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ORIGINAL ARTICLE

Quality of Life Is Significantly Impaired in Long-Term Survivors of Acute Liver Failure and Particularly in Acetaminophen-Overdose Patients

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Functional outcomes for long-term survivors of acute liver failure (ALF) are not well characterized. The aim of this prospective study was to determine health-related quality of life in long-term adult ALF survivors. Acute Liver Failure Study Group registry participants completed the Centers for Disease Control and Prevention Health-Related Quality of Life 14 and Short Form 36 (SF-36) questionnaires at 1- and/or 2-year follow-up study visits. Responses were compared among ALF subgroups and to those for available general US population controls. Among the 282 adult ALF patients, 125 had undergone liver transplantation (LT), whereas 157, including 95 acetaminophen overdose (APAP) patients and 62 non-APAP patients, were spontaneous survivors (SSs). APAP SS patients reported significantly lower general health scores and more days of impaired mental and

Additional Supporting Information may be found in the online version of this article.

Abbreviations: ALF, acute liver failure; ALFSG, Acute Liver Failure Study Group; APAP, acetaminophen overdose; BP, Bodily Pain; CDC, Centers for Disease Control and Prevention; GH, General Health; HRQOL, health-related quality of life; HRQOL-4, Health-Related Quality of Life 4; HRQOL-14, Health-Related Quality of Life 14; LT, liver transplantation; MCS, Mental Composite Score; MH, Mental Health; PCS, Physical Composite Score; PF, Physical Functioning; QOL, quality of life; RE, Role–Emotional; RP, Role–Physical; SF, Social Functioning; SF-36, Short Form 36; SS, spontaneous survivor; VT, Vitality.

The members and institutions participating in the Acute Liver Failure Study Group are listed in the Supporting Information.

Amol S. Rangnekar has no financial conflicts of interest. Robert J. Fontana has served as a consultant to Bristol-Meyers Squibb, Vertex Pharmaceuticals, Tibotec, Merck, GlaxoSmithKline, and Medtronic in the past year.

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physical health, activity limitations due to poor health, pain, depression, and anxiety in comparison with the other groups ($P \leq 0.001$). There were no significant differences in coma grade or in the use of mechanical ventilation or intracranial pressure monitoring among the patient groups during their ALF hospitalization, but APAP SSs had significantly higher rates of psychiatric disease and substance abuse ($P < 0.001$). In comparison with the general US population, a greater proportion of the combined SS patients reported fair or poor health and ≥14 days of impaired physical/mental health and activity limitations due to poor health. In addition, a greater proportion of LT recipients reported ≥14 days of impaired physical/mental health. Similar results were observed with the SF-36 across the 3 ALF subgroups and in comparison with population controls. In conclusion, long-term adult survivors of ALF reported significantly lower quality of life scores than US population controls. Furthermore, APAP SS patients reported the lowest quality of life scores, possibly because of higher rates of premorbid psychiatric and substance abuse disorders. ***Liver Transpl 19:991-1000, 2013***. © **2013 AASLD.**

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Acute liver failure (ALF) is defined as the development of severe liver dysfunction with associated coagulopathy and encephalopathy in patients without a known underlying liver disease. Although only 2000 to 3000 patients develop ALF in the United States each year, these patients are critically ill and require significant supportive care measures such as mechanical ventilation, vasopressors, and renal replacement therapy to achieve short-term survival.[1] Despite the high initial mortality rate among patients with ALF, nearly 67% will ultimately survive, with 29% of these patients undergoing emergency liver transplantation (LT).[2] The pathogenesis of cerebral edema in ALF patients remains unclear but can lead to severe global impairment, seizures, and even uncal herniation and death in some patients.[3-5] Pilot studies have suggested that ALF patients with cerebral edema may have impaired cognition and survival during short-term follow-up.[3-5] Whether ALF patients develop any long-term sequelae after such a catastrophic illness has not been well studied. In addition, there have been no large multicenter studies evaluating the long-term health-related quality of life (HRQOL) and functional outcomes in adult ALF survivors.

The Acute Liver Failure Study Group (ALFSG) is a consortium of 13 academic medical centers that has been prospectively studying the causes and outcomes of adult ALF patients in the United States since 1998. Much of the initial data from the ALFSG has been focused on short-term (ie, 3-week) outcomes such as survival and the need for LT. However, a large proportion of these patients have now been followed up to 2 years from illness onset to determine their long-term clinical and functional outcomes. The aim of this study was to determine differences in HRQOL during long-term follow-up among spontaneous survivors (SSs) and LT recipients. In addition, we set out to determine whether the severity of illness at ALF presentation was associated with long-term HRQOL outcomes. A secondary aim was to compare HRQOL outcomes for long-term survivors of ALF to those for age- and sex-matched US population controls.

PATIENTS AND METHODS

US ALFSG

The ALFSG is a consortium of 13 US academic referral centers funded by the National Institute of Diabetes and Digestive and Kidney Diseases to conduct an ongoing, prospective, observational study of the etiology, clinical features, and outcomes of adult patients with ALF. Enrollment criteria include the presence of coagulopathy defined as an international normalized ratio ≥ 1.5 and any level of hepatic encephalopathy within 26 weeks of illness onset in a patient with no known underlying liver disease. The current study population consisted of consecutive adult ALF patients who were enrolled between January 1, 1998 and July 1, 2010 and completed a long-term follow-up visit.

Data Collection

Local institutional review board approval was obtained at all participating sites, and written informed consent was obtained from each patient's durable power of attorney or next of kin at the time of enrollment. Detailed patient demographics, medical histories, clinical features, and laboratory values were collected at study enrollment. Serial laboratory and clinical parameters were prospectively recorded for up to 3 weeks after enrollment. At the end of 3 weeks, short-term outcomes were classified as spontaneous survival, LT, or death. SSs and LT recipients were to be followed up at 12 and 24 months by the site investigator. At the long-term follow-up study visits, subjects were queried about their current medication use, medical diagnoses, and interval health history since their ALF admission. In particular, subjects were queried about active substance abuse involving alcohol, prescription drugs, and illicit drugs. In addition, information regarding patients with active mood disorders or other psychiatric illnesses who required treatment, intervention, or monitoring were also recorded. Before February 2010, data forms were sent to the data coordinating center for review and entry into a central database. From February 2010 onward, data were entered into a Web-based study database by the study sites. Periodic site visits were conducted by the ALFSG leadership to verify source documents. A certificate of confidentiality was obtained from the National Institutes of Mental Health for the entire study.

Short Form 36 (SF-36) Questionnaire

The SF-36 (version 1.0) is a widely used quality of life (QOL) instrument. The questionnaire comprises 8

scales: Physical Functioning (PF), Social Functioning (SF), Role–Physical (RP), Role–Emotional (RE), Mental Health (MH), Vitality (VT), Bodily Pain (BP), and General Health (GH). Responses to questions in each scale are combined to create a score ranging from 0 (low) to 100 (high). In addition, these individual scale scores can be combined to create separate physical and mental health summary scores. The SF-36 questionnaire was to be completed 12 and 24 months after the onset of ALF. Population norms were obtained from the SF-36 scoring manual, which includes 2474 individuals (with 47% between the ages of 18 and 44 years and 57% female). Population norms were obtained only for the physical and health composite scores.

Centers for Disease Control and Prevention (CDC) Health-Related Quality of Life 14 (HRQOL-14)

The CDC Health-Related Quality of Life 14 (HRQOL-14) is a 4-item Healthy Days Core Module designed to assess the overall health of the general US population. Since 1993, the CDC HRQOL-4 has been integrated into the state-based Behavioral Risk Factor Surveillance System. The CDC HRQOL-14 is a 14-item questionnaire that includes questions from the Health Days Core Module as well as the Activity Limitations Module and the Healthy Days Symptoms Module.[6,7] Each 1-day change in any of the Healthy Days measures is considered clinically meaningful. As such, this instrument allows direct comparisons of mean healthy days among different patient groups, and the results can be compared to those for the general US population. The CDC HRQOL-14 questionnaire was completed by patients at the same study follow-up visit used for the SF-36. Population norms were obtained from Behavioral Risk Factor Surveillance System Web site data collected between 2006 and 2010.[8] The normalized population consisted of 1,934,859 individuals, with 28% between the ages of 18 and 44 years and 62% female. Population norms were aggregated for 2006 to 2010 by sex or age group (18-24, 25-34, 35-44, 45-54, 55-64, 65-74, and $\geq$75 years).

Statistical Analysis

SAS 9.2 (SAS Institute, Inc., Cary, NC) was used to perform statistical analysis. Baseline variables were described with counts and percentages for categorical data or with means and standard deviations (or medians and interquartile ranges) for continuous normal (or skewed) data. For variables identified as clinically relevant, statistical tests were performed with chi-square, analysis of variance, or Kruskal-Wallis tests. Survey items were reported as counts for the CDC QOL questionnaire and as standardized means and standard deviations for the SF-36 questionnaire. Measures between groups were compared with a global analysis of variance test or chi-square test followed by all Tukey multiple-comparison, adjusted, pairwise comparisons when there was significance. For pairwise comparisons against population norms, the Student *t* test or Wald test of proportions was used.

RESULTS

Demographic Characteristics and Clinical Parameters

From January 1, 1998 to July 1, 2010, there were 1850 adult ALF patients enrolled in the ALFSG. Among the 1138 survivors 3 weeks after enrollment, 773 patients had at least 1 long-term follow-up study visit completed via a clinic visit, telephone interview, or chart review or had died beyond 21 days (Fig. 1). There were 282 patients who completed at least 1 QOL survey at month 12 or 24. Among these patients, 277 completed the HRQOL-14 (76 completed it at both visits), and 281 completed the SF-36 (79 completed it at both visits). The baseline characteristics of the 282 study patients, including the need for life support and initial illness severity, were generally similar to those of the 405 excluded patients. However, the included patients were significantly older and were more likely to have undergone LT, have a higher body mass index, and be non-Hispanic in comparison with the excluded patients (see Supporting Table 1).

In the study population, 125 patients had undergone LT, whereas 157 were SSs; the latter included 95 with an acetaminophen overdose (APAP) and 62 with non-APAP etiologies. The APAP SS group included 58 subjects with an unintentional overdose, 28 subjects with an intentional overdose, and 9 subjects with unknown intent. The etiology was missing for 2 SS patients, and they were excluded from stratified analyses. The most common underlying etiologies for ALF among the LT recipients included drug-induced liver injury (25%), indeterminate etiologies (21%), and autoimmune hepatitis (18%); among the non-APAP SSs, the most common etiologies of ALF included drug-induced liver injury (26%), hepatic ischemia (13%), and hepatitis A (13%). Thirteen of the LT recipients (10.7%) had developed ALF because of APAP. No significant differences were noted in patient demographics, including age, sex, race/ethnicity, employment status, years of education, and marital status (Table 1). The APAP SSs demonstrated significantly higher rates of substance abuse and underlying psychiatric disease in comparison with the LT recipients and non-APAP SSs (Table 1). However, the 58 unintentional APAP SSs were significantly less likely to have a psychiatric comorbidity than the intentional APAP patients (48% versus 82%, $P = 0.003$), but the proportions with a history of substance abuse were similar (47% versus 43%, $P = 0.75$).

The LT recipients had significantly higher baseline serum total bilirubin levels and international normalized ratios than the SSs. The APAP SSs exhibited

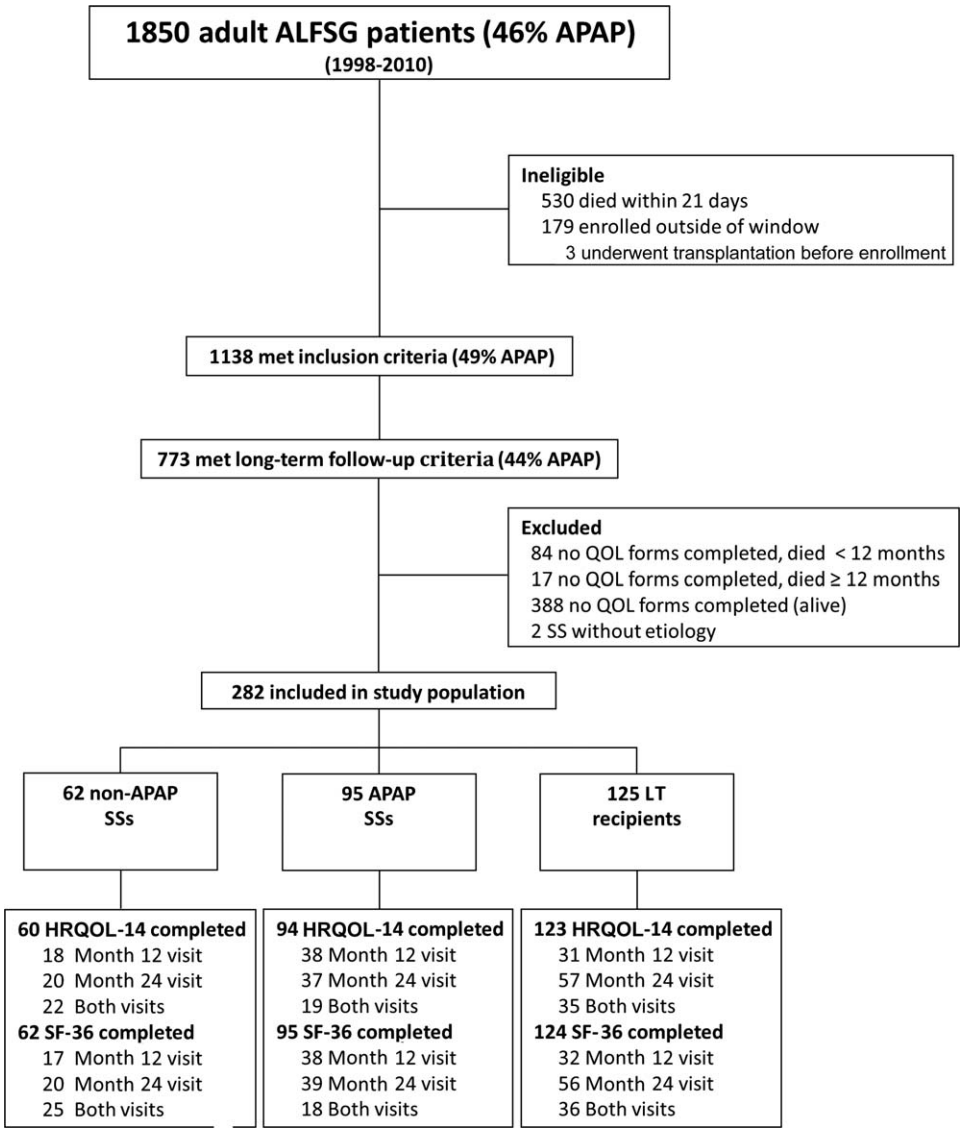

Figure 1. Flowchart for patients.

significantly higher aspartate aminotransferase and alanine aminotransferase levels in comparison with the LT and non-APAP SS groups. However, there were no significant differences in the baseline serum creatinine levels between the patient groups or in the rates of mechanical ventilation, renal replacement therapy, or intracranial pressure monitoring during their admission for ALF. The percentages of patients with a stage 3 or 4 coma grade were also similar among the LT recipients and the SS groups.

CDC HRQOL-14 Results

ALFSG Adult Cohort

The CDC HRQOL-14 form was completed by 277 ALF patients at a median of 708 days after enrollment (range = 127-3645 days). Within the Healthy Days Core Module, APAP SSs were more likely than non-APAP SSs and LT recipients to report fair or poor general health (34% versus 30% and 14%, $P = 0.001$; see Supporting Table 2). These patients also reported more days of impaired physical health (9.5 versus 5.6 and 6.2, $P = 0.012$), impaired mental health (11.2 versus 5.7 and 6.7, $P = 0.001$), and activity limitations due to poor physical or mental health (9.1 versus 4.9 and 4.5, $P < 0.001$).

Within the Healthy Days Symptoms Module, APAP SSs reported, in comparison with non-APAP SSs and LT recipients, more days of pain (10.8 versus 4.8 and 4.9, $P < 0.001$), depression (11.2 versus 5.3 and 5.7, $P < 0.001$), and anxiety (12.7 versus 4.8 and 6.7, $P < 0.001$). No significant differences were noted between the groups with respect to days of inadequate sleep or days of poor energy. Additionally, patients in these groups showed no significant differences in their responses to questions within the Activity Limitations Module. Among the 76 ALF patients who

TABLE 1. Baseline Characteristics of the Adult ALFSG Patient Population

	Patients (n)	Non-APAP SSs (n = 62)	APAP SSs (n = 95)	LT Recipients (n = 125)	*P* Value
Age (years)*	282	42.5 ± 14.2	38.2 ± 13.2	40.4 ± 13.0	0.52
Female (%)	282	71.0	74.7	64.8	0.27
Race (%)	282				0.17†
White		79.0	86.3	73.6	
Black		14.5	7.4	18.4	
Other		6.5	6.3	8.0	
Ethnicity: non-Hispanic (%)	282	96.8	97.9	92.0	0.13†
Full/part-time employment (%)	216	64.0	63.6	72.0	0.44
Education (years)*	181	13.8 ± 2.0	12.4 ± 2.2	13.3 ± 2.7	0.56
Marital status: married/significant other (%)	250	56.1	39.1	52.8	0.07
Etiology (%)	282				—‡
APAP		0	100	10.7	
Drug-induced liver injury		25.8	0	24.6	
Autoimmune hepatitis		11.3	0	18.0	
Hepatitis A		12.9	0	1.6	
Hepatitis B		6.5	0	13.1	
Ischemia		12.9	0	0	
Indeterminate		11.3	0	21.3	
Other§		19.4	0	10.7	
Medical history					
Body mass index (kg/m^2)*	231	28.8 ± 6.8	26.4 ± 7.0	28.8 ± 6.5	0.62
Psychiatric disease (%)	282	37.1	57.9	18.4	<0.001
Substance abuse (%)	282	9.7	48.4	11.2	<0.001
Intravenous drug user history (%)	278	3.3	6.4	2.4	0.32†
Hypertension (%)	282	24.2	13.7	13.6	0.13
Endocrine/diabetes (%)	282	30.7	11.6	14.4	0.005
Presenting features and clinical complications					
Time from jaundice to ALF (days)††	235	5.0 (2.0)	1.0 (2.0)	10.5 (17.3)	<0.001
International normalized ratio††	279	1.9 (1.7)	2.5 (1.7)	3.0 (1.8)	<0.001
Alanine aminotransferase (IU/L)††	279	1659 (3769)	3195 (3769)	711 (1776)	<0.001
Aspartate aminotransferase (IU/L)††	281	948 (6514)	2600 (6514)	622 (1511)	<0.001
Bilirubin (mg/dL)††	281	10.5 (3.2)	4.2 (3.2)	21.5 (15.7)	<0.001
Creatinine (mg/dL)††	282	1.3 (2.8)	1.4 (2.8)	1.1 (1.4)	0.30
Admission grade 3/4 encephalopathy (%)	280	36.1	40.0	34.7	0.71
Peak grade 3/4 encephalopathy (%)	282	43.6	47.4	55.2	0.27
Model for End-Stage Liver Disease score*	278	13.6 ± 4.7	11.4 ± 6.8	15.9 ± 5.1	0.001
Intubation (%)	281	30.7	41.1	30.7	0.22
Continuous venovenous hemofiltration or dialysis (%)	112	31.8	51.4	36.4	0.25
Intracranial pressure monitoring (%)	271	6.6	5.4	11.0	0.36†
Any infection (%)	282	38.7	40.0	37.6	0.94

*The data are presented as means and standard deviations.
†Fisher's exact test.
‡The *P* value is not provided because the definition of *strata* implies a different distribution.
§Other includes pregnancy, Budd-Chiari syndrome, hepatitis C, hepatitis E, mushrooms, Wilson's disease, and miscellaneous.
††The data are presented as medians and interquartile ranges; a nonparametric equivalent test (Kruskal-Wallis) was used.

completed the survey at both 12 and 24 months, there were no significant changes in the number of unhealthy days for the 41 SS patients during follow-up or for the 35 LT recipients during follow-up (data not shown).

ALFSG Versus Population Controls

In comparison with the general US population, a higher proportion of SSs (APAP and non-APAP SSs combined) reported fair or poor general health (32% versus 16%, $P < 0.001$; Figs. 2 and 3 and Supporting Table 4). This finding was confined primarily to women and patients who were 25 to 54 years old. Transplant recipients reported a general health status similar to that of the general US population. Higher percentages of both SSs and LT recipients reported >14 days per month of poor physical health in comparison with the general US population [28% versus 11% ($P < 0.001$) and 20% versus 11% ($P \leq 0.001$)], with

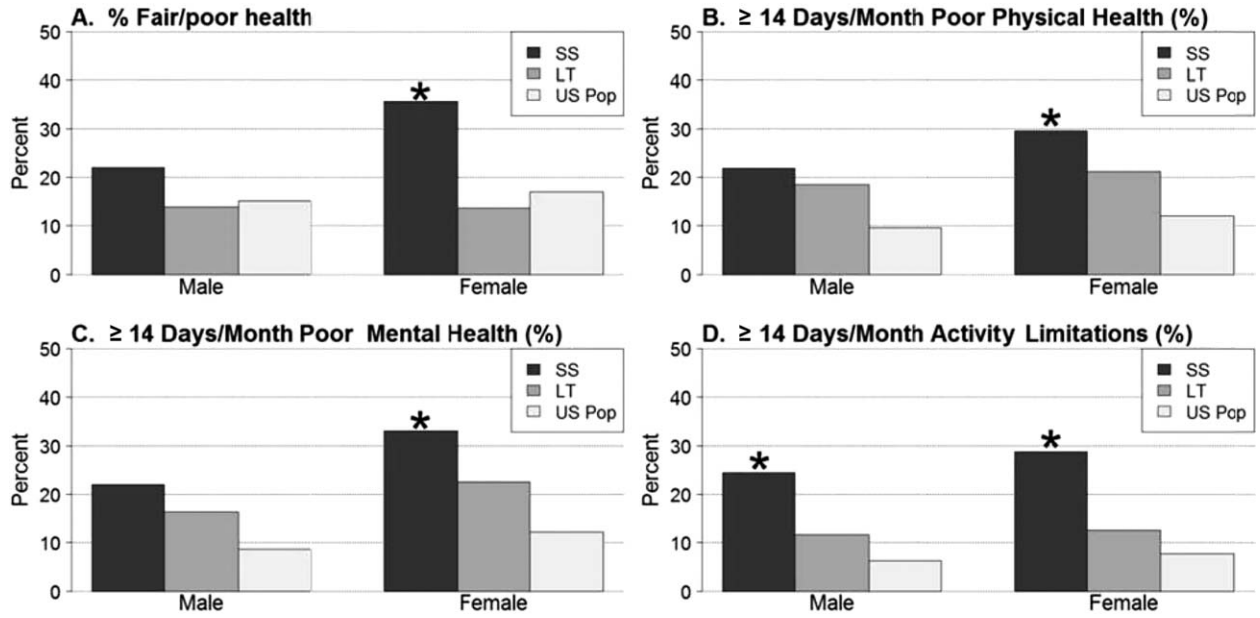

Figure 2. Results for CDC HRQOL Healthy Days Core Module questions from 156 SSs (41 males and 115 females) and 123 LT recipients (43 males and 80 females) stratified by sex. Overall, female SSs had significantly poorer HRQOL indices than the general population, whereas the scores for male SSs were significantly different only in days of activity limitations. The scores for male and female LT recipients were similar to those for the general US population. *$P \leq 0.001$ versus the general US population.

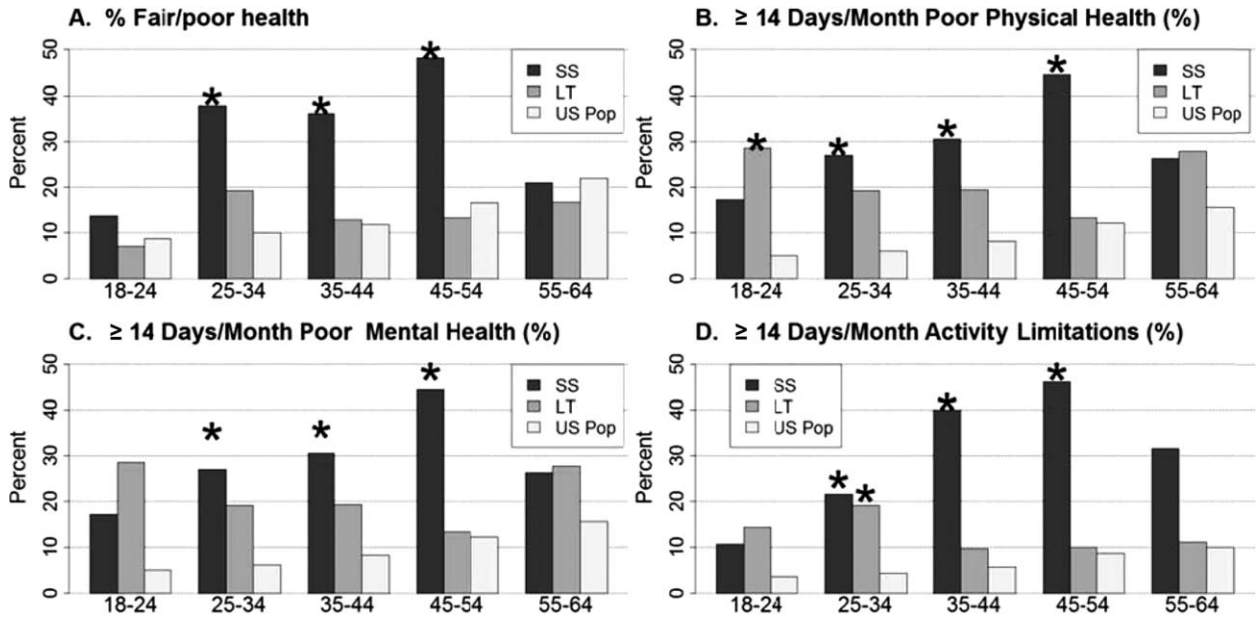

Figure 3. Results for CDC HRQOL Healthy Days Core Module questions from 148 SSs (n = 29 for 18-24 years, n = 37 for 25-34 years, n = 36 for 35-44 years, n = 27 for 45-54 years, and n = 19 for 55-64 years) and 119 LT recipients (n = 14 for 18-24 years, n = 26 for 25-34 years, n = 31 for 35-44 years, n = 30 for 45-54 years, and n = 18 for 55-64 years) stratified by age. The HRQOL scores were significantly lower for the SS patients in most age groupings, whereas the scores for the LT recipients were generally similar to those for age-matched population controls. *$P \leq 0.001$ in comparison with the general US population.

significant differences noted in SS patients of both sexes, female LT patients, SS patients under the age of 55 years, and LT patients between the ages of 18 and 44 years. Greater proportions of both SSs and LT recipients reported ≥14 days per month of poor mental health in comparison with the general US population [31% versus 10% ($P \leq 0.001$) and 20% versus 10% ($P < 0.001$)]. Among SSs, this finding was observed in both men and women between the ages of 25 and 54 years, but it was limited to women and patients between the ages of 18 and 24 years among transplant recipients. Both SSs and transplant

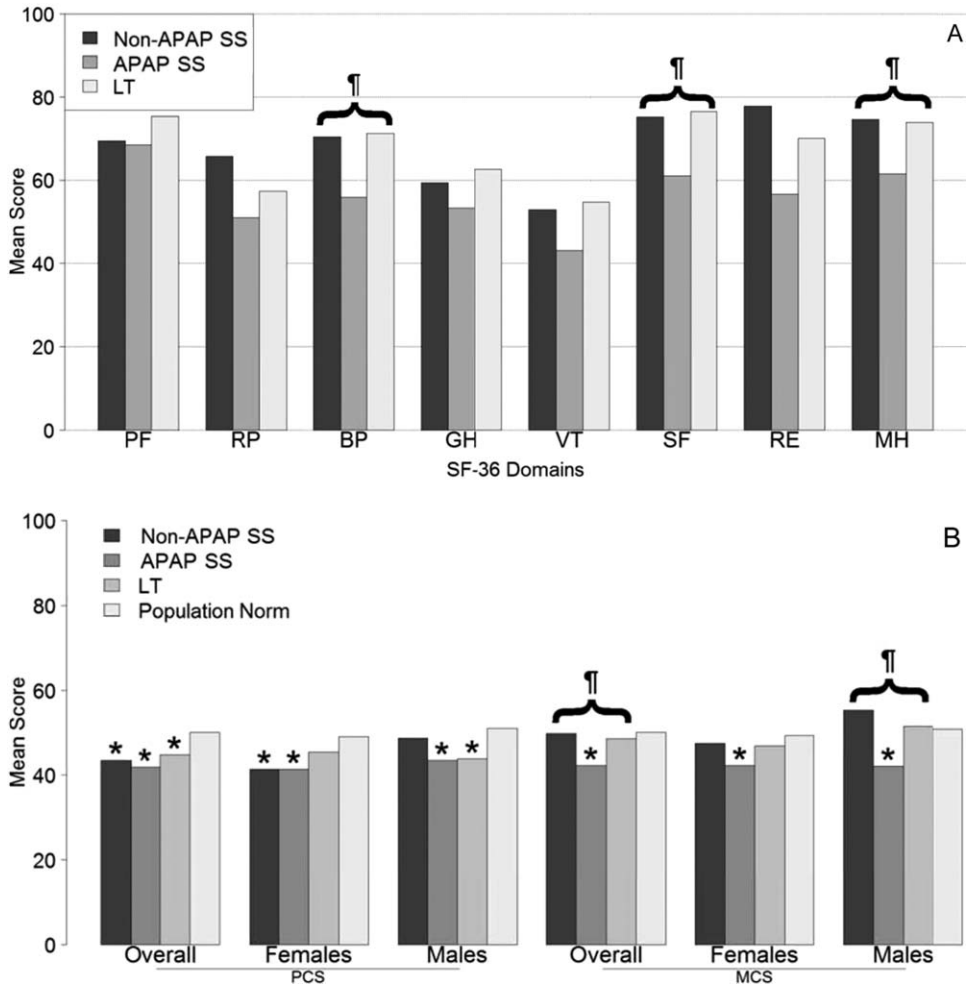

Figure 4. (A) SF-36 scores for 95 APAP SSs, 62 non-APAP SSs, and 124 LT recipients. The SF-36 domains are PF, RP, BP, GH, VT, SF, RE, and MH. (B) SF-36 component scores: PCS and MCS. *There was statistical significance at $p \leq 0.001$ in comparison with the general US population. ¶There was overall statistical significance at $p \leq 0.001$ for a comparison of non-APAP SSs, APAP SSs, and LT recipients.

recipients were more likely to report ≥14 days per month of activity limitations due to poor physical or mental health [28% versus 7% ($P \leq 0.001$) and 12% versus 7% ($P = 0.02$)]. Among SSs, this finding was confined to patients between the ages of 25 and 64 years; there were no differences in the LT population.

SF-36 Results

ALFSG Adult Cohort

The SF-36 questionnaire was completed by 281 ALF patients at a median of 706 days after enrollment (interquartile range = 448-859 days), and they included 95 APAP SSs, 62 non-APAP SSs, and 124 LT recipients. The demographic data were similar to those for the patient population completing the CDC HRQOL-14 questionnaire, and there were no significant differences between the 3 subgroups. In comparison with non-APAP SSs and LT recipients, APAP SSs reported lower scale scores for BP (56 versus 70 and 71, $P < 0.001$), GH (53 versus 59 and 63, $P = 0.024$), VT (43 versus 53 and 55, $P = 0.003$), SF (61 versus 75 and 76, $P < 0.001$), RE (57 versus 78 and 70, $P = 0.006$), and MH (62 versus 75 and 74, $P < 0.001$; Fig. 4A and Supporting Table 3). There were no significant differences in the scores between the 3 groups for the PF, RP, or physical health summary scales; however, the mental health summary scores were significantly lower for the APAP SS group versus the other patient groups (Fig. 4B). There were no significant differences in the mental or physical health summary scores over time for the 37 SSs or the 32 LT recipients with paired data (data not shown).

ALFSG Versus Population Controls

Sex-adjusted physical and mental health summary scale scores were significantly lower for the APAP SS group and for some of the other subgroups in comparison with US population norms (Fig. 4B).

DISCUSSION

This is the first large, prospective, multicenter study to assess QOL outcomes in long-term adult survivors

of ALF. The results of this study demonstrate that ALF SSs reported significantly more days of poor physical and mental health during long-term follow-up in comparison with the general US population. Among the ALF patient subgroups, APAP SSs were significantly more likely to report impairment than non-APAP SSs and LT recipients. Similar findings were noted with both the CDC HRQOL-14 and SF-36 questionnaires (Figs. 2–4).

Prior retrospective studies of HRQOL in ALF patients have focused primarily on patients who have undergone LT. During follow-up, ALF LT recipients have reported QOL scores similar to those of patients with cirrhosis undergoing LT.[9] In addition, no significant differences in QOL have been noted between APAP and non-APAP ALF transplant recipients.[10] However, ALF patients experience higher rates of depression, anxiety, and posttraumatic stress disorder after LT in comparison with LT recipients with cirrhosis, and this finding correlates with the higher rate of poor mental health among LT recipients observed in our study.[11] This observation may be due to the fact that ALF patients are previously healthy, generally young individuals who have suffered a sudden life-threatening illness, whereas most LT recipients with cirrhosis have been ill for several years and may have developed better coping skills. Furthermore, prior studies have shown that ALF LT recipients are less likely to resume employment than LT recipients with cirrhosis, despite their younger age.[9]

The SF-36 questionnaire has been used to assess HRQOL and functional outcomes in patients with other chronic diseases and in subjects who have experienced severe acute illness. In particular, the SF-36 has been administered to patients with various liver diseases, including chronic hepatitis C and primary biliary cirrhosis.[12-14] The SF-36 has also specifically been evaluated in LT recipients, and individual domain scores from the current study are similar to prior data reported 24 months after LT in patients with cirrhosis.[15] Although LT recipients with cirrhosis often report significantly improved QOL in the early posttransplant period in comparison with their pretransplant status, posttransplant QOL usually remains lower than that of age-matched population controls.[16,17] The durability of improved QOL after LT is also uncertain, with several studies suggesting that patients' psychological well-being may begin to erode as early as 1 year after LT.[18,19] In addition, episodes of rejection, osteoporosis, and recurrent disease are associated with further declines in QOL scores during long-term follow-up in LT recipients with cirrhosis.[20-22] However, the QOL scores of LT recipients remain better than those reported for patients with congestive heart failure.[23] Although the underlying etiology of cirrhosis affects HRQOL in the pretransplant period, no significant differences in QOL based on the etiology of cirrhosis have been noted 6 months after LT, but more recent studies suggest that patients with chronic HCV may have poorer HRQOL during long-term follow-up.[22,24]

Impaired QOL during long-term follow-up, as measured by the SF-36, has also been seen in previously healthy patients who have suffered from a severe acute illness such as acute renal failure, necrotizing pancreatitis, subarachnoid hemorrhaging, or acute respiratory distress syndrome.[25-28] A stay in the intensive care unit with associated vital organ dysfunction may be associated with reduced QOL, although this finding could also be attributable to preexisting disease.[29] Notably, we did not find a significant relationship between markers of disease severity (eg, the need for intubation or dialysis or the encephalopathy grade) and SF-36 or HRQOL-14 scores during long-term follow-up.

The CDC HRQOL-14 is a more recently developed instrument designed to assess the HRQOL of the general US population. The 4-item Healthy Days Core Module has been used to assess long-term QOL in patients with several chronic diseases, including osteoarthritis, rheumatoid arthritis, coronary artery disease, and diabetes mellitus.[30-32] Studies using the CDC HRQOL-4 have shown that survivors of severe, life-threatening diseases such as cerebrovascular accidents and breast cancer report more unhealthy days per month than the general US population. In addition, a study of older adults indicated that patients with lower CDC HRQOL-4 scores had higher rates of hospitalization and death during follow-up.[33] A key advantage of the CDC HRQOL-14 is its ability to quantify QOL impairment in terms of unhealthy days and further make direct comparisons with the general population. In our study, APAP SSs reported nearly twice as many days per month of impaired physical and mental health, activity limitation, pain, depression, and anxiety in comparison with the other groups (Fig. 2), and this indicated that they had the poorest functional status during follow-up.

Our findings of increased days of pain, depression, and anxiety for APAP SSs is consistent with prior data regarding the increased incidence of chronic pain and underlying psychiatric disease in this patient population.[34] As such, it is difficult to determine to what extent the long-term QOL impairment observed in this study is attributable to the ALF episode itself versus preexisting medical or psychiatric factors because baseline QOL scores were not available for these patients. Our findings also demonstrate that non-APAP SSs may experience substantial physical and mental health impairment during follow-up despite normalization of hepatic laboratory abnormalities. Among ALF LT recipients, impaired mental and physical QOL domains have been reported primarily for women and younger patients. As such, a significant subset of ALF survivors may benefit from targeted interventions, including counseling, psychiatric care, and physical therapy.

Because of the low incidence of ALF and the limited study population size, we were unable to identify presenting laboratory or clinical parameters that correlated with long-term QOL scores. However, there were no significant differences in the baseline coma grade

or need for intracranial pressure monitoring among APAP SSs, non-APAP SSs, and LT recipients. Although prior studies have suggested that adherence to follow-up and immunosuppression compliance may be lower among APAP LT recipients, we were not able to compare QOL outcomes for APAP LT recipients versus non-APAP LT recipients because of the small number of patients.[35]

There were 405 ALFSG patients who did not complete the HRQOL forms and were, therefore, excluded from this analysis (Supporting Table 1). Overall, the included patients were older, more likely to be non-Hispanic and have undergone LT, and less likely to have had APAP. Therefore, the QOL scores of the included ALFSG patients may intrinsically have been better in comparison with those who did not complete the surveys because the LT recipients had better QOL scores. The higher proportion of LT recipients captured in the current study group likely is related to the fact that LT recipients return more frequently for concurrent care than those who have recovered. In light of these limitations, confirmation of our findings in other large, independent cohorts of ALF patients is needed. Nonetheless, the current study represents the largest study of QOL outcomes in ALF patients completed to date. In addition, the prospective enrollment of patients from multiple sites and the administration of widely used and validated QOL instruments at predetermined study visits have helped to improve the generalizability and importance of our findings.

In conclusion, our study demonstrates that long-term adult survivors of ALF exhibit diminished QOL in comparison with age- and sex-matched population controls. Furthermore, APAP SSs reported decreased QOL across several domains in comparison with non-APAP SSs and LT recipients. These results were somewhat surprising because LT recipients are known to have more frequent and severe cerebral edema and require long-term use of potentially neurotoxic immunosuppressive agents.[36,37] We speculate that the observed differences in long-term HRQOL outcomes among the ALF patient groups may have been the result of other preexisting medical and psychiatric comorbidities rather than the patients' initial ALF illness and hospital course. Ongoing studies of neuropsychological function by our group and others will help us to better define the types and severity of potential cognitive impairments that many long-term ALF survivors report to their physicians.

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