

Liver Cirrhosis, Etiology and Clinical Characteristics Disparities among Minority Population

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Abstract

Background: Liver cirrhosis (LC) is a common disease with varied primary causes and ethnic disparities. We aimed to determine the frequency, clinical characteristics, and outcomes of LC among the Arab Bedouin (AB) population in southern Israel.

Methods: This retrospective and follow-up study enrolled all patients diagnosed with LC at the gastroenterology and hepatology department or the internal medicine ward. Patient records were reviewed for demographic, clinical data, and mortality. Clinical primary outcomes were defined as death, hepatocellular carcinoma or liver transplantation.

Results: We included 820 patients 69 (8.4%) AB and 752 (91.6%) Jewish patients. Incidence of cirrhosis found in our study was much lower among AB patients, 5-10/100,000/year, compared with 20-40/100,000 per year in Jewish patients. Age at diagnosis was 42.6 ± 16.9 years among Bedouins compared to 61 ± 13 years ($p < 0.001$) among Jews. The study included 25 (36.2%) male AB and 472 (63%) male Jewish patients ($p < 0.001$). The most frequent causes of LC among AB were cryptogenic (24.6%), hepatitis B (18.8%) and autoimmune hepatitis (17.4%), while hepatitis C (41.7%), fatty liver (16.5%) and alcoholic liver disease (15.5%) were most common among Jewish patients. An all-cause mortality of 41.8% was found in AB patients compared to 63.4% in Jewish patients ($p < 0.001$). Primary clinical outcomes were found by 34 (49%) AB patients and by 510 (67.9%) Jewish patients ($p = 0.002$), with 46 and 608 events, retrospectively.

Conclusions: The incidence of liver cirrhosis among Arab Bedouin is lower than that in the Jewish population, with disparities in etiology, age at diagnosis, presence of complications and mortality.

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 ones 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 etiologies, 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), central Israel, and northern Israel (the Galil). The AB population in southern Israel is estimated to be 250,000 [9].

Approximately 40% of Bedouins in the Negev reside in rural areas in semi-nomadic conditions. Families live in makeshift tin shacks for extended periods of time, without basic municipal services such as supply of water and electricity. Their homes are distant from the main roads, making them difficult to access. However, the rapid urbanization of the population over recent decades has shaken the socioeconomic foundations of Arabs 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

Patients: 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).

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 700,000 residents in the Southern district. Patients were diagnosed through liver biopsy results or clear clinical signs of cirrhosis (portal hypertension, ascites, esophageal varices, etc.).

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.

Primary clinical outcomes

Primary clinical outcomes were defined as death, hepatocellular carcinoma or liver transplantations.

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 \pm 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 Kruskal Wallis 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. All statistical analyses were performed using IBM SPSS version 24 (Chicago, USA). P-values less than 0.05 were considered statistically significant.

Results

Incidence of liver cirrhosis

In general, only 8.4% of our patients' cohort were AB. In this study, we calculated the incidence of LC in the AB and Jewish populations between the years 2002 and 2016. We found a high age-adjusted incidence rate in Jewish patients compared to that in AB, 20–40/100,000 per year and 5–10/100,000 per year, respectively. An unexplained drop in the curve was observed between the years 2004 and 2005 in the both

groups, and in the last years 2010–2016, a decline in incidence in the Jewish population was observed. The age-adjusted incidence of cirrhosis among AB and Jewish patients is described in figure 1.

Study population

The study included 820 participants diagnosed with LC during follow-up by a gastroenterologist/hepatologist or during hospitalization in the internal medicine ward; the mean age at diagnosis was 58.6 ± 14.6 , 498 (61%) patients of our cohort were male. The follow up time during the study ranged between 1–31 years, with a mean of 8.6 ± 4.9 years.

The AB patients tended to be diagnosed at younger ages than Jewish patients, at a mean of 42.6 ± 16.9 years, as opposed to 61 ± 13 years in Jewish patients ($p < 0.001$).

Female AB patients represented a larger portion of their group than Jewish women, 63.8% compared to 37%, respectively ($p < 0.001$).

At baseline, there was no significant difference in rates of hepatitis B, fatty liver, Wilson disease and primary sclerosing cholangitis (PSC) as an etiology of LC between the two groups. However, more Jewish patients suffered from LC due to alcoholic liver disease (15.5%) and hepatitis C (41.7%), while more AB patients had more cases of autoimmune hepatitis (17.4%) and cryptogenic cirrhosis (24.6%). Baseline characteristics of the two groups are described in table 1. The laboratory results including the values are shown in table 2. No significant differences were found between the two groups regarding the laboratory results.

Primary clinical outcome

The primary clinical outcomes were defined as either death, hepatocellular carcinoma or transplantation. The various complications and outcomes are summarized in table 3. Importantly, more AB patients had esophageal varices and bleeding events.

No significant difference in rates of hepatocellular carcinoma or spontaneous bacterial peritonitis were found between the two groups.

Lower all-cause mortality (41.8%) and younger age of death (51 ± 15.1 years) were demonstrated among AB patients as compared to Jewish patients (63.4% all-cause mortality [$p < 0.001$] and 67 ± 14.3 years [$p < 0.001$]).

One or more of the clinical primary outcomes was found in 34 (49.3%) AB patients and in 510 (67.9%) Jewish patients ($p = 0.002$), with a total of 46 and 608 events, respectively.

Survival

The Kaplan-Meier curve describing the survival rate among AB and Jewish patients is shown in figure 2. After the fourth year of follow-up, the curve representing survival rate among AB and Jewish patients diverges and demonstrates better survival rates among the AB up to 15 years of follow-up (about 30% among AB and 20% among Jewish patients), log rank = 0.02.

Discussion

To the best of our knowledge, the present study is the first to investigate LC in Israel with a focus on the AB population.

LC is one of the most frequent causes of death in Europe and the Middle East; however, it ranks low on the list of causes of mortality in Israel [3,8].

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, relevant to research on other minorities worldwide.

One of the important findings of our research is the frequency of LC among AB, 8.4% 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.

NAFLD has been shown to be associated with obesity in the literature, with 80% of NAFLD patients being obese [13,14]. 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 [15]. 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 [16]. Older

studies have shown that 29.9% of AB women overall are obese and 42% are overweight based on pre-pregnancy body mass index [17,18].

Given that obesity and hepatitis B are on the rise and that population is growing older, we project an increase in rates of LC among AB in the coming decades.

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. In contrast with our results, studies in other countries mostly attributed alcoholic liver disease, NAFLD and hepatitis C to the development of cirrhosis [19,20].

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, (64% compared to 37% 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 [21], 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 (42% versus 27%), 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 the didn't, however in these patients no cause for LC were found, but non alcoholic 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 13% 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% [22–24].

In the present study, the all-cause mortality among Jewish cirrhosis patients was significantly higher than in AB patients (63.4% compared to 41.8%, respectively). In our study, 61% 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 [25].

Mortality from LC in 2010 was estimated to be approximately 1 million worldwide, a significant global health burden [26]. This burden has variable geographic distribution due to the differences in the predominant etiologies of cirrhosis in each country.

The survival rate of our cohort estimated to be higher among AB, about 30% in a follow-up after 15 years, compared to 20% among Jewish patients.

However, the primary clinical outcomes defined in this study were significantly higher among Jewish patients than AB patients (67.9% and 49.3%, respectively), 608 versus 46 events.

Focusing on laboratory results, some laboratory values were abnormal as expected in both groups, including hemoglobin, platelets, liver enzymes, bilirubin, albumin and INR. A Child-Pugh score of 6 was assigned at diagnosis (Child A) and the last score was 7 and 8 (Child B) among AB and Jewish patients, respectively.

Despite the discrepancies between the two groups regarding clinical characteristics and outcomes, no significant differences were found in the laboratory results. Importantly, 58% of AB patients had normal ALT levels and 38% had normal AST levels. However, as calculated in table 2, the standard deviation of AST was relatively high (1200), which could be related to the high AST levels (up to 7000) among several AB patients recorded during previous hospitalizations. These high levels may be attributed to acute exacerbation or complication of the disease.

In summary, to the best of our knowledge this is the first study in Israel investigating cirrhosis in Bedouins 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. AB were diagnosed on average at a younger age, died at a younger age, and underwent more transplantations. 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.

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.

Conclusion

The incidence of liver cirrhosis is low among Arab Bedouin patients, with marked disparities in etiology, clinical characteristics, 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.

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: Aspartate transaminase

AP: Alkaline Phosphatase

GGT: Gamma-Glutamyl Transferase

Declarations

Acknowledgements

Not applicable

Ethics approval and consent to participate

The study protocol was approved by the Institutional Ethics Committee, Helsinki committee at the Soroka University Medical Center. A written informed consent was not needed because of the retrospective design of the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Author contributions:

- Conception and design of the study: MAT, NAF, OE, AF
- Generation, collection, assembly, analysis and/or interpretation of data: NAF, MAT, NK, AL, OE
- Drafting or revision of the manuscript: NAF, HAK, DY, ANS, AAG, LP
- Approval of the final version of the manuscript: MAT, LP, NK, AL, OE, HAK, AF, DY, ANS, AAG and NAF

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Tables Legend

Table 1: Basic Demographic and Clinical Characteristics of the included patients

Table 2: Summary of the laboratory results among Arab Bedouin and Jewish cirrhosis patients

Table 3: Clinical complications and Outcomes comparison between two study groups

Tables

Table 1: Basic Demographic and Clinical Characteristics of the included patients

P value	Characteristics		
	Jews N=751	Arabs N=69	
<0.001	(63.0) 472	(36.2) 25	Gender - Male
<0.001	66.4±12.7	49.9±14.8	Age
<0.001	61±13	42.6±16.9	Age at diagnosis
0.008	(27.1) 201	(42) 29	Liver biopsy
			Etiology of cirrhosis %
0.16	(12.8) 96	(18.8) 13	Hepatitis B
<0.001	(41.7) 313	(14.5) 10	Hepatitis C
0.89	(16.5) 124	(15.9) 11	Non-Alcoholic Fatty Liver Disease (NAFLD)
			Wilson Disease
0.46	(0.7) 5	(1.4) 1	Alcoholic Liver Disease
<0.001	(15.5) 116	(1.4) 1	Autoimmune Hepatitis
<0.001	(1.3) 10	(17.4) 12	Primary Biliary Cholangitis (PBC)
0.007	(0.8) 6	(4.3) 3	Primary Sclerosing Cholangitis (PSC)
			Cryptogenic
0.67	(0.3) 2	0 (0)	Others
<0.001	(9.1) 68	17 (24.6)	
	9 (1.1)	(1.4) 1	

Table 2: Summary of the laboratory results among Bedouin Arab and Jewish cirrhosis patients (mean ± SD, unless otherwise stated)

P value	Jews N=749	Arabs N=69	Characteristics
0.44	11.06±2.4	10.8±2.8	Hemoglobin (Hb) (gr/dl)
0.23	9.1±7.9	8±7.4	White Blood count (WBC) (10 ³ /ul)
0.09	119±78.2	102±70.4	Platelets (10 ³ /ul)
0.25	74±240	168±662	Alanine transaminase (ALT) (U/L)
0.29	155±623	310±1205	Asparatate transaminase (AST) (U/L)
0.29	166±159	187±176	Alkaline Phosphatase (AP) (U/L)
0.05	124±148	97±103	Gamma-Glutamyl Transferase (GGT) (U/L)
0.95	4±6.8	4±5.8	Bilirubin- Total - last (mg/dL)
0.71	2.02±3	2.1±2.5	Bilirubin-Total - at Diagnosis (mg/dL)
0.25	2.9±0.8	3.1±0.9	Albumin - last (gr/dL)
0.01	3.4±0.6	3.2±0.7	Albumin - at Diagnosis (gr/dL)
0.20	1.6±0.8	1.8±1.1	INR-Last
0.03	1.3±0.38	1.4±0.39	INR- at Diagnosis
0.61	137±8	138±5	Sodium (mEq/L)
0.16	6 (5; 8)	6 (5; 8)	Child-Pugh score- at Diagnosis (IQR)
0.39	8 (5; 10)	7 (5; 10)	Child-Pugh score last (IQR)

Table 3: Clinical complications and Outcomes comparison between two study groups

P value	Characteristics		
	Jews	Arabs	
	N=749	N=69	
0.003	(57.2) 416	52 (75.4)	Esophageal varices
0.02	(29.6) 206	(42) 29	Esophageal varices bleeding
0.86	(13.8) 103	(13) 9	Hepatocellular Carcinoma (HCC)
0.06	48±28	56±9	HCC - Age at diagnosis (mean±SD)
0.91	(23.8) 176	(23.2) 16	Spontaneous Bacterial Peritonitis (SBP)
0.75	131 (17.5)	11 (15.9)	Hepatorenal Syndrome
0.84	79 (11.9)	6 (9.5)	Hepatorenal Syndrome type 1
0.54	4 (0.5)	0 (0)	Hepatopulmonary
0.03	(4.3) 32	(10.1) 9	Transplantation
<0.001	(63.4) 473	(41.8) 28	Death
<0.001	67±14.3	51±15.1	Age of death
0.002	510 (67.9)	34 (49.3)	Primary Outcome (Death, HCC or transplantation)

Figures

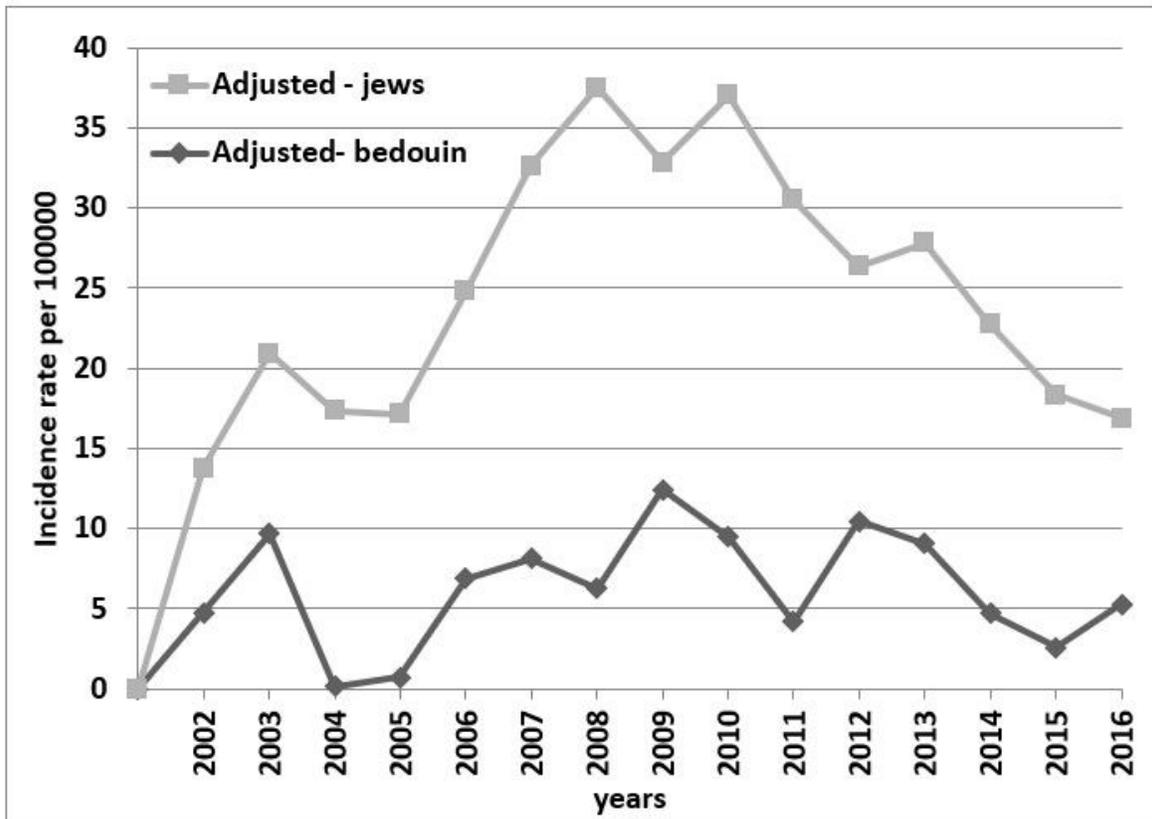


Figure 1

Age-adjusted incidence of cirrhosis among Arabs (Bedouin) and Jews population

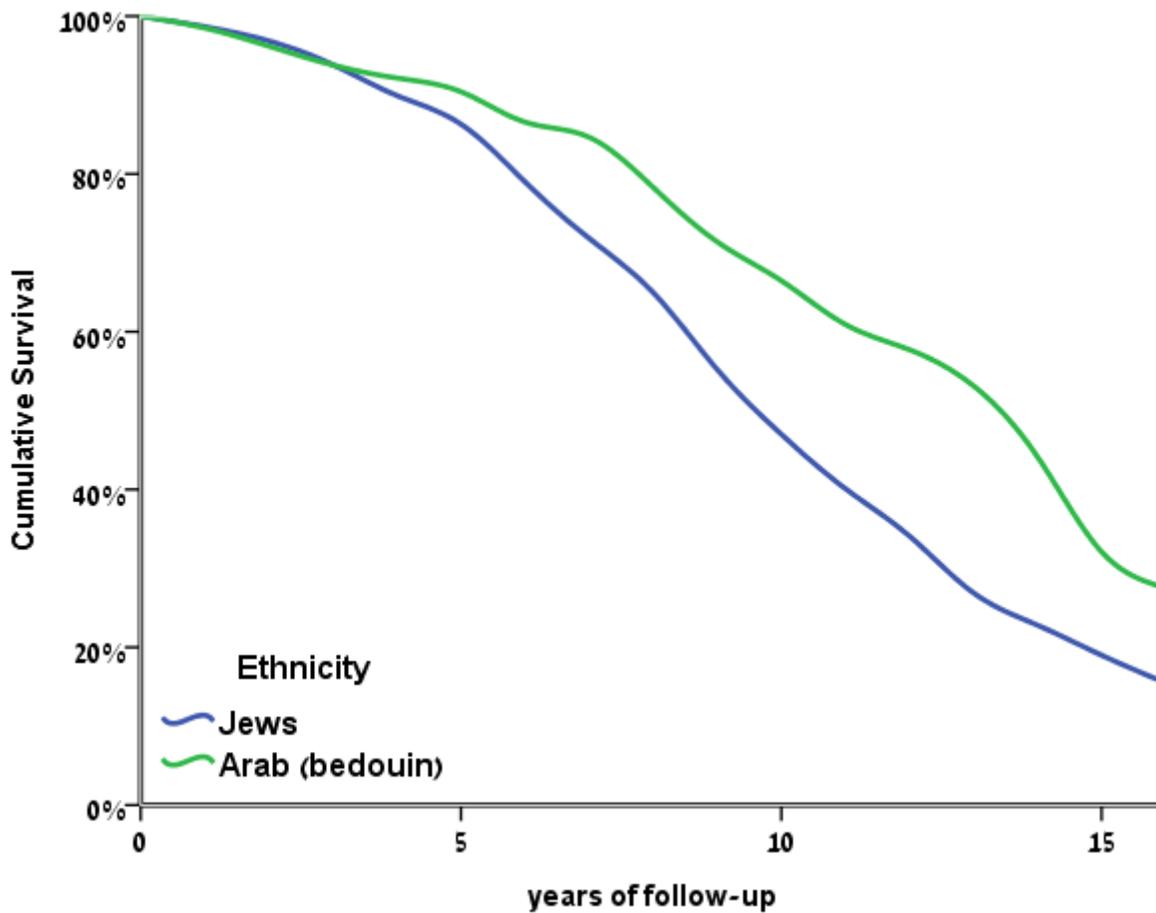


Figure 2

Kaplan-Meier survival analysis among Arab Bedouin and Jewish patients

Supplementary Files

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