Liver Cirrhosis, Etiology and Clinical Characteristics Disparities Among Minority Population

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Abstract
Liver cirrhosis (LC) is a common disease with varied primary causes and ethnic disparities. Clinical characteristics and outcomes of Arab Bedouin (AB) and Jewish patients with LC were retrospective collected and compared. We included 1048 patients, 95 (9%) Arab Bedouin and 953 (91%) Jewish patients. The incidence of cirrhosis was much lower among AB. Age at diagnosis was 47 ± 18 years among Bedouins compared to 61 ± 13 years (p < 0.001) among Jews. The most frequent causes of cirrhosis among Bedouin patients were fatty liver 21.1%, cryptogenic 20%, hepatitis B 17.9% and autoimmune hepatitis 15.8%, while hepatitis C (39.2%), fatty liver (17.2%) and alcoholic liver disease (14.4%) were most common among Jewish patients. An all-cause mortality of 48.4% was observed in AB patients compared to 66.4% in Jewish patients (p < 0.001). Significant disparities regarding incidence, clinical characteristics and outcomes of cirrhosis among Arab Bedouin compared with Jewish population were found.

Keywords Cirrhosis · Arab Bedouin · Jews · Complications · Mortality

Abbreviations
AB Arab Bedouin
LC Liver cirrhosis
HCC Hepatocellular Carcinoma
SBP Spontaneous Bacterial Peritonitis
NAFLD Non-Alcoholic Fatty Liver Disease (NAFLD)
PBC Primary Biliary Cholangitis
PSC Primary Sclerosing Cholangitis
Hb Hemoglobin
WBC White Blood Cells
PLT Platelets
ALT Alanine transaminase
AST Asparatate transaminase
AP Alkaline Phosphatase
GGT Gamma-Glutamyl Transferase

Introduction
Liver cirrhosis (LC) is a progressive scarring of liver tissue that occurs in advanced stages of chronic liver disease and is associated with several complications, including hepatocellular carcinoma (HCC) and mortality [1].

There are several causes of cirrhosis, some important being autoimmune, viral, metabolic, toxic, and cryptogenic etiologies (with no obvious cause). Alcoholic liver disease is one of the most common causes of LC worldwide. In Europe, excessive alcohol consumption accounts for 40–50% of all liver cancer cases [2].

In the Middle East, LC is still one of the top four causes of mortality [3]. Egypt, with the highest prevalence of hepatitis C worldwide, suffers from a high prevalence of cirrhosis complications and mortality, according to a recently published study [4–6]. In addition to the aforementioned
etologies, non-alcoholic fatty liver disease (NAFLD) may also be a significant source of cirrhosis. The rise in the disease in some developing countries may be explained partially by the transition to a more Western lifestyle and diet, thus increasing the incidence of NAFLD [7].

In contrast with its neighbors, Israel’s rates of cirrhosis are considerably lower. From 2010 to 2012, chronic liver disease was ranked as the tenth leading cause of death in males between the ages of 25 and 74 years. Only 4.2 out of 100,000 Israeli men died of chronic liver disease, with negligible rates among women [8]. However, to the best of our knowledge, little research has been conducted on liver disease in the AB population in Southern Israel.

AB in southern of Israel (Bedouin) are a subgroup within the Arab minority in Israel with historical, social, and cultural uniqueness. They reside in southern Israel (the Negev desert) and estimated to be 280,000 residents [9].

The rapid urbanization of the Bedouin population over recent decades has shaken the socioeconomic foundations of Arab society. The transition from tribal nomadism to a primarily urban, Western lifestyle makes this population of special interest due to a high prevalence of diseases associated with rapid urbanization, such as diabetes mellitus, ischemic heart disease, and smoking-related illnesses [10, 11].

The primary aim of this study is to conduct a retrospective review of epidemiologic and clinical data on a group of AB patients with LC and compare the data to that of Israeli Jewish patients in southern Israel.

The secondary aim is to observe the distinctions between the populations concerning LC complications, such as esophageal varices bleeding, hepatocellular carcinoma and mortality.

Methods

Population

In this retrospective study, patients with a confirmed diagnosis of LC were selected from the databases of the department of gastroenterology and liver disease and internal medicine wards at Soroka University Medical Center (SUMC). The database was searched for the term liver cirrhosis using the ICD-9 code 571, and only the patients with confirmed diagnosis of cirrhosis were included in the analysis. SUMC is a tertiary, 1100-bed hospital located in the city of Be’er-Sheva in southern Israel. It is the sole medical center providing primary care for approximately one million residents in the southern district. Patients were diagnosed through liver biopsy results or clear clinical signs of cirrhosis (portal hypertension, ascites, esophageal varices, etc.).

Israel has universal healthcare for all its residents as a fundamental right. All citizens are insured through one of four official health maintenance organizations (HMOs). Primary care is provided by family practices run directly by HMO or by privately-operated clinics. Specialty and outpatient care are provided by HMOs or hospitals.

Data Collection

Demographic and clinical data for all participants were gathered and reviewed using a number of computerized databases from the department of internal medicine and the department of gastroenterology and liver disease in SUMC. Demographic data collected from patient medical records included age, gender, and ethnicity; clinical data included etiology of cirrhosis, laboratory values, complications, and death. The Child–Pugh score for severity of cirrhosis of each patient was calculated at the time of diagnosis and a second score was calculated at the time of data collection or death (in cases, patients died before collection of the data). The Child–Pugh score calculation factored in values for albumin, international normalized ratio (INR) of prothrombin time (PT), total bilirubin, encephalopathy, and ascites.

The diagnoses of the cirrhosis etiologies were determined based on follow-up visits by a gastroenterologist/hepatologist, during hospitalization in the internal medicine department, laboratory results (hepatitis B surface antigen, Hb surface antibody, hepatitis C virus antibody, viral load for hepatitis B or C, anti-mitochondrial Ab, anti-smooth muscle cell Ab, anti-nuclear Ab, ceruloplasmin, and others), imaging findings, liver biopsy and endoscopy. The diagnosis of cirrhosis was determined in cases with significant findings support the diagnosis of cirrhosis as findings in the biopsy, portal hypertension (esophageal varices, ascites) or findings in the imaging. Cases without certain diagnosis were excluded. Finally, the data of AB Bedouins and Jews were compared.

The study was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Institutional Helsinki Committee.

Statistical Analysis

Patient characteristics were presented as mean ± SD for continuous variables and as percentages for categorical variables. Categorical variables were compared using the chi-square test. Continuous variables were examined with the student t-test. Continuous variables that were not normally distributed were reported as median (IQR) and compared in the Mann Whitney test. The rates of outcomes in follow-up were estimated using the Kaplan–Meier method, and differences between AB and Jewish patients were assessed by the log-rank test. We performed a logistic regression analysis to investigate the predictors of one-year mortality in all population studies to define the effect of ethnicity on the one-year outcome. All statistical analyses were performed using IBM
SPSS version 26 (Chicago, USA). P-values less than 0.05 were considered statistically significant.

Results

Study Population

The study included 1048 participants diagnosed with LC during follow-up by a gastroenterologist or hepatologist, baseline characteristics of the two groups are described in Table 1. The mean age at diagnosis was 54 ± 15 years among AB patients and 67 ± 12 years among Jews patients (p < 0.001). Female AB patients represented a larger portion of their group than Jewish women, 57.9% vs 36.6%, respectively (p < 0.001).

Incidence of Cirrhosis

Ninety-five (9%) of our patient’s cohort were AB. We calculated the incidence of LC in the AB and Jewish populations between the years 2002 and 2019. We found a high age-adjusted incidence rate in Jewish patients compared to that in AB, 20–30/100,000 per year and 5–10/100,000 per year, respectively. An unexplained drop in the incidence was observed in the both groups in different periods. The age-adjusted incidence of cirrhosis among AB and Jewish patients is described in Fig. 1.

Causes of Cirrhosis, Laboratory and Mortality

Significant difference in rates of hepatitis B, hepatitis C, alcoholic liver disease, autoimmune hepatitis and cryptogenic as a cause of LC between the two groups. More Jewish patients suffered from LC due to alcoholic liver disease (14.4%) and hepatitis C (39.2%), while more AB patients had more cases of autoimmune hepatitis (15.8%) and cryptogenic cirrhosis (20%). The laboratory results of both groups are presented in Table 2. Significant differences were found regarding platelets, GGT, albumin at diagnosis and INR at diagnosis. The Child–Pugh scores and stages are shown in Table 3, with no significant difference between the two groups. The various complications and outcomes are summarized in Table 4. Importantly, more AB patients had esophageal varices and bleeding events. No significant

| Characteristics                        | Bedouin n=95 | Jews n=953 | p-value |
|----------------------------------------|--------------|------------|---------|
| Age - mean ± SD                        | 54 ± 15      | 67 ± 12    | <0.001  |
| Age at diagnosis mean ± SD             | 47 ± 18      | 61 ± 13    | <0.001  |
| Gender - female (%)                    | 55 (57.9)    | 349 (36.6) | <0.001  |
| Hepatitis B (%)                        | 17 (17.9)    | 85 (8.9)   | 0.005   |
| Hepatitis C                            | 14 (14.7)    | 374 (39.2) | <0.001  |
| Fatty Liver                            | 20 (21.1)    | 164 (17.2) | 0.34    |
| Alcoholic liver disease                | 2 (2.1)      | 137 (14.4) | 0.01    |
| Autoimmune Hepatitis                   | 15 (15.8)    | 9 (0.9)    | <0.001  |
| Cryptogenic                            | 19 (20.0)    | 84 (8.8)   | <0.001  |
| Hepatitis C + Alcoholic Liver disease  | 1 (1.1)      | 40 (4.2)   | 0.13    |
| Hepatitis B + Hepatitis C              | 0 (0.0)      | 13 (1.40)  | 0.25    |
| Hepatitis B + Alcoholic Liver disease  | 1 (1.1)      | 11 (1.20)  | 0.93    |
| Liver biopsy                           | 37 (38.9)    | 225 (23.9) | 0.001   |

*Values within parenthesis represent percentage
difference in rates of hepatocellular carcinoma or spontaneous bacterial peritonitis were found between the two groups.

Lower all-cause mortality (48.4%) and younger age of death (56 ± 14 years) were demonstrated among AB patients as compared to Jewish patients (66.4% all-cause mortality [p < 0.001] and 68 ± 12 years [p < 0.001]). The final model of the study demonstrates that the predictors of one-year mortality included age at diagnosis, male gender, HCC, and alcohol use. The model is shown in Table 5 and was adjusted to ethnicity group, hepatitis B, Hepatitis C, and fatty liver. Male gender, HCC and alcoholic liver disease were significant predictors for one year mortality.

**Survival**

The Kaplan–Meier survival analysis among AB and Jewish patients is shown in Fig. 2. After the five years of follow-up, the curve representing survival rate among AB and Jewish patients diverges and demonstrates better survival rates among the AB up to end of follow-up period (log rank = 0.01).
Discussion

One of the important findings of our research is the frequency of LC among AB, 9% of all patients in the cohort. This percentage is much lower than that of the AB in the general population in southern Israel, which is about 33% [9]. Our data showed a significantly lower rate of incidence of cirrhosis among AB compared with the incidence rate among the Jewish population during the follow-up time of the study. The low incidence may be specific to the Bedouin population of southern Israel due to their unique characteristics, while the incidence among the Jewish patients of southern Israel are largely representative of the general Israeli population. Given the young average age of the AB (about 59% of the Arabs are younger than age 19 years) [9], rates of cirrhosis might be expected to be low. However, it has also been suggested that it is the low frequency of hepatitis C and alcohol liver disease among AB—generally the most common causes of cirrhosis—that may explain this low prevalence. Currently, since the approval of the direct-acting antivirals (DAA) for hepatitis C treatment with a sustained viral clearance of over 95% [12], the division of cirrhosis etiologies is likely to change in most countries. Hepatitis C may no longer be considered the main cause for cirrhosis. Rather, NAFLD, with its increasing incidence and no promising effective treatment on the horizon, as well as hepatitis B that is on the rise in some regions, are projected to climb higher on the list of common causes of cirrhosis in the near future. Both etiologies are responsible for many cases of cirrhosis in the AB in southern Israel. In the past three decades, the AB of southern Israel have undergone a major shift in lifestyle. This transition from a seminomadic to western lifestyle makes this population of special interest, and different studies showed increasing in diseases related to the lifestyle such as diabetes mellitus, ischemic heart disease and inflammatory bowel diseases [10, 11, 13].

In contrast to the results of the present study regarding causes of cirrhosis, there are notable disparities in etiology between AB and Jewish patients. We observed that the most common causes of cirrhosis among AB patients were cryptogenic, hepatitis B, autoimmune hepatitis and NAFLD, while cases in Jewish patients were mainly derived from hepatitis C, NAFLD, alcoholic liver disease, and hepatitis B. NAFLD has been shown to be associated with obesity in the literature, with 80% of NAFLD patients being obese [14, 15]. The rates of obesity in the Arab population in Israel are higher than that of the Jewish population; 19.8% of Arab men and 24.3% of Arab women are obese, while the rates among Jews are 18% and 16%, respectively [16]. Obesity in the AB age groups of 45–44, 55–64 and 65+ years are 34%, 47% and 45%, respectively. The rates among women are higher, up to 60% in some age groups [17]. Older studies have shown that 29.9% of AB women overall are obese and 42% are overweight based on pre-pregnancy body mass index [18, 19]. Given that obesity and hepatitis B are on the rise and that population in growing older, we project an increase in rates of LC among AB in the coming decades, particular due to lack of treatment for fatty liver and adherence for treatment of about 67% among patients with HBV in our region as we found in previous study [20]. In contrast with our results, studies in other countries mostly attributed alcoholic liver disease, NAFLD and hepatitis C to the development of cirrhosis [21, 22]. In the Middle East, the most common factors leading to LC are hepatitis B and hepatitis C, with the highest prevalence of hepatitis C in Egypt (14%) [3–5].
When focusing on clinical characteristics, we find that a large proportion of AB patients with cirrhosis were female, (57.9% compared to 36.6% of Jewish patients), and the AB patients were significantly younger at the time of diagnosis (by an average of twenty years). These findings are possibly related to the etiology, since cryptogenic and autoimmune hepatitis are more common among females [23], while hepatitis C, alcoholic liver disease and NAFLD are more common in males.

Our data also show that more AB patients underwent liver biopsy than Jewish patients (38.9% versus 23.9%), which may stem from the etiology of the cirrhosis. A large portion of AB was diagnosed with cryptogenic or autoimmune hepatitis, and liver biopsies are necessary to formulate a complete and accurate diagnosis in these cases; such diagnostic methods are utilized less often in patients with hepatitis C or alcoholic liver disease.

Cryptogenic cirrhosis still high among AB patients, part of the patients underwent liver biopsy and some of them didn’t, however in these patients no cause for LC were found, but nonalcoholic steatohepatitis still in the differential diagnosis, which is not diagnosed in the liver biopsy due to the advanced liver disease.

Notably, AB patients were diagnosed at a younger age, but had more esophageal varices, more bleeding esophageal varices, and more liver transplantations. There is no clear explanation for this finding; however, the younger age at diagnosis with poorer adherence to follow-up and treatment during the compensation period of the cirrhosis might be a risk factor for accelerated disease progression. We found no differences in HCC and SBP. Approximately 14.5% of cirrhotic patients developed HCC in the two groups. Patients with LC have an increased risk for development of HCC and depending on the etiology and risk factors, the risk for HCC can reach 24% [24–26].

In the present study, the all-cause mortality among Jewish cirrhosis patients was significantly higher than in AB patients (66.4% compared to 48.4%, p < 0.001 respectively). In our study, 64.7% of all cirrhosis patients died throughout the follow-up time, a relatively high mortality rate. Fleming et al. estimated a hazard ratio (HR) of 4.7 for death among patients with compensated cirrhosis and 9.7 among patients with decompensated cirrhosis compared to the general population [27]. Mortality from LC in 2010 was estimated to be approximately 1 million worldwide, a significant global health burden [28]. This burden has variable geographic distribution due do the differences in the predominant etiologies of cirrhosis in each country.

In summary, to the best of our knowledge this is the first study in Israel investigating cirrhosis, and in our study, we compared different populations, Bedouin Arab and Jews in southern Israel. The strength of our study is in the large sample of cirrhosis patients, the findings of the study showed huge disparities among the AB patients compared with the Jewish patients. Significant differences were found regarding LC causes, complications, transplantations rate, and mortality. Yet these AB patients still had a lower all-cause mortality and better survival rates, possibly due to cirrhosis etiology, time of diagnosis, and the seeking of medical services. The interest of our study and findings lies in the lifestyle change, with modernization to western lifestyle of AB in the last decades, our findings could be extrapolated to other populations in the world, which undergoing the process of lifestyle changes recently. Additionally, the findings can help for decision making for future intervention for the specific causes of the cirrhosis in such population, such as interventions for preventions of NAFLD and hepatitis B.

There are some limitations of the present study: first, the retrospective design of the study, and second, the incomplete data on treatment, hospitalization and precise causes of death. Another limitation of the study is the possibility of missing of a very small number of patients, who were in follow up in outpatient clinics outside the hospital.

Conclusion

The incidence of cirrhosis is low among Arab Bedouin patients, with marked disparities in causes, age, complications and all-cause mortality as compared to Jewish patients. Arab Bedouin patients were diagnosed at a younger age, underwent more liver transplantation, but had lower all-cause mortality rates and higher survival rates.

New Contribution to the Literature

This is the first report regarding the cirrhosis among Bedouin population, disparities were found in term of causes and outcomes among this specific population, however it could be addressed to other minority in other regions in the world.

Author Contributions All authors have contributed significantly to the work and have approved the final version of the manuscript.

Declarations

Conflict of interest There are no conflicts of interest for any of the authors, and no financial disclosures.

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