Gender and ethnic differences in the post-liver transplant outcomes of patients with autoimmune hepatitis with acute liver failure at initial presentation: a case-control study

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Abstract

Introduction: Autoimmune hepatitis (AIH) may initially present as acute liver failure (ALF). The outcome of liver transplantation (LT) in patients with AIH and ALF is not very well defined. We determined the outcome of LT in UNOS (United Network for Organ Sharing) status 1 adult patients with and without AIH using post-MELD (Model for End-Stage Liver Disease) UNOS data.
Material and methods: For each AIH patient, 3 patients with non-AIH, matched for age ±5 years and donor risk index (DRI) ±5 years, were identified; 200 patients (50 AIH, 150 non-AIH) were found eligible for the study.
Results: Patients with AIH were more likely to be female (p = 0.003), non-Caucasian (p = 0.009), have higher bilirubin (p = 0.003), longer waiting time (p = 0.01), and lower creatinine (p = 0.019). African American patients with AIH were younger (p = 0.003), had lower bilirubin (p = 0.037), and were more likely to have had a prior LT compared to Caucasians (p = 0.02). Kaplan-Meier analysis showed that 5-year post-LT survival was similar in those with and without AIH (p = 0.3). African American with AIH showed a trend for lower 5-year survival compared to Caucasians (55% vs. 80%, p = NS). Women had a better outcome, especially in those with non-AIH (p = 0.002).
Conclusions: Patients with AIH transplanted as status 1 have similar outcomes to those without AIH. Women with non-AIH-related ALF have better survival than their male counterparts.

Key words: autoimmune hepatitis, acute liver failure, liver transplantation.

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory disorder of the liver characterized by a female preponderance, presence of autoantibodies, increased gamma globulins, and liver histology showing interface hepatitis that is predominantly lymphoplasmocytic [1]. While AIH can have protean manifestations, the majority of patients present with chronic or subclinical disease. In 10–25% of patients, however, the course can be more acute, with a fulminant presentation [2–4]. Acute liver failure (ALF), a serious clinical condition occurring in patients with no prior history of liver disease, is characterized by development of he-

patic encephalopathy and coagulopathy [5], often resulting in multi-organ failure. In a survey in the US carried out between 1998 and 2008, AIH was found to be the underlying etiology in 5% of patients with ALF [6]. Similar data were reported from Europe, where 2–5% of patients with fulminant hepatic failure (FHF) had AIH as the underlying etiology [7, 8].

There is a paucity of published data in patients with fulminant onset of AIH, and therefore their clinical characteristics, response to immunosuppression, and outcomes with and without liver transplantation (LT) remain poorly defined. Much of the controversy hinges on a critical management issue, i.e. whether such patients should be given a trial of corticosteroids, be priority listed for LT, or both. This is confounded by the variable response rates to corticosteroids (8–50%) in patients with AIH who present with liver failure [3, 9, 10]. Furthermore, there are concerns whether initiating steroids in such ill patients could predispose them to an increased risk of infections without any additional benefits. Previous studies had suggested that patients transplanted for AIH have 5-year survival in the range of 74–92% [11–13]. These studies, however, had included mostly patients with chronic AIH. There are only limited data available on the long-term post-LT outcomes of patients with AIH who were transplanted for fulminant disease. The aim of this study, therefore, was to assess 5-year patient survival of patients with AIH transplanted as UNOS status 1 (assuming that all adult patients who were transplanted as UNOS status 1 had presented with acute liver failure) and compare that to patients without AIH, who were also transplanted as UNOS status 1 during the same time period.

Material and methods

Because of the heterogeneity of the patient population, we conducted a case-controlled study to adjust for some important confounders that may impact survival. For this study, we included only those adults (≥ 18 years) who were transplanted as UNOS status 1 LT between 2002 and 2007, and hence all data were collected in the post-MELD era. We excluded those patients who were re-transplanted as status 1 for early graft failure after the initial liver transplantation [14]. For every patient with AIH (n = 50), we selected three age (±5 years) and donor risk index (DRI) (±0.2 points) matched patients (n = 150) with non-AIH who were transplanted during the same period. The DRI was calculated, as previously described, using 3 variables that were shown to independently predict survival: donor age > 40 years, donation after cardiac death (DCD), and split/partial grafts [15].

The following data were recorded for recipients: age (in years), body mass index (BMI), ethnicity (Caucasian, African American (AA), Hispanic, Asian, and Others), patient status (alive or dead), serum bilirubin, creatinine and albumin, days on waiting list and number of prior LT. Donor characteristics recorded were age, BMI, ethnicity, gender, DRI, cold ischemic time (CIT), warm ischemic time (WIT), and serum creatinine.

The outcome variable of interest was patient survival in years. All subjects who were lost to follow-up or had not reached the primary endpoint of patient survival, defined as death, were censored and assumed to have the same underlying survival function as the non-censored subjects.

Statistical analysis

The data are presented as the mean ± standard deviation (SD) or frequency followed by the relative frequency. Differences between continuous and categorical variables were analyzed by the Mann-Whitney and by Fisher's exact or χ^2 test respectively. A 2-tailed p value of less than 0.05 was considered significant. Kaplan-Meier survival analysis was performed to assess outcomes between the AIH and non-AIH groups, with the variable time of patient survival in years, where the end point of patient survival was defined as death. The differences between groups were assessed using a log-rank test. Cases with missing data for any particular measurement were omitted from analyses involving that variable. The statistical software used was SAS version 9.13 (Cary, NC, USA).

Results

Fifty patients with AIH were transplanted during the study period as status 1. By study design, these 50 patients were compared to 150 patients with non-AIH. Table I compares the baseline demographic data in the AIH and non-AIH groups. Those with AIH were more likely to be female (80% vs. 44.7%, p = 0.0002), have higher serum bilirubin (p = 0.003), and to have spent a longer time on the waiting list (p = 0.01) compared with their non-AIH counterparts. In contrast, the latter were more likely to be Caucasian (38% vs. 64%, p = 0.036), and have higher serum creatinine levels (p = 0.019). The BMI, MELD scores at time of listing, and number of previous LT were comparable in the two groups (Table I). There were no significant differences in donor characteristics between those with and without AIH as regards donor age, BMI, gender, DRI, CIT, and WIT. Those in the AIH group, however, were more likely to receive a graft from a Hispanic donor (p = 0.04) (Table I).

Since AA were reported to have relatively worse outcomes compared to Caucasians, we compared

Table I. Characteristics of patients with and without AIH and ALF

Recipient factors	AIH (*N* = 50)	Non-AIH *N* = 150	Value of *p*
Age	44.0 ±14.3	33.5 ±13.8	0.68
BMI	27.9 ±7.4	26.8 ±6.2	0.32
Ethnicity:			0.009
White	19 (38)	96 (64)	0.036
African American	13 (26)	27 (18)	0.27
Hispanic	11 (22)	20 (13)	0.18
Asian	6 (12)	7 (4.6)	0.08
Other	1 (2)	0	0.08
Gender:			
Female	40 (80)	67 (44.7)	0.003
Bilirubin	20.7 ±13.5	15.1 ±12.8	0.003
Serum albumin at time of TX	2.73 ±0.70	2.65 ±0.70	0.59
Days on wait list	24.2 ±110.8	14.6 ±65.5	0.01
MELD	30.3 ±8.1	28 ±11.4	0.59
Number of previous TX	0.26 ±0.56	0.38 ±0.51	0.07
Creatinine	1.5 ±1.5	1.6 ±1.2	0.019
Donor factors:			
Age	36.1 ±16.0	38.7 ±17.9	0.42
BMI	24.9 ±4.2	25.5 ±5.5	0.71
Ethnicity:			0.20
White	32 (64)	115 (76.7)	0.37
African American	5 (10)	16 (10.7)	0.90
Hispanic	12 (24)	17 (11.3)	0.04
Asian	1 (2)	1 (0.67)	0.41
Other	0	1 (0.67)	0.56
Gender:			0.39
Male	30 (60)	100 (66.7)	0.61
Female	20 (40)	50 (33.3)	0.49
DRI	1.53 ±0.41	1.53 ±0.40	1.00
Cold ischemia time	8.62 ±8.57	7.38 ±3.64	0.54
Warm ischemia time	39.3 ±13.7	34.8 ±13.1	0.26
Creatinine	1.32 ±2.87	1.53 ±2.96	0.15
Mortality:			
Death	13 (26)	58 (38.7)	0.78

BMI – Body mass index, TX – transplant, MELD – model for end stage liver disease, DRI – donor risk index.

the characteristics of these two groups (Table II). African American were younger (p = 0.003), have lower serum bilirubin (p = 0.037), but were more likely to have had a prior transplant in comparison to the Caucasians (p = 0.025). There were no significant differences in donor characteristics, ex-

Table II. Characteristics of African Americans and Caucasians with AIH and ALF

Recipient factors	African American (*N* = 13)	Caucasian (*N* = 19)	Value of *p*
Age	42.9 ±16.4	50.4 ±10.4	0.003
BMI	26.0 ±5.1	29.0 ±8.3	0.95
Gender:			0.78
Male	4 (30.8)	5 (26.3)	0.37
Bilirubin	15.8 ±8.6	24.0 ±12.3	0.037
Serum albumin at time of TX	2.9 ±0.91	2.6 ±0.72	0.59
Days on wait list	2.9 ±2.6	4.6 ±3.1	0.13
MELD	30.7 ±6.6	31.9 ±8.8	0.86
Number of previous TX	6 (46)	2 (11)	0.025
Creatinine	2.1 ±1.6	1.7 ±1.8	0.36
Donor factors:			
Age	34.7 ±17.1	33.00 ±16.90	0.74
BMI	26.2 ±4.3	24.6 ±4.9	0.41
Ethnicity:			0.18
White	11 (84.6)	12 (63.1)	0.28
African American	0	3 (15.8)	0.56
Hispanic	1 (7.7)	4 (21.1)	0.08
Asian	1 (7.7)	0	0.23
Other	0	0	1.00
Gender:			0.22
Female	4 (30.8)	10 (52.6)	0.020
DRI	1.46 ±0.39	1.56 ±0.46	0.55
Cold ischemia time	9.3 ±11.9	7.6 ±2.8	0.23
Warm ischemia time	41.6 ±7.8	40.5 ±10.8	0.77
Creatinine	0.83 ±0.28	2.05 ±4.62	0.43
Mortality:			
Death	5 (38.5)	4 (21.1)	0.83

cept that the Caucasians were more likely to receive a graft from a female donor ($p = 0.02$) (Table II).

Table III compares gender differences in those with and without AIH. Among the AIH group, no significant differences were observed both in the recipient and donor characteristics, except that females with AIH were more likely to have a female donor ($p = 0.0013$). In those with non-AIH, men had a higher serum creatinine ($p = 0.0002$) and mortality ($p = 0.019$), but serum bilirubin was higher in the females ($p = 0.02$). In addition, men in the non-AIH group were more likely to receive a graft from a donor with a greater BMI ($p \leq 0.0001$), and serum creatinine ($p = 0.002$), though with a shorter CIT ($p = 0.028$). Men with non-AIH had a higher mortality compared to women (49% vs. 25%, $p = 0.019$).

The 5-year survival was similar in those with and without AIH (Figure 1, $p = 0.29$). The survival was similar in AA and Caucasians (Figure 2 A), but there was a lower survival in AA with AIH compared to Caucasians (65% vs. 80%), though the difference was not statistically significant (Figure 2 B). Overall, women had a better outcome (Figure 3 A, $p = 0.002$). When stratified by disease, there were no gender differences in those with AIH (Figure 3 B, $p = 0.67$), but women with non-AIH had a significantly better survival compared to men (Figure 3 C, $p = 0.004$).

Discussion

This case-controlled study showed that patients with AIH transplanted as UNOS status 1 were more likely to be female, non-Caucasian, and have higher serum bilirubin and longer waiting times, but lower serum creatinine compared to a non-AIH cohort. The 5-year survival, however, was similar in those with and without AIH transplanted as UNOS status 1. AAs with AIH were 8 years younger than their Caucasian counterparts, and despite their younger age, showed a lower (though statistically non significant) 5-year surviv-

Table III. Gender differences in those with and without AIH and ALF

Recipient factors	AIH (*N* = 50)			Non-AIH (*N* = 150)		
	Male (*n* = 10)	Female (*n* = 40)	Value of *p*	Male (*n* = 83)	Female (*n* = 67)	Value of *p*
Age	43.7 ±16.5	44.1 ±14.0	1.00	45.0 ±13.1	41.6 ±14.6	0.17
BMI	27.1 ±10.3	28.2 ±6.6	0.27	26.9 ±5.6	25.9 ±6.8	0.066
Ethnicity:			0.41			0.83
White	5	14	0.49	53	43	0.98
African American	4	9	0.33	14	13	0.71
Hispanic	1	10	0.37	11	9	0.97
Asian	0	6	0.96	5	2	0.39
Other	0	1	0.62	0	0	1.00
Bilirubin	19.53 ±10.20	21.02 ±14.35	1.00	13.20 ±12.68	17.56 ±12.62	0.019
Serum albumin at time of TX	2.72 ±1.04	2.74 ±0.60	0.65	2.64 ±0.82	2.67 ±0.52	0.72
Days on wait list	3.0 ±1.9	29.6 ±123.5	0.11	23.9 ±87.2	3.0 ±3.4	0.14
MELD	32.8 ±7.9	29.7 ±8.1	0.20	29.1 ±12.9	28.2 ±9.3	0.46
Number of previous TX	0.6 ±1.0	0.2 ±0.4	0.11	0.39 ±0.54	0.37 ±0.49	0.97
Creatinine	1.85 ±1.12	1.39 ±1.56	0.07	1.90 ±1.34	1.24 ±0.82	0.0002
Donor factors	**Male**	**Female**	**Value of *p***	**Male**	**Female**	**Value of *p***
Age	31.5 ±15.6	37.2 ±16.1	0.30	37.45 ±18.16	40.31 ±17.63	0.34
BMI	26.1 ±5.7	24.6 ±3.8	0.61	27.1 ±5.9	23.6 ±4.3	< 0.0001
Ethnicity:			0.62			0.23
White	7	25	0.79	62	53	0.76
African American	0	5	0.0013	12	4	0.11
Hispanic	3	9	0.67	7	10	0.24
Asian	0	1	0.62	1	0	0.37
Other	0	0	1.00	1	0	0.37
Gender:			0.15			0.048
Female	6	14	0.26	22	28	0.11
DRI	1.40 ±0.36	1.56 ±8.15	0.27	1.57 ±0.41	1.50 ±0.38	0.30
Cold ischemia time	6.19 ±2.14	9.18 ±9.38	0.43	7.77 ±3.49	6.95 ±3.78	0.028
Warm ischemia time	37.86 ±6.54	39.62 ±14.81	0.98	35.43 ±13.77	34.09 ±12.40	0.43
Creatinine	0.82 ±0.41	1.45 ±3.20	0.40	1.17 ±0.57	1.98 ±4.35	0.002
Mortality:						
Death	3	10	0.78	41	17	0.019

al compared to Caucasians. Additionally, women, especially those in the non-AIH group, had significantly better survival compared to men.

Acute liver failure accounts for 6% to 7% of all LT in the United States and 11% in Europe [16, 17]. In the pre-transplantation era, survival of patients who presented with ALF was only 6–22% [18, 19]. Recent data from the European Liver Transplant Registry suggest that there has been significant improvement in survival among patients transplanted for ALF with 1-, 5- and 10-year patient and graft survival rates of 74%, 68%, 63%,

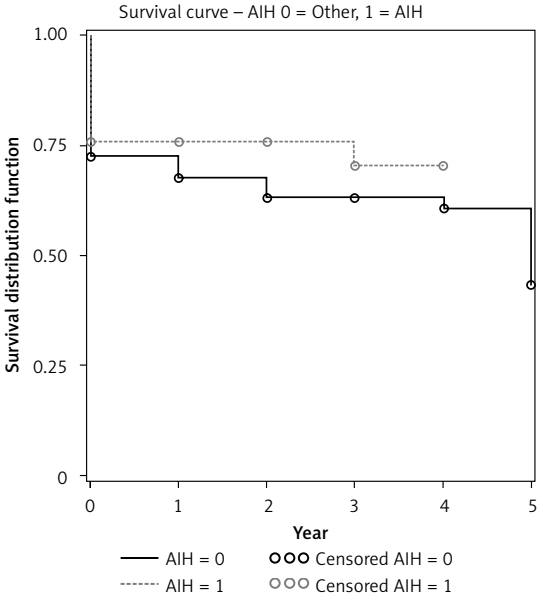

Figure 1. Kaplan-Meier survival curves in UNOS status 1 patients with AIH and non-AIH (log rank χ^2 test = 1.10, p = 0.29)

and 63%, 57%, 50% respectively [20]. In fact in Europe, the 10-year survival gap between patients transplanted for ALF versus chronic liver disease has decreased from 15% to 5% [16]. Similarly, results from the US Acute Liver Failure Study Group indicate excellent 3-year survival in ALF (82%) over the last decade [21]. Factors predictive of poor outcome after LT for ALF are donor BMI > 30 kg/m^2, non-Caucasian ethnicity, serum creatinine > 2 mg/dl, recipient age > 50 years, donor age > 60 years, history of life support and non-viral etiology of the ALF [21–23].

Previous studies had reported that overall patient/graft survival in patients with AIH at 1 year (97.5%/97.5%), 2 years (93%/91.2%) and 5 years (93%/87%) is excellent, but the majority of these patients presented with chronic liver failure [12]. There are only limited data on patients with AIH and a fulminant presentation. A small Spanish study reported better survival for patients with AIH and ALF (n = 7) at 1 and 5 years compared to those with chronic AIH (n = 8) [24]. The 5-year post-LT survival of 62.5% in patients with AIH and ALF in their study corroborates our data, as our 5-year survival in this cohort was just over 60%. In another study where just over a third had ALF due to AIH, with the others having chronic AIH, after a median follow-up period of 530 days, the overall patient and graft survival rates were > 90% [25].

Bacterial and fungal sepsis are responsible for almost one third of deaths after LT for ALF and in conjunction with multisystem failure are the most common cause of death [20, 22, 26, 27]. Because patients with AIH are likely to be on corticosteroids before the transplant, there is a perception that they may be at increased risk of sepsis-related morbidity and mortality. In this study, data on corticosteroid use and subsequent development of sepsis were not available. We have previously shown that in patients with AIH and initial presentation with liver failure, a lower MELD score at admission (≤ 28), more severe hepatic fibrosis, and an early (within 4 days of steroid therapy) im-

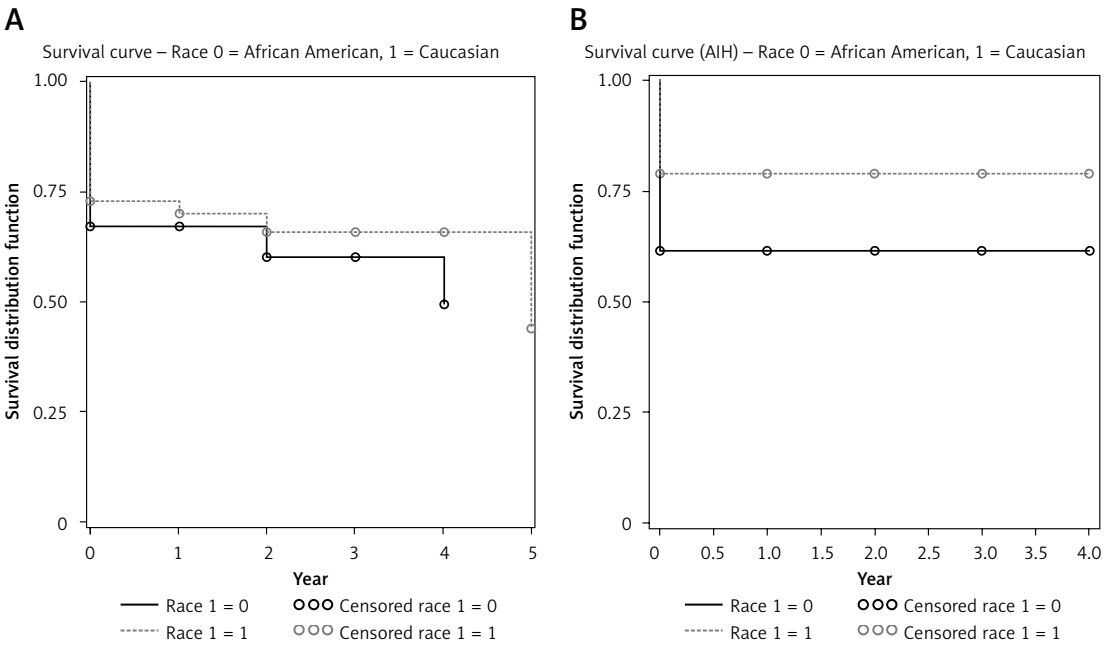

Figure 2. A – Kaplan-Meier survival curves of UNOS status 1 patients (overall) stratified by ethnicity (AA vs. Caucasian; log rank χ^2 =1.17, p = 0.28); **B** – Kaplan-Meier survival curves of UNOS status 1 patients with AIH, stratified by ethnicity (AA vs. Caucasian; log rank χ^2 = 1.12, p = 0.29)

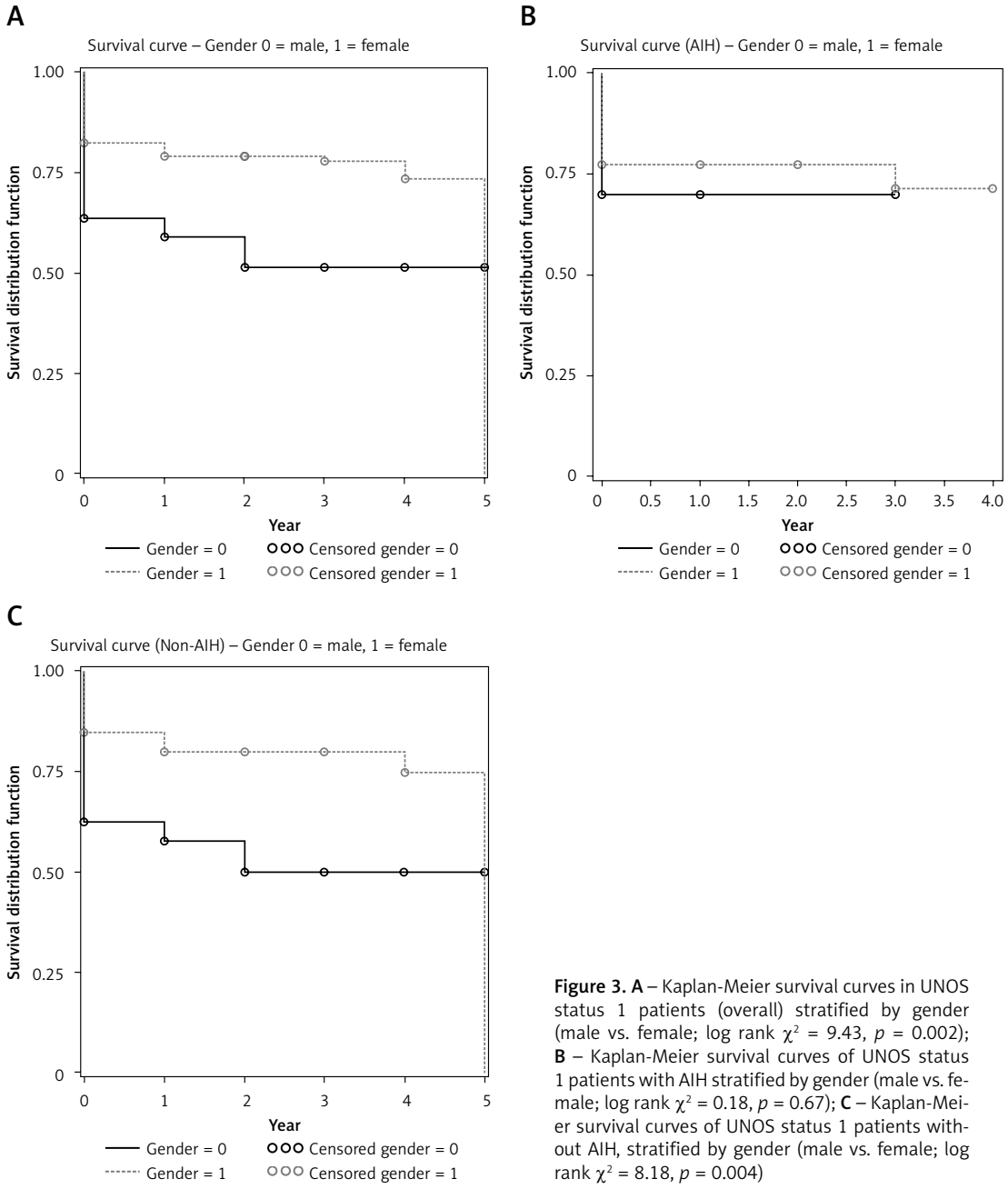

Figure 3. A – Kaplan-Meier survival curves in UNOS status 1 patients (overall) stratified by gender (male vs. female; log rank χ^2 = 9.43, p = 0.002); **B** – Kaplan-Meier survival curves of UNOS status 1 patients with AIH stratified by gender (male vs. female; log rank χ^2 = 0.18, p = 0.67); **C** – Kaplan-Meier survival curves of UNOS status 1 patients without AIH, stratified by gender (male vs. female; log rank χ^2 = 8.18, p = 0.004)

provement or stabilization in serum bilirubin and INR, identified those who were likely to respond to corticosteroid therapy, and thereby survive without LT [28]. Such an early stratification strategy could optimize care of patients with AIH who present with liver failure, and avoid unnecessary treatment with corticosteroids. In the current study, 5-year survival was no different in those with and without AIH, and hence we can speculate that even if corticosteroid usage was associated with increased risk of infections, it did not appear to impact the long-term survival of those with AIH and ALF.

Other factors that may be associated with poorer post-LT outcomes in those with AIH included a higher risk of acute cellular rejection (reported incidence between 75% and 83%) and possibly disease recurrence in the graft [2, 12, 29]. European studies have suggested that there is a progressive increase in AIH recurrence, reaching more than 60% after 5 years of follow-up [30, 31]. Because of the retrospective nature of our study, we did not have access to data on incidence of rejection and disease recurrence. Núñez-Martínez *et al.*, however, reported no differences between ALF and chronic AIH patients as regards acute and chronic rejection episodes, and biliary and arterial graft complications [24].

A review of the UNOS database from 1988–2004 found that AIH was more frequently found amongst blacks [32]. This is consistent with our

data, and in our study only 38% of those in the AIH group were Caucasians compared to 64% in the non-AIH group (p = 0.036). This over-representation of non-Caucasians in those with AIH may be related to more aggressive disease in this ethnic group. We in fact had previously reported that at presentation, black patients with AIH were more likely to have cirrhosis (56.7% vs. 37.5%, p = 0.061), liver failure (37.8% vs. 9.3%, p = 0.001), be referred for LT (51.3% vs. 23.4%, p = 0.004), and consequently have higher mortality (24.3% vs. 6.2%, p = 0.009) [28]. In this study, although not statistically significant perhaps because of the smaller sample size, the survival curves in those with AIH showed a lower (though statistically non significant) 5-year survival in AA compared to Caucasians (65% vs. 80%). Furthermore, another recent study found significantly lower 2-year graft survival (68% vs. 74%) and 2-year and 5-year patient survival (74% and 48% and 83% and 58%, respectively) in AA compared to White Americans [33]. In addition to a propensity towards more aggressive disease, another factor contributing to the lower post-LT survival in AA could be the higher incidence of chronic rejection in AA compared to White Americans (12% vs. 6%) [34]. We in fact observed that AAs with AIH were more likely to have had a prior LT (46% vs. 11%, p = 0.025), as has been reported by others [34]. Whether this is related to more severe disease at onset [28], racial differences in pharmacokinetics of immunosuppressants [34], pharmacogenomics or non-compliance remains uncertain. Since this was a retrospective study, data on corticosteroid usage and corticosteroid-related septic events, the incidence of graft loss due to acute/chronic rejection and disease recurrence were unavailable. These are some of the inherent limitations of the UNOS database.

An interesting observation in our study was the significantly better survival in women, especially those in the non-AIH group listed as UNOS status 1. This may have been related to greater BMI and serum creatinine at the time of listing in men, as well as receiving a graft from a heavier donor. These factors have been associated with poorer outcomes after LT for ALF in prior studies [22].

In conclusion, patients with and without AIH, listed as UNOS status 1, seem to have similar 5-year survival after LT, but in those with AIH, there was a lower (statistically non significant) survival in AA compared to Caucasians. Further prospective studies are needed to address this issue.

Conflict of interest

The authors declare no conflict of interest.

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