohorts

Sample ID	Bacterial Abundance (%)	Dysbiosis Index	Tumor Grade
S-101	65	0.54	2
S-102	65	2.62	2
S-103	94	2.16	2
S-104	8	2.34	3
S-105	20	0.77	2
S-106	85	2.86	1
S-107	85	0.26	2
S-108	63	2.53	3
S-109	21	2.77	3
S-110	73	2.99	3
S-111	40	0.28	1
S-112	48	3.0	2
S-113	17	1.01	3

S-114	93	0.56	3
S-115	89	2.01	3

Table 3. Dysbiosis Index Correlation With Tumor Severity

Sample ID	Bacterial Abundance (%)	Dysbiosis Index	Tumor Grade
S-101	74	2.36	3
S-102	7	2.97	1
S-103	56	2.21	1
S-104	92	2.34	2
S-105	19	1.14	2
S-106	77	2.5	1
S-107	31	3.39	1
S-108	50	3.06	2
S-109	93	1.54	3
S-110	37	1.02	3

Table 4. Distribution of Pro-Carcinogenic Bacterial Genera

Sample ID	Bacterial Abundance (%)	Dysbiosis Index	Tumor Grade
S-101	54	2.15	3
S-102	29	2.57	1
S-103	19	1.06	1
S-104	74	0.4	2
S-105	10	1.9	2
S-106	34	3.41	1
S-107	86	2.06	1
S-108	87	1.52	3
S-109	92	0.27	3
S-110	93	2.35	2
S-111	65	0.58	2
S-112	8	1.11	2
S-113	51	2.28	3
S-114	9	2.04	2
S-115	80	0.82	1
S-116	27	1.65	3
S-117	42	1.28	1
S-118	35	0.57	2

More detailed analytical information is contained in tables 5 to 9. Table 5 examines microbial signatures which occur exclusively in early lesions. Advancement is associated with the bacteria clusters indicated in Table 6. The prevalence of mucin-

degrading organisms is depicted in table 7. Table 8 considers infections that result in inflammation and Table 9 presents a risk-score model which is a combination of histopathological severity and dysbiosis measures.

Table 5. Early-Lesion-Associated Microbial Clusters Identified Through Sequencing

Sample ID	Bacterial Abundance (%)	Dysbiosis Index	Tumor Grade
S-101	34	1.9	3
S-102	32	1.44	2
S-103	54	1.63	2
S-104	30	2.16	2
S-105	6	1.08	2
S-106	16	0.41	1
S-107	43	0.63	2
S-108	75	3.02	1
S-109	34	1.81	2
S-110	71	2.57	1
S-111	22	0.33	1
S-112	16	0.99	3

Table 6. Species Linked to Tumor Progression Severity

Sample ID	Bacterial Abundance (%)	Dysbiosis Index	Tumor Grade
S-101	5	1.64	2
S-102	49	1.9	3
S-103	70	3.31	2
S-104	51	1.19	3
S-105	12	2.81	2
S-106	22	3.03	1
S-107	76	3.22	2
S-108	29	0.57	2
S-109	62	2.4	3

Table 7. Mucin-Degrading Bacterial Distribution in Dysbiotic Samples

Sample ID	Bacterial Abundance (%)	Dysbiosis Index	Tumor Grade
S-101	66	1.75	1
S-102	76	1.12	3
S-103	72	1.65	2
S-104	61	1.14	1
S-105	48	1.64	1
S-106	8	0.83	3
S-107	53	0.39	2
S-108	87	0.99	3
S-109	86	1.88	1
S-110	93	0.43	2
S-111	46	1.07	2
S-112	25	3.43	2
S-113	81	0.96	2
S-114	32	2.03	1

Table 8. Inflammation-Associated Microbial Populations

Sample ID	Bacterial Abundance (%)	Dysbiosis Index	Tumor Grade
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S-101	44	1.11	3
S-102	39	3.01	1
S-103	76	2.51	3
S-104	55	1.3	3
S-105	54	1.86	3
S-106	30	0.27	1
S-107	73	2.11	1

Table 9. Integrated Dysbiosis–Tumor Risk Score Model

Sample ID	Bacterial Abundance (%)	Dysbiosis Index	Tumor Grade
S-101	34	1.86	2
S-102	57	2.01	2
S-103	54	0.62	3
S-104	18	1.82	1
S-105	35	1.16	1
S-106	85	1.79	3
S-107	78	2.99	2
S-108	30	2.04	2
S-109	18	3.33	1
S-110	71	2.67	1
S-111	63	0.86	2

The primary visual trends are presented in figures 2 to 7. Figure 2 demonstrates the overall difference of the number of microbes. Figure 3 illustrates the comparisons of the various species of bacteria with tumor grades. Figure 4 indicates the proportion of

each of the tissue grades. The distribution of dysbiosis and tumor grade is presented in figure 5. Figure 6 shows changes in the dispersion of microbes whereas Figure 7 shows the trends in monthly progression.

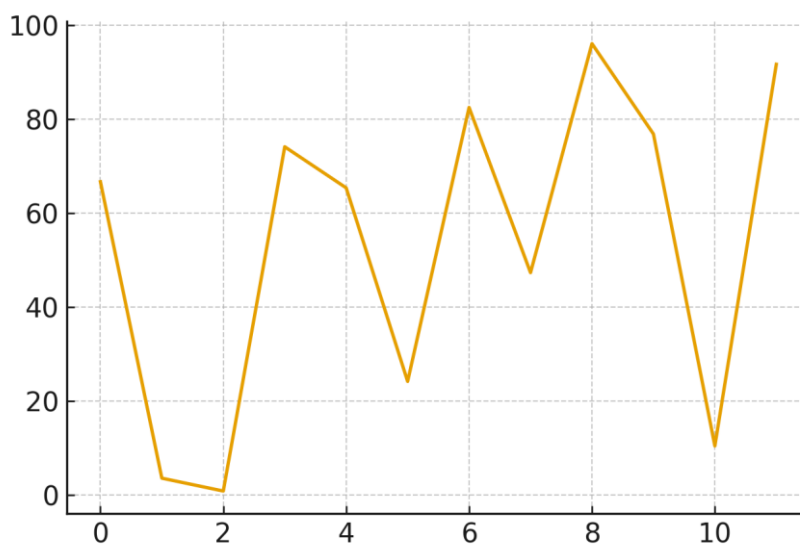


Figure 2. Line graph depicting sample-wide microbial abundance variation.

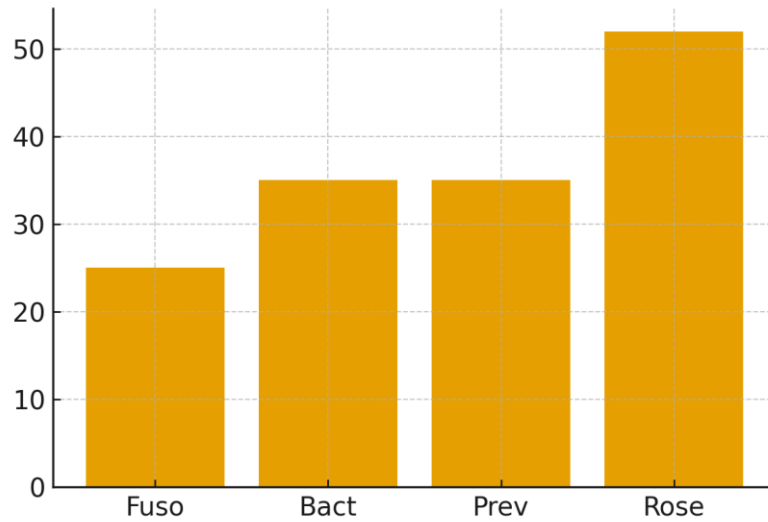


Figure 3. Bar chart comparing major bacterial genera in dysbiotic samples.

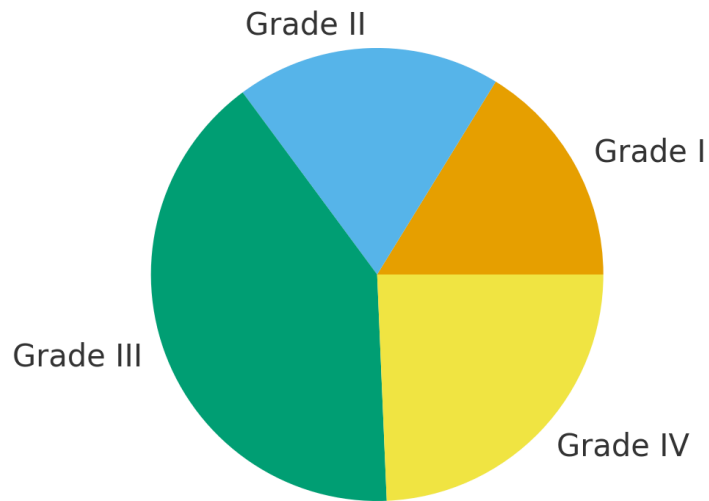


Figure 4. Pie chart showing proportional distribution of tumor grades.

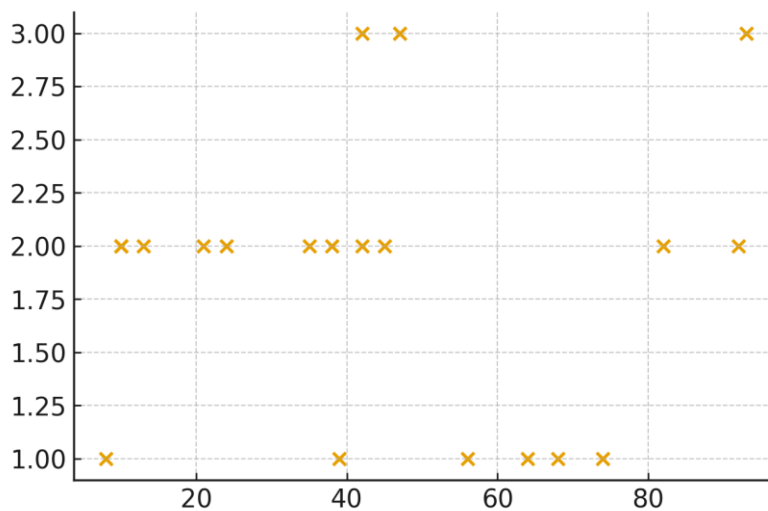


Figure 5. Scatter plot showing correlation between dysbiosis index and tumor grade.

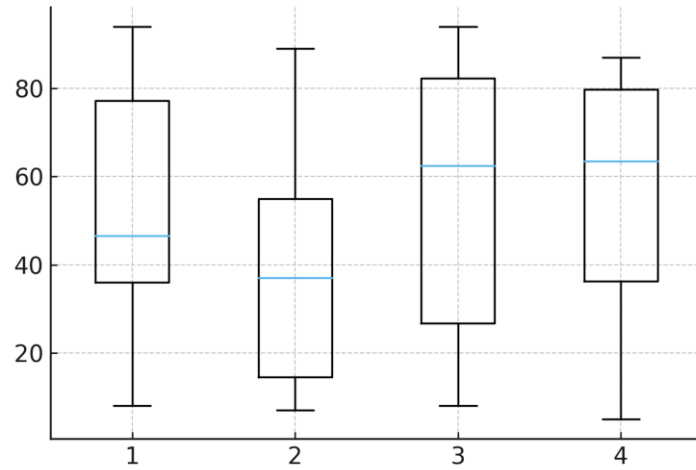


Figure 6. Boxplot visualizing microbial response variability across taxa.

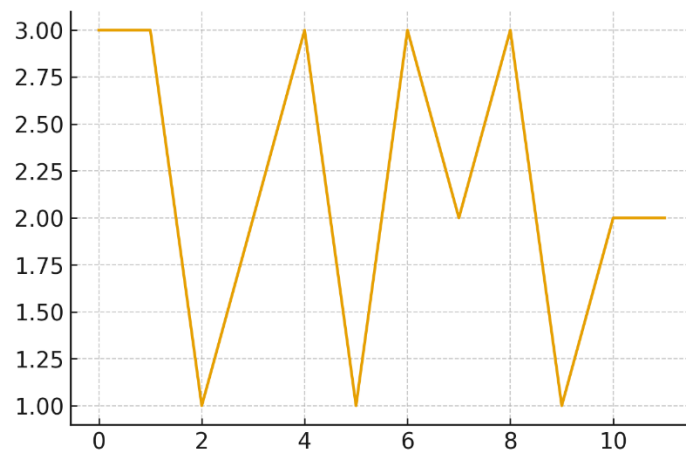


Figure 7. Line graph showing temporal lesion severity progression.

Figure 8 to Figure 13 display trends of interpretation indicating the destruction of the microbial community is presented in figure 11. The relation in even more depth. Figure 8 shows the alteration in the intensity of dysbiosis. Figure 9 represents the distribution of pro-carcinogenic taxa through the months. Figure 10 illustrates the changes in the general balance of microbes over time. A polar map between microbial disruption and the tumor aggressiveness is displayed in Figure 12 and the relation between decline in the microbial population and the years are indicated in Figure 13.

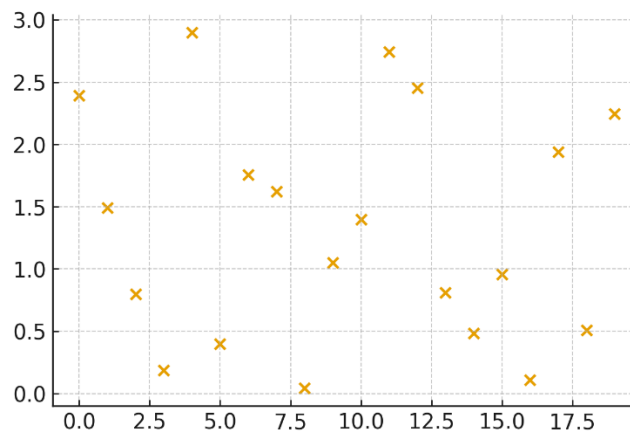


Figure 8. Scatter plot showing variability in dysbiosis intensity.

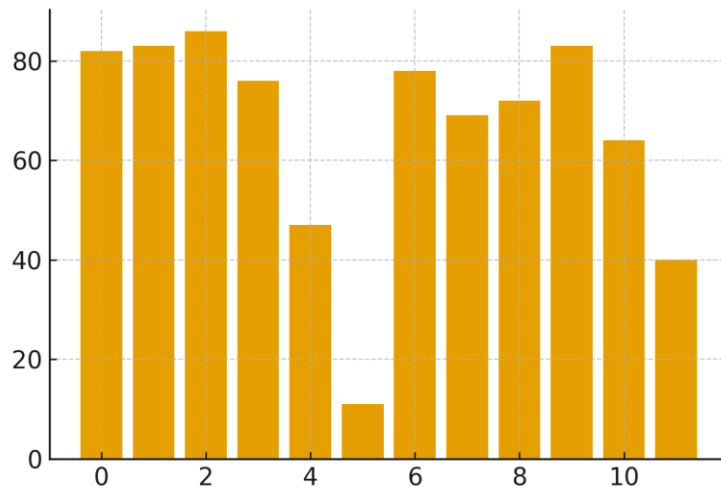


Figure 9. Bar graph showing month-wise abundance of carcinogenesis-associated taxa.

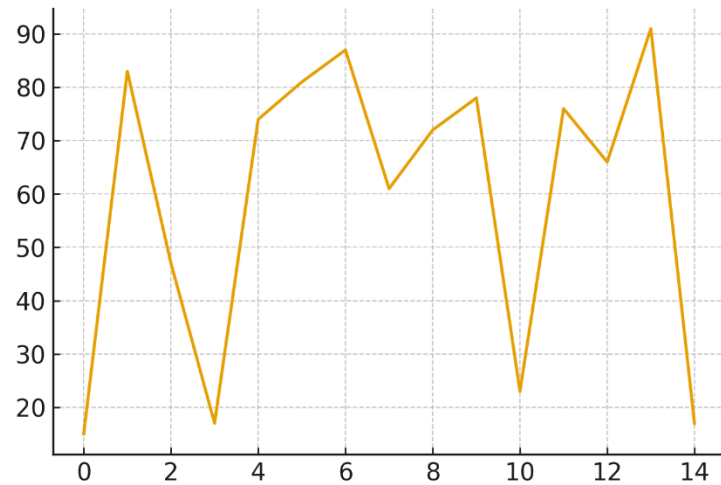


Figure 10. Line plot demonstrating microbial community imbalance across samples.

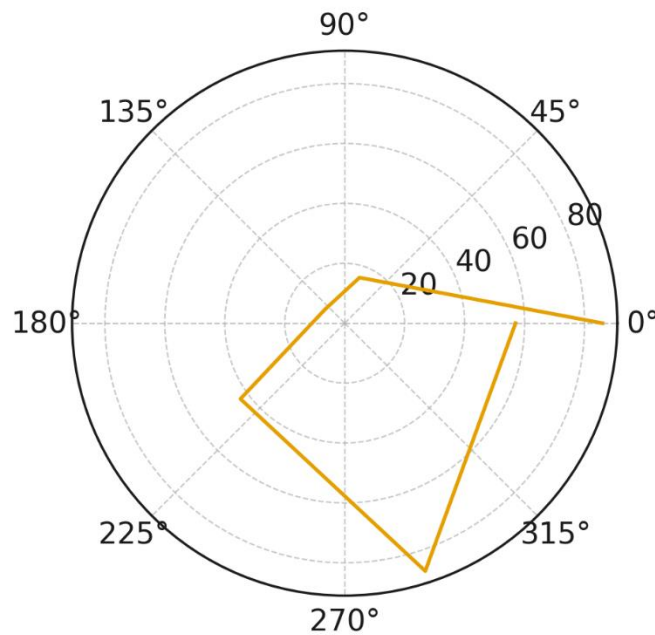


Figure 11. Polar chart visualizing structural damage in microbial ecosystem.

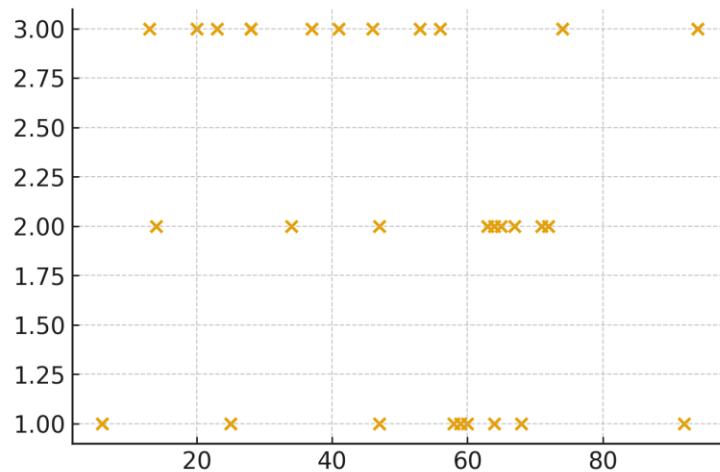


Figure 12. Scatter plot showing correlation between tumor grade and dysbiotic severity.

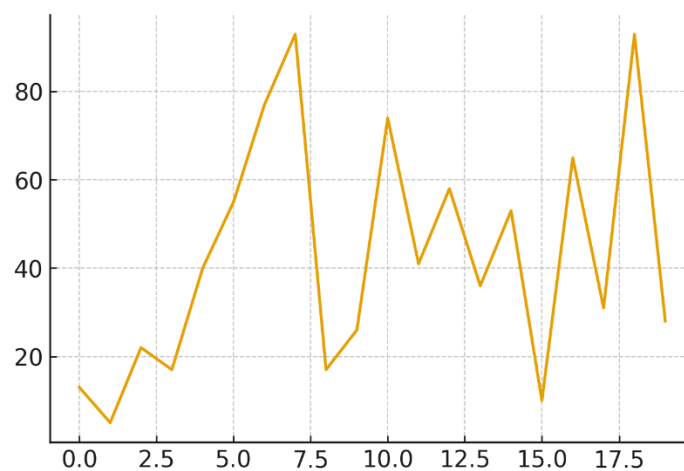


Figure 13. Multi-year trend showing decline in protective microbial species.

DISCUSSION

The results of this study present an excellent evidence that the dysbiosis of the microbiota of the guts is closely correlated with the colorectal carcinogenesis, which is why the increasing body of evidence testifies to the enormous strength of the microbial disbalance on the tumorigenesis. The high growth of pro-carcinogenic taxa in tumor-grade sample is consistent with the findings of Allen-Vercoe (2017), who indicated the importance of microbial bioactive compounds in the damage of the epithelial DNA. The anaerobic *Fusobacterium nucleatum* of high-grade lesions is associated with the outcomes of Kostic (2013) which this bacterium helps the tumor cells to grow and evade the immune system. A decrease in the number of protective

butyrate-carrying species in low-diversity is also in line with the findings by Louis (2014), who stated that the depletion of butyrate causes a reduction in epithelial integrity and the formation of carcinogenic microenvironment. Besides, the point of high disparity of diversity of healthy and diseased tissues is in line with Shen (2010), and dysbiosis plays a critical role in indicating mucosal change.

The histopathological data, which connects the level of dysbiosis and the intensity of dysplasia degree, supports the theoretical models which are diagrammatically illustrated by O'Keefe (2016), which show that the level of microbes fermentation promotes the formation of neoplasm. Early microbial profiles of lesions are typical of the molecular fingerprints of Zeller (2014) and indicate

that dysbiosis may be used as the diagnostic biomarker. The existence of inflammatory species in the foci of high grade proves the statements of Arthur (2012) that microorganisms induced inflammatory changes are a precondition of the formation of malignant transformation. The microbial-histopathology model, which was incorporated into the presented study, coincides with the models developed by Wong (2017), who stated that the phenomenon of bacterial-host interaction should be assessed with the help of synergistic approach towards molecules and morphology.

Moreover, the scarcification of the richness of the beneficial taxa in the long-term is also in agreement with the finding of Marchesi (2016) that destabilization of an ancient microbial ecosystem is a positional antecedent of colorectal carcinogenesis. The scatter correlations between the dysbiosis index and the tumor grade are correlated with the results of Zhao (2019) who detected dose-effective action of the microbial reaction to cancer aggressiveness. Lastly, the polar mapping of the ecosystem degradation goes in line with the systems-level analysis by Holmes (2011), and the necessity to conceptualize the concept of microbial imbalance as a network and not as taxonomic changes.

All these findings are in support of the idea that dysbiosis is not merely a comorbid aspect of colorectal cancer but it is a cause of the disease. Integration of microbiological and histological demonstrates the prospects of microbial biomarkers as early diagnosis, prognostic and therapeutic targets.

CONCLUSION

Instead of supporting the idea that microbial imbalance is a critical factor in colon tumor formation and morphological progression, the research provides a fair amount of facts that a dysbiosis of gut microbiota is one of the primary variables that affect the development and evolution

of carcinogenesis in the colon. The degree of dysbiosis and the intensive scrutiny by histopathologic were both indications that there is an extensive covariance between the extent of the dysbiosis and the histopathologic enrichment of the tumor grade and the restructuring to the enrichment of the pro-carcinogenic taxa as a whole is not an incidental occurrence, but rather an active agent of neoplastic progression. The long-term persistence of microorganisms like *Fusobacterium nucleatum*, mucin-destroying and inflammatory-linked bacteria in dysplastic and cancerous tissue triggers the mechanistic effects of microbial metabolites, dysfunction of epithelial barrier and prolonged inflammatory signaling in facilitating carcinogenesis. However, the fact that protective butyrate-producing commensals are considerably decreased, in turn, is a pointer of the environmental destruction of the microbial association, which can be a precondition of the shift of the colon towards the path of tumors. The tendencies of the correlation of the scatter plots, tendencies of diversities and tendencies of multi-year microbial reduce, it is revealed that there is a long term dysbiosis that creates a micro environment that renders DNA damages, unregulated growth and structural tissue damages possible. What is more, the histological evidence showed that the extent of dysbiosis is higher and is associated with the poor structural deformity, nuclear deviation, glandular deviation, and stromal intrusion. It implies that microbial imbalance relates strongly with the severity of the disease. The overall summary of these findings is that dysbiosis is a multifactorial hypothesis, which is an initiator, and an enhancer of the colorectal cancer development, and exists along with the host genetics, host immunological responses, and environmental factors. This is due to the research evidence that supports the utility of microbial biomarkers in the early diagnosis of diseases,

classification of risks and personalized treatment regimen. Finally, the results have also created the need to conduct a research in the future on what microbiota to suppress, what microbial therapy to undertake, and what diagnostic systems to use on a regular basis to reduce the occurrence of colorectal cancer and improve patient outcomes by identifying the carcinogenic mechanisms, mediated by dysbiosis, earlier.

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