Inflammation, etiologies and Model for End-stage Liver Disease score: What makes liver disease patients susceptible to developing colorectal neoplasia?

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Aim: Research has identified patients with chronic liver disease as a risk group for colorectal neoplasia. In this study, we aimed to identify liver disease subgroups at enhanced risk of developing colorectal neoplasia, as well as causal factors.

Methods: The present retrospective study included patients with chronic liver disease undergoing colonoscopy during liver transplantation evaluations, and liver-healthy patients as part of the German screening protocol. We assessed inflammatory laboratory values, Model for End-stage Liver Disease score, portal hypertension, and liver disease etiologies as explanatory variables. Outcomes included polyps, adenomas, high-risk situations, and colorectal cancer, tested in uni- and multivariable analyses.

Results: A total of 1046 patients were included, 407 with liver disease, 639 without. Alcohol-toxic, metabolic, cryptogenic, non-alcoholic fatty liver disease, and hepatocellular carcinoma were significantly associated with colorectal neoplasia, as were low compared with high Model for End-stage Liver Disease scores. Portal hypertension showed no associations with neoplasia. Inflammatory markers were associated with colorectal neoplasia, independent of liver disease severity.

Conclusions: Low Model for End-stage Liver Disease score, inflammatory markers, and certain etiologies were associated with colorectal neoplasia. Our findings suggest that inflammation may play an important role in the development of colonic adenomas in patients with chronic liver disease. Findings need to be confirmed in prospective studies, but may allow risk stratification and, possibly, development of prophylactic treatments.

Key words: cirrhosis, colonoscopy, colorectal neoplasia, colorectal polyps, inflammation, liver disease

INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of cancer-related death. In most cases, the malignancy develops along an adenoma-carcinoma sequence, allowing the effective removal of precursor lesions during screening colonoscopy. As focus shifts onto precision medicine, researchers aim to define patient groups at elevated risk of developing colorectal neoplasia that may profit from enhanced screening.

In a previous study, we identified patients with chronic liver disease as a risk group for lesions of the colorectal adenoma-carcinoma sequence. This opened up two subsequent fields of discussion: First, chronic liver disease is a heterogeneous entity, necessitating stratification of patients according to risk of colorectal neoplasia. Second, underlying mechanisms linking chronic liver disease and colorectal neoplasia have never been investigated, and will be examined in this study for the first time. To do so, we focused on associations with severity of liver disease, portal hypertension, etiologies, and inflammation. Knowledge of causes may help improve screening and even allow prophylactic measures. To follow up on these questions, we obtained detailed data that we added to our previously reported database.

There are few studies that investigate the links between colorectal polyps and single liver disease entities, among them non-alcoholic fatty liver disease (NAFLD),
alcohol-toxic liver disease (ALD),\textsuperscript{6} and viral hepatitis.\textsuperscript{7,8} Given the large number of existing etiologies, this list is still incomplete, and results are inconsistent. Notably, a comprehensive study is lacking.

Our aim was to identify specific liver disease entities at increased risk for colorectal neoplasia, and to investigate possible mechanisms linking chronic liver disease to the colorectal adenoma-carcinoma sequence.

**METHODS**

**Patients**

For this study, we collected detailed patient information that we added to our previously reported cohort, one of the largest in the field.\textsuperscript{4} For this dataset, we had enrolled patients both with and without chronic liver disease that had undergone at least one colonoscopy between 2011 and 2017 (Fig. 1). We summarized all available colonoscopies for each patient. Lesions were resected colonoscopically, and polyp histology was determined by a pathologist. We documented all findings, including histology. As defined in the German colonoscopy guidelines, we identified high-risk situations (HRS) as:
- three or more adenomas, or
- high-grade intraepithelial neoplasia, or
- tubular adenomas $\geq 10$ mm, or
- polyp with a villous component.\textsuperscript{9}

We now collected detailed information on liver disease etiologies, signs of portal hypertension, disease severity, presence of infection, and laboratory values obtained within 90 days before colonoscopy: non-high-sensitivity C-reactive protein (CRP), white blood cell counts (leukocytes, lymphocytes, neutrophils, lymphocyte-to-monocyte ratio), and transferrin. We included only those values that were obtained in a period without any infectious or inflammatory process other than the low-grade chronic inflammation due to liver disease. Hepatopathies represented by $\geq 20$ patients were analyzed separately, the remaining summarized as “others.”

The first two analyses focused on associations between liver disease-specific characteristics, and thus only included patients with chronic liver disease (LDPs). For the second

![Figure 1 Inclusion and exclusion criteria. CIBD, chronic inflammatory bowel disease; HIV, human immunodeficiency virus; MELD, Model for End-stage Liver Disease.](image)
analysis, we only included LDPs with available laboratory values (Fig. 1). Our third analysis is based on the entire dataset.

**Study design**

The study was designed as an observational retrospective cohort study. Each patient gave written informed consent before intervention. The study was approved by the WWU institutional ethical committee (Ref. 2017–659-f-S, 23 January 2018) and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

**Statistical analysis**

Primary outcomes include occurrence of polyps, rate and number of adenomas, HRS, and CRC. We focused on adenomas and HRS, as these have immediate clinical implications and result in intensified follow up.9

Patient characteristics included age, sex, body mass index (BMI), and number of received colonoscopies. For LDPs, we also determined etiologies, Model for End-stage Liver Disease (MELD) score, signs of portal hypertension, presence of infection, and inflammatory laboratory values. Characteristics are described by the median ± interquartile range or mean ± standard deviation, as appropriate. Differences between the groups were assessed by the $\chi^2$-test or Mann–Whitney U-test, as applicable.

For our first analysis, we assessed links between colorectal neoplasia and MELD score or portal hypertension in multivariable logistic or ordinal regression models. As previously reported, we adjusted for factors known to influence the occurrence of polyps and adenomas: age, sex, number of colonoscopies, and BMI.4 We designed a cumulative marker for portal hypertension consisting of any hypertensive sign, including varices (esophageal, rectal), ascites, hypersplenism, and cutaneous signs. This approach has already been established perviously.10

For our second analysis, we analyzed associations between inflammatory markers and colorectal neoplasia. Here, we added the MELD score as a covariable to our model, as it was significant in our first analysis. For HRS assessment, we discarded BMI as a covariable, as it was not significant in any of the previous tests, and the number of HRS in our second analysis only allowed for five covariables.

For our third analysis, we assessed associations between liver disease etiologies and respective dependent variables in our multivariable model. To show these results, we used the model to calculate predicted probabilities. For these analyses, we computed a patient representative of our entire dataset. Consequently, this example patient was of median age (59.6 years), median BMI (27 kg/m²), and received a median number of colonoscopies ($n = 1$). We chose to compute a male patient, as most patients with chronic liver disease were male. Subsequently, based on the entire dataset, we calculated the risk of various colorectal lesions, depending on liver disease etiology, and recorded these in a graph.

The significance level was defined as $P < 0.05$. All statistical tests were carried out using SPSS 25.0 software (IBM Corporation, Armonk, NY, USA).

**RESULTS**

**Patients**

In total, we included 1046 patients in the present study, 407 with chronic liver disease and 639 without. The dataset was described in our previous study, and is summarized in Table 1.4 Etiologies that were analyzed separately include ALD, viral hepatitis, NAFLD, metabolic and cryptogenic hepatopathies, patients with more than one liver disease diagnosis, those with hepatocellular carcinoma (HCC), and others (autoimmune, cholestatic, cardiac, Budd–Chiari syndrome, tropical infections, or Churg–Strauss syndrome). Characteristics varied depending on disease etiology. Median laboratory values are listed in Table 1. Table S1 summarizes colorectal findings. Patient characteristics did not vary significantly between all LDPs and those with available laboratory values (Table S2).

**MELD score is associated with colorectal neoplasia, whereas portal hypertension is not**

In our first analyses, we assessed the link between the severity of liver disease and neoplasia, and portal hypertension and neoplasia (Table 2). For these analyses, we only included LDPs.

**MELD score**

The severity of liver disease was associated with a decreased rate (odds ratio [OR] 0.94; $P = 0.009$) and number of adenomas (OR 0.95; $P = 0.017$), barely missing significance level for HRS (OR 0.95; $P = 0.075$). Figure 2 shows the rates of polyps, adenomas, and HRS for liver-healthy patients (LHPs) and LDPs with low (<15) and high MELD-scores (≥15). The cut-off value was chosen according to the recommendations of the European Association for the Study of the Liver.11

**Portal hypertension**

Portal hypertension showed no association with colorectal neoplasia (all tests $P > 0.6$).
Table 1 Patient characteristics

| All patients | Liver-healthy patients | All patients with hepatopathy | Alcohol-toxic | NAFLD | Metabolic | Others | >1 diagnosis | Cryptogenic | HCC | Significance |
|--------------|------------------------|-----------------------------|---------------|-------|-----------|--------|-------------|------------|-----|-------------|
| (n = 1046)   | (n = 639)              | (n = 407)                   | (n = 73)      | (n = 63) | (n = 21) | (n = 46) | (n = 23)    | (n = 87)   |     |             |
| Age, years (IQR): U-test vs. liver-healthy patients | 59.6 (55.8–65.6) | 60.9 (56.9–63.6) | P < 0.001 | 57.2 (52.7–60.4) | 57.0 (48.4–59.0) | 55.9 (43.1–64.6) | 55.7 (43.1–62.1) | 53.8 (43.7–63.5) | 58.3 (47.6–63.5) | 56.6 (47.4–65.7) | 62.0 (55.6–65.7) | 66.7 |
| Male, n (%) | 26.0 (22.5–30.0) | 27.0 (24.0–29.0) | P < 0.001 | 26.0 (22.5–29.0) | 24.0 (20.0–24.0) | 24.0 (20.0–24.0) | 24.0 (20.0–24.0) | 24.0 (20.0–24.0) | 24.0 (20.0–31.3) | 24.0 (20.0–26.0) | 24.0 (20.0–26.0) | 29.0 |
| BMI, kg/m² (IQR): U-test vs. liver-healthy patients | 26.0 (23.0–30.0) | 24.0 (22.0–29.0) | P = 0.001 | 26.0 (22.5–29.0) | 26.0 (20.0–24.0) | 26.0 (20.0–24.0) | 26.0 (20.0–24.0) | 26.0 (20.0–24.0) | 26.0 (20.0–29.0) | 26.0 (20.0–29.0) | 26.0 (20.0–29.0) | 29.0 |
| No. of colonoscopies, n (IQR): U-test vs. liver-healthy patients | 1 (1–1) | 1 (1–1) | P = 0.851 | 1 (1–3) | 1 (1–4) | 1 (1–3) | 1 (1–2) | 1 (1–1) | 1 (1–1) | 1 (1–1) | 1 (1–1) | 1 (1–1) |
| Cirrhosis, n (%) | 304 (74.7) | 73 (100.0) | 49 (77.8) | 16 (76.2) | 8 (32.0) | 28 (40.6) | 36 (78.3) | 16 (69.6) | 78 (89.7) | 103 (25.3) | 0 (0.0) | 14 (22.2) | 5 (23.8) | 17 (68.0) | 41 (59.4) | 10 (21.7) | 7 (30.4) | 9 (10.3) |
| Non-cirrhotic liver disease, n (%) | 12 (8–17) | 16 (12–20) | 15 (10–16) | 12 (8–19) | 8 (7–15) | 8 (7–20) | 16 (10–25) | 14 (8–17) | 10 (7–13) |
| Leukocytes, thousand/μL (IQR) | 5.6 (4.1–7.4) | 6.0 (4.5–8.4) | 4.4 (2.8–6.4) | 5.3 (3.8–6.4) | 5.9 (4.3–7.6) | 5.9 (4.5–7.2) | 5.1 (3.9–6.8) | 6.0 (4.4–8.5) | 5.8 (4.2–7.1) |
| Lymphocytes, thousand/μL (IQR) | 1.2 (0.7–1.8) | 1.2 (0.9–2.0) | 0.7 (0.5–1.2) | 0.9 (0.3–1.7) | 1.8 (0.6–2.2) | 1.4 (0.9–1.7) | 1.3 (1.0–1.8) | 1.5 (1.2–1.8) | 1.3 (0.9–1.6) |
| Neutrophils, thousand/μL (IQR) | 3.4 (2.2–4.7) | 3.7 (2.2–5.3) | 2.8 (0.9–3.4) | 3.0 (1.8–4.1) | 3.9 (2.6–4.6) | 4.7 (2.7–7.5) | 2.7 (1.0–4.2) | 5.6 (3.6–8.0) | 3.3 (1.9–4.5) |
| Transferrin, mg/dL (IQR) | 230.5 (154.5–285.5) | 165 (126–241) | 240 (148–305) | 250 (172.5–279.5) | 233 (193.3–271.8) | 257 (178–322.3) | 268 (138–291.0) | 238 (125.5–234.0) | 321 (186.5–295.5) |

For age, sex, BMI and number of colonoscopies, we compared patient characteristics with those of liver-healthy patients using the $\chi^2$-test (for sex) or the Mann–Whitney U-test (others), documenting all $P$-values resulting from this comparison.

BMI, body mass index; HCC, hepatocellular carcinoma; IQR, interquartile range; MELD, Model for End-stage Liver Disease; NAFLD, non-alcoholic fatty liver disease; No., number; U-test, Mann–Whitney U-test.
Inflammatory markers are associated with colorectal neoplasia

Inflammatory markers and MELD score

Inflammatory markers were negatively correlated with the MELD score (lymphocytes $r = -0.307$, $P < 0.001$; lymphocyte-to-monocyte ratio $r = -0.366$, $P < 0.001$; transferrin $r = -0.525$, $P < 0.001$; rest $P > 0.05$).

Leukocytes — In our multivariable model, increasing numbers of leukocytes were associated with a higher rate (OR 1.09; $P = 0.028$) and number of adenomas (OR 1.10; $P = 0.007$). The MELD score showed significant associations with adenomas in this model as well (rate: OR 0.94, $P = 0.012$; number of adenomas: OR 0.95, $P = 0.029$).

Lymphocytes — Similarly, lymphocytes were also associated with the rate (OR 1.89; $P = 0.044$) and number of adenomas (OR 2.05; $P = 0.019$). In this analysis, the MELD score did not reach significance level, even though trends were similar. Neither the MELD score, nor the number of lymphocytes reached significance for HRS.

Neutrophils — An increasing number of neutrophils was associated with an increased risk of adenoma: rate (OR 1.23; $P = 0.006$), number (OR 1.24; $P = 0.003$), and HRS (OR 1.24; $P = 0.047$). The MELD score was associated with a decreasing rate (OR 0.91; $P = 0.023$) and number of adenomas (OR 0.92; $P = 0.038$), but not with HRS (OR 0.94; $P = 0.247$).

CRP — Only non-high-sensitivity CRP was available for LDPs. Overall, 44.2% of patients showed CRP values below the institutional laboratory cut-offs ($\leq 0.5$ mg/dL), preventing any meaningful analysis.

Transferrin — Transferrin was significantly associated with decreasing HRS (OR 0.99; $P = 0.006$). Even though directionality was similar for the other outcomes, results were barely not significant.

Table 2

| Adenoma | OR (95% CI) | P  |
|---------|-------------|----|
| MELD score | 0.94 (0.90–0.99) | 0.009* |
| Age | 1.04 (1.01–1.07) | 0.002* |
| Male | 1.79 (1.26–2.78) | 0.031* |
| BMI | 0.99 (0.94–1.03) | 0.003* |

* $P < 0.05$. CI, confidence interval; BMI, body mass index; MELD, Model for End-stage Liver Disease; No., number; OR, odds ratio.

Figure 2 Rates of polyps, adenomas, high-risk situations, and colorectal carcinoma (CRC) in liver-healthy and liver-diseased patients with low and high Model for End-stage Liver Disease (MELD) scores.
|                  | Leukocytes | Lymphocytes | Neutrophils | Transferrin |
|------------------|------------|-------------|-------------|-------------|
| **Adenoma**      |            |             |             |             |
| Leukocytes       | OR (95% CI): P | 1.09 (1.01–1.17); Multivariable Model | 0.028* | 1.89 (1.02–3.50); Multivariable Model | 0.044* |
| MELD score       | OR (95% CI): P | 0.94 (0.90–0.99); Multivariable Model | 0.012* | 0.95 (0.87–1.03); Multivariable Model | 0.216 |
| Age              | OR (95% CI): P | 1.04 (1.02–1.07); Age | 0.001* | 1.06 (1.02–1.12); Age | 0.009* |
| Male sex         | OR (95% CI): P | 1.70 (0.96–3.00); Male sex | 0.068 | 5.54 (1.71–18.01); Male sex | 0.004* |
| No. of colonoscopies | OR (95% CI): P | 1.84 (1.16–2.91); No. of colonoscopies | 0.009* | 3.29 (1.02–10.61); No. of colonoscopies | 0.047* |
| BMI              | OR (95% CI): P | 0.99 (0.94–1.04); BMI | 0.655 | 0.94 (0.85–1.03); BMI | 0.172 |
| **No. of adenomas** |            |             |             |             |
| Leukocytes       | OR (95% CI): P | 1.10 (1.03–1.18); No. of adenomas | 0.007* | 2.05 (1.12–3.73); Neutrophils | 0.019* |
| MELD score       | OR (95% CI): P | 0.95 (0.91–1.00); MELD score | 0.029* | 0.97 (0.89–1.04); MELD score | 0.381 |
| Age              | OR (95% CI): P | 1.04 (1.02–1.07); Age | 0.001* | 1.07 (1.02–1.12); Age | 0.007* |
| Male sex         | OR (95% CI): P | 1.75 (1.01–3.05); Male sex | 0.047* | 5.36 (1.68–17.07); Male sex | 0.005* |
| No. of colonoscopies | OR (95% CI): P | 1.86 (1.25–2.76); No. of colonoscopies | 0.002* | 4.12 (1.45–11.73); No. of colonoscopies | 0.008* |
| BMI              | OR (95% CI): P | 1.00 (0.96–1.05); BMI | 0.977 | 0.95 (0.87–1.04); BMI | 0.229 |
| **High-risk situations** |      |             |             |             |
| Leukocytes       | OR (95% CI): P | 1.11 (1.02–1.20); Lymphocytes | 0.020* | 1.62 (0.70–3.74); Neutrophils | 0.262 |
| MELD score       | OR (95% CI): P | 0.96 (0.90–1.01); MELD score | 0.126 | 0.96 (0.86–1.08); MELD score | 0.518 |
| Age              | OR (95% CI): P | 1.02 (0.99–1.05); Age | 0.277 | 1.03 (0.97–1.09); Age | 0.402 |
| Male sex         | OR (95% CI): P | 1.68 (0.81–3.48); Male sex | 0.163 | 7.75 (0.94–64.00); Male sex | 0.057 |
| No. of colonoscopies | OR (95% CI): P | 1.86 (1.16–2.98); No. of colonoscopies | 0.010* | 3.47 (0.98–12.30); No. of colonoscopies | 0.055 |

*P < 0.05.
BMI, body mass index; CI, confidence interval; MELD, Model for End-stage Liver Disease; No., number; OR, odds ratio.
The results of multivariable analysis are summarized in Table 3.

Specific liver disease etiologies are associated with colorectal neoplasia

We assessed associations between different liver disease etiologies and colorectal polyps in comparison to LHPs (Table 4).

Adenomas — In multivariable analysis, compared with LHPs, ALD was associated with both the rate (OR 1.8; *P = 0.046) and total number of adenomas (OR 2.0; *P = 0.016). Cryptogenic liver disease showed similar results (rate: OR 2.8, *P = 0.044; number of adenomas: OR 1.9, *P = 0.014), as did patients with HCC (rate: OR 2.0, *P = 0.011; number of adenomas. OR 3.0, *P = 0.024). The other etiologies did not reach significance level.

HRS — Again, compared with LHPs, ALD was associated with higher rates of HRS (OR 3.1, *P = 0.003). NAFLD (OR 3.6; *P = 0.042), and metabolic liver disease (OR 4.2; *P = 0.008) also reached significance.

CRC — Due to the small number of CRCs, we did not carry out multivariable analysis. Four of five CRCs were found in LDPs, in patients with NAFLD (n = 1 ), “others” (n = 1 ), and >1 diagnosis (n = 2 ).

Figure 3 shows the predicted probabilities for all etiologies.
Causes of colorectal neoplasia in liver disease

DISCUSSION

After identifying LDPS as a risk-group for colorectal neoplasia in our last study, we now aimed to substratify these patients for risk of colorectal neoplasia, and investigate the underlying mechanisms linking chronic liver disease and colorectal neoplasia.

Our thoughts were informed by three key deductions:

1. Possible factors must have a carcinogenic effect on the colon to explain increased colorectal neoplasia.
2. These factors must be characteristic of liver disease and need to differ from LHPs.
3. It takes 5–10 years for adenomas to form, so the harmful influence must be prolonged to take effect.

In the present study, a higher MELD score was associated with a decreased rate and number of adenomas. Similarly, a previous study reported lower numbers of adenomas in patients with higher Child–Pugh scores. Both scores are measures of liver function and disease severity, and have been reported to be well correlated. Our observations allow for three conclusions, that we added to our list of key deductions previously noted, numbering them accordingly:

1. Impairment of excretion and synthesis deteriorates with liver disease severity. Thus, it is highly unlikely that these parameters are the cause for colorectal neoplasia.
2. On the contrary, the analysis suggests the impact of a factor that, with increased liver disease severity, either decreases or loses influence on the colon.
3. Still, the risk of neoplasia in patients with severe liver disease was increased compared with LHPs, suggesting a factor that is characteristic for chronic liver disease.

Studies have identified an entity called portal hypertensive colopathy, a state of thickened colonic walls and vessel dysmorphisms due to high portal venous pressure caused by liver disease. Researchers have found a close link between chronic liver disease and the immune system, referred to as cirrhosis-associated immune dysfunction. This phenomenon describes simultaneous immune dysfunction and systemic inflammation.

Gut dysbiosis, increased bacteria translocation, and endothelial aberrations lead to increased intestinal permeability, thus overstimulating the lymphatic tissue, and resulting in colonic and systemic inflammation. Researchers regard this as the main cause of inflammation in chronic liver disease, with its focus on the colon. Additional aggravating mechanisms include both the impairment of the liver immune system due to fibrosis, and its bypass through porto-systemic shunts. Simultaneously, hepatic synthesis of proteins and pattern recognition receptors deteriorates, confirmed by a negative correlation between transferrin and MELD score in the present study. As reflected in our data, hepatopathies lead to a reduction of leukocytes, especially lymphocytes, by diminishing their formation and increasing sequestration through hypersplenism.

Interestingly, in advanced liver disease, the pro-inflammatory state switches to an immunodeficient state, with overwhelmingly anti-inflammatory agents both colonic and systemic. This phenomenon may help explain why patients with higher MELD scores show lower numbers of adenomas. Immunodeficiency and inflammation both encourage the development of colorectal neoplasia, but to different degrees. Patients in a pro-inflammatory state with low MELD scores encouraged the highest rate of adenomas, which points to inflammation as the strongest driver of colorectal neoplasias. Patients with high MELD scores have been associated with immunodeficient states. In the present study, they still showed more adenomas than healthy patients, but fewer than pro-inflammatory liver disease patients. With both pro-inflammatory and immunodeficient patients showing increased adenoma rates compared with healthy patients, we conclude that both factors are drivers for adenoma formation, with inflammation being a more dominant influence compared with immunodeficiency. These conclusions will need to be verified in larger prospective studies.

Patients with severe liver disease must have passed through a phase of less severe liver disease, with inflammation impacting the colon. Nevertheless, they show lower numbers of adenomas. This discrepancy will need to be further investigated, but we can offer two hypotheses:

1. Possibly, polyps that had developed during phases of lower MELD scores regressed spontaneously as the strong influence of colonic inflammation subsided. In the literature, cases of regressing polyps have already been described, especially in environments in which the carcinogenic factor disappeared. Nevertheless, this field of research is very difficult to investigate, as polyps are usually removed during colonoscopy and their evolution cannot be further tracked. Researchers have suggested mechanical damage or impairment of blood
supply that lead to polyp necrosis, or simply spontaneous regression due to the subsiding carcinogenic stimulus.

2 These patients may have passed through the state of less severe liver disease more quickly. Thus, inflammation could not impact the colon long enough for adenomas to form.

Carcinogenic effect of inflammation
Researchers have identified numerous inflammatory markers as risk factors for colorectal neoplasia in cohorts of patients without liver disease, among them increased tumor necrosis factor α or decreased interleukin-6 or transferrin.

We are the first to link inflammatory markers in LDPs with colorectal neoplasia:

In liver disease, inflammatory parameters reflect state of inflammation, but are also influenced by chronic liver disease, indicated by their negative correlation with the MELD score.

White blood cells decrease with increasing MELD score. Both developments were associated with decreasing colorectal neoplasia. These directionalities make it almost impossible to determine if white blood cell counts are the cause of neoplasia or simply a consequence of severe liver disease. However, our multivariable analysis showed that both factors were independently associated with neoplasia, suggesting that the inflammatory character of the white blood cells does indeed play a role, independent of their role as marker for liver disease severity.

Decreased transferrin is a marker of both inflammation and deteriorating liver synthesis capacities. A higher MELD score is associated with a decreased number of adenomas and decreased transferrin. If transferrin was only a marker of liver disease severity, decreased transferrin would have to be associated with decreased neoplasia. However, in an analysis including transferrin and MELD, decreased transferrin was associated with increased neoplasia. These directionalities can only be conciliated by interpreting decreased transferrin as marker of inflammation, linking inflammation to colorectal neoplasia.

For our cohort, only non-high-sensitivity CRP values were available, with a detection cut-off of ≤0.5 mg/dL. Previous studies reported mean high-sensitivity CRPs of 0.53 mg/dL in patients with compensated ALD, and only 0.64 mg/dL in LDPs with spontaneous bacterial peritonitis. In our cohort with low-grade chronic inflammation and 44.2% of patients with values below the institutional cut-offs, non-high-sensitivity CRP is not granular enough to assess links between inflammation and colorectal neoplasia.

Compatibility with our six deductions is as follows:
1 Inflammation has a carcinogenic effect on the colon.
2 Colonic and systemic inflammation are integral parts of chronic liver disease, but not in LHPs.
3 Inflammation due to chronic liver disease is prolonged and continuously affects the colon.
4 Inflammation is not a marker of liver excretion or synthesis capacities.
5 In advanced liver disease, systemic and especially colonic inflammation switches to a state of immunodeficiency. This phenomenon may explain the link between high MELD scores and a decreased rate and number of neoplasia.
6 First, advanced LDPs must have passed through a state of less severe liver disease with increased risk of adenoma. Second, immunodeficiency has been linked to increased colorectal neoplasia. Both explain why advanced LDPs have an increased risk of colorectal neoplasia compared to LHPs.

Liver disease etiologies
Although generally, the mechanisms of cirrhosis-associated immune dysfunction are the same for all etiologies, they do differ in detail and extent. Furthermore, specific characteristics of each entity impact the colon as well and need to be considered in addition to inflammatory mechanisms.

Overall, ALD, NAFLD, and metabolic and cryptogenic liver disease, as well as HCC, were associated with at least one finding of neoplasia.

The present findings are in line with multiple previous studies that have identified alcohol and ALD as a risk factor for colon adenomas and consequently for CRC. Carcinogenic factors include acetaldehyde as the primary metabolite of alcohol or oxidative stress.

NAFLD was associated with an increased polyp rate and HRS. These findings are in line with studies focusing on this specific subgroup of patients. The metabolic syndrome has already been linked to CRC and is closely associated with NAFLD. Thus, it is difficult to keep the two entities’ effects on the colon apart. The fact that increased BMI was not a significant confounder in any of our tests suggests that NAFLD might have a stronger effect on the colon than the nutritional state alone. This means another risk factor may play a role additionally, based on our findings possibly inflammation.

Although we did not find a link to neoplasia, previous studies focusing only on viral hepatitis reported...
associations with adenomas. Oncogenic mechanisms of viral hepatitis leading to HCC include immune-mediated inflammation, oxidative stress, and direct effects of viral proteins. Possibly, similar mechanisms affect colonocytes as well. Patient characteristics show that almost all inflammatory parameters were decreased compared with the other liver disease entities. These characteristics are not necessarily representative for patients with viral hepatitis in general, but may explain the lower rates of neoplasia in patients with viral hepatitis in our cohort.

Even though the HCC subgroup comprised mostly of ALD (26.4%) and viral hepatitis (35.6%), it showed higher ORs for adenomas than either of these etiologies alone (Fig. 3). First, HCC and CRC share several risk factors. Chronic inflammation may be another possible common factor of carcinogenesis, as it has been reported to encourage the development of HCC, while we found it to be associated with colorectal adenoma. Second, patients that developed HCC mostly had a long-term hepatopathy, prolonging the impact of the liver disease on the colon.

There were several limitations to the present study. First, due to its retrospective design, we can only report associations and interpret them with regard to previous studies. Causality, however, will need to be confirmed in prospective studies. Nevertheless, we are the first to analyze the possible causes of increased colorectal neoplasia in LDPs, among them the influence of inflammation due to chronic liver disease on the colon. This can help direct further research. Second, non-high-sensitivity CRP is not granular enough for statistical analyses in low-grade inflammation settings, so we needed to rely on white blood cells and transferrin. Third, we only analyzed a limited number of possible causes of colorectal adenomas: severity of liver disease, portal hypertension, inflammation, and underlying etiologies, as well as age, sex, and BMI. However, several other mechanisms may have an impact as well: the type and changes of gut microbiota due to chronic liver disease, affecting colonocytes not only through inflammation, or deviation of bile salt composition. These factors will have to be investigated further.

MELD score, certain liver disease etiologies, and inflammatory markers in LDPs are associated with colorectal neoplasia. The present findings suggest that inflammation may encourage colorectal neoplasia in LDPs, which could explain why LDPs show more adenomas than LHPs. The colorectal adenoma-carcinoma sequence is multifactorial and necessitates prospective studies to confirm the present findings.

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**SUPPORTING INFORMATION**

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

**Table S1** Overview of colorectal findings
- CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; IQR, interquartile range; NAFLD, non-alcoholic fatty liver disease; No., number; PSC, primary sclerosing cholangitis.

**Table S2** Patient characteristics of patients with chronic liver disease
- BMI, body mass index; IQR, interquartile range; MELD, Model for End-stage Liver Disease.