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Association of metabolic dysfunction-associated fatty liver disease with gastrointestinal infections: insights from National Inpatient Sample Database

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ABSTRACT

Objectives The study aimed to compare the risk of gastrointestinal infections among patients with and without metabolic dysfunction-associated fatty liver disease (MAFLD).

Methods This was a population-based, retrospective, observational study using data from the National Inpatient Sample (NIS), the largest all-payer US inpatient care database.

Setting Hospitalisation of adults aged ≥18 years old admitted in 2020 was identified using the NIS. Patients were stratified by the presence and absence of MAFLD.

Participants 26.4 million adults aged ≥18 years old were included in the study. Patients younger than 18 and those with missing demographic or mortality data were excluded.

Primary and secondary outcomes Primary outcome was to assess the overall risk of gastrointestinal infections in patients with and without MAFLD. Secondary outcomes were demographics and comorbidities stratified by the presence or absence of gastrointestinal infection, and the risk of specific gastrointestinal pathogens.

Results Of 26.4 million patients admitted in 2020, 755 910 (2.85%) had the presence of MAFLD. There was a higher prevalence of bacterial gastrointestinal infections in patients with MAFLD than those without (1.6% vs 0.9%, p<0.001). The incidence of *Clostridioides difficile* (1.3% vs 0.8%, p<0.001), *Escherichia coli* (0.3% vs 0.01%, p<0.001), and *Salmonella* (0.07% vs 0.03%, p<0.001) was higher in patients with MAFLD. The presence of MAFLD was associated with higher odds of developing gastrointestinal infections (adjusted OR (aOR) −1.75, 95% CI −1.68 to 1.83, p<0.001). After adjusting for confounders, results remained statistically significant (aOR −1.36, 95% CI - 1.30-1.42, p<0.001).

Conclusion Even after adjusting for confounding factors, our study demonstrates an increased risk of gastrointestinal infections in patients with MAFLD, specifically of *C. difficile*, *E. coli*, and *Salmonella*. The immune and microbiota changes seen within MAFLD potentially contribute to the increased risk of gastrointestinal infections.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immune and microbiota changes are associated with the pathogenesis of metabolic dysfunction-associated fatty liver disease (MAFLD). These changes have been implicated with an increased risk of various pathogens. There is a paucity of data that have investigated the association between the presence of MAFLD and its associated risk of bacterial gastrointestinal infections.

WHAT THIS STUDY ADDS

⇒ Patients with MAFLD were found to have an increased risk of bacterial gastrointestinal infections. The incidence of *Clostridioides difficile*, *Escherichia coli*, and *Salmonella* was higher in patients with MAFLD. The microbiota and immune changes may contribute to this association.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further studies are needed to clarify the findings of this study. Future studies can focus on better detailing the exact microbiota changes and mechanisms that predispose patients with MAFLD to bacterial gastrointestinal infections.

INTRODUCTION

Metabolic dysfunction-associated fatty liver disease (MAFLD), with a prevalence rate of 20–25% worldwide, is the second most common cause of liver transplants in the USA and Europe.[1 2] It has become a significant public health problem worldwide, with a higher prevalence of disease noted in the Middle East (31%) and South America (32%) and the lowest in Africa (14%).[3] MAFLD is a multisystem disease characterised by hepatic

steatosis in over 5% of hepatocytes while excluding secondary causes of liver damage, including alcohol misuse, steatogenic medications, or monogenic genetic disorders.[4] With further progression, inflammatory damage can develop, causing steatohepatitis and eventually hepatic fibrosis.[1]

MAFLD has a complex multifactorial pathogenesis similar to metabolic syndrome, ultimately leading to hepatocyte lipotoxicity, increased intestinal permeability, endotoxaemia, gut dysbiosis, and an impaired immune response.[5] Insulin resistance-inducing lipotoxicity is still considered the critical pathway leading to the development of non-alcoholic steatohepatitis (NASH).[6] This triggers the local immune response leading to the recruitment of leucocytes and other inflammatory cells, further stimulating the transdifferentiation of hepatic stellate cells to myofibroblasts. This in turn leads to fibrotic changes within the hepatocytes.[6 7] Liver fibrosis is seen as the most crucial predictor of all-cause and liver-related mortality in patients with MAFLD.[8] The altered gut microbiome is implicated in multiple hits to the gut–liver axis leading to increased translocation of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns.[9] These molecular patterns result from tissue injury or cell death. They associate sterile inflammation with life-threatening disease and end-organ damage.[10] This leads to altered innate and adaptive immunity and further progression of MAFLD.[9] In addition to this, MAFLD has been associated with other alterations in immune function such as derangements in the function of Kupffer cells, neutrophils, and hepatic natural killer cells. Although common metabolic factors among patients with MAFLD can contribute to increased infection risk through immune dysregulation, prior reports suggest that MAFLD may independently put patients at risk of severe infections. A prior study on a Swedish cohort found that patients with non-alcoholic fatty liver disease were at increased risk of respiratory infections, peritonitis, urinary tract infections, musculoskeletal infections, and skin and soft tissue infections. Although worsening fibrosis was associated with an increased risk of infection, patients with non-alcoholic fatty liver disease experienced a similar spectrum of infection as compared with the general population, with respiratory and urogenital being the most common. It was proposed that non-alcoholic fatty liver disease may itself be associated with an increased susceptibility and severity of infection.[11]

Thus, our study compared patients with and without MAFLD and the risk of bacterial gastrointestinal (GI) infections using publicly available national data. The aim was to assess if MAFLD was independently associated with an increased risk of bacterial GI infections.

MATERIALS AND METHODS
Data source
Healthcare Cost and Project (HCUP) maintains the National Inpatient Sample (NIS), the nation's largest database of inpatient hospital stays.[12] It collects data from a 20% stratified sample of US hospitals from 37 states and has been reliably used to estimate disease burden and outcomes. Each hospitalisation is de-identified and maintained in the NIS as a unique entry.

Study population
The International Classification of Diseases 10th Version, Clinical Modification (ICD-10-CM) diagnosis codes were used to identify all patients admitted from 1 January 2020 through 31 December 2020. Patients aged less than 18 years were excluded from the analysis. Patients with missing demographic and mortality data were also excluded. In total, 26.4 million cases met the inclusion criteria. Patients were stratified into two groups, those with and without the diagnosis of MAFLD.

Definition of MAFLD
Adult hospitalisation with MAFLD was identified by first using ICD codes for liver disease without mention of alcohol (ICD-9: 571.5, 571.8-9, 567.23, 572.2-4, 456.0-2x, 789.5x; ICD-10: I85.xx, K65.2, K72.1x, K72.9x, K74.0-2, K74.6x, K75.8x, K75.9, K76.0, K76.6-9, K77, R18.x) and then excluding patients with chronic liver disease with mention of alcohol or alcohol use disorder. A similar approach has been used by Minhas *et al* to identify patients with the diagnosis of MAFLD.[13]

Study variables
Patient demographics, including age (divided into three groups: <44 years, 45–64 years, and >65 years), gender, race, primary insurance, and median income quartile, were collected. Hospital characteristics such as region, bed size, and rural/urban location, prespecified by HCUP, were also collected. Data were also collected on the common comorbidities associated with MAFLD, such as diabetes, hypertension, obesity, obstructive sleep apnoea (OSA), hyperlipidaemia, gastro-oesophageal reflux disease (GERD), inflammatory bowel disease (IBD), and smoking. Information on tobacco use was also collected. The Charlson-Deyo Comorbidity Index (CCI) was used to assess the comorbidity burden. This is a well-validated index based on ICD-10-CM codes meant to be used in large administrative data to predict mortality and hospital resource use.[14]

Study outcomes
Our study aims to assess if an association exists between MAFLD and GI infections. We also assessed the rates of common infections such as *Clostridioides difficile, Escherichia coli,* and *Salmonella* in patients with and without MAFLD. These were ascertained using ICD-10 codes.

Statistical analysis
Hospital-level discharge weights provided by NIS were used to generate national estimates. X^2 test was used to compare categorical variables, while an independent sample t-test was used for continuous variables. Univariate and multivariate logistic regression analyses were

performed. We adjusted for patient demographics, hospital comorbidities, CCI, smoking, diabetes, hypertension, obesity, OSA, hyperlipidaemia, GERD, and IBD. The unadjusted and adjusted ORs (aORs) were calculated with a 95% CI. A type I error of <0.05 was considered statistically significant. Data analysis was done using STATA V.17.0 (Texas).

RESULTS
Patient characteristics based on presence or absence of MAFLD
A total of 26 million patients were admitted in 2020. Of these, 755 910 (2.85%) patients had the presence of MAFLD. The majority of the patients in the MAFLD group were >65 years of age (46.1%), female (54.2%), had Medicare (51.4%), and were in the lowest income quartile (30.9%). On unadjusted analysis, patients with MAFLD had a higher prevalence of GERD (27.6% vs 18.6%), hyperlipidaemia (39.5% vs 32.7%), diabetes (46.07% vs 27.9%), hypertension (68.0% vs 58.6%), obesity (32.9% vs 18.2%), OSA (13.4% vs 7.3%), and IBD (1.7% vs 1.0%), and incidence of bacterial GI infections (1.6% vs 0.9%) compared with patients without MAFLD (all p<0.05). A complete list of demographic differences and comorbidities between patients with MAFLD and those without is presented in table 1.

Patient characteristics based on presence or absence of GI infection
We also stratified the total admissions into patients with GI infections and those without. Out of the total admissions to US hospitals in 2020, 0.92% of admissions had GI infections. The majority of the patients in the bacterial GI infections group were elderly aged >65 years (57.18%), female (56.03%), had Medicare (61.96%), and were in the lowest income quartile (28.96%). On unadjusted analysis, patients with GI infections were more likely to have GERD (24.03% vs 18.78%), hyperlipidaemia (36.37% vs 32.88%), diabetes (34.26% vs 28.45%), hypertension (68.57% vs 56.83%), and IBD (4.98% vs 1.07%). GI infections were less associated with obesity (15.1% vs 18.57%). Caucasian patients were more likely to have GI infection compared with African American, Hispanic, and Asian/Pacific Islander patients. Medicare patients were more likely to have GI infection compared with patients with Medicaid, private insurance, or those uninsured. A complete list of demographic differences and comorbidities between patients with GI infections and those without is presented in table 2.

Incidence of specific enteric pathogens with MAFLD
There was a higher incidence of *C. difficile*, *E. coli*, and *Salmonella* in the MAFLD group compared with the non-MAFLD group. The presence of fatty liver was associated with statistically significant higher odds of developing GI infections (aOR −1.75, 95% CI −1.68 to 1.83, p<0.001). A slightly higher incidence of other GI infections was noted

in the MAFLD group; however, the difference was not statistically significant. Results are expressed in table 3.

Results of multivariate analysis assessing the risk of MAFLD on the risk of developing GI infections
Multivariable analysis on risk of bacterial GI infections is presented in table 4 and further highlighted in figure 1. Even after adjusting for confounding factors, the positive relationship between MAFLD and bacterial GI infections continued to stay statistically significant (aOR 1.36, 95% CI 1.30 to 1.42, p<0.001). Compared with younger patients aged 18–44 years of age, patients 45–64 and >65 years of age were more likely to have bacterial GI infections (aORs 1.82 and 1.69, respectively). Females were also more likely than males to have GI infections (aOR 1.13). African American, Hispanic, and Asian/Pacific Islander patients were less likely to have GI infections than Caucasians, while Native Americans were more likely to have GI infections (aOR 1.12). Patients with GERD (aOR 1.13, 95% CI 1.11 to 1.16) were more likely to have GI infections. Patients with a smoking history (aOR 0.84, 95% CI 0.82 to 0.86), diabetes (aOR 0.90, 95% CI 0.88 to 0.92), obesity (aOR 0.75, 95% CI 0.73 to 0.77), and OSA (aOR 0.84, 95% CI 0.81 to 0.87) were less likely to have bacterial GI infections. Increasing levels of comorbidities were noted to have an increased risk. IBD also had an increased risk of bacterial GI infections (aOR 5.02, 95% CI 4.79 to 5.23). All the above results achieved statistical significance (p<0.05).

DISCUSSION
In our nationally representative population-based study on a US patient sample, after adjusting for confounding factors, we found that patients with MAFLD were more likely to have GI infections, particularly with *C. difficile*, *E. coli*, and *Salmonella*. Prior studies demonstrated similar results involving other features of metabolic syndrome, such as obesity, hyperglycaemia, and diabetes.[15 16] Most prior research involving infections and MAFLD has investigated the role of the gut and associated infections in the pathogenesis and progression of MAFLD. The role of infectious agents such as *Helicobacter pylori*,[17] hepatitis C and HIV,[18 19] and even SARS-CoV-2 in the development and progression of steatosis has been well described in the literature.[20] However, the effects of MAFLD on the patients' risk of developing various bacterial infections have not been well elucidated.[21]

Ebrahimi *et al* also found that patients with MAFLD were more likely to have severe infections versus control counterparts, most notably respiratory and urinary tract infections. Although this was a Swedish cohort evaluating both inpatient and outpatient care, after adjusting for comorbidities, they found a similar increased risk of GI infections in patients with MAFLD (HR 1.95, 95% CI 1.76 to 2.16). The specific microorganism cause of infections was not expressed, as was in our study. This risk was seen across all stages of MAFLD, with worsening risk

Table 1 Patient demographics and comorbidities, stratified by the presence or absence of MAFLD

Demographics	Absence of MAFLD n (%)	Presence of MAFLD n (%)	P value
Age category			**<0.001**
18–44	7 414 871 (28.9)	121 360 (16.0)	
45–64	7 014 496 (27.3)	285 945 (37.8)	
>65	11 247 555 (43.8)	348 605 (46.1)	
Sex			**<0.001**
Male	11 167 501 (43.5)	345 810 (45.7)	
Female	14 509 421 (56.5)	410 100 (54.2)	
Race			**<0.001**
Caucasian	16 892 682 (65.8)	502 850 (66.5)	
African American	4 088 746 (15.9)	82 285 (10.9)	
Hispanic	3 006 105 (11.7)	120 835 (15.9)	
Asian/Pacific Islander	734 530 (2.9)	20 560 (2.7)	
Native American	178 830 (0.7)	1935 (0.8)	
Other	797 395 (3.0)	6080 (2.5)	
Primary expected payer			**<0.001**
Medicare	11 965 204 (46.6)	388 210 (51.4)	
Medicaid	4 837 650 (18.8)	112 135 (14.8)	
Private	6 895 562 (26.9)	200 250 (26.5)	
Uninsured	1 084 341 (42.2)	30 575 (4.0)	
Median household income			**<0.001**
Lowest quartile	7 852 345 (30.6)	233 275 (30.9)	
Second quartile	6 970 118 (27.1)	209 720 (27.7)	
Third quartile	5 869 792 (22.9)	175 630 (23.2)	
Highest quartile	4 984 667 (19.4)	137 285 (18.1)	
Charlson Comorbidity Index			**<0.001**
0	8 884 263 (34.6)	13 150 (1.7)	
1	4 856 220 (18.9)	142 715 (18.9)	
2	3 453 565 (13.4)	128 725 (17.0)	
>3	8 482 874 (33.0)	471 320 (62.3)	
Underlying comorbidity			
Gastro-oesophageal reflux disease	4 769 150 (18.6)	208 425 (27.6)	**<0.001**
Hyperlipidaemia	8 400 750 (32.7)	298 605 (39.5)	**<0.001**
Smoking	9 359 320 (36.4)	266 205 (35.2)	**<0.001**
Diabetes	7 186 560 (27.9)	348 225 (46.07)	**<0.001**
Hypertension	14 537 211 (56.6)	514 100 (68.0)	**<0.001**
Obesity	4 685 809 (18.2)	249 200 (32.9)	**<0.001**
Obstructive sleep apnoea	1 866 635 (7.3)	101 180 (13.4)	**<0.001**
Bacterial gastrointestinal infections	231 405 (0.9)	11 850 (1.6)	**<0.001**
Inflammatory bowel disease	278 615 (1.0)	12 950 (1.7)	**<0.001**

Numbers are presented as absolute numbers with percentages.
Significant differences between groups highlighted in bold (p<0.05).
Income data provide quartile classification of the estimated median household income of residents in the patient's zip code. The quartiles are identified by values of 1–4, indicating the poorest to wealthiest populations. Because these estimates are updated annually, the value ranges for the income quartile categories vary by year. For the year 2020, the national income quartiles were: (1) $1–49 999, (2) $50 000–64 999, (3) $65 000–85 999, (4) $86 000+.
MAFLD, metabolic dysfunction-associated fatty liver disease.

Table 2 Patient demographics and comorbidities, stratified by the presence of GI infection

Demographics	Absence of GI infection n (%)	Presence of GI infection n (%)	P value
Age category			
18–44	7 504 751 (28.66)	31 480 (12.94)	**<0.001**
45–64	722 775 (27.6)	72 690 (29.88)	
>65	11 457 075 (43.75)	139 085 (57.18)	
Sex	26 189 577	26 432 932	
Male	11 406 361 (43.55)	106 950 (43.97)	0.1174
Female	14 783 216 (56.45)	136 305 (56.03)	
Race			
Caucasian	17 220 462 (65.75)	175 070 (71.97)	**<0.001**
African American	4 137 746 (15.8)	33 285 (13.68)	
Hispanic	3 105 236 (11.86)	21 705 (8.92)	
Asian/Pacific Islander	21 705 (2.86)	5180 (2.13)	
Native American	178 830 (.68)	1935 (0.80)	
Other	797 395 (3.05)	6080 (2.50)	
Primary expected payer			
Medicare	12 202 689 (46.59)	150 725 (61.96)	**<0.001**
Medicaid	4 917 785 (18.78)	32 000 (13.15)	
Private	7 047 957 (26.91)	47 855 (19.67)	
Uninsured	1 108 266 (4.23)	6650 (2.73)	
Median household income			
Lowest quartile	8 015 175 (30.6)	70 445 (28.96)	**<0.001**
Second quartile	7 112 998 (27.96)	66 840 (27.48)	
Third quartile	5 987 652 (22.86)	57 770 (23.75)	
Highest quartile	5 073 752 (19.37)	48 200 (19.81)	
Charlson Comorbidity Index			
0	8 855 363 (33.81)	42 050 (17.29)	**<0.001**
1	4 958 355 (18.93)	40 580 (16.68)	
2	3 543 335 (13.53)	38 955 (16.01)	
>3	8 832 524 (33.72)	121 670 (50.01)	
Comorbidity			
Gastro-oesophageal reflux disease	4 919 115 (18.78)	58 460 (24.03)	**<0.001**
Hyperlipidaemia	8 610 875 (32.88)	88 480 (36.37)	**<0.001**
Smoking	9 539 595 (36.43)	85 930 (35.33)	**<0.001**
Diabetes	7 451 445 (28.45)	83 340 (34.26)	**<0.001**
Hypertension	14 884 506 (56.83)	166 805 (68.57)	**<0.001**
Obesity	4 898 289 (18.57)	36 720 (15.1)	**<0.001**
Obstructive sleep apnoea	1 950 410 (7.45)	17 405 (7.16)	**0.02**
MAFLD/NASH	744 060 (2.84)	11 850 (4.87)	**<0.001**
Inflammatory bowel disease	279 440 (1.07)	12 125 (4.98)	**<0.001**

Numbers are presented as absolute numbers with percentages.
Significant values are in bold (p<0.05).
GI, gastrointestinal; MAFLD, metabolic dysfunction-associated fatty liver disease; NASH, non-alcoholic steatohepatitis.

with increasing fibrosis severity.[11] Similar findings were seen by Nseir *et al* who found an increased risk of bacterial infections in patients with MAFLD independent of metabolic syndrome.[22] The metabolic pathologies associated with MAFLD have long been known to be associated with an increased risk of infection. Studies have indicated

Table 3 Gastrointestinal (GI) conditions, stratified by presence of fatty liver

Bacterial infection	Absence of MAFLD n (%)	Presence of MAFLD n (%)	P value
Bacterial GI infections	231 405 (0.9)	11 850 (1.6)	**<0.001**
Clostridioides difficile	197 390 (0.8)	9555 (1.3)	**<0.001**
Escherichia coli	3495 (0.01)	215 (0.3)	**<0.001**
Salmonella	8075 (0.03)	530 (0.07)	**<0.001**
Other	2030 (0.008)	90 (0.012)	0.10

Numbers are presented as absolute numbers with percentages.
Significant values are in bold (p<0.05).

that nearly 6% of patients with diabetes have at least one hospital admission secondary to an infectious cause.[23] However, the prior studies suggest that the increased risk seen in MAFLD may be due to mechanisms independent of metabolic syndrome.[11] This is reflected in our analysis, where an increased risk in patients with MAFLD was seen with statistical significance after adjusting for confounding culprits for increased infection risk, such as obesity and diabetes.

On adjusted analysis, female patients were more likely to have bacterial GI infections than their male counterparts. This is in contrast to prior research, which has suggested that males are at an increased risk of GI infections, particularly *C. difficile* and *Salmonella,* while females are at increased risk of genitourinary infections. This has been suggested due to gender differences in hygiene and eating practices, inflammatory response, and hormones.[24] Patients with GERD were more likely to have bacterial GI infections than those without GERD. These patients are more likely to be on proton-pump inhibitor (PPI) therapy which leads to a reduction in gastric acid secretion. An Asian study by Kuo *et al* found that PPI therapy was associated with an increased risk of enteric infections (aOR 5.526, 95% CI 5.274 to 5.791). This increased risk is thought to be due to a reduction in gastric acid, making the stomach more hospitable to pathogenic, enteric organisms. Furthermore, PPI use can alter the gut microbiome and alter the function of immune cells, both of which may contribute to an increased infection risk.[25] We acknowledge that PPI use was not assessed in our study.

Patients with IBD were also more likely to be diagnosed with enteric infections than those without. This is in line with prior studies that have shown an increased risk of *C. difficile* and *Salmonella* in patients with IBD.[26] This is likely due to an altered gut microbiome, decreased immunity, frequent hospitalisation, and use of immunosuppressive medications such as steroids. Notably, diabetes and obesity were associated with a decreased risk of bacterial GI infections. This was not expected, as the immune deficits seen among diabetics have been associated with an increased risk of infection.[11]

Patients with MAFLD have been found to be at increased risk of *C. difficile* infections. This has been previously demonstrated by Nseir *et al* in a retrospective study of 230 patients with MAFLD who were found to have a greater risk of *C. difficile* infection.[27] Similar results were seen by Samadan *et al,* who found that MAFLD was associated with increased rates of recurrent *C. difficile* infection.[28] The microbiota of the intestines encompasses the microbial community inhabiting the GI tract, with an estimated presence of more than 100 trillion microorganisms.[29] Colonisation begins at birth, matures over time, and is affected by various dietary, environmental, and genetic factors.[30] In a healthy patient, the host and bacterial colonisers within the microbiota display a delicate symbiotic homeostasis. The host provides a source of nutrients and an environment, while the microorganisms produce crucial amino acids and vitamins, while breaking down some indigestible parts of the diet.[31] In addition, the microbiota fulfils an important role in immune homeostasis, counteracting the colonisation of pathogenic bacteria and maintaining intestinal barrier integrity.[32 33] Any disruption to this relationship can lead to the pathological growth of colonising bacteria. This dysbiosis generally involves the loss of beneficial bacteria, the loss of bacteria diversity, or the expansion of harmful bacteria.[34] This complex interplay can potentially explain the increased rates of *C. difficile* infection in patients with MAFLD seen in our study.

While there has been extensive research regarding *C. difficile* and MAFLD, not much has been reported regarding the association between MAFLD and *Salmonella* and *E. coli.* Prior studies have reported that *E. coli* has a higher abundance in patients with MAFLD than in healthy patients.[35 36] The association of *Salmonella* with MAFLD has not been discussed in the literature. The microbiota changes that predispose patients to *C. difficile* may also be associated with an increased risk of *Salmonella* and *E. coli* infections. Further studies are needed to clarify these associations.

Patients with MAFLD exhibit increased gut permeability with associated dysbiosis.[6] The gut barrier consists of immune cells, structural elements of mucus and epithelial cells, and soluble mediators such as IgA, which prevent bacterial translocation while allowing for the transport of nutrients across tight junctions.[37] The permeability of this barrier can lead to translocation to the liver of PAMPs, which can lead to NASH development and

Table 4 Results of multivariate logistic regression analysis assessing the relationship between MAFLD and gastrointestinal conditions

	OR	95% CI	P value
Fatty liver	1.36	1.30 to 1.42	**<0.001**
Age categories			
18–44	Reference		
45–64	1.82	1.74 to 1.89	**<0.001**
>65	1.69	1.60 to 1.77	**<0.001**
Sex			
Male	Reference		
Female	1.13	1.11 to 1.6	**<0.001**
Race			
Caucasian	Reference		
African American	0.86	0.83 to 0.89	**<0.001**
Hispanic	0.84	0.81 to 0.88	**<0.001**
Asian/Pacific Islander	0.76	0.71 to 0.81	**<0.001**
Native American	1.21	1.06 to 1.37	**<0.001**
Other	0.87	0.81 to 0.93	**<0.001**
Median household income			
Lowest quartile	Reference		
Second quartile	0.86	0.83 to 0.90	**<0.001**
Third quartile	0.79	0.76 to 0.82	**<0.001**
Highest quartile	0.77	0.72 to 0.82	**<0.001**
Income quartiles			
Lowest quartile	Reference		
Second quartile	1.05	1.01 to 1.08	**<0.001**
Third quartile	1.08	1.04 to 1.12	**<0.001**
Highest quartile	1.06	1.02 to 1.11	**<0.001**
Comorbidities			
Gastro-oesophageal reflux disease	1.13	1.11 to 1.16	**<0.001**
Hyperlipidaemia	0.81	0.79 to 0.83	**<0.001**
Smoking	0.84	0.82 to 0.86	**<0.001**
Diabetes	0.90	0.88 to 0.92	**<0.001**
Hypertension	1.06	1.03 to 1.09	**<0.001**
Obesity	0.75	0.73 to 0.77	**<0.001**
Obstructive sleep apnoea	0.84	0.81 to 0.87	**<0.001**
Charlson Comorbidity Index			
0	Reference		
1	1.47	1.42 to 1.53	**<0.001**
2	1.87	1.79 to 1.95	**<0.001**
3 or more	2.40	2.30 to 2.50	**<0.001**
Inflammatory bowel disease	5.02	4.79 to 5.23	**<0.001**

Significant values are in bold (p<0.05).
MAFLD, metabolic dysfunction-associated fatty liver disease.

augment progression.[9] We propose that the increased gut permeability seen in MAFLD can also predispose patients to GI infections. Worsening fibrosis in MAFLD has been associated with an increased risk of bacterial infections.[11] Similar findings have been well described in cirrhosis, where retrospective studies have indicated that increased
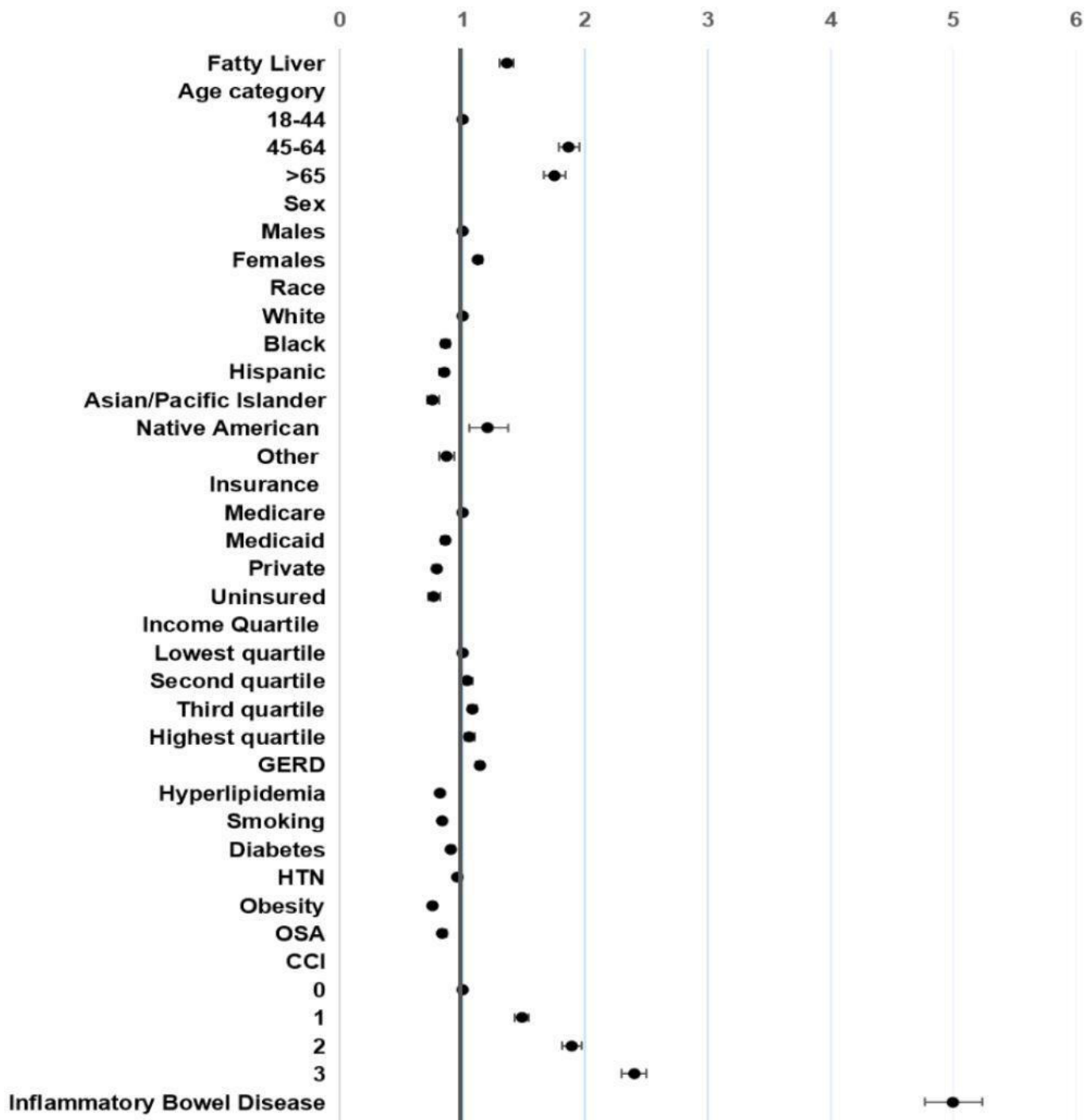
Figure 1 Logistic regression model depicting the association of patient characteristics and comorbidities with the development of bacterial GI infections. CCI, Charlson Comorbidity Index; GERD, gastro-oesophageal reflux disease; GI, gastrointestinal; HTN, hypertension; OSA, obstructive sleep apnoea.

intestinal permeability has been associated with pathological bacterial translocation, subsequent infections, and increased mortality.[38]

Changes in the microbiota have also been noted in patients with MAFLD. The gut microbiome's main intestinal phyla are *Firmicutes* and *Bacteroidetes*, which amass more than 90% of the entire microorganism population.[30] A disruption in population sizes and ratios may contribute to the pathological effects seen in MAFLD.

A prospective cross-sectional study by Wang *et al* found that patients with MAFLD had higher levels of *Bacteroidetes* and lower levels of *Firmicutes* versus healthy subjects. Patients with MAFLD also had lower levels of *Lachnospiraceae*, *Peptostreptococcaceae*, *Lactobacillaceae*, and *Ruminococcaseae*, among others.[39] These findings are notable as prior reports suggest that *Firmicutes* produce more butyrate, which has been shown to increase insulin sensitivity and metabolism, and have anti-inflammatory

effects.[36] Another study by Tsai *et al* noted that patients with NASH and MAFLD had lower levels of *Lentisphaerae* and *Clostridia*.[40] Although it is evident that microbiota changes are present and likely contribute to the development of MAFLD and its complications, such as infections and progression, the exact mechanism still needs to be elucidated.

Another mechanism of increased susceptibility to infections is the possible immune-related deficiencies of MAFLD. The liver plays a crucial role in the human immune system. The Kupffer cells and lymphocytes contribute around 20% of the total cells of the liver.[41] They play a critical role in GI immune defence as they are the first immune cells to detect and process pathogens and antigens from the GI system. It has therefore been suggested that their atypical activation contributes to the development of MAFLD and an increased risk of infection.[42 43] In addition, the insulin resistance seen in MAFLD can contribute to the impaired function of neutrophils.[44] Worsening MAFLD and fibrosis can potentially worsen the risk of infection. This has been manifested by Nseir *et al* when they found stronger associations of community-acquired pneumonia with worsening fibrosis in patients with MAFLD.[45] Similar immune dysfunction has been noted in patients with cirrhosis who experience increased susceptibility to bacterial infection in the setting of extensive immunoparesis.[46] Findings in cirrhotics of intestinal dysmotility, intestinal permeability, and gut microbiome dysbiosis that contribute to infections can also explain the increased infection risk seen in MAFLD.[47]

A strength of our study is the analysis of a large, population-based cohort and the ability to test the associations of a variety of patient comorbidities and demographics. We acknowledge the following limitations of the study. Our study relies on a national database subject to observational data limitations in a retrospective manner. NIS does not provide patient identifiers; therefore, it is difficult to track readmissions. Due to the nature of the database, we rely on ICD-10 diagnosis codes to identify patients, and the possibility of coding errors could not be ruled out. It is difficult to ascertain the fibrosis stage in patients with MAFLD, as the database lacks objective data. PPI use was not tested for in our study in relation to risk of *C. difficile* and other enteric infections. We also acknowledge the lack of specific data on laboratory testing for diagnosing enteric infections, as these are unable to be analysed using the NIS.

CONCLUSIONS AND FUTURE PERSPECTIVES

MAFLD is associated with a complex interplay of metabolic disease, altered gut microbiota, and dysfunctional immunity. Prior studies have shown that other disease processes with these factors have been associated with increased infection risk. The association between MAFLD and infection risk has not been clearly established. Our study found an increased risk of enteric bacterial

infections due to *C. difficile*, *E. coli*, and *Salmonella* in patients with MAFLD. Alterations in the gut microbiome, immunity, and gut permeability may be responsible for this association. Further prospective, multicentre studies are needed to explore the association between MAFLD and infections.

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