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Assessment of Dietary Habits, Lifestyle and Trimethylamine N-oxide Status in Colorectal Cancer Patients in Morocco: A Cross-Sectional Study

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ABSTRACT

Background: Trimethylamine-N-oxide (TMAO) is a hepatic metabolic co-product derived from dietary precursors via gut microbiota-mediated biotransformation. Although recently implicated as a critical molecular bridge relating dietary patterns to diverse systemic pathologies, the precise impact of TMAO on colorectal cancer (CRC) pathogenesis, etiology, and progression remains largely unresolved.

Aims: This study aimed to investigate the association between circulating TMAO levels and various clinical, dietary, and behavioral risk factors associated with colorectal carcinogenesis within a cohort of Moroccan patients.

Patients and Methods: In this cross-sectional study, patients were consecutively recruited over a 12-month period from the Ibn Rochd University Hospital in Casablanca and the Mohammed V Military Hospital in Rabat. Face-to-face interviews were conducted to evaluate dietary intake, nutritional patterns, lifestyle behaviors, and clinical phenotypes. Whole blood samples were collected, and serum TMAO concentrations were quantified through liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS).

Results: Globally, no significant correlation was observed between circulating TMAO concentrations and the overall CRC risk. However, highly significant specific associations were identified between elevated TMAO levels and tumor localization at the Hepatic flexure. Furthermore, significant correlations emerged between TMAO concentrations and distinct CRC symptomatologies, including rectal bleeding volume, chronic diarrhea, narrowed stool caliber, tenesmus (the sensation of incomplete rectal emptying), and fatigue. Regarding dietary habits, high-protein dietary adherence was positively correlated with elevated circulating TMAO concentrations, whereas a high consumption of plant-based whole foods was inversely associated with serum TMAO concentrations. Additionally, socioeconomic status and alcohol intake were found to modulate serum TMAO profiles.

Conclusions: While these findings demonstrate no direct association between circulating TMAO levels and overall CRC risk, they underscore the clinical necessity of considering dietary patterns when interpreting TMAO biomarkers in oncological cohorts. These outcomes highlight the critical imperative to develop tailored nutritional guidelines for CRC patients and to implement structured nutritional education programs within oncology centers to promote a healthy and balanced diet as an essential component of comprehensive CRC management.

Keywords: Colorectal Cancer; Trimethylamine-N-oxide (TMAO); Diet; Morocco.

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1 Introduction

Globally, colorectal cancer (CRC) remains one of the most prevalent malignancies, ranking third in incidence and second in cancer-related mortality (Bray *et al.,* 2024). According to the latest epidemiological estimates, approximately 1.9 million new cases and over 900,000 deaths were attributed to CRC worldwide in 2022 (Bray *et al.,* 2024; Ferlay *et al.,* 2024). In Morocco, the incidence of CRC has increased markedly over recent decades in both men and women, reaching annual age-standardized rates of 10.6 and 10.4 per 100,000 individuals, respectively (Registre des Cancers, 2024). Scientific evidence indicates that shifts in

dietary habits and lifestyle behaviors significantly alter gut microbial homeostasis, which is turn plays a critical role in the initiation and progression of CCR (Zheng *et al.,* 2021).

Trimethylamine-*N*-oxide (TMAO), an organic compound belonging to the amine oxide family, is an indirect byproduct of gut microbiota (GM) metabolism. This constituent is generated via the hepatic oxidation of trimethylamine (TMA), which is produced by intestinal bacteria during the breakdown of dietary nutrients such as choline, L-carnitine, betaine, and phospholipids (lecithin) (Papandreou *et al.,* 2020). These precursors are predominantly abundant in red meat, deep-water fish, eggs, whole milk, and cheese (Lombardo *et al.,* 2022). Following microbial synthesis, TMA is absorbed into the portal circulation and transported to the liver, where it is oxidized by hepatic flavin-containing monooxygenase 3 (FMO3) to form TMAO (Ji *et al.,* 2020). In the general population, elevated circulating TMAO levels have been associated with several pathological conditions, including cardiovascular disease (Li *et al.,* 2024), chronic kidney disease (Cheng *et al.,* 2025), and severe neurological disorders (Wang *et al.,* 2023a; Wang *et al.,* 2022b), thereby influencing the occurrence, severity, and prognosis of conditions such as ischemic stroke (Xu *et al.,* 2015), Parkinson's disease, and cognitive decline (Keshavarzian *et al.*, 2015; Wang *et al.,* 2021).

In parallel, emerging evidence implicates TMAO in oncogenic processes (Wang *et al.,* 2022a). Mechanistically, TMAO activates the NLRP3 inflammasome (Yue *et al.,* 2017) — a central inflammatory pathway implicated in the tumorigenesis of various cancers, including colorectal, oral, lung, and hepatocellular carcinomas (He *et al.,* 2018; Wang *et al.,* 2018). Epidemiological studies indicate that individuals with plasma TMAO levels in the highest quartile exhibit a 3.4-fold increased risk of developing rectal cancer compared to those in the lowest quartile (Bae *et al.,* 2014). Furthermore, *in vitro* investigations suggest that TMAO may promote tumor cell proliferation and induce angiogenesis by upregulating vascular endothelial growth factor A (VEGFA), thereby exerting potentially pro-carcinogenic effects (Yang *et al.,* 2022).

Systemic TMAO concentrations are modulated by several interdependent determinants, primarily the composition and functional capacity of the GM (Rath *et al.,* 2017), dietary patterns (Wang *et al.,* 2019), physical activity (Argyridou *et al.,* 2020), pharmacological interventions (Milks *et al.,* 2018), hepatic FMO3 expression (Bennett *et al.,* 2013), and renal excretion efficiency (Janeiro *et al.,* 2018). Diets rich in animal proteins and saturated fats are associated with greater abundance of bacteria from phylum Firmicutes, which has been correlated with increased TMAO production (Koeth *et al.,* 2013). Conversely, plant-based and vegetarian diets rich in oligosaccharides promote the growth of the genus *Prevotella*, presenting a promising dietary strategy to attenuate circulating TMAO levels (Benítez-Páez *et al.,* 2019). A recent systematic review highlighted that targeted dietary interventions can enhance microbiome diversity and stimulate the production of beneficial metabolites such as short-chain fatty acids in populations at risk of CRC; however, the magnitude of these effects varies considerably based on food matrix, culinary processing, and intervention duration (Pandey *et al.,* 2025). Additionally, high adherence to the Mediterranean diet and targeted probiotic supplementation have been demonstrated to mitigate the systemic adverse effects associated with TMAO (Cheng *et al.,* 2021). Nevertheless, the precise cellular and metabolic pathways driving these protective effects remain insufficiently understood.

Accordingly, the present study aimed to evaluate circulating TMAO levels in Moroccan CRC patients and assess their associations with clinical characteristics, dietary habits, and behavioral risk factors. By elucidating these relationships, this work seeks to contribute to the development of evidence-based, targeted preventive and therapeutic strategies, providing actionable clinical recommendations to optimize CRC management within the Moroccan population.

2 Patients and Methods

2.1 Patient Recruitment and Ethical Considerations

Patients with a histologically confirmed diagnosis of colorectal cancer (CRC) were recruited from the Ibn Rochd University Hospital in Casablanca and the Mohammed V Military Hospital in Rabat, Morocco. The study protocol was approved by the Ethics Committee of the University Hospital of Tangier (Approval No: AC13FV/2023). Written informed consent was obtained from all participants prior to enrollment. The study was conducted in strict adherence to the ethical principles outlined in the Declaration of Helsinki, ensuring full participant confidentiality and data protection.

2.2 Study Design and Data Collection

Face-to-face interviews were conducted to collect sociodemographic data, including age, sex, geographical origin, place of birth, marital status, and occupational status. Clinical parameters—including weight, height, waist circumference, histological cancer type, tumor stage, and anatomical disease site—were extracted from institutional medical records.

2.2.1 Anthropometric Assessment

Because most patients experienced marked disease-related weight loss at initial presentation, body weight recorded at

diagnosis did not reliably reflect habitual nutritional status. Consequently, anthropometric parameters—specifically body mass index (BMI) and waist circumference—were retrieved from medical records completed two months prior to diagnosis, capturing a more representative pre-pathological nutritional baseline.

2.2.2 Lifestyle and Behavioral Characteristics

Lifestyle attributes were systematically evaluated using a structured clinical questionnaire. Alcohol consumption was categorized by frequency (daily, weekly, or occasional). Smoking status was recorded dichotomously (smoker vs. non-smoker). Self-reported physical activity was assessed by recording whether patients engaged in regular exercise and, where applicable, the specific modality (e.g., walking, moderate-intensity, or vigorous-intensity exercise) and weekly frequency (sessions per week).

2.2.3 Dietary Assessment and Scoring

Habitual dietary intake was evaluated using a semi-quantitative approach modeled on the principles of the Food Frequency Questionnaire (FFQ), a validated instrument for assessing dietary exposure over specified periods (INDDEX Project, 2018). The dietary collection tool was structured in tabular format across four daily meal occasions: breakfast, lunch, afternoon snack, and dinner. The tool was content validated prior to deployment by an expert panel comprising a clinical nutritionist and an oncologist.

For each meal, participants reported the specific food items and beverages consumed (e.g., dairy products, hot beverages, soft drinks, juices, cereals, eggs, fruits, vegetables, and protein-dense foods). Portions were estimated using standardized household measures. To quantify intake, participants reported the daily quantity consumed per meal alongside the weekly frequency of consumption for each item. An individual dietary score was computed for each food item according to the following formula:

$$\text{Dietary Score} = \text{Daily Quantity Consumed} \times \text{Weekly Frequency of Consumption}$$

2.2.4 Socio-Economic Status (SES) Determination

Socio-economic status was classified according to multi-indicator metrics inspired by the framework established by the High Commission for Planning (*Haut-Commissariat au Plan*, HCP) in *Les indicateurs sociaux du Maroc* (HCP, 2023) which suggests a classification of household living standards based on national representative surveys covering employment, income, living conditions, and consumption (Maaroufi, 2023). Stratification incorporated monthly household income, primary occupation, and household crowding ratio (number of cohabitants per dwelling). Based on these composite criteria, participants were categorized into low, medium, or high SES tiers.

2.3 Biological Analyses and Laboratory Assessments

Venous blood samples were collected following an overnight fast (minimum 8–10 hours) using serum separator tubes containing a clot activator and gel barrier. Samples were centrifuged at 3,000 rpm for 10 minutes; serum was immediately aliquoted and stored at –20°C until mass spectrometry analysis.

2.3.1 Quantification of Serum TMAO

Serum trimethylamine-*N*-oxide (TMAO) concentrations were quantified via liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) at the LIMMS Laboratory (MBNext Group Europe), utilizing an established, high-sensitivity analytical assay.

2.3.2 Routine Metabolic Parameters

Routine fasting biochemical analyses were performed at the ISO 9001:2015-certified Biolife Medical Analysis Laboratory (Rabat, Morocco). Fasting blood glucose (FBG) was determined via the hexokinase/glucose-6-phosphate dehydrogenase (HK/G6PDH) enzymatic assay. Total cholesterol (TC) and triglycerides (TG) were measured using the CHOD-PAP and GPO-PAP enzymatic colorimetric methods, respectively, on an automated Beckman Coulter® clinical analyzer. Glycated hemoglobin (HbA1c) was quantified by high-performance liquid chromatography (HPLC) using the Bio-Rad D-10™ system.

Biochemical variables were categorized according to established clinical threshold guidelines:

- **Fasting Blood Glucose (FBG):** Classified per American Diabetes Association (ADA) criteria as normal (0.70 – 1.10 g/L) or elevated (> 1.10 g/L) (ADA, 2024).
- **HbA1c:** Classified per ADA guidelines as normal (< 5.7%) or elevated (≥ 5.7%).
- **Triglycerides (TG):** Categorized according to European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines as normal (≤ 1.50 g/L) or elevated (> 1.50 g/L).
- **Total Cholesterol (TC):** Thresholds were established based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, defining hypercholesterolemia as TC ≥2.50 g/L (≥250 mg/dL) (Expert Panel, 2001).

2.4 Statistical Analysis

Data analysis was performed using Jamovi software (version 2.6.26). Descriptive statistics were computed for all baseline variables. Continuous data were assessed for normality visually using quantile-quantile (Q-Q) plots and formally using the Shapiro-Wilk test. Normally distributed continuous variables are reported as mean ± standard deviation (SD), whereas non-normally distributed variables are expressed as median and interquartile range (IQR). Categorical variables are presented as absolute counts (n) and relative percentages (%).

Bivariate correlation analyses between continuous variables and raw serum TMAO levels were conducted using Pearson's correlation coefficient (r) for normally distributed data or Spearman's rank correlation coefficient (ρ) for non-parametric distributions.

For comparative and risk factor analyses, serum TMAO levels were dichotomized into low/normal (< 4.7 μM) and high (≥ 4.7 μM) subgroups. Differences in categorical variables between TMAO tiers were evaluated using Pearson's chi-squared (χ^2) test or Fisher's exact test where expected cell counts were < 5. Continuous variables were compared using Student's independent *t*-test or the Mann-Whitney *U* test, as appropriate. Variables exhibiting statistically significant associations ($p < 0.05$) in univariate analysis were subsequently entered into a multivariate binary logistic regression model to identify independent predictors of high serum TMAO while adjusting for potential confounding factors. Adjusted odds ratios (aOR) and corresponding 95% confidence intervals (95% CI) were reported. Statistical significance was set at a two-tailed *p*-value < 0.05.

3 Results

3.1 Baseline Characteristics of the Study Population

A total of 65 patients diagnosed with CRC were enrolled in this study, comprising 39 men and 26 women(male-to-female ratio: 1.5:1). The mean age of the cohort was 58.92 ± 13.01 years (range: 36 – 85 years) with the majority of patients (81.5%) being older than 45 years. Most participants resided in urban area (63.1%). Regarding lifestyle risk factors 70.8% of patients reported no history of tobacco smoking, 55.38% reported no prior alcohol consumption, and 50.8% engaged in no regular physical activity. Socio-economically, 56.9% of participants were economically inactive, and only nine patients (13.8%) reported high household income levels, as displayed in Table 1.

Clinical evaluation revealed that rectal tumors were the most prevalent malignancy (67.7%), comprising both peritoneal (31.08%) and non- peritoneal (32.43%) localizations. Among patients with colon cancer, tumors located in the right colon and sigmoid colon were most frequently reported, each accounting for 9.46% of total cases. Notably, a significant majority presented with advanced-stage disease at diagnosis, with 44.6% classified as stage III and 36.9% as stage IV. Anthropometric assessment yielded a mean waist circumference of 91.95 ± 18.55 cm, and a mean body mass index (BMI) of 25.06 ± 5.10 kg/m². Overall, 15.4% of patients were classified as obese, with 12.3% presenting moderate obesity (Class I) and 3.1% severe obesity (Class II/III) (Table 2).

Evaluation of habitual dietary patterns employing composite scores demonstrated that dairy products were the least consumed food group, yielding a median score of 0.00 (IQR = 0.00), indicating that over half of the cohort consumed negligible or no dairy items. Conversely, higher consumption scores were observed for hot beverages—predominantly green tea—and cereal products, with median scores of 2.00 and 2.26 respectively (Table 3).

Table 1. Sociodemographic Characteristics of the Recruited Participants

Parameters	N (%)
Gender	
Female	26 (40.0 %)
Male	39 (60.0 %)
Age	
Age < 45	12 (18.5 %)
Age > 45	53 (81.5 %)
Geographical origin	
Urban	41 (63.1 %)
Rural	24 (36.9 %)
Past alcohol consumption	
No	36 (55.38 %)
Yes	24 (36.92 %)
Tobacco use	
No	46 (70.8 %)
Yes	19 (29.2 %)
Physical activity	
Does not exercise	33 (50.8 %)
Low: less than once a week	14 (21.5 %)
Moderate: 1 to 2 times per week	10 (15.4 %)
High: 3 times per week or more	8 (12.3 %)
Employment status	
Economically inactive	37 (56.9%)
Employed part-time	16 (24.6%)
Employed full-time	12 (18.5%)
Socioeconomic status	
Low income	15 (23.1 %)
Moderate income	41 (63.1 %)
High income	9 (13.8 %)

Note: N=number of patients; %= percentage of patients

Circulating serum trimethylamine-*N*-oxide (TMAO) concentrations spanned a broad range, with a median level of 2.90 μM (IQR: 3.21). Stratification by TMAO status revealed that 26.2% of patients exhibited elevated TMAO concentrations (> 4.7 μM), whereas 73.8 % presented normal (0.6 – 4.7 μM) or low TMAO levels (< 0.6 μM) (Table 4).

Table 2. Clinical Attributes and Anthropometric Parameters of the Participants

Parameters	N (%)
Cancer type	
Colon	21 (32.3%)
Right colon	7 (9.46%)
Transverse colon	0 (0.0%)
Left colon	6 (8.11%)
Sigmoid colon	7 (9.46%)
Hepatic flexure	5 (6.76%)
Splenic flexure	2 (2.7%)
Rectum	44 (67.7%)
Peritoneal rectum	23 (31.08%)
Non- Peritoneal rectum	24 (32.43%)
Cancer stage	
Early	10 (15.4%)
Stage 0	0.0
Stage I	1 (1.5%)
Stage II	9 (13.8%)
Advanced	53 (81.5%)
Stage III	29 (44.6%)
Stage IV	24 (36.9%)
BMI	
Underweight	8 (12.3%)
Normal weight	23 (35.4%)
Overweight	24 (36.9%)
Moderate obesity	8 (12.3%)
Severe obesity	2 (3.1%)
Waist circumference (cm)	
Abdominal obesity	26 (40,0%)
Non abdominal obesity	39 (40%)

Note: N=number of patients; %= percentage of patients

Table 3. Descriptive Statistics of Food Scores for Each Food Group

Food	Median (IQR)	Mean ± SD
Fruits	0.42 [0.142, 0.999]	----------
Vegetables	----------	1.42 ± 0.75
Egg	0.28 [0.00,0.428]	----------
Cereal products	----------	2.26 ± 0.84
Fat	1.00 [1.00, 1.857]	----------
Starchy	0.14 [0.000, 0,285]	----------
Protein-rich food	0.99 [0.713, 1.428]	----------
Sweet products	0.14 [0.000, 0.428]	----------
Dairy products	0.00 [0.000, 0.285]	----------
Soft beverages	0.14 [0.000, 0.571]	----------
Hot beverages	2.00 [1,142, 2.000]	----------

Note: IQR= Interquartile Range; SD= Standard Deviation

Table 4. Results of Biochemical Parameter Assessment

Parameters	N (%)
TMAO	
Normal (0.6 - 4.7 μM) and Low (<0.6 µM)	48 (73.8%)
High TMAO (> 4.7 μM)	17 (26.2%)
Glycemia	
Hypoglycemia (< 0.70 g.L^{-1}l)	6 (9.2%)
Normal glycemia (0.70 et 1.10 g.L^{-1})	44 (67.7%)
Hyperglycemia (> 1.10 g.L^{-1})	15 (23.1%)
HbA1c	
Normal glycaemia (< 5.7 %)	39 (60.0%)
Hyperglycemia (> 5.7 %)	26 (40.0%)
Triglycerides	
Normal triglyceridemia (0 – 1.50 g.L^{-1})	57 (87.7%)
Hypertriglyceridemia (> 1.50 g.L^{-1})	8 (12.3%)
Cholesterol	
Hypocholesterolemia (< 1.4 g.L^{-1})	8 (12.3%)
Normal total Cholesterol (1.4 – 2.5 g.L^{-1})	48 (73.8%)
Hypercholesterolemia (> 2.5 g.L^{-1})	9(13.8%)

Note: N = number of patients; % = Percentage of patients; HbA1c: glycated hemoglobin

Regarding metabolic and biochemical profiles, the median fasting blood glucose (FBG) was 0.88 g L^{-1} (IQR = 0.32) and mean glycated hemoglobin (HbA1c) was 5.50 % ± 0.80. The median serum triglyceride level was 0.92 g.L^{-1} (IQR = 0.54), and the mean total cholesterol level was 1.73 g.L^{-1} ± 0.48. Overall, 23.1% of the cohort presented with fasting hyperglycemia; among whom, 40% exhibited suboptimal glycemic control with HbA1c levels exceeding 5.7 %. Hypertriglyceridemia and hypercholesterolemia were documented in 12.3% and 13.8% of patients, respectively (Table 4).

3.2 Association Between Serum TMAO Levels and Population Parameters

To investigate potential determinants of circulating TMAO levels, bivariate comparative analyses were conducted across various clinical, demographic, metabolic, and dietary variables.

3.2.1 Association Between Categorical Serum TMAO Levels and Dietary Intake Scores

Bivariate comparative analyses revealed distinct distribution patterns of composite dietary scores when comparing patients with normal versus high circulating TMAO levels (> 4.7 μM).

Descriptive evaluation demonstrated that median intake scores for protein-dense foods and hot beverages were noticeably elevated in the high TMAO group relative to the normal TMAO subgroup. Conversely, median scores for vegetable consumption and total fat intake were higher among individuals in the normal TMAO tier. Cereal intake

scores exhibited identical median distributions across both TMAO categories. These shifts highlight differential dietary habits between patients presenting with normal and elevated systemic TMAO concentrations.

A statistically significant association was observed between circulating TMAO tiers and the composite consumption scores for both eggs and protein-dense foods ($p < 0.01$). No statistically significant differences were detected across the remaining dietary parameters (Table 5). Notably, vegetable consumption exhibited a non-significant trend toward lower TMAO levels ($p = 0.091$), suggesting a potential inverse relationship that warrants further investigation in a larger cohort.

Table 5. Association between TMAO and eating habits

	Normal TMAO (median IQR)	High TMAO (median IQR)	*p-value*
Hot beverage score	1.71 [0.05 - 2.00]	2.00 [1.28 - 2.00]	0.363
Cereal score	2.29 [1.82 - 3.00]	2.29 [1.43 - 186]	0.675
Vegetables' score	1.43 [1.99 - 2.04]	0.85 [0.71 - 1.86]	0.091
Eggs score	0.14 [0.00 - 0.28]	0.57 [0.28 - 1.00]	< .001
Sugar and sweet food score	0.142 [0.00 - 0.42]	0.07 [0.00 - 0.42]	0.869
Fruits score	0.428 [0.28 - 1.00]	0.285 [0.00 - 0.57]	0.218
Protein food score	0.999 [0.57 - 1.14]	1.71 [0.99 - 1.86]	< .001
Soft drink score	0.035 [0.00 - 0.42]	0.285 [0.00 - 1.00]	0.139
Fat intake score	1.21 [1.00 - 1.89]	1.00 [0.99 - 1.43]	0.310

Note: IQR= Interquartile Range

3.2.2 Clinical, Behavioral, and Symptom-Related Correlates of Serum TMAO

Evaluation of categorical demographic, clinical, and behavioral variables according to TMAO status revealed several statistically significant associations (Table 6). Systemic TMAO levels were strongly associated with past alcohol consumption ($p < 0.001$) and lower socio-economic status ($p < 0.001$). Furthermore, several clinical manifestations frequently reported in CRC patients demonstrated significant associations with elevated TMAO levels, including:

- **Rectal bleeding volume**: ($p < 0.001$)
- **Diarrhea**: ($p = 0.029$)
- **Narrow-caliber / pencil-thin stools**: ($p = 0.016$)
- **General fatigue**: ($p = 0.034$)
- **Sensation of incomplete rectal evacuation:** ($p = 0.051$)

In contrast, no significant associations were observed between TMAO levels and personal history of diabetes mellitus ($p = 0.069$) or the presence of visible hematochezia.

Regarding anatomical tumor distribution, localization within the hepatic flexure of the colon was positively associated with elevated TMAO levels. However, comparing distal versus non-distal tumor sites yielded no statistically significant difference ($p = 0.139$) (Table 7).

Table 6. Association Between TMAO and Sociodemographic, Lifestyle and Clinical Factors

Variables		Total cases	TMAO normal	High TMAO			*p-value*
			N	%	N	%	
Age	Age < 45	12	8	66.7	4	33.3	0.531
	Age > 45	53	40	75.5	13	24.5	
Past alcohol consumption	No	36	32	88.9	4	11.1	< .001
	Yes	24	11	45.8	13	54.2	
Smoking	No	46	37	80.4	9	19.6	0.060
	Yes	19	11	57.9	8	42.1	
Physical activity	No	33	27	81.8	6	18.2	0.079
	Yes	32	21	65.6	11	34.4	
Financial Situation	Low income	15	11	73.3%	4	26.7	< .001
	Moderate income	41	35	85.4%	6	14.6	
	High income	9	2	22.2%	7	77.8	
Obesity	Non obese	54	41	74.6	14	25.5	0.764
	Obese	10	7	70	3	30	
Abdominal obesity	Abdominal Obesity	26	19	73.1	7	26.9	0.908
	General obesity	39	29	74.4	10	25.6	
Diabetes	No	37	24	64.9	13	35.1	0.069
	Yes	27	23	85.2	4	14.8	
Total cholesterol	Normal TC	48	34	70.8	14	29.2	
	Hypercholesterolemia	9	7	77.8	2	22.2	

Table 7. Association Between TMAO and Clinical and Biological Factors

Variables		Total cases	TMAO normal		High TMAO		*p-value*
			N	%	N	%	
Diarrhea	No	41	34	82.9	7	17.1	0.029
	Yes	24	14	58.3	10	41.7	
Constipation	No	50	36	72	14	28	0.536
	Yes	15	12	80	3	20	
Alternating diarrhea and constipation	No	51	35	68.6	16	31.4	0.068
	Yes	14	13	92.7	1	7.1	
Arrow stool	No	33	20	60.6	13	39.4	0.016
	Yes	31	27	87.1	4	12.9	
Incomplete evacuation sensation	No	25	15	60	10	40	0.051
	Yes	39	32	82.1	7	17.9	
Abdominal pain	No	25	18	72	7	28	0.835
	Yes	39	29	74.4	10	25.6	
Gas	No	21	16	76.2	5	23.8	0.727
	Yes	43	31	72.1	12	27.9	
Fatigue and weakness	No	9	4	44.4	5	55.6	0.034
	Yes	55	43	78.2	12	21.8	
Nausea and vomiting	No	31	24	77.4	7	22.6	0.485
	Yes	33	23	96.7	10	30.3	
Anemia	No	41	31	75.6	10	24.4	0.599
	Yes	23	16	69.6	7	30.4	
Accumulation of fluid in the abdomen	No	34	26	40.6	8	12.5	0.559
	Yes	30	21	32.6	9	14.1	
Blood in stool	No	11	9	81.8	2	18.2	0.254
	Yes	54	39	72.2	15	27.8	
Amount of bleeding	Scant bleeding	34	31	91.2	3	8.8	< .001
	Profuse bleeding	19	7	36.8	12	63.2	
Cancer type	Colon cancer	21	16	76.2	5	23.8	0.766
	Rectum cancer	44	32	72.7	12	27.3	
Tumor location	Right colon	7	6	85.7	1	14.3	0.449
	Left colon	5	5	100	0	0.0	0.126
	Sigmoid colon	3	3	100	0	0.0	0.166
	Hepatic flexure	5	1	20	4	80	0.004
	Splenic Flexure	1	1	100	0	0.0	0.547
	Peritoneal rectum	22	18	81.8	4	18.2	0.544
	Non- Peritoneal rectum	21	14	66.7	7	33.3	0.153
Cancer stage	Early	10	6	60	4	40	0.247
	Advanced	53	41	77.4	12	22.6	
Triglyceride ($g.L^{-1}$)	Normal triglyceridemia	57	42	73.7	15	26.3	0.937
	Hypertriglyceridemia	8	6	75	2	25	
Total cholesterol ($g.L^{-1}$)	Hypocholesterolemia.	8	7	87.5	1	12.5	0.586
	Normal total Cholesterol	48	34	70.8	14	29.2	
	Hypercholesterolemia	9	7	77.8	2	22.2	

Note: N=number of patients, %= percentage of patients

3.3 Bivariate Correlation Analyses

Bivariate correlation testing between continuous serum TMAO levels and quantitative clinical, dietary, and biological parameters identified statistically significant positive correlations with both the egg consumption score and the total protein food score ($p = 0.909$) ($p = 0.016$), respectively.

Conversely, no statistically significant correlations were observed between TMAO levels and other studied quantitative variables, including age, BMI, or scores for hot beverages, cereals, fruits, vegetables, and added sugars ($p > 0.05$). Similarly, continuous metabolic and biological markers—including fasting blood glucose, HbA1c, serum

triglycerides, and total cholesterol—exhibited no significant correlation with serum TMAO concentrations ($p > 0.05$).

3.4 Multivariable Logistic Regression Analysis of Factors Associated with High TMAO Levels

A multivariable binary logistic regression analysis was performed to identify independent predictors of elevated serum TMAO adjusting for potential confounding variables identified in univariate screening. (Table 7).

- **Sex:** While female sex was associated with TMAO tiers in univariate analysis, this effect lost statistical significance after multivariable adjustment ($p = 0.387$).
- **Waist Circumference:** Central adiposity remained a significant independent predictor of elevated TMAO levels. Each 1 cm increase in waist circumference was associated with an 18% increase in the odds of presenting with elevated TMAO levels (OR = 1.18; 95% IC: 1.03 – 1.35; $p = 0.019$).
- **Underweight status**: Pre-diagnosis underweight status demonstrated a strong positive association with elevated TMAO levels (OR = 34.17; 95% IC: 1.23 – 944.90; $p = 0.037$). However, the wide confidence interval reflects reduced precision attributable to small subgroup sample sizes.
- **Vegetable consumption**: High vegetable consumption was independently and inversely associated with elevated TMAO levels (OR = 0.13; IC95 %: 0.03 – 0.60; $p = 0.008$), indicating and 87% reduction in the odds of high serum TMAO among high-intake consumers.
- **Fruit consumption:** Conversely, high fruit consumption was independently associated with increased odds of high serum TMAO (OR = 16.30; 95% CI: 2.15 – 106.38; $p = 0.003$). As with underweight status, the broad confidence interval underscores limited sample density within this stratum.

4 Discussion

Colorectal cancer (CRC) remains a major global health challenge and a leading cause of cancer-related morbidity and mortality worldwide. Although historically considered a pathology predominantly affecting older populations, recent epidemiological data highlight an alarming rise in early-onset CRC among younger populations (Loomans-Kropp *et* Umar, 2019; Sung *et al.*, 2025). This shifting demographic profile prompted major advisory bodies, including the U.S. Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS), to lower the recommended age for initiating routine screening to 45 years. These updated guidelines are supported by epidemiological analyses and predictive models demonstrating a significant prevalence of precancerous lesions in younger adults (Knudsen *et al.,* 2021).

In our Moroccan cohort, the mean rank was 30.50 for participants under 45 of age, and 33.57 for those over 45, with no statistically significant difference between the two groups. These results revealed that the association between age and the onset of CRC is not evident and merits to be deeply investigated. Moreover, global epidemiological data indicate a rising incidence of early onset CRC, with an increasing incidence of younger individuals being affected. This trend supports the hypothesis of a shift toward earlier disease onset.

These findings align with historical data from the same university hospital center, which reported as early as 1988 that 27% of CRC cases presented in individuals under 40 years of age (Sahraoui *et al.,* 2000).

4.1 Role of TMAO in Colorectal Carcinogenesis

Current evidence implicates trimethylamine-*N*-oxide (TMAO) in oncogenic processes; however, its specific role in colorectal carcinogenesis remains nuanced and, at times, paradoxical across epidemiological cohorts (Budoff *et al.*, 2025; Jarmukhanov *et al.*, 2024; Sun *et al.*, 2024; Wang et *al.*, 2022b). In our univariate analyses, continuous TMAO levels were not directly associated with overall clinical disease stage.

This aligns with findings by Guertin *et al.* (2017), who reported no direct association between serum TMAO and CRC risk ($p = 0.25$), but identified a significant association with dietary choline status Because TMAO is synthesized from microbial cleavage of dietary choline and L-carnitine—nutrients concentrated in animal-derived foods—colorectal carcinogenesis may be driven primarily by choline metabolic intermediates and host microbial imbalances rather than TMAO in isolation (Yao *et al.,* 2023). Conversely, *in vitro* and *in vivo* models suggest that TMAO directly promotes tumor cell proliferation and fuels tumor angiogenesis via vascular endothelial growth factor (Yang *et al.,* 2022). However, most of the available data is derived from small sample sizes or experimental in vitro and/or in vivo models (Crowe *et al.,* 2022; Huang *et al.,* 2024), underscoring the need of further in-depth investigation through large-scale longitudinal studies including appropriate control groups, to better assess the potential role of TMAO in the colorectal cancer development and/or progression.

4.2 Lifestyle Modulators: Physical Activity, Smoking, and Alcohol

Lifestyle factors significantly modulate gut microbial composition and systemic TMAO concentrations:

- **Physical Activity:** During last decades, a substantial interest has been offered to the role of physical activity in disease prevention and overall well-being. Although clinical trials demonstrate that moderate-to-vigorous physical activity (MVPA) reduces circulating TMAO levels (e.g., a 0.584 μM daily reduction per 30 minutes of MVPA; Argyridou *et al.,* (2020), no correlation was detected in our cohort. This discrepancy likely stems from self-reported measurement limitations; participants frequently categorized light domestic chores or short walks as exercise due to perceived fatigue, whereas such activities do not meet formal physiological thresholds for MVPA (Murphy *et al.,* 2013).
- **Tobacco Smoking:** The association between TMAO level and smoking status has been well documented in relation with several diseases, particularly thromboangiitis obliterans (Buerger's disease) and ischemic stroke (Wang *et al.,* 2025). However, to the best of our knowledge, there's no data on the potential role of smoking in modulating TMAO levels and its involvement in the pathogenesis of CRC. In the present study, a borderline association was found between tobacco use and TMAO status (p = 0.06). Excreted tobacco metabolites entering the gastrointestinal tract via biliary secretion may induce DNA damage, disrupt mucosal barrier integrity, and alter the gut microbial niche favorizing TMA-producing bacteria. These effects may have potential effect on CRC development and/or progression, although further investigation in larger and controlled studies is warranted.
- **Alcohol Consumption:** Alcohol intake demonstrated a strong positive association with serum TMAO levels (p < 0.001). This finding aligns with previous research. Oh *et al.* (2024) observed that plasma levels of TMAO and its dietary precursors increased with the severity of alcoholic liver disease (ALD). Similarly, Helsley *et al.* (2022) noticed a significant elevation of TMA in patients with alcoholic hepatitis and demonstrated that inhibiting microbial TMA production reduced ethanol-induced liver damage in mice.

4.3 Adiposity, Malnutrition, and Dietary Patterns

In our study, general obesity (measured via BMI) was not significantly associated with TMAO levels. This finding is consistent with previously reported data, suggesting that neither BMI nor metabolic syndrome is necessarily correlated with elevated TMAO levels even in patients at high risk (Naghipour *et al.*, 2024). However, However, following multivariable adjustment, waist circumference emerged as a strong independent predictor. This indicates that visceral/central adiposity—rather than total body mass—is the primary metabolic driver of altered TMAO dynamics.

Another notable finding of the present study is the significant correlation between TMAO level and underweight status adjustment for all covariates. This trend could be attributed to the malnutrition reported in the studied cohort, as observed by Yuan *et al.* (2023) in malnourished patients. Accordingly, negative correlation has been observed between TMAO levels and body mass index as well as dietary protein intake (Hu *et al.,* 2022). Moreover, patients exhibiting protein energy wasting (PEW), a severe form of malnutrition characterized by deficiencies in both protein and energy, exhibited elevated TMAO levels compared to those without PEW (Hu *et al.,* 2022). In the current study, univariate analysis did not reveal any correlation with vegetarian diets and TMAO levels. However, after adjusting for all relevant factors in multivariate analysis, a significant correlation emerged. Vegetarian diets, being rich in oligosaccharides, are associated with an elevated abundance of the bacterial genus Prevotella, potentially reducing the availability of choline for TMA synthesis (Benítez-Páez *et al.,* 2019). Consistent with this trend, healthy individuals following plant-based diets, such as the Mediterranean diet, vegetarian or vegan diets, tend to display lower plasma TMAO concentrations (Lombardo *et al.,* 2022). Moreover, the consumption of fiber-rich food has been demonstrated to attenuate TMAO formation following meat intake, ultimately contributing to reduced circulating TMAO levels (Haas *et al.,* 2025).

intake of protein-dense foods (red meat, eggs) strongly correlated with elevated TMAO, consistent with feeding trials demonstrating marked surges in circulating TMAO following animal protein consumption (Wang *et al.,* 2019; Wilcox *et al.,* 2021). Similarly, individuals consuming fish exhibited 4 – 6 times higher urinary TMAO levels than those consuming red meat (Yin *et al.,* 2020).

4.4 Gastrointestinal Symptom Profiles and Tumor Localization

Elevated TMAO levels correlated with key gastrointestinal symptoms that serve as clinical "red flags" for CRC:

- **Diarrhea & Mucosal Inflammation:** Diarrhea constitutes one of the four "red flags" symptoms in CRC. Alongside abdominal pain, rectal bleeding, and iron deficiency anemia, diarrhea is associated with earlier diagnosis of CRC (Fritz *et al.,* 2023). In the present study, a strong and significant association of TMAO to diarrhea has been identified. TMAO has been implicated in the development and persistence of chronic diarrhea and correlates is significantly with

inflammatory markers such as IL-1β, TGF-β1 and NLRP3 ($p < 0.05$) (Xie *et al.,* 2024b). In an animal model, some studies have suggested that TMAO may contribute to diarrhea indirectly by GM composition (Xie *et al.,* 2024a).

- **Pencil-Thin Stools & Hematochezia:** Significant high levels of TMAO were observed in patients with narrow-caliber stools and in those with a high amount of blood in the stool. This may be explained by inflammation that makes the intestinal mucosa edematous and infiltrated. In addition, recurrent inflammation can lead to scarring and fibrosis, resulting in thickening of the intestinal wall, causing permanent stenosis and luminal narrowing (Stenke *et al.*, 2017).

  To the best of our knowledge, this is the first study highlighting an association between TMAO level and the amount of blood in the stool. This relationship may reflect increased intestinal permeability accompanied by morphological and hemodynamic alterations in the colon (Jaworska *et al.,* 2017). Dysregulation of pro-inflammatory proteins that regulate intestinal permeability, such as zonolin may contribute to these variations (Al-Obaide *et al.,* 2017).

- **Tumor Anatomical Site:** Additionally, TMAO can also cause functional damage to vascular endothelial cells via the PKC/NF-κB pathway, and activation of protein kinase C further contributing to intestinal and vascular alterations (Ma *et al.,* 2017). Rectal tenesmus is defined as a persistent sensation of needing to defecate, even where no stool or only a minimal amount is present (Mawer & Alhawaj, 2025; Mueller *et al.,* 2020). In our patients, a borderline association was observed between TMAO levels and rectal tenesmus ($p = 0.051$), which may be mediated by intestinal inflammation. The GM possesses further unpredictable characteristics. GM can influence enteric neuronal and glial activity and affect plasticity via its metabolites such as short-chain fatty acids (SCFAs) and lipopolysaccharides (LPS) (Giuffrè *et al.,* 2020). In response to these microbial signals, enteric glial cells (EGCs) release pro-inflammatory cytokines including IL-1β. IL-6. TNF-α which contribute to intestinal inflammation (Liñán-Rico *et al.*, 2016; Turco *et al.,* 2014) and induce therefore modifications in smooth muscle contractility leading to spasms and hypomotility (Giuffrè *et al.,* 2020).

In the present study, patients suffering from fatigue exhibited high levels of TMAO. TMAO is generated through the conversion of L-carnitine by the GM. L-carnitine itself plays a crucial role in mitochondrial energy production and the improvement of physical and cognitive functions (Longo *et al.,* 2016), particularly in elderly individuals (Vecchio *et al.,* 2021). While L-carnitine may reduce fatigue by enhancing mitochondrial function and reducing inflammation, its conversion to TMAO promotes systemic inflammation and oxidative stress (Yue *et al.,* 2017), leading to muscle fatigue and impair skeletal muscle function (Davis *et al.,* 2025). Additional significant correlation was detected between elevated TMAO levels and CRC located in the hepatic flexure of the colon. To date, few studies have explored the association between TMAO and tumor location. Previous research correlated high TMAO levels with an elevated risk of distal CRC, particularly in the descending colon and rectum (Byrd *et al.,* 2024). Similarly, some researchers have found a positive correlation between TMAO and rectal cancer in postmenopausal women (Bae *et al.,* 2014), although no specific association with the proximal colon tumors possibly due to regional differences in gut microbiota composition or metabolic mechanisms that are not yet fully elucidated. Overall, these results suggest that TMAO levels could be associated not only with dietary habits and gastrointestinal symptoms but also with specific clinical characteristics and tumor locations in CRC.

4.5 Study Limitations

The present study is specifically informative and clearly demonstrates that a diet with high protein intake and alcohol consumption is closely associated with a higher blood TMAO levels, and conversely plant-based food consumption is associated with lower TMAO levels.

When interpreting these findings, several methodological limitations should be considered:

- **Cross-Sectional Design & Sample Size:** The single-center, cross-sectional design restricts our ability to establish direct temporal or causal relationships, and the moderate sample size led to wide confidence intervals in specific subgroup analyses (e.g., underweight status).
- **Subjective Lifestyle Assessments:** Dietary intake and physical activity were quantified using self-reported questionnaires rather than objective biosensors or double-labeled water methods, introducing potential recall bias.
- **Absence of Direct Microbiome Profiling:** Fecal 16S rRNA or metagenomic sequencing was not performed, preventing direct correlation between specific bacterial taxa abundances and serum TMAO concentrations.

5 Conclusions

The present study provides evidence that high animal protein intake, central adiposity, and alcohol consumption are independent determinants of elevated circulating TMAO levels in Moroccan CRC patients. Conversely, adherence to fiber-rich, plant-based dietary patterns exerts a marked protective effect against systemic TMAO accumulation. Furthermore, elevated TMAO levels correlate with distinct clinical symptom profiles (diarrhea, narrow stools, rectal bleeding) and specific anatomical tumor sites, particularly the hepatic flexure.

These findings highlight the clinical utility of integrating targeted dietary assessments and nutritional interventions into standard oncology care in Morocco. Promoting plant-based dietary patterns and limiting red meat consumption could reduce systemic TMAO exposure, potentially improving metabolic and clinical outcomes in CRC management. Prospective, large-scale longitudinal and interventional studies are warranted to further elucidate the causal pathways linking gut microbial metabolites to colorectal carcinogenesis.

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