Mortality Analysis of Acute Liver Failure in Uruguay

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ABSTRACT

Background. Acute liver failure (ALF) is a syndrome with high mortality.

Objective. Describe characteristics and outcomes of patients with ALF in Uruguay, and identify factors associated with mortality.

Methods. A retrospective analysis of 33 patients with ALF was performed between 2009 and 2017.

Results. The patients' median age was 43 years, and 64% were women. Average Model for End-Stage Liver Disease (MELD) score at admission was 33. The median referral time to the liver transplant (LT) center was 7 days. The most common etiologies were viral hepatitis (27%), indeterminate (21%), autoimmune (18%), and Wilson disease (15%). Overall mortality was 52% (71% of transplanted and 46% of nontransplanted patients). Dead patients had higher referral time (10 vs 4 days, $P = .008$), higher MELD scores at admission (37 vs 28) and highest achieved MELD scores (42 vs 29; $P < .001$), and higher encephalopathy grade III to IV (94% vs 25%, $P < .001$) than survivors. Patients without LT criteria (n = 4) had lower MELD score at admission (25 vs 34, $P = .001$) and highest achieved MELD score (27 vs 37, $P = .008$) compared with the others. Patients with LT criteria but contraindications (n = 7) had higher MELD scores at admission (38 vs 31, $P = .02$), highest achieved MELD scores (41 vs 34, $P = .03$), and longer referral time (10 days) than those without contraindications (3.5 days) or those without LT criteria (7.5 days, $P = .02$). Twenty-two patients were listed; LT was performed in 7, with a median time on waiting list of 6 days.

Conclusions. ALF in Uruguay has high mortality associated with delayed referral to the LT center, MELD score, and encephalopathy. The long waiting times to transplantation might influence mortality.

ACUTE LIVER FAILURE (ALF) is a syndrome characterized by the development of coagulopathy and encephalopathy in patients without previous liver disease [1]. The incidence is low: 2000 cases per year in the United States (estimated at 6.2 per million inhabitants per year) [2,3], 1 to 8 cases per million inhabitants per year in the United Kingdom [4,5], and 1.4 per million inhabitants per year in Spain [6].

ALF has a high mortality rate, although the prognosis has dramatically improved since the introduction of liver transplantation (LT) in the late 1980s along with advances in critical care. In the 1970s, the global mortality rate was 83% to 85% [7,8], and currently the rates are 38% in Europe [8] (42% in Spain [6]) and 33% in the United States [9].

There was a difference in the survival of patients who did not receive a transplant compared with those who did in Europe between 2004 and 2008 (48% and 86%, respectively)

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[8], as well as in the United States between 1998 and 2001 (43% and 84%, respectively) [9].

ALF accounted for 8% of indications for LT in Europe. Survival rates at 1, 3, and 5 years have improved over the past 20 years and are currently 79%, 75%, and 72%, respectively. However, survival is lower than that of elective transplant [10]. In the United States, ALF accounted for 3.3% of the indications for LT, and the survival rate at 1 year is above 80% [3,11].

The utilization of LT in ALF varies between different countries (18.2% in Europe [7], 29% in the United States [9], and 54% in Argentina [12]), transplant centers in the same country, and different etiologies [1]. In Europe the most common cause is drug-induced hepatotoxicity [8]; in United Kingdom, induced by Paracetamol [4], and in other areas such as Spain induced by non-Paracetamol drugs [6]. In the United States, Paracetamol hepatotoxicity is also the leading cause [9]. Viral hepatitis is the most frequent cause in South America [12], Asia [13,14], and Africa [15].

The following factors are recognized to contribute to a poor prognosis in ALF: advanced age, unfavorable etiologies (such as indeterminate, non-Paracetamol drug hepatotoxicity, and Wilson disease), subacute impairment, advanced encephalopathy, severe liver injury, extrahepatic failure (particularly renal failure), and late referral to a specialized unit [1,8,9,12,16,17].

The prognosis after listing for LT depends on the availability of a compatible donor organ, which depends on the number of available donors (donation rate and population) and the organ allocation system [18].

Mortality determinants after LT in ALF patients have been studied. Data from the European Liver Transplant Register identify the following determinants: recipient age >50 years and male sex, donor age >60 years, and incompatible ABO group [10]. The United Network for Organ Sharing cites the following determinants: recipient age >50 years, body mass index $\geq$ 30 kg/m^2, creatinine >2 mg/dL, and history of life support [19]. King College Hospital identifies 4 variables: age of the recipient >45 years, requirement of vasopressors, and suboptimal donor defined by the presence of 2 of the following: age >60 years, steatosis, nonidentical ABO group, and reduced graft [20]. Other factors that have been shown to be associated with post-transplant mortality are elevated Model for End-Stage Liver Disease (MELD) scores [21] and a prolonged waiting list time [22].

Uruguay has a population of 3,440,000 (in 2014) [23] and has a single National Liver Transplant Program, which operates in the Military Hospital, and is an adult-only program. There is only one national waiting list; ALF has the highest priority, categorized as an emergency.

Our objective is to describe the characteristics and outcomes of patients with ALF in Uruguay and identify the possible factors associated with mortality.

METHODS

Patients and Methods

A retrospective analysis of 33 charts of adult patients (older than 14 years) hospitalized with ALF at the National Liver Transplant Program between April 2009 and April 2017 was performed. Approval from the Institutional Research Board was obtained.

All enrolled patients met entry criteria for ALF: presence of coagulopathy (international normalized ratio $\geq$1.5) and any grade of hepatic encephalopathy (HE) within 26 weeks of the onset of symptoms, without underlying liver disease. Patients with Wilson disease, hepatitis B virus infection, or autoimmune hepatitis with cirrhosis were included if their disease had been recognized for <26 weeks [7].

Demographic, clinical, etiologic, laboratory, therapeutic, organizational data (referral time defined as the period between the first medical appointment and the contact with the LT program, waiting list time), and outcomes (mortality at discharge) were collected. The HE was graded from I to IV according to the West Heaven criteria [24].

ALF was classified as hyperacute, acute, or subacute impairment according to O'Grady classification [25]. Etiologic diagnoses were made based on accepted diagnostic criteria, including clinical history, laboratory values, imaging studies, and, in some cases, histologic characteristics. ALF was considered indeterminate when clinical, laboratory evaluation including toxicologic screening, serologic markers for viruses and antibodies, imaging studies, and histology (when available) were inconclusive.

The management of the patients followed published guidelines. Medical treatment measures included prevention of hypoglycemia, bacterial and fungal infections, upper gastrointestinal tract bleeding and renal failure, treatment of HE, correction of blood volume and electrolyte and acid-base disorders, administration of coagulation factors if active bleeding or performing invasive procedures, and specific etiologic treatment if was available. Patients with HE grade $\geq$ II were given *N*-acetylcysteine. Extracorporeal hepatic support (Prometheus, Fresenius Medical Care, Germany) was performed in 2 patients.

Candidacy for LT was determined according to the King's College criteria (KCC) proposed by O'Grady et al [16]. The MELD score [26] was determined.

The following contraindications for LT were defined: irreversible brain injury, unsolved active infection, multiple organ dysfunction with more than 3 organs compromised, extrahepatic cancer, and severe extrahepatic diseases that could not be solved with combined transplantation. In the patients who were transplanted, orthotopic LT of cadaveric donor was performed.

Statistical Analysis

Numerical variables are expressed as means and standard deviations in case of normal variables and median and interquartile range (IQR) in case of non-normal variables. The statistical significance of differences between groups was calculated using a Student *t* test for independent samples in the case of normal variables and a Wilcoxon rank test in case of non-normal variables. χ^2 Test with Yates correction was used for categorical variables, which are expressed in percentages. The statistical software used was R (version 3.4.0; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was tested with a 95% of confidence (exceptions were clarified on the text).

RESULTS

Thirty-three patients were included. The estimated incidence of ALF during the study period was 1.2 cases per million inhabitants per year (this may be underestimated due to patients not being referred to the LT program).