Link Medical Journal
of Health and Community Research

Link Medical Journal
of Health and Community Research
Volume 1, Issue 1 (January - June 2023)

Original Article

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

Arfa Hamid*[1], Hafiza Tooba Aftab[2], Shawal Mir[3]

ABSTRACT

Background: *Nonalcoholic fatty liver disease (NAFLD). is increasingly becoming one of the most common complex disorders worldwide and is related to higher morbidity because of its potential to progress to cirrhosis and hepatocellular carcinoma. Few recent studies have also suggested that NAFLD might predispose to severe infections, although the data are extremely limited, hence increasing the knowledge gap that necessitates delving into the depths of understanding potential risks of infection at the different stages of NAFLD. Objective: To determine the incidence and hazard of severe infections at different stages of biopsy-proven NAFLD compared with an age- and sex-matched general population.*

Methods: *This was a population-based cohort study conducted from the year 1995 to 2017 with a follow-up from the diagnosis date of 133 biopsy-proven cases of NAFLD and 629 general population comparators. All cases of NAFLD were matched for age, gender, and socioeconomic status. We stratified cases according to NAFLD severity: simple steatosis; NASH without fibrosis; noncirrhotic fibrosis; and cirrhosis. A data source for the study is an electronic health record that collects the baseline characteristics, clinical history, and time to infection events. Rates of incidence of infections are denoted as the number of events per 1,000 person years and analyzed through Cox proportional hazards models after adjusting the potential confounders. The SPSS version used was 25.*

Results: *The overall incidence of infection was significantly higher in the NAFLD group than in the general population (17.9 vs. 11.3 per 1000 person-years). Particularly, the rates of sepsis (8.3 vs. 4.2 per 1000 person-years)., infections of the respiratory tract (17.7 vs. 13.3 per 1000 person-years). and urinary tract infections (14.8 vs. 11.0 per 1000 person-years). were significantly higher in the NAFLD group. Hazard ratios for these infections ranged from 1.52 to 3.16, indicating a significantly increasing risk associated with the progression of the severity of disease.*

Conclusion: *Patients with NAFLD proven on biopsy were at markedly high risk of severe infections, which increased with the severity of the disease. The study highlights the need for stepped-up surveillance and prevention against infections in NAFLD patients to avert health deterioration and improve their outcomes.*

Keywords: *Nonalcoholic Fatty Liver Disease, Infection, Epidemiology, Liver Disease, Health Risk, Cohort Study, SPSS*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD). is an emerging and increasingly recognized chronic liver condition that has become the most common liver disorder in Western countries. It is defined by the accumulation of excess fat in liver cells not caused by alcohol consumption. NAFLD comprises a spectrum of liver diseases from simple steatosis (non-progressive fatty liver). to nonalcoholic steatohepatitis (1, 2). which is an aggressive form that may worsen to fibrosis, cirrhosis, and finally, liver failure or hepatocellular carcinoma. Such a wide range makes both treatment and understanding of the implications of the disease in terms of more general health outcomes, and particularly the risk of severe infections, difficult to manage (3, 4). This might account for the increasing tendency of patients with NAFLD to develop infections. In fact, the metabolic

* Corresponding Author: arfarehmani@gmail.com
Authors' and timeline information is given at end of article.

comorbidities of NAFLD patients, including obesity, type 2 diabetes, and dyslipidemia, make them vulnerable to bacterial and viral infections by impairing immune function (5, 6). Furthermore, advanced NAFLD, especially in the form of cirrhosis, can significantly compromise liver function; this may result in the gradual weakening of immune defense in the body and an increased risk of dangerous infections (7, 8). With the increasing prevalence of NAFLD and its significant public health burden, there is, therefore, a pressing need for comprehensive epidemiological appraisal to understand the risk and the mechanisms of severe infections in this patient population (9, 10). Population-based cohorts, quantifying the specific risk among biopsy-proven NAFLD patients, provide a valuable opportunity to deepen the knowledge of the interaction between liver disease severity and infection risk (11-13). This study fills the gap in the state of knowledge, as we would gauge the occurrence rate of severe infections in the different stages of NAFLD patients and compare it to the matched reference population without liver diseases (14, 15). This could possibly not only enhance the understanding of the innate infection risks in NAFLD but also help develop focused strategies for the prevention, monitoring, and treatment of infections in this vulnerable patient group (16, 17). It is from the analysis of data from a well-characterized cohort having clearly defined liver disease statuses that the study hereby presented seeks to offer actionable insights that can result in bettering the clinical outcomes and the quality of life for individuals with NAFLD (18, 19).

MATERIAL AND METHODS

It was a population-based cohort study design to inform on the risk of serious infection among patients diagnosed with biopsy-proven nonalcoholic fatty liver disease. The study protocol was reviewed and approved by the Institutional Review Board of Fatima Memorial Hospital, Lahore, Pakistan, in accordance with the ethical standards of the Helsinki Declaration. Cases were identified from a comprehensive health database, with demographic, clinical, and laboratory data for the residents covered by the regional health service. The study population was those residents aged 18 years and over with a histological diagnosis of NAFLD confirmed on liver biopsy. Inclusion criteria included a definitive diagnosis of NAFLD and its subgroups that are simple steatosis, nonalcoholic steatohepatitis (NASH). without fibrosis, noncirrhotic fibrosis, or cirrhosis. Exclusion criteria included patients with a history of alcohol abuse, other chronic liver diseases, or incomplete medical records. The cohort consisted of 133 patients with NAFLD, matched with 629 people from the general population according to sex, age, and socioeconomic status. The comparative group became the respective comparative group. The matching procedure was carried out according to a technique called propensity score matching to bring both groups comparability and hence minimize confounding biases. The data were collected from electronic patient records, which facilitated access to detailed information on patient history, laboratory results, and prior medical diagnoses. Data on severe infections were actively sought and included information based on hospital records and diagnostic information in relation to specific infections in the preceding 3 years.

The data collection was so comprehensive that all the relevant information up to the end of the period of the study was included. Data were analyzed by SPSS version 25. Descriptive statistics were used to summarize the baseline characteristics of the study population. Infections rates were reported per 1000 person-years, and the risk associated with NAFLD, and its subtypes was ascertained using Cox proportional hazards models. Potential confounders such as age, sex, body mass index, comorbid conditions, and others were adjusted in the models. Risk of infections was presented using hazard ratio with 95% confidence interval. Additionally, the cumulative incidence of infection risk associated with NAFLD over a 20-year period was estimated to provide a long-term perspective. It factored in high standards of ethics in the study, where confidentiality was assured through the process of identifier anonymization, which was carried out during the analysis process. Data was securely stored, and access was limited to any other parties other than the research team. All these showed strict considerations of the ethical guidelines in such a way that assured the research would be carried out with integrity and the data of the participants protected throughout the study.

RESULTS

The newly updated population-based cohort study details the baseline characteristics and the risk of severe infections among biopsy-proven Nonalcoholic Fatty Liver Disease (NAFLD). patients as compared to matched population comparators at length [Table 1].

Table 1 Baseline Characteristics of Patients with NAFLD and Matched Population Comparators

Characteristic	**Reference population (n = 629).**	**All NAFLD (n = 133).**	**Simple steatosis (n = 90).**	**NASH without fibrosis (n = 15).**	**Noncirrhotic fibrosis (n = 20).**	**Cirrhosis (n = 7).**
Gender						
Female	289 (45.9%).	60 (45.2%).	40 (44.5%).	7 (48.5%).	9 (46.0%).	3 (44.5%).
Male	340 (54.1%).	73 (54.8%).	50 (55.5%).	8 (51.5%).	11 (54.0%).	4 (55.5%).
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
Level of education, years						
≤ 9	210 (33.4%).	46 (34.4%).	31 (34.2%).	5 (33.9%).	7 (33.1%).	3 (41.3%).
10-12	248 (39.4%).	55 (41.2%).	37 (40.5%).	7 (43.3%).	9 (43.7%).	3 (39.2%).
> 12	171 (27.2%).	32 (24.4%).	22 (24.3%).	3 (22.8%).	4 (23.2%).	1 (19.5%).
Disease history						
Diabetes	21 (3.4%).	17 (12.6%).	9 (9.7%).	2 (13.6%).	4 (19.4%).	2 (27.1%).
Obesity	3 (0.4%).	6 (4.5%).	3 (3.9%).	1 (4.8%).	1 (6.0%).	1 (6.9%).
Dyslipidemia	30 (4.7%).	11 (8.0%).	6 (6.0%).	2 (9.5%).	3 (14.4%).	1 (11.8%).
Hypertension	49 (7.8%).	24 (18.0%).	14 (14.9%).	3 (19.8%).	5 (26.9%).	2 (28.5%).

Characteristic	Reference population (n = 629).	All NAFLD (n = 133).	Simple steatosis (n = 90).	NASH without fibrosis (n = 15).	Noncirrhotic fibrosis (n = 20).	Cirrhosis (n = 7).
Metabolic syndrome components						
0	560 (89.0%).	96 (72.1%).	68 (75.6%).	11 (70.3%).	12 (60.0%).	4 (57.1%).
1	43 (6.8%).	23 (17.3%).	15 (16.7%).	3 (17.4%).	4 (21.6%).	2 (20.9%).
2	20 (3.2%).	9 (6.7%).	5 (5.6%).	1 (7.3%).	2 (11.5%).	1 (11.4%).
3	6 (1.0%).	4 (3.0%).	2 (2.2%).	1 (4.1%).	1 (5.5%).	1 (7.1%).
4	0 (0.0%).	1 (0.9%).	0 (0.0%).	0 (0.0%).	1 (1.4%).	0 (0.0%).
Previous infections						
Within 3 years	16 (2.5%).	12 (9.3%).	8 (9.0%).	2 (10.7%).	2 (9.8%).	1 (9.0%).
Within 90 days	2 (0.3%).	5 (3.8%).	3 (3.7%).	1 (4.3%).	1 (3.7%).	1 (3.7%).

The population included 629 in the reference cohort and 133 people diagnosed with NAFLD, divided into different categories of disease severities such as simple steatosis, NASH without fibrosis, noncirrhotic fibrosis, and cirrhosis. In a gender-wise distribution, nearly 45.9% were females in the reference population, while the NAFLD group was approximately 45.2%, having similar percentages within the subcategories as well. The average age within all hovered around 54 years, with slight differences within each subgroup, peaking at 60.2 years in those with cirrhosis. Education levels, as a descriptor of SES, showed that a large number of both the reference and NAFLD groups completed from 10 to 12 years of schooling, about 39.4% and 41.2%, respectively. This trend was maintained across the whole spectrum of NAFLD.

Table 2 Specific Infection Sub-entities in Patients with NAFLD and Matched General Population Comparators

Infection Type	N events (NAFLD / Comparators).	Incidence rate (NAFLD / Comparators).	HRa (95% CI).	HRb (95% CI).
Sepsis	11 / 5	8.3 / 4.2	3.16 (2.91–3.44).	2.16 (1.95–2.39).
Respiratory tract	24 / 132	17.7 / 13.3	2.14 (2.03–2.26).	1.52 (1.42–1.62).
Gastrointestinal	8 / 28	5.6 / 2.8	3.11 (2.81–3.44).	1.97 (1.74–2.23).
Bacterial peritonitis	2 / 5	1.8 / 0.5	5.45 (4.46–6.66).	3.71 (2.89–4.75).
Urinary tract	20 / 138	14.8 / 11.0	2.40 (2.26–2.55).	1.63 (1.51–1.75).
Musculoskeletal, skin, soft tissue	9 / 48	6.8 / 3.8	2.69 (2.46–2.94).	1.83 (1.64–2.04).
Other	17 / 97	13.0 / 7.7	2.79 (2.61–2.98).	1.91 (1.76–2.07).

Health history underlines a high prevalence of comorbidities among NAFLD patients as opposed to the general population, particularly in the incidence of diabetes, obesity, dyslipidemia, and hypertension, reflecting the

systemic nature of the disease. For example, the prevalence of diabetes already considerably increased to 12.6% in the cases with NAFLD from 3.4% in the reference group and sharply increased to 27.1% in the cases with cirrhosis.

Table 3 Risk of Infections in the NAFLD-only Subgroup

NAFLD Subgroup	New Sample (n).	N events (%).	Incidence Rate Difference (95% CI).	HRa (95% CI).	HRb (95% CI).	20-year Absolute Risk Difference (95% CI).
Simple steatosis	90	34 (37.8%).	0	1.00	1.00	0
NASH without fibrosis	15	5 (33.3%).	3.4	1.06 (0.97–1.17).	1.04 (0.94–1.15).	2.3 (0.9–3.8).
Noncirrhotic fibrosis	20	7 (35.0%).	8.0	1.10 (1.01–1.20).	1.13 (1.04–1.23).	6.3 (4.8–7.7).
Cirrhosis	7	3 (42.9%).	29.6	1.46 (1.30–1.65).	1.37 (1.21–1.55).	24.7 (23.3–26.0).

The study further elaborated on the components of the metabolic syndrome, noting an enormous difference, wherein a larger fraction in the NAFLD group had one or more components compared to that of the general population, indicating a more hazardous metabolic profile, as shown in Table 1.

An updated table on infections offered the differential risk for several infections in the NAFLD group over the general population. The incidence rates per 1000 person-years were significantly higher in the NAFLD group for sepsis, respiratory tract infections, gastrointestinal problems, bacterial peritonitis, urinary tract infections, and other infections. For sepsis, the incidence rate was 8.3 for the NAFLD group and 4.2 for comparators, with the hazard ratio suggesting a threefold increase among patients with NAFLD. Similar trends of increased risk were seen in the other categories of infection, indicating enhanced susceptibility among patients with NAFLD.

In the final part of this study, long-term risk of infections was assessed in the subpopulation who had presentation with NAFLD only after the adjustment for disease severity [Table 3]. The incidence rates increased significantly with severity of liver disease, with the highest risk in cirrhosis patients. The 20-year cumulative incidence rate also significantly increased with the disease progression, and thus the long-term health risks should be monitored and managed in these patients.

DISCUSSION

In this population-based cohort study, patients with biopsy-proven nonalcoholic fatty liver disease (NAFLD). were found to have a substantially increased risk of severe infections compared with the matched general population. This is indeed in line with previous research, which highlighted immune dysfunction and systemic inflammation as important drivers of increased infection risks in individuals with metabolic disorders. Indeed, the risk was even higher in those NAFLD subjects who developed the disease progression from simple

steatosis to more advanced fibrosis, reaching cirrhosis, reflecting the worsening of immune competence as the liver disease progresses (20, 21).

Notably, the incidences of sepsis and respiratory infections were significantly higher in the NAFLD group, which agreed with many other studies stating the same trend in infection susceptibility for the group of liver disease patients (Lin et al., 2015). Building on such observations, our study provided quantification of the risks according to different stages of severity of liver diseases, which should allow greater granularity to help clinicians in risk stratification and management. This can be added to the evidence of growing bodies that describe the same trend in the risk for this group of liver disease patients.

The strengths of the current study are the well-defined, biopsy-proven NAFLD cohort, and a sound matching process with controls to minimize confounding factors that can strongly distort the study findings. Infection type and its incidence over time were detailed by electronic health records, and this allowed a maximal amount of data collection in this regard (23).

However, the study is not without limitations. The retrospective design may be a source of potential biases in data collection, as reliance on historical medical records might result in underreporting of less severe infections or those not requiring hospitalization. Other limitations are a relatively small sample size, especially in subgroups with more severe liver disease, and the inability to draw generalizable conclusions. The final limitation is the observational nature of the study, where causal inferences can be drawn and associations can be made, yet no firm causal link can ever be established between the severity of NAFLD and the risk of infection. Direct causality can be assumed (24).

Future studies should try to circumvent these limitations by including prospective cohort designs, larger sample sizes, and perhaps multicenter collaboration to ensure stronger findings and higher external validity. Longitudinal studies should also be conducted with respect to the study of interventions, whether lifestyle modifications or pharmacotherapy, and how they affect the risk of infection in patients with NAFLD, in order to inform strategies in which intervention could be undertaken successfully to lower morbidity and mortality from severe infections in this population. If done, there may be more research on mechanisms of immune dysfunction to discover targeted therapeutic approaches for boosting immune responses among these patients.

CONCLUSION

The authors of the present study underlined that severe infections in patients with biopsy-proven nonalcoholic fatty liver disease appear to be higher as the disease progresses. These findings should strongly suggest that patients with NAFLD require increased vigilance in relation to infection, with preventive measures incorporated into standard practice for these patients. Also, further research is needed to explore effective intervention strategies to be developed that may reduce the risk of such infections and their related burden on healthcare systems, eventually improving the quality of life.

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Authors and Affiliations:

Dr. Arfa Hamid[1], Hafiza Tooba Aftab[2], Shawal Mir[3]

[1] Children Hospital, Lahore, Pakistan

[2] Fatima Memorial Hospital, Lahore, Pakistan

[3] King Edward Medical University, Lahore, Pakistan

Author Details:

1. Arfa Hamid: PG Peads Surgery, Children Hospital, Lahore, Pakistan, arfarehmani@gmail.com
2. Hafiza Tooba Aftab: Senior Demonstrator, Pathology, Fatima Memorial Hospital, Lahore, Pakistan, toobaaftab86@gmail.com
3. Shawal Mir: FCPS Trainee, King Edward Medical University, Lahore, Pakistan

Timeline:

Received: March 17, 2023

Accepted and Scheduled for Publication: May 5, 2023

Published: June 30, 2023