Association between NAFLD and Infectious Diseases

Subjects: Others

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Non-alcoholic fatty liver disease (NAFLD) is the most prevalent chronic liver disease, affecting one third of the Western population. The hallmark of the disease is excessive storage of fat in the liver. Most commonly, it is caused by metabolic syndrome (or one of its components).

NAFLD infectious disease community acquired pneumonia

1. NAFLD and Community Acquired Pneumonia

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality worldwide [1]. There have only been a few studies evaluating the relationship between NAFLD and CAP.

Nseir et al. published a case-control retrospective study in 2017 that included 141 patients who were hospitalized for the treatment of CAP during a 3-year period. The patients with CAP were older than 18 years and had imaging data of the liver by abdominal ultrasonography. Structural lung disease and immunocompromised patients were excluded. A control group was made up of 141 patients who were hospitalized in the same study period matched for age, gender and BMI, and no evidence of current infectious disease. A total of 40.4% of the subjects from the study group showed evidence of Non-alcoholic fatty liver disease (NAFLD) vs. only 27.6% from the control group. Mean CRP levels were significantly higher in patients with CAP. A multivariate analysis showed that NAFLD was associated with CAP.

The same group later reported a retrospective cohort study including 561 patients with CAP and assessed the impact of NAFLD on CAP survival. The prevalence of NAFLD was 35.6%. Significant differences were found between the NAFLD and non-NAFLD group in BMI, CURB-65 (a clinical prediction rule for the purpose of predicting mortality in community-acquired pneumonia including five risk factors, each worth one point: confusion of new onset, blood urea nitrogen greater than 7 mmol/L (19 mg/dL), respiration rate of 30 breaths per minute or above, blood pressure less than 90 mmHg, systolic or diastolic blood pressure of 60 mmHg or less and age of 65 or older), ALT, GGT, and CRP. The mortality in the NAFLD group was 17%, and in controls it was 5.8%. In multivariate logistic regression analysis, NAFLD with fibrosis score 0–2, NAFLD with fibrosis score > 2 were associated with 30-day all-cause mortality, independently of other components of metabolic syndrome [2].

Several other studies examined the impact of T2DM or obesity on CAP outcomes, however none of them included NAFLD as a variable. Patients with T2DM have reduced neutrophil function (thereby increasing their likelihood of

acquiring infectious illnesses) and a generally poorer prognosis for CAP (increased rating of pleural effusions and mortality) [3][4]. There appears to be no substantial difference in mortality between obese patients with pneumonia and normal-weight patients, even though obese patients are more susceptible to respiratory tract infections. However, studies examining the relationship between obesity, T2DM, and pneumonia demonstrates that obese people with T2DM have a higher incidence and severity of infection [5][6].

The term “obesity paradox” (a lower mortality rate for overweight or obese people within certain subpopulations) has also been recorded by some researchers in patients with CAP [7]. This finding is mainly based on observational studies that might be biased by patients’ selection since obese patients more frequently develop CAP and they might be overrepresented in cohorts [7]. Another possible explanation includes so called reversal causation, where normal weight patients might have other risk factors for worse outcomes [7]. One of the interesting research topics is the alteration of gut microbiota in obese patients that might modulate immune response and have an impact on survival. This connection depends on the gut metagenome, and changes in the microbial population might result in modifications to the normal metabolism. Additionally, it has been discovered that the gut microbiota influences lipid metabolism, inflammation, and atherogenesis via lipopolysaccharides and peptidoglycans [8]. Further research on this topic is necessary.

2. NAFLD and COVID-19

There is growing evidence that NAFLD is a risk factor for acquiring the SARS-CoV2 infection. Angiotensin-converting enzyme 2 (ACE2), a cellular entrance receptor for SARS-CoV-2, is also present in the hepatobiliary and gastrointestinal epithelial cells, making the entire gastrointestinal (GI) system susceptible to infection [9].

In patients with NASH, the expression of genes that enhance the affinity of coronaviruses for hepatic tissue is also elevated. This also suggests that people with advanced NAFLD may be even more susceptible to COVID-19 [10]. Additionally, compared to patients without NAFLD, those with NAFLD seem to have a greater chance of disease progression and a longer viral shedding time [11].

Younossi et al. used electronic medical record data of adult COVID-19 patients hospitalized between March and December 2020 to identify the determinants of mortality and hospital resource consumption among patients with NAFLD. Imaging methods or a liver biopsy were used to detect NAFLD in the absence of other liver disorders. Out of the 4835 patients hospitalized with COVID-19, 553 had NAFLD. Of those, 58% were obese, 15% were morbidly obese (BMI > 40kg/m^2), 51% had T2DM, and 63% had arterial hypertension. When compared to patients without NAFLD, patients with NAFLD experienced more pronounced respiratory symptoms, a higher body temperature and heart rate, and higher levels of alanine and aspartate aminotransferases. Only 3.9% of individuals with NAFLD had acute liver damage. With a crude inpatient mortality rate of 11%, the NAFLD group had considerably longer lengths of stay, more ICU admission, and they more frequently required mechanical ventilation. Older age, morbid obesity, a higher Fibrosis-4 Index (FIB-4) score were independent predictors of mortality in patients with NAFLD, but not sex, race/ethnicity, or other comorbidities.

Between February and April 2020, all consecutive patients hospitalized with COVID-19 were enrolled in a cohort study undertaken by Forlano et al. Patients were categorized based on their FIB-4 index and imaging results. The study involved 193 patients. A total of 59 patients (30%) died, nine (5%) remained in the hospital, and 125 (65%) were released. When compared to the non-NAFLD cohort (*n* = 132), the NAFLD cohort (*n* = 61) was younger (60 vs. 70.5 years). The diagnosis of NAFLD was not linked to worse outcomes. However, the NAFLD group had higher CRP levels. While intermediate/high risk FIB-4 or liver cirrhosis were not linked with in-hospital mortality among NAFLD patients, male gender, ferritin, and early warning score (EWS) were. Mortality in the NAFLD group was associated with male gender and inflammatory response [12].

Early in 2020, Ji et al. reported data on 202 consecutive patients with NAFLD (based on HSI index) and COVID-19 from two China-based hospitals. On admission and throughout hospitalization, liver damage was detected in 101 (50%) and 152 (75.2%) individuals, respectively. Only 2.6% (4/152) of liver injuries exhibited ductular or mixed patterns, making up most hepatocellular injuries. From admission to discharge, 67 patients (33.2%) had persistently abnormal liver function. Of total patients, 163 (80.7%) and 39 (19.3%) had stable disease, whereas 39 had progressing disease. Patients with disease progression tended to be older, had higher BMIs, higher comorbidity rates, and NAFLD. When compared to patients without NAFLD, patients with NAFLD had a higher likelihood of impaired liver function from admission to discharge, and a longer viral shedding period. One of the patients' postmortem liver biopsies revealed only microvesicular steatosis and overactive T cells, indicating that the liver damage in COVID-19 is probably immune-mediated [13].

Electronic medical record data of 6700 persons with a positive SARS-CoV-2 PCR between 1 March 2020, and 25 August 2020 were retrospectively analyzed by Bramante et al. The probabilities of hospital admission were calculated using logistic regression and competing risk. A history of NAFLD/NASH was associated with increased odds of admission for COVID-19. After adjusting for NAFLD/NASH, people who were obese had lower risks of being hospitalized for COVID-19. In all racial/ethnic categories, including men and women, NAFLD/NASH increased hospitalization risk [14].

Adult patients with severe COVID-19 who were consecutively hospitalized between March and June 2021 were included in the prospective observational study by Vrsaljko et al. A total of 120 of the 216 included patients had NAFLD. The C-reactive protein, interleukin-6, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase levels were higher in the NAFLD group. Patients with NAFLD more frequently required noninvasive ventilation or high-flow nasal cannulas, had longer hospitalization, and were more frequently diagnosed with pulmonary thromboembolism. NAFLD was found to be a risk factor for pulmonary thrombosis and to have a negative correlation with time to recovery [15].

The two primary ways by which SARS-CoV-2 affects the liver are direct cytopathic damage induced by the virus itself, and indirect inflammation resulting in hepatic ischemia or the exacerbation of preexisting liver illness. Typically, both mechanisms are present at the same time [15]. Another mechanism of liver damage is drug-induced liver injury (DILI) due to the treatment, which is also relatively common in patients with preexisting liver disease [16]. COVID-19 is characterized by a hepatocellular pattern of liver abnormalities. Associations of NAFLD with COVID-

19 outcomes might be the result of persistent lipotoxicity, chronic inflammation, insulin resistance, oxidative stress, and immunological response. Additionally, IL-6 (which is typically elevated in people with NAFLD) is overproduced during COVID-19 infection, resulting in a 'cytokine storm' that exacerbates the organism's inflammation [10][11][12][13][14][15][16][17][18].

3. NAFLD and H. pylori

The human stomach is commonly colonized by the Gram-negative, microaerophilic bacterium *Helicobacter pylori*. The colonization is approximately 20% prevalent in wealthy nations and up to 70% prevalent in developing nations. While some research implies a possible link between *H. pylori* and NAFLD, others do not support it. Also, the underlying pathogenic process is not entirely understood. This suggests that the eradication of *H. pylori* may play an important role in the treatment of NAFLD [19].

According to a recent meta-analysis, *H. pylori* infection was associated with an increased incidence of NAFLD. *H. pylori* was an independent risk factor for NAFLD related to a higher degree of steatosis. The *H. pylori*-positive group, however, had a considerably higher proportion of patients with arterial hypertension, as well as higher BMI, total cholesterol, triglycerides, and LDL levels, while having lower HDL values.In addition, a recent study found that individuals with NASH who test positive for *H. pylori* are more likely to have hepatocyte ballooning. This shows that *H. pylori* may not be directly related with NAFLD but may contribute to the progression of the disease to NASH [20][21].

4. NAFLD and Urinary Tract Infections

The studies examining the association between NAFLD and urinary tract infections (UTIs) are limited.

Nseir et al. conducted a study in 2019 on the association between NAFLD and recurrent urinary tract infections (rUTI) in premenopausal women without metabolic syndrome. This was a 3-year retrospective case-control study including 1009 premenopausal women hospitalized and treated for UTI. Ultimately, 372 participants were enrolled in the trial (186 participants with rUTI and 186 controls without a history of rUTI). As part of the inclusion criteria, abdominal ultrasonography was performed on each subject. The two groups were compared to identify factors associated with rUTI, including maternal history of rUTI, use of contraceptives, frequency of sexual activity, metabolic syndrome, obesity, usage of probiotics, serum vitamin D levels, and NAFLD. A recurrent UTI was defined as three or more bouts of UTI within one year. Mean age of the 372 participants was 39.7 ± 5 years. NAFLD was diagnosed in 43.5% of subjects with rUTI vs. 21.5% controls. Women with rUTI were more often obese and presented with lower serum levels of vitamin D. A multivariate analysis showed that NAFLD was associated with rUTI in premenopausal women independent of metabolic syndrome [22]. This entry also did not stratify the severity of liver disease and its correlation with the severity of UTIs and their outcomes.

A few studies have also examined the association between NAFLD and urolithiasis. All have established that NAFLD is an independent risk factor for the development of urolithiasis. Given that urolithiasis is a predisposing

factor for UTI, this is an important finding [23].

Studies that investigated the association between serum 25(OH)D concentrations and NAFLD found that persons with NAFLD have lower serum 25(OH)D concentrations. This is intriguing because reduced blood 25(OH)D levels have a direct effect on the occurrence of a higher rate of rUTI [24][25].

5. NAFLD and C. difficile

Due to the high correlation between *C. difficile* associated diarrhea (CDAD) and prior antibiotic usage, it has been determined that disruptions in the gut flora are a key factor in CDAD. Proton pump inhibitor use and advanced age are also risk factors for acquiring CDAD. These elements are linked to modifications in the gut microbiota's constitution. Studies have revealed a link between lower microbiota diversity and the presence of *C. difficile*, either as a colonizer or as a pathogen. Changes in the representation of microbial populations (e.g., taxa) appear to be linked to *C. difficile* infection per se and may either function to increase susceptibility to *C. difficile* infection or to act as a barrier to *C. difficile* colonization of the gut [26].

NAFLD was reported as an independent predictor for the development of *C. difficile* associated diarrhea (CDAD).

Papić et al. conducted a study in 2019 which identified NAFLD as an independent predictor of CDAD. This was a retrospective cohort study that included patients ≥ 65 years, treated with antimicrobial therapy ≥ 24 h, and hospitalized ≥ 72 h during a 36-month period. Of the 314 patients included in the study, 83 had NAFLD. Diabetes and obesity were more common in the NAFLD group. A total of 16% of the patients with NAFLD and 7.4% of patients in the control group developed in-hospital CDAD. The study concluded that NAFLD is an independent predictor of CDAD [27].

Nseir et al. conducted a similar study in 2020. This was a retrospective study of patients admitted to the hospital for CDAD during a period of 4 years. The control group consisted of patients with CD toxin (CDT) negative diarrhea. The controls were matched for age and gender. A total of 230 patients were included in the study (115 CDT positive, 115 CDT negative). The mean age was 69.57 ± 18 years. NAFLD was found in 66% of patients with CDAD vs. 30.4% with CDT negative diarrhea. In addition, the CDAD group had significant associations with metabolic syndrome. A multivariate analysis showed that NAFLD is significantly associated with CDAD [28].

In 2021 Šamadan et al. published a study on NAFLD being a risk factor for recurrent CDAD. This was a retrospective cohort study that included patients ≥ 60 years hospitalized with CDAD. The cohort was divided into two groups: those who were and were not readmitted with CDAD within 3 months of index discharge. Of the 329 patients included, 32.5% experienced recurrent CDAD. Chronic kidney disease and NAFLD were also more common in this group, with no other major differences in the two groups. Analysis showed that age > 75 years, NAFLD, Charlson Age–Comorbidity Index (CACI) > 6, chronic kidney disease, statins and immobility were associated with recurrent CDAD, making NAFLD a possible host-related risk factor associated with recurrent

CDAD [29]. These studies did not stratify the severity of liver disease and its correlation with the severity of CDAD and its outcome.

6. NAFLD, Bacteremia and Recurring Bacterial Infections

One of the first studies to assess this was conducted by Nseir et al. (2011). A total of 296 hospitalized NAFLD patients were assessed over a three-year period for the occurrence of recurrent bacterial infections (RBI) and were compared with 100 age and gender-matched patients without NAFLD who were hospitalized over the same period due to non-recurrent bacterial infections. NAFLD patients had significantly more RBIs than the patients without NAFLD (22% vs. 8%). Analysis showed that age, BMI, male waist circumference, serum 25(OH)D, triglycerides, serum malondialdehyde and paroxonase-1 are associated with RBIs in NAFLD patients. It is important to mention that these factors were associated with RBIs, irrespective of metabolic syndrome [30].

NAFLD patients have increased intestinal mucosal permeability in comparison to healthy people [31]. Small intestine bacterial overgrowth contributes to the etiology of mucosal permeability, as exogenous and endogenous causes can change the gut microbiome. Modulation of the gut microbiota is associated with increased intestinal permeability, which precedes the onset of metabolic endotoxemia, inflammation, and associated diseases. Gut dysbiosis may result in the translocation of gut bacteria into the circulation [32].

Nseir et al. did a study in 2016 on the relationship between primary bacteremia (PB) with a likely GI origin and NAFLD. At least two positive cultures of *Salmonella enterica*, *Proteus*, *Klebsiella* spp., *Citrobacter*, *Escherichia coli*, and *Enterococci* were found in PB that was thought to have originated from the gastrointestinal system. The presence of fatty liver by ultrasonography and the lack of secondary causes of NAFLD were used to make the diagnosis of NAFLD. In total, 946 distinct cases of bacteremia were examined and 14% had PB. Out of them, 71 patients with PB and hepatic ultrasonography were included. Between the two groups with and without NAFLD, there were no differences in the mean age, CRP, DM, chronic renal failure, or malignancy. However, there was a substantial difference in the proportion of women, obesity, and PB thought to originate from the GI tract. Most patients with PB were found to have NAFLD (68.5%). The most common bacteria in the NAFLD group (77%) of patients was *Escherichia coli* (50% of patients in the group without NAFLD had *E. coli*). This retrospective analysis of PB cases revealed a correlation between NAFLD and PB in patients with PB thought to have gastrointestinal origin [33].

Gjurašin et al. examined mortality in patients with NAFLD and invasive group B streptococcus (GBS) disease. TThis was a retrospective cohort analysis. Cellulitis/erysipelas (34.3%), pneumonia (12.7%), endocarditis (7.8%), and bacteremia without a specified source (36.3%) were the most common syndromes among the 102 patients who entered the study. Diabetes (41.2%), dyslipidemia (38.2%), cardiovascular disease (33.3%), peripheral vascular disease (20.6%), obesity (20.6%), and cancer (9.8%) were the most prevalent comorbidities. The patients were divided into two groups based on the findings of the abdominal ultrasound: those with steatosis (43.1%) and those without steatosis (56.9%). Clinical presentations and comorbidities between groups did not differ significantly. Patients with NAFLD had in-hospital mortality rate of 29.5%, compared to 10.3% in the control group. Acute renal

failure, qSOFA ≥ 2, endocarditis, and NAFLD were all independently linked to in-hospital mortality. The study concluded that NAFLD is associated with higher mortality in individuals with invasive GBS disease [34]. These studies did not stratify the severity of liver disease and its correlation with the severity of bacteremia, RBIs and their outcome.

7. NAFLD and Hepatitis B, C and HIV

Liver steatosis occurs in approximately 50% of patients with HCV, while NASH is found in 10%. Because HCV genotype 3 directly induces fatty liver deposition, it is associated with the highest prevalence and severity, whereas other HCV genotypes demonstrated a lower prevalence of steatosis. In general, HCV alters lipid and glucose metabolism, leading to the accumulation of fats in the liver. It has also been pointed out by Adinolfi et al. that HCV-associated NAFLD has accelerated development of NASH, hepatic fibrosis, and ultimately hepatocellular carcinoma (HCC). This is due to elevated liver inflammation and oxidative stress levels. This environment also leads to HCV persistence and replication. Some extrahepatic symptoms of chronic HCV infection are influenced by HCV-associated steatosis (diabetes, metabolic syndrome, and atherosclerosis) [35].

Similarly, human immunodeficiency virus (HIV) infection also results in fatty liver due to various viral and host factors, as well as the anti-viral medications used to treat HIV. Liver disease is one of the primary causes of death among HIV-positive individuals, particularly if they are also coinfected with HCV. Development of insulin resistance, the release of free fatty acids from adipose tissue, hepatic triglyceride deposition, and oxidative stress-cytokine-mediated damage explains the mechanism. The high incidence of lipid and glucose abnormalities is a consequence of HIV infection and/or antiretroviral medications (some of which cause direct hepatotoxicity and steatosis). HIV also causes persistent inflammation in the majority of infected individuals. HIV-infected individuals have a prevalence rate of approximately 30% for NAFLD, whereas those coinfected with HCV have an incidence rate of 40–72%. In their study, Maurice et al. concluded that, possibly independent of dysbiosis and intestinal translocation, monocyte activation associated with central adiposity appears to be a critical factor in the development of NAFLD and severe liver fibrosis in HIV-monoinfected patients [36].

8. NAFLD and Periodontitis

Gram-negative bacteria present in dental plaque are the main cause of most periodontal diseases. It is generally recognized that *Porphyromonas gingivalis* (*P. gingivalis*) causes periodontitis [37].

Yoneda et al. showed that NAFLD patients had considerably higher detection rates of *P. gingivalis* (46.7% vs. 21.7%) than non-NAFLD controls. Additionally, *P. gingivalis* was found more frequently (52%) in NASH patients than in participants without NAFLD. The majority of *P. gingivalis* fimbria found in NAFLD patients belonged to the invasive genotypes, particularly type II (50.0%). The three-month non-surgical periodontal therapies for NAFLD patients improved the liver function measures, including the serum AST and ALT levels [27]. This finding implies that *P. gingivalis* infection may be implicated in the development of NAFLD because *P. gingivalis* or the endotoxins

produced by the bacteria can easily reach the bloodstream. In addition, *A. actinomycetemcomitans* is frequently discovered in severe periodontitis. According to research, the administration of *A. actinomycetemcomitans* to test animals has been linked with an increase in metabolic diseases [38].

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