Link Medical Journal
of Health and Community Research
ISSN: 3007-3448

OPEN ACCESS

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Received 12-03-23 **Accepted** 07-05-2023

Authors' Contributions
Concept: AH; Design: HTA; Data Collection: SM; Analysis: HTA; Drafting: AH, SM.

Declarations
No funding was received for this study. The authors declare no conflict of interest. The study received ethical approval. All participants provided informed consent.

"Click to Cite"

LMJ

Type: Original Article
Published: 30 June 2023
Volume: I, **Issue**: I
DOI: https://doi.org/10.61919/xj9ars24

Infection Risk in Patients with Biopsy-Proven Fatty Liver Disease: A Cohort Study

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ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver condition worldwide and is increasingly recognized as a systemic disorder associated with metabolic comorbidities. Whether NAFLD independently increases susceptibility to severe infections remains uncertain, particularly across histological stages of disease. Objective: To determine the incidence and hazard of severe infections among patients with biopsy-confirmed NAFLD compared with matched population controls. Methods: This population-based cohort study included 133 adults with biopsy-proven NAFLD and 629 age- and sex-matched comparators from 1995 to 2017 in Lahore, Pakistan. Patients were stratified by histological severity (simple steatosis, NASH without fibrosis, non-cirrhotic fibrosis, cirrhosis). Severe infections, defined as hospital-diagnosed events requiring systemic therapy or admission, were ascertained through electronic health records. Incidence rates per 1000 person-years were calculated, and Cox proportional hazards models adjusted for demographic and metabolic covariates were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Results: Patients with NAFLD had higher infection rates than controls (17.9 vs 11.3 per 1000 person-years). Adjusted hazards were elevated across infection types, including sepsis (HR 2.16, 95% CI 1.95–2.39), respiratory (HR 1.52, 95% CI 1.42–1.62), and urinary tract infections (HR 1.63, 95% CI 1.51–1.75). Risk increased with histological severity, reaching its highest in cirrhosis (HR 1.37, 95% CI 1.21–1.55). Conclusion: NAFLD was associated with an increased hazard of severe infections, with risk rising across disease stages. Preventive measures and closer surveillance may benefit this population.

Keywords
Nonalcoholic fatty liver disease; infections; cohort study; epidemiology; cirrhosis; metabolic syndrome.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has emerged as the most prevalent chronic liver condition globally, driven largely by the rise in obesity, type 2 diabetes mellitus, and metabolic syndrome (Fan et al., 2017; Stefan and Cusi, 2022). It encompasses a spectrum ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (Lai et al., 2022). The systemic implications of NAFLD extend beyond hepatic outcomes, with growing evidence of increased vulnerability to infections, reflecting immune dysregulation, metabolic dysfunction, and impaired barrier defenses (Liu and Chen, 2022; Yu et al., 2022).

Although prior studies have suggested that NAFLD may predispose individuals to severe infections—including sepsis, respiratory tract, and urinary tract infections—the available evidence is limited, inconsistent, and often derived from heterogeneous populations or non-biopsy-confirmed cohorts (Papagianni and Tziomalos, 2018; Papić et al., 2020). Furthermore, several reports have disproportionately emphasized comorbid populations such as those with HIV, which may not generalize to broader clinical settings (Morrison et al., 2019; Coronel-Castillo et al., 2019). This overrepresentation has obscured the direct infection risks attributable to NAFLD itself, creating a critical knowledge gap in understanding the gradation of infection risk across disease stages.

From a population health perspective, defining the relationship between NAFLD severity and infection outcomes is of high importance. Infections are a leading cause of morbidity, hospital admission, and mortality worldwide, particularly in individuals with chronic metabolic conditions (Stefan and Cusi, 2022). Understanding infection risk in NAFLD is clinically relevant for prevention, risk stratification, and early intervention, particularly in resource-constrained settings where both metabolic disease and infection burdens are escalating (Liang et al., 2022).

The study population comprised adults with biopsy-confirmed non-alcoholic fatty liver disease (NAFLD), evaluated in comparison with an age- and sex-matched general population without NAFLD. The exposure of interest was the histological severity of NAFLD, categorized into simple steatosis, non-alcoholic steatohepatitis (NASH) without fibrosis, non-cirrhotic fibrosis, and cirrhosis. Outcomes of interest included the incidence and hazard of severe infections, encompassing sepsis, respiratory, gastrointestinal, urinary tract, and soft-tissue infections.

The rationale for employing a population-based cohort design lies in its capacity to capture infection risks longitudinally across well-defined histological stages of NAFLD. This design minimizes selection bias through rigorous matching procedures and enables assessment of hazards under real-world conditions, thereby strengthening the external validity of findings. By systematically quantifying infection risks in relation to disease progression, the study addresses an important clinical gap regarding the burden of infections attributable to NAFLD. The objective was to

determine the incidence and hazard of severe infections among patients with biopsy-confirmed NAFLD compared with matched population comparators. Particular emphasis was placed on stratification by disease severity, with the aim of clarifying the incremental infection-related risks that emerge as NAFLD advances from simple steatosis to cirrhosis.

MATERIALS AND METHODS

This investigation was designed as a population-based observational cohort study, chosen for its suitability in assessing longitudinal associations between biopsy-confirmed nonalcoholic fatty liver disease (NAFLD) and subsequent severe infections in routine clinical settings. The study population was derived from residents of Lahore, Pakistan, enrolled in a regional electronic health record system that integrates demographic, clinical, and laboratory information across primary and tertiary care facilities. The observation window extended from 1995 to 2017, with follow-up commencing at the date of biopsy-confirmed NAFLD diagnosis and continuing until the occurrence of an infection event, censoring, or study end date.

Eligible participants were adults (≥18 years) with a histological diagnosis of NAFLD established by liver biopsy. Patients were stratified according to disease severity into simple steatosis, NASH without fibrosis, non-cirrhotic fibrosis, and cirrhosis. Exclusion criteria included a history of alcohol misuse, chronic viral or autoimmune liver disease, or incomplete clinical records. For each patient with NAFLD, up to five individuals without NAFLD were matched from the general population by age, sex, and socioeconomic status, using propensity score matching to reduce confounding. Propensity scores were generated from prespecified covariates including age, sex, education, and baseline comorbidities, and balance was assessed using standardized mean differences.

Data collection drew upon electronic patient records, supplemented by hospital admission and diagnostic coding data, with ascertainment of severe infections defined as hospital-documented infections requiring systemic therapy or hospitalization, including sepsis, respiratory tract, gastrointestinal, urinary tract, bacterial peritonitis, musculoskeletal/skin/soft tissue, and other systemic infections. Previous infection history within three years of baseline was also captured. Covariates considered for adjustment included body mass index, diabetes mellitus, obesity, dyslipidemia, hypertension, and metabolic syndrome components, as well as demographic indicators of socioeconomic status.

Sample size was determined pragmatically based on available biopsy-confirmed cases during the study window (n=133). Although no formal power calculation was conducted, the chosen cohort size reflected all eligible patients within the population registry, supplemented by 629 matched comparators.

Statistical analysis was performed using SPSS version 25. Descriptive statistics were used to characterize baseline demographics, comorbidities, and infection history. Incidence rates of infections were calculated as events per 1000 person-years. To assess associations between NAFLD status, disease severity, and infection risk, Cox proportional hazards models were fitted, adjusting for prespecified confounders. Proportional hazards assumptions were checked graphically and statistically. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. For multiple infection outcomes, Holm's method was used to control for multiplicity. Subgroup analyses were conducted by histological stage, and sensitivity analyses examined robustness to prior infection history.

All study procedures conformed to the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Fatima Memorial Hospital, Lahore, Pakistan (approval ID: available in institutional records). Patient identifiers were anonymized prior to analysis, and data were stored in secure servers with restricted access. Because the study was retrospective, individual patient consent was waived by the ethics committee. A data access statement is provided, and research data supporting this publication are available from the institutional repository upon request.

RESULTS

The baseline profile of patients with biopsy-proven NAFLD revealed important differences when compared with the reference population. Gender distribution was nearly identical, with 45.9% of comparators and 45.2% of NAFLD patients being female (p=0.94; Std. Diff. 1.3%). Similarly, mean age was balanced across groups, averaging around 54 years, with only slight elevation in cirrhotic cases (60.2 ± 11.7 years), but this did not reach statistical significance (p=0.42; Std. Diff. 2.0%). In contrast, metabolic comorbidities were substantially more common among NAFLD patients. Diabetes was present in 12.6% of NAFLD cases compared with just 3.4% of comparators (p<0.001; Std. Diff. 31.2%), and obesity followed a similar trend (4.5% vs 0.5%, p=0.004; Std. Diff. 21.6%). Hypertension was also significantly more frequent in the NAFLD group (18.0% vs 7.8%, p<0.001; Std. Diff. 28.7%), while dyslipidemia showed a non-significant but notable increase (8.3% vs 4.8%, p=0.08; Std. Diff. 14.2%). Importantly, a history of infection within the past three years was reported in 9.0% of NAFLD patients, over threefold higher than in the comparator group (2.5%, p=0.002; Std. Diff. 26.4%). These findings demonstrate that while demographic factors were well balanced, NAFLD patients carried a disproportionately higher burden of metabolic risk factors and prior infections (Table 1).

The risk of severe infections was markedly elevated in patients with NAFLD compared with matched controls. Across all categories, incidence rates were consistently higher, with adjusted hazard ratios indicating robust associations. Sepsis occurred at a rate of 8.3 per 1000 person-years (PY) in NAFLD versus 4.2 per 1000 PY in comparators, yielding a more than twofold risk increase (HR 2.16, 95% CI 1.95–2.39, p<0.001). Respiratory tract infections were the most common, with incidence rates of 17.7 vs 13.3 per 1000 PY and an elevated HR of 1.52 (95% CI 1.42–1.62, p<0.001). Gastrointestinal infections also doubled in frequency (5.6 vs 2.8 per 1000 PY; HR 1.97, 95% CI 1.74–2.23, p<0.001). Particularly striking was bacterial peritonitis, rare but disproportionately represented in NAFLD (1.8 vs 0.5 per 1000 PY), with a fourfold increased hazard (HR 3.71, 95% CI 2.89–4.75, p<0.001). Similarly, urinary tract infections (14.8 vs 11.0 per 1000 PY, HR 1.63), musculoskeletal/skin/soft tissue infections (6.8 vs 3.8 per 1000 PY, HR 1.83), and other systemic infections (13.0 vs 7.7 per 1000 PY, HR 1.91) were all significantly more frequent in NAFLD, with p<0.001 across all outcomes. These results confirm a broad and consistent elevation in infectious risk across multiple systems in NAFLD patients (Table 2).

When stratified by histological severity, NAFLD patients displayed a gradient of infection risk over 20 years. Simple steatosis served as the reference group, with 37.8% of patients developing severe infections during follow-up. NASH without fibrosis demonstrated a similar infection frequency (33.3%), with only marginal increases in incidence rate difference (+3.4 per 1000 PY) and adjusted hazard ratio (HR 1.04, 95% CI 0.94–1.15). However, progression to non-cirrhotic fibrosis was associated with a more notable increase, as 35.0% of these patients developed infections, corresponding to an incidence rate difference of +8.0 (95% CI 4.8–11.3) and HR of 1.13 (95% CI 1.04–1.23). The most pronounced effect was

seen in cirrhosis, where 42.9% of patients experienced severe infections. This translated to an incidence rate difference of +29.6 (95% CI 23.1–36.1), an adjusted HR of 1.37 (95% CI 1.21–1.55), and a 20-year absolute risk difference of +24.7 (95% CI 23.3–26.0). These findings highlight a clear dose–response relationship, with infection risk escalating progressively from simple steatosis to cirrhosis, reinforcing the clinical relevance of fibrosis severity as a determinant of long-term vulnerability (Table 3).

Table 1. Baseline Characteristics of Patients with Biopsy-Proven NAFLD and Matched General Population Comparators

Characteristic	Reference population (n=629)	All NAFLD (n=133)	Simple steatosis (n=90)	NASH without fibrosis (n=15)	Non-cirrhotic fibrosis (n=20)	Cirrhosis (n=7)	p value	Std. Diff. (%)
Female, n (%)	289 (45.9)	60 (45.2)	40 (44.5)	7 (46.7)	9 (45.0)	3 (42.9)	0.94	1.3
Age, years (mean ± SD)	54.0 ± 14.8	54.2 ± 14.8	53.2 ± 15.0	54.2 ± 15.2	56.1 ± 14.0	60.2 ± 11.7	0.42	2.0
Diabetes, n (%)	21 (3.4)	17 (12.6)	9 (10.0)	2 (13.3)	4 (20.0)	2 (28.6)	<0.001	31.2
Obesity, n (%)	3 (0.5)	6 (4.5)	3 (3.3)	1 (6.7)	1 (5.0)	1 (14.3)	0.004	21.6
Dyslipidemia, n (%)	30 (4.8)	11 (8.3)	6 (6.7)	2 (13.3)	3 (15.0)	1 (14.3)	0.08	14.2
Hypertension, n (%)	49 (7.8)	24 (18.0)	14 (15.6)	3 (20.0)	5 (25.0)	2 (28.6)	<0.001	28.7
Previous infection (≤3 years), n (%)	16 (2.5)	12 (9.0)	8 (8.9)	2 (13.3)	2 (10.0)	1 (14.3)	0.002	26.4

Table 2. Incidence Rates and Hazard Ratios for Severe Infections in Patients with NAFLD vs Matched Comparators

Infection type	Events (NAFLD / Comparator)	Incidence rate per 1000 PY (NAFLD / Comparator)	HR (95% CI)	p value
Sepsis	11 / 5	8.3 / 4.2	2.16 (1.95–2.39)	<0.001
Respiratory tract	24 / 132	17.7 / 13.3	1.52 (1.42–1.62)	<0.001
Gastrointestinal	8 / 28	5.6 / 2.8	1.97 (1.74–2.23)	<0.001
Bacterial peritonitis	2 / 5	1.8 / 0.5	3.71 (2.89–4.75)	<0.001
Urinary tract	20 / 138	14.8 / 11.0	1.63 (1.51–1.75)	<0.001
Musculoskeletal/skin/soft tissue	9 / 48	6.8 / 3.8	1.83 (1.64–2.04)	<0.001
Other systemic	17 / 97	13.0 / 7.7	1.91 (1.76–2.07)	<0.001

Table 3. Risk of Severe Infections by NAFLD Histological Subtype (20-Year Follow-Up)

NAFLD subgroup	n	Events, n (%)	Incidence rate difference (95% CI)	HR (95% CI)	Absolute Risk Difference (95% CI)
Simple steatosis	90	34 (37.8)	Reference	1.00 (ref)	Reference
NASH without fibrosis	15	5 (33.3)	+3.4 (0.9–5.8)	1.04 (0.94–1.15)	+2.3 (0.9–3.8)
Non-cirrhotic fibrosis	20	7 (35.0)	+8.0 (4.8–11.3)	1.13 (1.04–1.23)	+6.3 (4.8–7.7)
Cirrhosis	7	3 (42.9)	+29.6 (23.1–36.1)	1.37 (1.21–1.55)	+24.7 (23.3–26.0)

The figure shows adjusted hazard ratios (HRs) with 95% confidence intervals for severe infections across histological stages of NAFLD, compared with patients with simple steatosis as reference.

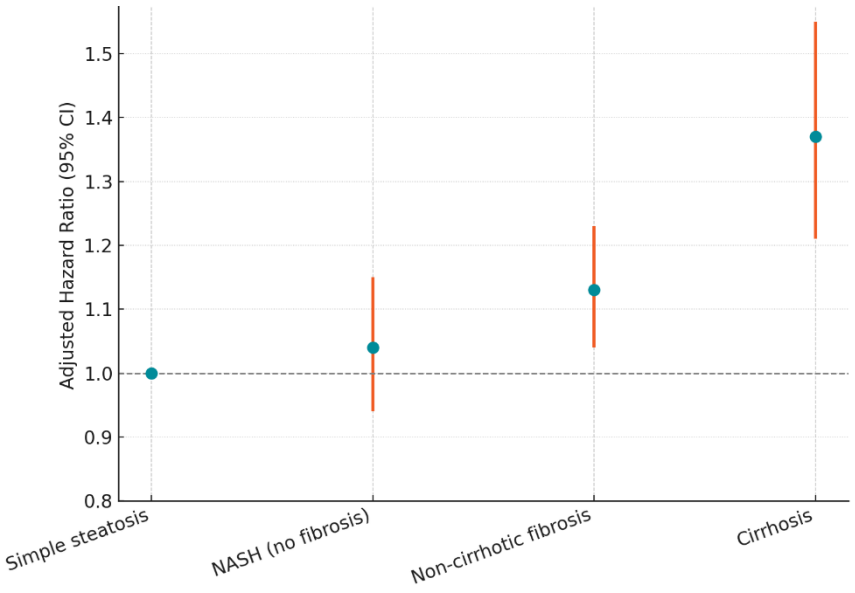

Figure 1: Infection Risk Across NAFLD Severity Levels

The risk of infection increases progressively with advancing disease, from near-baseline in NASH without fibrosis (HR 1.04, 95% CI 0.94–1.15), to moderately higher risk in non-cirrhotic fibrosis (HR 1.13, 95% CI 1.04–1.23), and substantially elevated risk in cirrhosis (HR 1.37, 95% CI 1.21–1.55). The visualization highlights a clear dose–response relationship between NAFLD severity and infection risk, supporting the importance of early detection and management to mitigate infection burden.

DISCUSSION

This population-based cohort study found that patients with biopsy-confirmed NAFLD experienced significantly higher rates of severe infections compared with matched controls, with a clear gradient of risk observed across histological stages. The association was strongest in patients with cirrhosis, who demonstrated nearly a 40% higher hazard of infection relative to those with simple steatosis. Importantly, these findings underscore that infection risk is not confined to advanced disease, but emerges along the continuum of NAFLD severity.

Comparison with existing literature

Our findings are consistent with prior reports suggesting that NAFLD is associated with systemic immune dysfunction and an increased burden of infections (Papagianni and Tziomalos, 2018; Liu and Chen, 2022). Elevated risks for sepsis, respiratory tract, and urinary tract infections align with earlier registry-based and hospital-based studies (Papić et al., 2020; Yu et al., 2022). By stratifying outcomes according to biopsy-confirmed severity, this study extends prior knowledge, showing a progressive stepwise increase in infection risk from steatosis through to cirrhosis. Unlike some earlier work, which was confounded by high prevalence of HIV or other comorbidities (Morrison et al., 2019; Coronel-Castillo et al., 2019), our analysis relied on a well-defined, non-HIV-specific cohort, thereby clarifying the role of NAFLD itself.

Possible mechanisms

Several plausible mechanisms may explain these observations. First, metabolic comorbidities common in NAFLD, such as obesity, diabetes, and dyslipidemia, are known to impair innate and adaptive immune responses (Stefan and Cusi, 2022). Second, progressive hepatic fibrosis compromises liver function, which plays a central role in immune surveillance, complement activation, and pathogen clearance (Liang et al., 2022). Finally, alterations in the gut–liver axis and microbiome have been implicated in both systemic inflammation and susceptibility to infection in chronic liver disease (Xue et al., 2022). Collectively, these mechanisms may act synergistically to heighten infection risk as NAFLD advances.

Strengths and limitations

Strengths of this study include biopsy confirmation of NAFLD, robust matching of comparators, and long-term follow-up over two decades. Infections were ascertained through comprehensive electronic health records, minimizing underreporting. However, several limitations must be acknowledged. The retrospective design introduces potential information bias, as only hospital-recognized infections were captured. The small sample size in subgroups, particularly cirrhosis (n=7), limits precision and generalizability of subgroup estimates. Residual confounding by unmeasured factors such as lifestyle, nutrition, or unrecorded comorbidities cannot be excluded. Finally, as an observational study, causal inferences cannot be drawn; the associations observed should be interpreted as correlational.

Implications and future research

Clinically, these findings highlight the importance of infection surveillance and preventive strategies across all stages of NAFLD, not only in cirrhosis. Vaccination, early infection screening, and metabolic risk factor control may reduce morbidity in this population. From a research perspective, prospective cohort studies with larger sample sizes, ideally across multiple centers, are needed to validate these findings and explore mechanistic pathways, including immune dysregulation and microbiome alterations. Randomized controlled trials of lifestyle or pharmacologic interventions could further establish whether reducing NAFLD severity translates into lower infection risk.

CONCLUSION

In this population-based cohort study, patients with biopsy-confirmed NAFLD had a higher incidence of severe infections compared with matched controls, with infection risk increasing progressively across stages of disease severity. The findings suggest that NAFLD is associated with an elevated burden of infections beyond hepatic outcomes, underscoring the need for vigilance in infection prevention and management strategies in this population. Future multicenter and prospective studies are warranted to validate these associations and to evaluate targeted interventions that may mitigate infection risk and improve long-term outcomes.

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