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Survival after severe liver failure requiring intensive care with and without liver transplantation: a 10-year retrospective study.

Degree Project in Medicine

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Abbreviations

ACLF	Acute-on-Chronic Liver Failure
ALF	Acute Liver Failure
CIVA	Central intensivvårdsavdelning /general intensive care unit
CLIF-SOFA	Chronic Liver Failure-Sequential Organ Failure Assessment
HE	Hepatic Encephalopathy
ICD-10	International statistical Classification of Diseases and related health problems 10th rev.
ICU	Intensive Care Unit
INR	International Normalized Ratio
KCC	King´s College Criteria
ltx	Liver transplantation
SOFA	Sequential Organ Failure Assessment
TIPS	Transjugular Intrahepatic Portosystemic Shunt

Abstract

Title: Survival after severe liver failure requiring intensive care with and without liver transplantation: a 10-year retrospective study.
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Introduction: Severe liver failure is treated in the intensive care unit (ICU) and carries a high mortality rate. Acute liver failure (ALF), without previous liver disease, and ´acute-on-chronic´ liver failure (ACLF), with previously known liver disease, are treated with aetiology-specific and supportive treatments. If the patient deteriorates in spite of medical treatment, transplantation may be lifesaving. Survival over time after intensive care is however not well studied in Sweden.

Aim: This study aims to evaluate survival after severe liver failure requiring intensive care with and without transplantation, and regarding liver failure syndrome and sex, at the general intensive care unit at Sahlgrenska University Hospital, Gothenburg.

Methods: A descriptive retrospective cohort study of patients diagnosed with liver failure treated in the general ICU ward 96 (CIVA) between January 1st, 2010 and September 7th, 2020 was implemented. Adults with ICD-10 diagnosis liver failure, K70-72, with mechanical ventilation and/or dialysis were included. Patients with previous or elective liver transplantation and metastatic cancer were excluded.

Results: 168 patients--60 ALF and 108 ACLF--were included. Overall survival is higher in patients transplanted while in the ICU compared to not transplanted ($p<0.001$). ALF patients have a higher survival rate than ACLF patients ($p=0.001$). Both transplanted and non-transplanted ACLF patients have a low one-year survival rate: 65% and 20%, respectively.

Conclusion: The high mortality of transplanted and non-transplanted ACLF patients point to the need to consider earlier examination of aetiology and evaluations for possible transplant in order to increase the overall survival of patients with severe liver failure.
Key words: survival, intensive care, liver failure, ALF, ACLF, transplantation

Introduction

The liver

The liver has many interdependent functions which become evident when it fails, disturbing multiple body systems simultaneously. The liver, to briefly summarize its main functions, filters and stores blood; forms coagulation factors and bile; stores fat-soluble vitamins together with iron and copper ions; and metabolizes proteins, fat, and carbohydrates together with hormones and foreign chemicals. Due to the metabolic characteristics of the liver, intake of substances such as alcohol and certain medications over longer periods, or intensively over shorter periods, can affect the liver acutely or diminish its function over time. (1, 2)

Liver failure – acute and acute-on-chronic

Liver failure occurs when homeostasis of the liver declines to a level at which symptoms occur. Liver failure can be classified either as acute or chronic, where chronic failure can become acute if the compensation mechanisms are insufficient to maintain basic functions (3).

Acute liver failure

Acute liver failure (ALF) is a syndrome in which a person without previously known liver disease develops symptoms of liver failure with severe acute liver injury. The liver injury causes a sharp increase in transaminases, impaired liver function with jaundice, coagulopathy (PK ≥1.5), and development of hepatic encephalopathy (HE). (4) According to O´Grady et al., the number of weeks between debut of jaundice and development of HE defines the prognosis and gives a hint as to aetiology. In “hyperacute” ALF, HE occurs within one week of jaundice and is usually caused by paracetamol or hepatitis A and E. In “acute” ALF this interval is

between one to four weeks and hepatitis B is a typical cause. In “subacute” it is five to 12 weeks and is usually caused by a non-paracetamol drug-induced liver failure. In “subacute” ALF, even a low grade of HE implies an extremely poor prognosis. (4, 5)
Acute presentations of Wilson´s disease, chronic autoimmune hepatitis, and Budd-Chiari syndrome, all are classified as ALF in the presence of HE if these chronic liver diseases have *not* been diagnosed previously (4).

The main causes of ALF vary geographically due to variation in living conditions and vaccinations available. (4, 6). Viral hepatitis is the predominant cause in developing countries such as Bangladesh and India (hepatitis E) while in Europe, ALF is primarily drug-induced, with paracetamol as the most prevalent cause in the United Kingdom, and USA (4). In Sweden, the most common aetiologies are paracetamol (42%) followed by other drugs, and viral hepatitis (7). Other aetiologies, include anything from mushroom intoxication and autoimmune hepatitis, to Budd-Chiari and congenital diseases like Wilson´s disease (8). Aetiology is unknown in 11% of the Swedish patients and is referred to as either cryptogenic liver failure or seronegative hepatitis (9). The prognosis depends on cause, age, and grade of consciousness (7). Transplantation-free two-year survival in non-paracetamol-induced ALF is 76% compared to 90% in paracetamol-induced (1). Within a cohort of Swedish ALF patients from 2007, 63% recovered spontaneously (after medical treatment without transplantation), with the highest survival rate in paracetamol-induced ALF (9) . Hepatitis B virus, autoimmune hepatitis, and drug-induced acute liver failure have a low transplantation-free survival, and in fulminant Wilson´s disease it is rare that a patient survives without transplantation (1).

Acute-on-chronic liver failure

Chronic liver failure, on the other hand, presupposes a pre-existing liver diagnosis (3). Alcoholic hepatitis is the exception and is always classified as acute-on-chronic liver failure even without cirrhosis given the excessive alcohol consumption that has occurred before contracting the diagnosis, even in the absence of previous known liver diagnosis (3).

A compensated disease can show symptoms such as tiredness and itchy skin, an overall quite disease. When decompensating, these diseases come with secondary effects such as ascites, oesophagus varices, jaundice and more (3).

There are no tests that predict the development of acute decompensation (AD), only tests for the severity of decompensation and corresponding short-term mortality prognosis are available (10), described later on.

Compensated chronic liver disease can rapidly progress to acute-on-chronic liver failure (ACLF) due to a precipitating cause such as ascites, gastrointestinal haemorrhage, bacterial peritonitis, hepatorenal syndrome and hepatic encephalopathy (3). In about a third of patients, further complications such as kidney failure and/or failure in other extra hepatic organs occur (2, 3). Not only organ failure itself but also *which* organ is failing, are important variables in predicting the short-term prognosis, which is reflected in the classification of decompensation with and without acute-on-chronic liver failure into four main groups: acute decompensation without ACLF and ACLF 1-3 depending on number of failing organs (2, 3), referred to as the ACLF grading system, or simply “ACLF-grading”, Table 1 (2).

Kidney failure is the most prevalent organ failure in ACLF 1 in contrast to ACLF 2, when liver failure dominates, and ACLF 3, when the prevalence of all organ failures is high or

moderately high. Short-time survival is related to the ACLF stage and diminishes at each additional level. The main cause of death in non-transplanted ACLF patients is multiple organ failure without hypovolemic or septic shock, followed by septic and hypovolemic shock. Twenty-eight day mortality in ACLF vary in relation to ACLF-grade, with the chance of survival decreasing with the number of organ failures (Table 1). (2)

Overall one-year survival without liver transplantation in ACLF patients is 28% (11).

Table 1 - Grading of ACLF according to type and number of organ failures and 28- and 90-day mortality

ACLF-grade	Organ	28-/90-day mortality
No ACLF	No organ failure	4.7% / 14.0%
	Single "non-kidney" organ failure and s-creatinine <133 mmol/L with no HE	
	Single cerebral failure with s-creatinine <133 mmol/L	
ACLF 1	Patients with single kidney failure	22.1% / 40.7%
	Single "non-kidney" failure w. s-creatinine 133-177 mmol/L and/or moderat HE	
	Single cerebral failure with s-creatinine 133-177 mmol/L	
ACLF 2	2 organ failures	32.0% / 52.3%
ACLF 3	3 or more organ failures	76.7% / 79.1%

ACLF, acute-on-chronic liver failure; s-, serum; HE, hepatic encephalopaty, w., with

Prognostic scores

Several prognostic scores are used to identify patients with poor prognosis in determining possible transplantation candidates. The goal is to distinguish patients who will recover from medical treatment alone, from those who will die without transplantation. Transplantation criteria depend on the aetiology of ALF and severity of ACLF. Different scores are used in different parts of the world including different sets of factors, and all have pros and cons. Patients with ALF are evaluated using guiding prognostic models. O´Grady's model, King´s Collage Criteria (KCC) (12), is widely used in Europe as prognosis guideline (4), Sweden included (13, 14). The criteria differ depending on the aetiology as seen in Table 2, and KCC gives an early prediction of prognosis where medical treatment might not be enough (12). KCC is validated (7) and has a fair specificity but lower sensitivity (4, 7)

Table 2 - King´s College Criteria. Used to identify patients with poor prognosis without liver transplantation in acute liver failure patients, divided in aetiology.

Paracetamol-induced ALF	**Non-paracetamol-induced ALF**
• Arterial pH <7.30	• INR >6.5 (PT >100 sec)
Or all of the following:	*Or* any ≥3 of the following:
• INR >6.5 (PT >100sec)	• Age <10 years or >40 years
• S-creatinine >300 µmol/L	• Aetiology: non-A, non-B, (non-C) hepatitis, idiosyncratic drug-induced hepatitis
• HE grade 3-4	• Duration of jaundice before onset of encephalopathy >7days
	• INR >3.5 (PT >50sec)
	• Bilirubin >300 µmol/L

ALF, acute liver failure; INR, International Normalized Ratio; PT, prothrombin time; HE, hepatic encephalopathy; sec, seconds; s-, serum

Scientific methods to evaluate if an ACLF patient will benefit from transplantation is lacking (3). Several prognostic tests are used as a base in prioritizing and inactivation on the transplant waiting list. Listed below are those mentioned in the Swedish National Liver Transplantation guideline (14) and the ICU liver version of SOFA (Sequential Organ Failure Assessment).

The Model for End-stage Liver Disease (MELD)[1] predicts the three-month survival in chronic liver failure irrespective of cirrhosis aetiology. MELD scoring has further developed with an updated formula and, since 2016, there is also a MELD Sodium (MELD-Na). (15)

Child-Turcotte-Pugh Score (CPT), Child-Pugh in short, is used to forecast prognosis in liver cirrhosis and derives the patient´s score from clinical features and grades into three classes, A-C, A being the least severe with the highest five-year survival rate of 80% (16).

The Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) is a further development of the SOFA score and was created in association with the CANONIC study focusing on symptoms of liver failure. CLIF-SOFA use hepatic encephalopathy (HE) instead

[1] The formulas are as follows:
MELD = 11.2 x ln(INR) + 3.78 x ln(bilirubin, *in mg/dL*) + 9.57 x ln(creatinine, *in mg/dL*) + 6.43
MELD-Na = MELD - Na – [0.025 x MELD x (140-Na)] + 140

of the Glasgow Coma Scale (GCS) when measuring cerebral function, and International Normalized Ratio (INR) instead of platelets for measuring coagulation, but excludes the use or non-use of mechanical ventilation as a criterion. (2)

Treatment

Liver disease causes 800-900 deaths per year in Sweden, the majority of which are alcohol-related, followed by liver fibrosis and liver cirrhosis (17). Acute liver failure and ACLF are very severe conditions that usually requires intensive care (3, 4). Supporting intensive care including, but not limited, to antibiotics, vasoactive drugs, ventilatory support, and renal replacement therapy aims to counteract the life-threatening symptoms of liver failure such as severe encephalopathy, cerebral oedema, multiorgan failure, and sepsis (4, 18).

The usual management of patients with severe acute liver failure is ICU care, preferably in a hospital with a transplant centre when transplantation is considered a possible treatment. Careful monitoring of patients is of utmost importance to be able to treat complications in a timely manner. (4) The medical treatment involves identifying and then eliminating the triggering agents (e.g., N-acetylcysteine in case of paracetamol intoxication and non-paracetamol-induced liver injury; antibiotics and antifungal drugs in case of sepsis; and dialysis in regard to certain poisonings) (4, 18). Liver support systems and plasma exchange are two alternative treatments, used either to promote recovery or as a bride for liver transplantation, but they have not advanced into standard treatments (4).
If the liver failure cannot be reversed medically, the remaining lifesaving treatment is liver transplantation (3, 4).

Transplantation

In Sweden, liver transplantation is performed in two centres, Karolinska University Hospital, Huddinge and Sahlgrenska University Hospital, Gothenburg. Scandiatransplant is an established collaboration between the Nordic countries, including Estonia, within which approximately 2000 patients receive a liver transplant every year. This organisation covers a 29-million population with organ exchange and resource allocation. (19)

The transplant centre at the Sahlgrenska University Hospital in Gothenburg was established in 1985 and is the largest in Scandinavia with 80-100 transplantations a year. Patients of all ages receive transplants of livers or partial livers from either living or deceased donors with the use of different techniques (20).

Evaluation for liver transplantation

As soon as severe liver failure is diagnosed, it is important to establish aetiology as early as possible and determine whether the patient will survive with medical therapy alone, or will require transplantation. The medical dilemma is that a possible listing for transplant will not guarantee that a suitable organ will be at hand while the patient is still well enough to handle an operation. There is also a chance that the course can take a positive or negative turn without the transplant, resulting in removal from the list.

The transplantation investigation contains a detailed medical history with the patients´ psycho-social situation; results from extensive blood tests; results from examinations and consultants such as psychiatrist; CT and MR imagery of stomach; and when needed, CT of the chest (21). Poor prognostic factors such as HE need to be identified (22).

Transport to a transplant centre by contact with a hepatologist at an early stage is of vital importance (7). Close monitoring of the patient's clinical state and development, often in the ICU, enables early detection of progression and need for further interventions (6).
If a patient in the ICU is deemed in need of a transplant, a multidisciplinary conference is convened. Blood tests and evaluations are done on a daily, or even hourly basis, to make sure the patient on the list is still in need of a new liver and fit enough to undergo the operation. Information is shared with the patient in the ICU at the discretion of medical personnel depending on the patient's cognitive function. Evaluation and decision to transplant will result in listing for a transplant. (23)

Prognosis after transplantation

One-year survival after elective liver transplant for adults is about 90% and five-year survival around 70%, including all reasons for liver transplantation, comparable with survival after kidney transplantation (23). Acute liver failure patients had an up to 80% overall mortality rate before the widespread availability of liver transplantation. In the last decade, studies from the UK and USA show a decrease in mortality rate to 33%, due largely to an increased transplantation rate in ALF patients. (1) After liver transplantation due to ALF, the one-year survival is around 80% in Europe and five-year survival around 70%, with most deaths occurring within the first three months (6). In ACLF patients, survival is highly related to ACLF-grade with an overall one-year survival of 85% (11).

Research regarding sex and outcome can not be found when searching current research data, therefore no one knows if there is a difference in incidence as has been seen in other diseases.

Knowledge gaps

There are fewer studies of medically treated ALF and ACLF patents. To the authors knowledge, published peer-reviewed studies of survival over time after liver failure requiring intensive care — with or without liver transplantation — did not include Swedish data.

The intention of this study is to evaluate the quality of the highly specialized intensive care at the general ICU (CIVA) at the liver transplantation centre at Sahlgrenska University Hospital, Gothenburg. This study will exploit previously unexplored data from the general ICU at Sahlgrenska University Hospital to evaluate survival after ICU stay in relation to transplantation, type of liver failure and sex.

Aim

This study aims to evaluate survival after severe liver failure requiring intensive care with and without transplantation, and regarding liver failure syndrome and sex, at the general intensive care unit at Sahlgrenska University Hospital, Gothenburg.

Research questions

- The study aims to investigate survival of patients with severe liver failure requiring intensive care, with and without acute liver transplantation in order to establish:
- What demography and characteristics do patients with severe liver failure who requires ICU care have?
- What survival rates does patient have after ICU treatment with respect to type of liver failure syndrome (ALF/ACLF) and sex? Further, does it differ weather the patients have received an acute liver transplant or not?
- How many patients survive ICU care and get a transplant later in time, as well as how many patients need a re-transplantation after transplantation in the ICU?

Material and Methods

Study design and patients

A descriptive retrospective cohort study comprising patients diagnosed with liver failure and treated in the general ICU ward 96 (Central Intensivvårdsavdelning) at the Sahlgrenska University Hospital in Gothenburg between January 1st, 2010 and September 7th, 2020.

The outcome measures were demographic profile of the patient group; survival at discharge from the ICU; and survival from date of admission to the ICU to 30 days, and 1 year. Furthermore, the number of acute liver transplantations during ICU care; and the number of transplantations and re-transplantations after the ICU were examined.
Finally, an evaluation of survival comparing type of liver failure (ALF or ACLF), sex, and acute transplantation or no transplantation was performed.

Inclusion criteria

Adults 18 years or older admitted to the ICU during the study period with liver failure diagnosis K70-72[2] (with sub-groups) according to ICD-10[3], and submitted to mechanical ventilation and/or dialysis were included.

Exclusion criteria

Patients with previous liver transplantation or admission to the ICU after elective liver transplantation were excluded. Cases of malignancy, except non-metastasized primary liver cancer; effectively treated cancer with a low long-term mortality; or a history of previous healed cancer, were also excluded.

[2] K70 Alcoholic liver disease, K71 Toxic liver disease or K72 Hepatic failure, not elsewhere classified
[3] The International statistical classification of diseases and related health problems 10th rev. (ICD-10)

Data collection

Local databases IVArätt (year 2010-2016) and PasIva (year 2017-2020) were screened in accordance to the inclusion and exclusion criteria. Patients admitted to ICU from theatre were excluded if registered with NOMESCO Classification of Surgical Procedures operation code "JJC Transplantation of liver and related operations"[4]. The IVArätt and PasIva data contained information on need of medical ventilation and dialysis. Mechanical ventilator as an inclusion criterion was defined as both invasive and non-invasive (NIV) ventilation, while dialysis included continuous and intermittent haemodialysis. Demographic comorbidity information enabled exclusion of AIDS and malignancy. Individual medical records in Melior were reviewed for other malignancies and accuracy of the diagnosis registered in the databases. Clinical information was collected from medical records in Melior.

An attempt to calculate ACLF, CLIF-SOFA and CPT scores was performed. However, the hepatic encephalopathy grading was inconsistent, often mentioned in the context of "the patient is encephalopathic" or "the patient is confused", without an exact grading. Furthermore, the Child-Pugh requires a subjective grading of the amount of ascites, only found in very few of the medical records.

Survival status and length of stay was missing from patients' resident outside the region of Västra Götaland Region (VGR). Information about ICU stay for the Swedish patients was supplemented with data from the Nationell Patient Översikt (NPÖ) for patients alive at the time of data collection, as NPÖ is not available after death. Some patients had their one-year

[4] JJC00 allogenic transplantation of liver; JJC60 Total excision of transplanted liver; or JJC96 Other transplantation of liver or related operation

follow up at Sahlgrenska while one was lost to follow-up upon return to their local hospital. IVArätt and PasIva occasionally contained data about date of death.

Data on previous liver transplantation of patients in Gothenburg (1985-2020), information about enrolment on the transplant waiting list; time on the list; and removal from the list was obtained with the help of the transplantation coordinators from Scandiatransplant's closed pages. The Scandiatransplant data was only screened for ID of the patients in this study.

Statistical methods

The predefined subgroups used in the analysis were category of liver failure (ALF/ACLF), and sex (male/female), with and without transplantation.

Transplantation was defined as transplantation performed while the patient was still in intensive care. The patients who were transplanted after ICU discharge (9 patients) were allocated to the "no transplantation" group in the statistical analysis.
The Kaplan-Meier model show survival over time, Log-Rank for statistical calculations.

Descriptive statistics used mean and standard deviation, or median and range depending on group size and distribution. For continuous variables Student's t-test (normally distributed data) or Mann-Whitney U-test (non-normally distributed data) was used.
Chi-square test or Fischer's exact test was used in analyses of categorical data depending on subgroup size.
The results are presented as number and percentage of total, mean with standard deviation, or as median with range. Numerical and percentage results are presented rounding to the nearest whole number (with zero-decimal level). All results were defined as statistically significant at

a level of $p < 0.05$. Computations were performed using Excel (v16.38, Microsoft Corp, Redmond, WA, USA) and SPSS (v26, IBM Statistics, IBM 166 Corp, Armonk, NY, USA).

Ethical considerations

Access to the databases and the medical records was granted by the Head of the Department of Anesthesia and Intensive care, Division 5, Sahlgrenska University Hospital. Due to the retrospective nature of the study and the long time period covered by the patient sample, individual consent was deemed unnecessary in relation to the breach of integrity of the individual patient. Intensive care patients at the general ICU at Sahlgrenska University Hospital are informed on a regular basis that their data can be used to evaluate the quality of care. The intrusion into patient privacy was assessed as limited and only the responsible researchers had access to the data.

The results are presented on group level without individual identifying information.

Results

Patient demographics and characteristics

A total of 689 patients with liver failure as a diagnosis were found in databases IVArätt and PasIva during the period January 1st, 2010 and September 7th, 2020. Screening and enrolment of patients in relation to set criteria, as described in method, excluded 438, and the review of each remaining individual record excluded another 83 patients. A total of 168 patients with severe liver failure treated in the ICU with mechanical ventilation and/or dialysis were included in the study.

As shown in Table 3, the sample had an even sex distribution, with a total of 60 ALF and 108 ACLF cases. When comparing the two subgroups of liver failure, ALF and ACLF, comorbidities such as hypertension, other cardiovascular, respiratory, gastrointestinal diseases, and viral hepatitis were equally distributed. The ALF patients were younger and physically healthier with fewer cases of diabetes, metabolic, and renal disease, but with a

Table 3 - Patient characteristics and demography at admission to the general ICU

Characteristic	All patients (n=168)	ALF (n=60)	ACLF (n=108)	p-value[O]	Male (n=84)	Female (n=84)	p-value[¨]
Age, mean (±SD)	53 (±13)	46 (±15)	57 (±10)	< 0.001	53 (±13)	53 (±14)	0.936
Male	84 (50)	26 (31)	58 (69)	0.001			
On transpl. wl. at ICU	83 (49)	42 (70)	41 (40)	< 0.001	43 (51)	46 (55)	0.757
Alcohol misuse	69 (41)	15 (25)	54 (50)	0.002	39 (46)	30 (36)	0.209
Mixed drug misuse	11 (7)	6 (10)	5 (5)	0.178	5 (6)	6 (7)	1.0
Comorbidity, n (%)							
Viral hepatitis	18 (11)	3 (5)	15 (14)	0.074	14 (17)	4 (5)	0.023
Hypertension	29 (17)	7 (12)	22 (20)	0.153	15 (18)	14 (17)	1.0
Diabetes mellitus	25 (15)	2 (3)	23 (21)	0.002	12 (14)	13 (16)	1.0
Other cardiovascular	25 (15)	8 (13)	17 (16)	0.674	17 (20)	8 (10)	0.081
Other metabolic	22 (13)	3 (5)	19 (18)	0.02	13 (16)	9 (11)	0.493
Respiratory	19 (11)	5 (8)	14 (13)	0.364	10 (12)	9 (11)	1.0
Renal	14 (8)	1 (2)	13 (12)	0.02	7 (8)	7 (8)	1.0
GI-tract	19 (11)	3 (5)	16 (15)	0.054	11 (13)	8 (10)	0.627
Neurological	10 (6)	3 (5)	7 (7)	1.0	5 (6)	5 (6.0)	1.0
Malignant	7 (4)	3 (5)	4 (4)	0.701	2 (2)	5 (6.0)	0.443
Psychiatric	34 (20)	21 (35)	13 (12)	< 0.001	11 (13)	23 (27)	0.034
Other	33 (20)	7 (12)	26 (24)	0.052	9 (11)	24 (29)	0.006
Abdominal surgery	24 (14)	2 (3)	22 (20)	0.002	11 (13)	13 (16)	0.826

NOTE. All data is expressed as means in years (±SD) or number of patients, n, and percentage (%).
[O]p-value for comparison of ALF and ACLF; [¨]p-value for comparison of male and female
Discription of the content in all comorbidity categories in Appendix, Supplement 1.
ICU, intensivie care unit; ALF, acute liver failure; ACLF, acute-on-chronic liver failure; transpl., transplantation; wl, waiting list; GI, gastro intestinal

disproportionately higher number of reported psychiatric diseases. Furthermore, female sex was more prevalent in ALF together with a higher likelihood of being on the transplantation list at ICU stay. Previous abdominal surgery was significantly more prevalent in the ACLF group.

Overuse of alcohol and drugs (previous and/or current), was seen in both ALF and ACLF patients, with a significantly higher alcohol overuse in the ACLF group. Due to the high extent to which patients withhold the truth about alcohol consumption, and absence of B-Peth in the study group, the exact amount of active alcohol overuse at admission was not documented and further investigation would be needed to assess its influence on the results. In addition, there was an unknown alcohol intake in the ´mixed drug use´ group.
Viral hepatitis was more widespread in men, while psychiatric and other diagnosis were more common in women.

Among the women, 40% had ALF and 60% had ACLF, compared to 31% and 69%, respectively, among men (p 0.20). There was no significant difference in transplantation listing between the sexes (p=0.757). Out of the 62 liver transplantations during ICU stay, 38 (61%) were women, a significant majority (p<0.037).
Removal from the transplantation list was more prevalent in the male group, 15/39 (38%) than the female group 5/44 (9%), (p=0.078).

Both mechanical ventilation and dialysis were utilized in majority of all patients, Table 4.

Table 4 - mechanical ventilation and dialysis

	All n=168	ALF n=60	ACLF n=108	Male n=84	Female n=84
Mechanical ventilation	157 (93)	56 (60)	101 (94)	81 (96)	77 (92)
Dialysis	103 (61)	45 (75)	58 (54)	50 (60)	53 (63)

ALF, acute liver failure; ACLF, acute on chronic liver failure

Aetiology of ALF

As shown in Figure 1, there is a great variety of aetiologies to acute liver failure. The three most prevalent in this study were paracetamol intoxication, dose-independent drug-induced, and unknown causes.

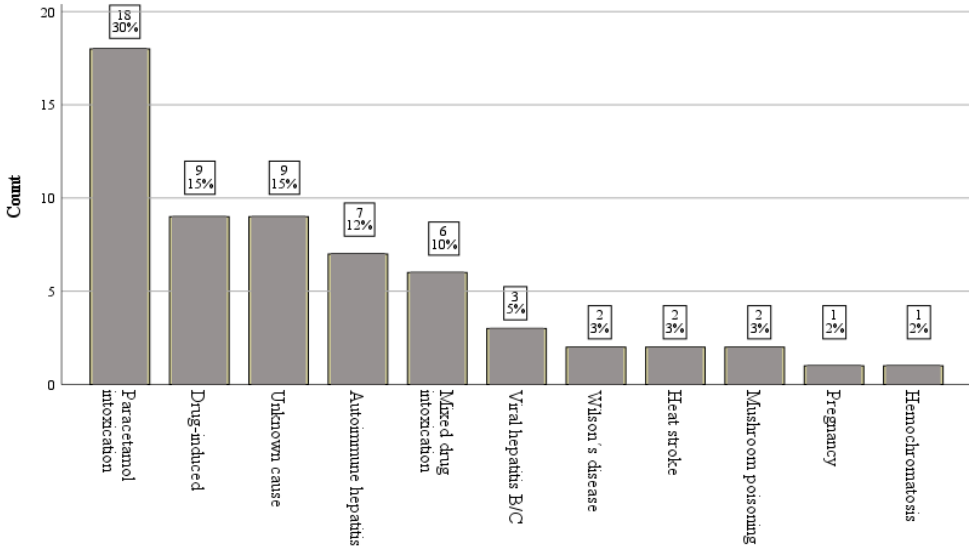


Figure 1 – Aetiology of severe acute liver failure (ALF) in 60 patients in the general ICU at Sahlgrenska University Hospital during a 10-year period (2010-2020). The medications believed to cause the medicine-induced liver injury were disulfiram, heracillin, nitrofurantoin, diklofenak, ibuprofen, or NSAID uns. Mixed drug intoxication includes alcohol, paracetamol, oxascand, fluoxetin, zopiklon, postafen, NSAID uns., and unknown substances.

Out of the 18 paracetamol intoxications and the six mixed drug intoxications, 16/24 (89%) patients had a previous history of psychiatric disease and 9/24 (38%) intoxications had an acknowledged suicidal purpose. Patients with drug-induced ALF had used prescribed doses of pharmacological treatments, two of whom used Antabus (disulfiram).

Precipitation events of ACLF

Precipitating events for ACLF in this study were dominated by bacterial infection, gastrointestinal bleeding, and alcohol, as shown in Table 5. When more than one precipitating event was identified, they were divided accordingly to the existing categories and ´one reason´ before lastly being classified as ´several reasons´. Patients with chronic diseases that

have a natural decrease in function over time were coded as ´unknown cause´ where no obvious cause was found.

Table 5 – Categories of precipitation events of acute-on-chronic liver failure
The same patient can have more than one precipation event (data is overlapping).

Bacterial infection, n (%)	34 (31)
GI-bleeding, n (%)	22 (20)
Alcohol, n (%)	21 (19)
Other reason, n (%)	16 (15)
Unknown cause, n (%)	18 (17)
Several reasons, n (%)	3 (3)

NOTE Data is presented in numbers and percentage. Other reasons include porta venous thrombosis, Budd-Chiari syndrome, heart failure, herniated umbilical hernia, hyperkalemia, hydrothorax, dehydration due to diuretics, fungemia, DILI and fracture w. operation. Several reasons include obstipation, theralen, TIPS, dehydration, hypokalemia, hyperglycaemia, herniation of umbilical hernia. GI, gastrointestinal; DILI, Drug induced liver injury; PBC, primary biliary cirrhosis; TIPS, Transjugular Intrahepatic Portosystemic Shunt

Figure 2 shows the diagnosis associated with ACLF. Cirrhosis caused by alcohol (31%) is the most prevalent chronic liver diagnosis followed by “unknown cause”, and alcoholic hepatitis. Thereafter follows the non alcohol-related causes. “Unknown cause” includes both cryptogenic liver disease and disease not yet diagnosed at the time of the data collection.

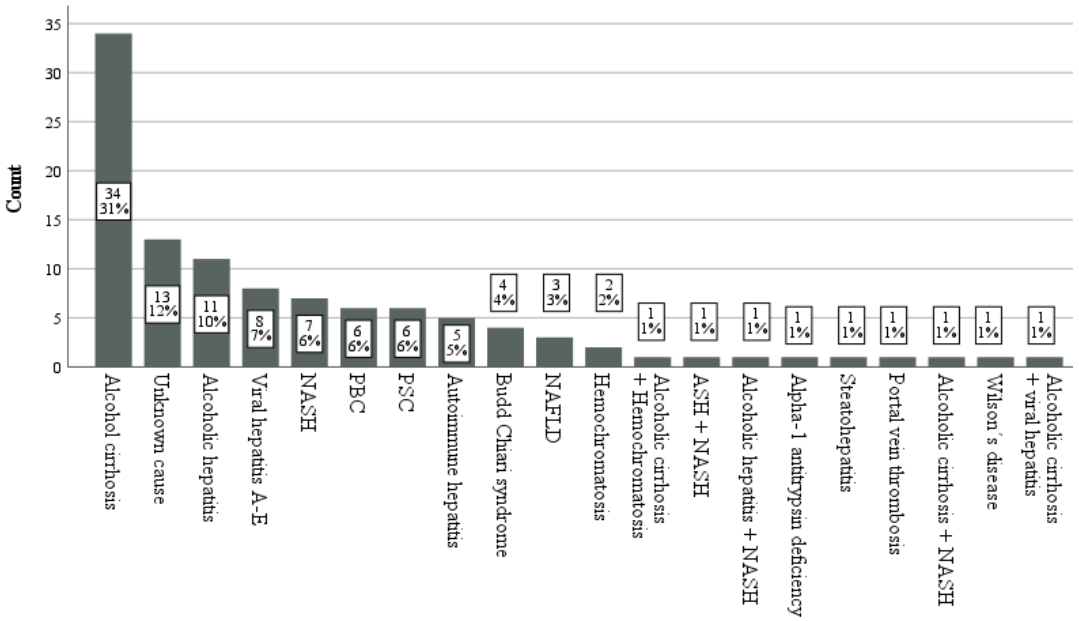


Figure 2 – Diagnosis in 108 patients with severe acute-on-chronic liver failure (ACLF) in the general ICU at Sahlgrenska University Hospital during a 10-year period (2010-2020). Notice that some patients have more than one diagnosis. NASH, Non-alcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, Primary Sclerosing cholangitis; NAFLD, Non alcoholic fatty liver disease; ASH, Alcoholic steatohepatitis

Transplantation versus no transplantation

Considerations for transplantation in the entire cohort of 168 patients, Figure 3. In 18 cases transplantation was not discussed as an option in the medical record. A liver review board was convened in 95 cases, in which 12 patients were denied, and 83 patients were accepted for transplant waiting list. Out of the 83 patients on the waiting list, 62 patients were transplanted during their ICU stays and 18 patients were removed from the list, of whom 8 due to death and 10 due to other causes (6 too ill for transplantation and 4 recovered). From the waiting list, 3 were transplanted later from another ward, within or outside the hospital stay accounted for in this study. Another 6 patients were listed and transplanted after ICU stay. In another 49 medical records transplantation was considered, and in some cases a transplantation investigation was initiated, but did not lead to an acute multidisciplinary conference.

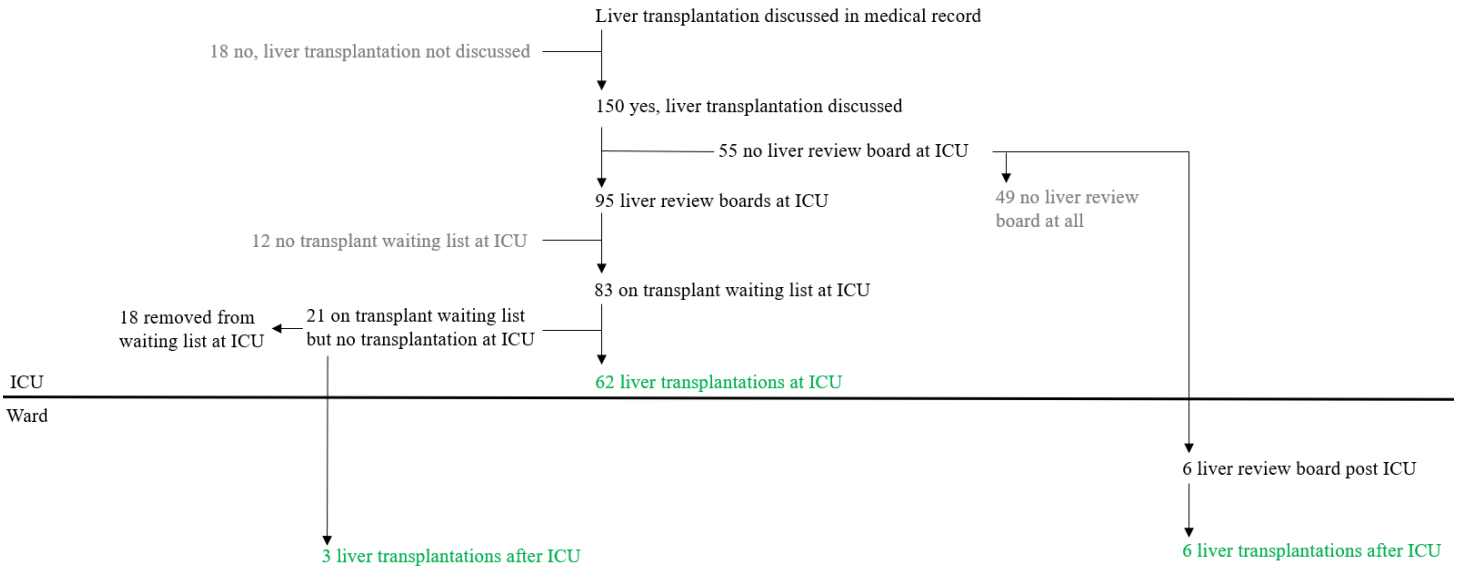


Figure 3 – Transplantation in the ICU, from discussion to transplantation. A patient flowchart of this study sample with all stages of decision-making. Transplantation is a process in which the discussion of transplantation is the start. Thereafter, if the patient is considered after anamnesis and testing, a liver review board is convened. If the transplantation criteria are met the patient is accepted to the liver transplant waiting list. If a suitable donor organ is matched to the receiver, a transplantation will take place.
ICU, intensive care unit; ward, other ward than the ICU; green patients who received a transplant; grey patients never on the transplant waiting list.

Transplantation was performed in a total of 62/168 (37%) patients out of whom 35/60 (58%) ALF patients and 27/108 (25%) ACLF patients received a transplant.

Among the 35 transplanted patients with ALF, the underlying cause was drug-induced in 8 (23%); paracetamol, autoimmune hepatitis or unknown cause in 6 (17%) each, viral hepatitis in 3 (9%); mixed drug intoxication and Wilson´s disease in 2 (6%) each, and, finally, hemochromatosis and mushroom poisoning in 1 (3%) case each.

In the 27 transplanted ACLF patients, the main underlying diagnoses were related to alcohol in 8 (32%) cases (cirrhosis from alcohol, alcohol hepatitis) followed by an even distribution of all other causes.

Survival

There was one patient completely lost to follow-up while survival data was partly missing in 9 patients, reported as censored in the analysis.

As shown in table 6, transplantation gives a significantly higher survival in both ALF and ACLF patients. Out of the 35 transplanted ALF patients, five died during ICU stay out of whom all were women.

Table 6 – Survival after severe liver failure treated in the ICU at specific points in time - by type of liver failure, and type of liver failure with and without transplantation

	ALF n=60	ALF ltx n=35	ALF no-ltx n=25	p-value
ICU discharge	46 (78)	30 (86)	16 (67)	0.113
30-days	44 (75)	30 (86)	14 (58)	0.031
1-year	44 (75)	30 (86)	14 (58)	0.031
	ACLF n=108	ACLF ltx n=27	ACLF no-ltx n=81	p-value
ICU discharge	62 (61)	25 (96)	37 (49)	<0.001
30-days	53 (49)	26 (96)	27 (33)	<0.001
1-year	33 (31)	17 (65)	16 (20)	<0.001

NOTE. All results are in number, n, and percent (%).
p-value comparing transplanted/non-transplanted is calculated using Fischer´s Exact Test.
ICU, intensive care unit; ALF, acute liver failure; ACLF, acute on chronic liver failure; ltx, liver transplantation

ICU survival in the non-transplanted ACLF when divided into “never transplanted” and “transplanted after ICU” is 28/67 (42%) and 9/9 (100%), respectively.

The 30-day survival in non-transplanted ACLF when divided into “never transplanted” and “transplanted after ICU” is 18/72 (25%) and 9/9 (100%), respectively.

The one-year survival in non-transplanted ACLF when divided into “never transplanted” and “transplanted after ICU” is 9/72 (13%) and 7/9 (78%), respectively.

There is no significant difference in survival between men and women at ICU discharge (p=1.0), 30-days (p=0.738) or one-year survival (p=0.355). Transplantation gives a significantly better short-term and long-term survival in both men and women at all points in time, Table 7.

Table 7 – Survival after severe liver failure treated in the ICU at specific points in time - by sex, and sex with and without transplantation

	Male n=84	Male ltx n=24	Male no ltx n=60	p-value
ICU discharge	53 (65)	23 (96)	30 (52)	<0.001
30-days	45 (54)	24 (100)	21 (36)	<0.001
1-year	35 (43)	20 (87)	15 (25)	<0.001
	Female n=84	Female ltx n=38	Female no ltx n=46	p-value
ICU discharge	55 (69)	32 (84)	23 (55)	0.007
30-days	52 (62)	32 (84)	20 (44)	<0.001
1-year	42 (50)	27 (71)	15 (33)	<0.001

NOTE. All results are in number, n, and percent (%).
p-value comparing transplanted/non-transplanted is calculated using Fischer´s Exact Test.
ICU, intensive care unit; d, days; ltx, liver transplantation

Re-transplantation and transplantation after ICU stay

Re-transplantation after acute transplantation at ICU stay was needed in 3 cases: 1 ALF and 2 ACLF, all alive at follow up.

Another 9 ACLF patients were transplanted after the ICU stay, 7 alive at follow up while the other 2 passed away within the first year of transplantation.

Survival over time

Is there a difference in survival according to type of liver failure (ALF/ACLF) among all patients, and in ALF/ACLF with and without transplantation?

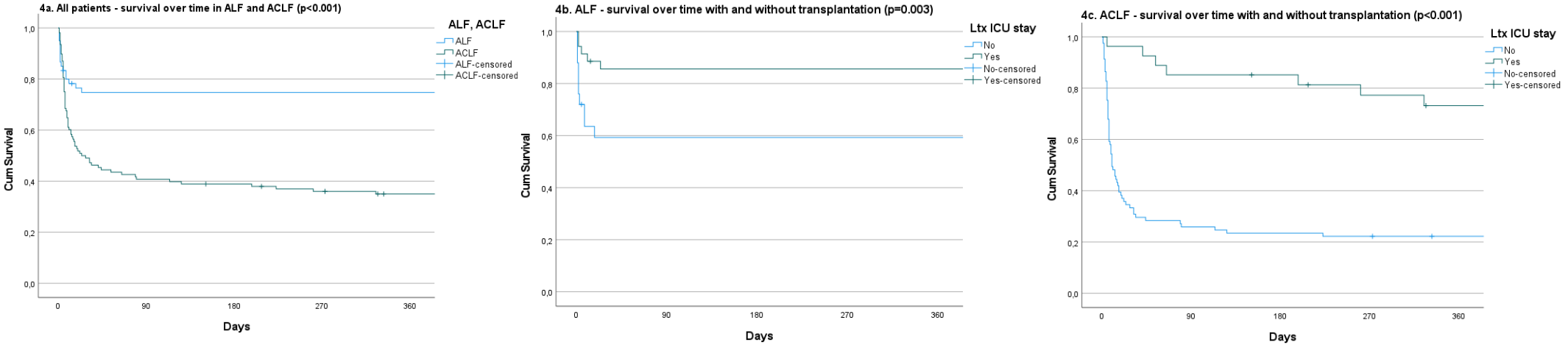


Figure 4a-c: Survival over time in all patients in relation to syndrome (ALF/ACLF), and transplantation in relation to syndrome (ALF/ACLF).
Time scale from day one of ICU admission until one-year from ICU admission. All patients are 168 in total, here divided in sub-groups with 60 ALF and 108 ACLF; ALF patients: 35 transplanted, 25 not transplanted, 60 in total; ACLF patients: 27 transplanted, 81 not transplanted, 108 in total. ALF, acute liver failure; ACLF, acute-on-chronic liver failure; ICU, intensive care unit; ltx, transplantation

ALF patients have a higher overall survival than ACLF patients. Survival is higher in transplanted than non-transplanted patients in both ALF (p=0.003) and ACLF (p <0.001) subgroups.

Is there a difference in survival between the sexes, and between transplanted and non-transplanted in male and female patients?

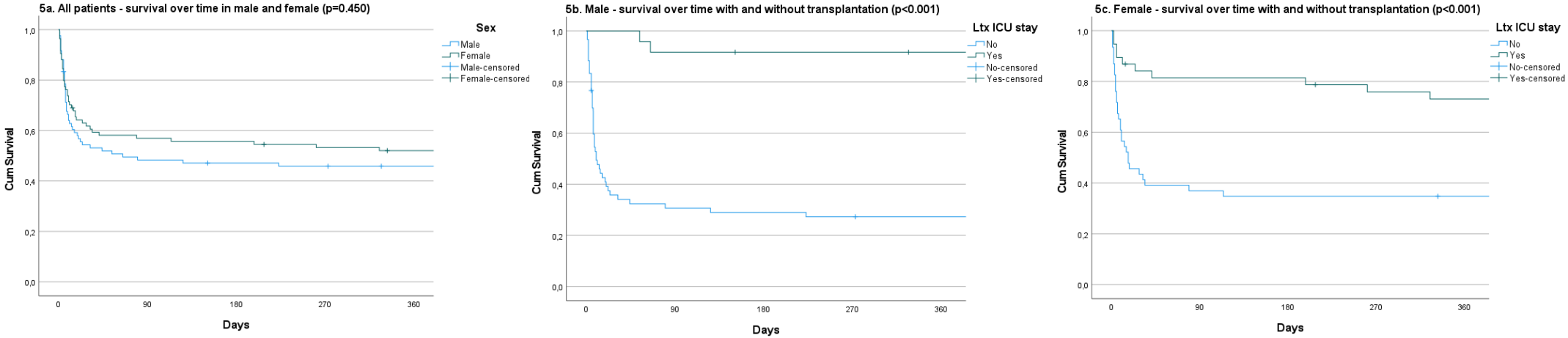


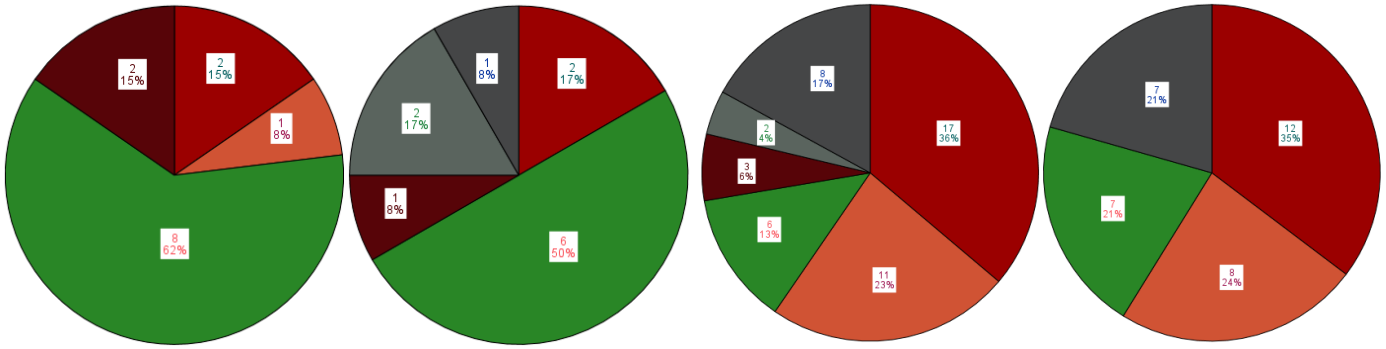
Figure 5a-c – Survival over time in all patients in relation to sex, and transplantation in relation to sex.
Time scale from day one of ICU admission until one-year from ICU admission. Male patients: 24 transplanted and 60 not transplanted, 84 in total. Female patients: 38 transplanted and 46 not transplanted, 84 in total. ltx, transplantation; ICU, intensive care unit

There is no significant survival difference between men and women. Transplantation gives a significantly higher survival in both men

(p<0.001) and women (p<0.001).

Reasons for not receiving a liver transplant

There were 106 patients not transplanted at ICU stay. The reasons for no transplantation are categorized by type of liver failure (ALF/ACLF) and sex, as seen in Figure 11a-d.



11a. ALF and male (13 pat.) **11b. ALF and female (12 pat.)** **11c. ACLF and male (47 pat.)** **11d. ACLF and female (34 pat.)**

Figure 11 – Reason behind no transplantation in 106 patients during ICU stay categorized by type of liver failure and sex (ALF in male and female, and ACLF in male and female). The results are shown in both number and percent. **Red:** liver failure that is too severe to survive a transplantation. **Orange**: active addiction. **Green**: improvement from medical treatment. **Burgundy:** other physical reasons such as severe obesity; subcutaneous oedema; unhealed wounds; toxic epidermal necrolysis; cancer; bowl hypoxia/infection/perforation; and anastomosis insufficiency. **Light grey:** psychological reasons including severe obsessive-compulsive disorder, bipolar disorder and low cognitive function. **Dark grey:** liver transplantation not mentioned. ALF, acute liver failure; ACLF, acute-on-chronic liver failure; pat., patients; ICU, intensive care unit ltx, liver transplantation

Reasons behind no transplantation vary between the ALF and ACLF group but not according to sex, Figure 11.

In ALF the most common reason for non-transplantation is improvement during intensive care, in contrast with the ACLF group, in which the liver failure is too severe for an operation, followed by an active addiction to alcohol and/or other substances. A larger sample would be needed to determine whether there is a significant relationship between the reason for non-transplantation and survival.

Discussion

The main findings in this descriptive, retrospective analysis of a cohort of patients with severe liver failure treated in the ICU are that both transplanted and non-transplanted ACLF patients have a lower overall survival rate than found in the literature; and that the entire group of transplanted patients show a better survival than non-transplanted patients.

Type of liver failure

Spontaneous recovery, or responses to aetiology-specific treatments was seen in 56% of ALF cases in this study, contrasting to the 63% in the Swedish study (2007), but due to our small sample this difference corresponds to 2 patients only. A repeated national survey like the Swedish study that Wei et al. performed, is warranted to investigate if the ALF result is on the same level or if it has declined.

Transplantation is the only treatment that avoids imminent death for a large proportion of the ACLF patients treated in the ICU, who are prone to have a high short-term mortality (24). The non-transplanted ACLF patients in our study had a 30-day survival of 33%. The 28-day survival is highly related to ACLF-grading, which in the CANONIC study ranges from 59% in ACLF-1 to 21% in ACLF-3 (2). Given the level of ICU supportive measure, the ACLF patients in our study could rather be compared to the ACLF-3 group in studies with better formal grading. This suggests that it is very important to evaluate ACLF-grade and its fluctuation to predict survival without transplantation.

Stabilizing of ACLF patients in the ICU can open for transplantation in a later stage with a more optimised patient. When divided into “never transplanted” and “transplanted after ICU stay”, a 30-day survival of 18/78 (23%) and 3/3 (100%), respectively was seen. As concluded

earlier, transplantation gives a higher survival in these patients, allowing a better long-term survival when surviving ICU stay and thereafter being transplanted at the ward.

Transplantation

Transplantation in ALF patients is associated with a higher survival among both men and women compared to no transplantation, and the one-year survival in this study is 86% compared to 80% in a previous study (6). Out of the 35 transplanted, 30 were alive at follow-up and the other 5 died in the ICU, indicating a promising prognosis after ICU discharge alive.

The transplantation rate of ACLF patients in this study, 25%, is consistent with the Austrian study with 23% (24), note that Austrian study is not using the ACLF-grading according to the CANONIC study (2). Transplantation in ACLF patients in this study was associated with a low one-year survival (65%) compared with previous studies of ACLF patients with a one-year survival of 75-88%, depending on time to transplantation and number of organ failures (25, 26). Mechanical ventilation was utilized in 94% of all ACLF patients in this study, only seen in 3.6-66% of ACLF-1, -2, and -3 in other ACLF studies (25, 26). ACLF-grading was not possible in this study, which prevents further comparison on a deeper level. Intubation is normally instituted from hepatic encephalopathy-grade 3 and higher, suggesting that most patients in the present study had HE 3 or higher. Patients using mechanical ventilation are found to have a lower survival (75%) compared to those without (85%) (27). This might indicate the need for a transplantation at a lower ACLF-grading and taking the mechanical ventilator use into consideration when assessing the prognosis.

Reason behind no transplantation

Advanced multi-organ failure, most often driven by terminal exhaustion of the liver function, and an ongoing addiction are two of the reasons eliminating patients from a potentially lifesaving transplantation, factors that might be affected by intervention at an earlier stage.

A low survival rate is seen in non-transplanted ACLF patients. A few of these patients were in the hospital for their investigation to be on the transplant waiting list. “Reasons behind no transplantation” show that about 36% of ACLF patients, both men and women, are too ill to be transplanted. The questions are why, and can anything be done about it?
Symptom development, like ascites and jaundice, are first detectable by the patients themselves, and there might be a patient delay in seeking medical attention, with a risk of a further progression of the liver failure before arrival at the hospital. Do transplantation investigations start too late and if so, how can we find these patients in time? How do we deal with potential doctors’ delay in relation to diagnosis and treatment of bacterial and fungal infections (28)? When in hospital for liver failure, either acute or acute-on-chronic, is the patient taken to the ICU too late?

Secondary prevention of overuse of alcohol and/or drugs might need to be prioritized more highly to save these lives. It is of importance to treat the underlying cause of the liver disease, preferably before transplantation. Only a minority of these patients had participated in an addiction treatment program prior to transplantation investigation, and Weinreib found that behavioural interventions reduced intake, as did medical treatment with baclofen (29). Predictors of relapse need to be investigated further. Factors such as abstention from alcohol for more than 6 months, a negative family history of addiction, co-inhabitants being sober, and no current drug dependency might create better conditions for remaining sober. (29)

In this study, 24% of ACLF patients are denied transplantation due to an ongoing overuse of alcohol and/or drugs. An exclusion rate of 51% due to alcohol/drug use was seen in a previous Austrian study (24). As many as 25% on the waiting list consumed alcohol in a review by Weinreib from the USA, concluding that as much as 50% of transplanted patients return to abusing alcohol within five years after transplantation (29). Finding these patients gives a condition to treat the ongoing alcohol addiction. It is of great importance that all patients on the transplant waiting list comply with transplantation criteria. Alcohol intake after transplantation contributes to a more rapid fibrosis progress in the allograft and a higher 10 year mortality (30).

The recommendation of an addiction specialist in the transplantation team, together with greater knowledge about medications that might not be suitable in end-stage liver disease might reduce the risk of alcohol intake after transplantation, and the risk of alcohol being the precipitating event for a patient with chronic liver failure (30).

The final decision to perform a transplant in a critically ill patient depends on the degree of perturbation of physiologic and laboratory values.
Using lactate increases the sensitivity for predicting a poor outcome in ALF patients and might help deciding between transplantation or not (31, 32).

Few scoring models are to be used in cirrhotic patients in hospital before onset of ACLF to predict prognosis, but the CLIF Consortium Acute Decompensation score (CLIF-C ADs) is one of them (33). Are models like this used or are there tools we are not yet using?

Further use of more than one test at the time, MELD-Na and ACLF as an example, might increase the chance of giving the correct treatment at the correct point in time (27). A low MELD score in patients receiving a transplant is associated with a higher risk of mortality after one year than for patients with a low MELD score remaining on the transplant waiting list (15). In the same time, a low MELD-Na but with a high ACLF-grade at the same time indicates a higher mortality rate than a higher MELD-Na with a low ACLF-grade (27).

Studies trying to invent a method to predict mortality and liver failure outcomes are, and have been taking place with comparing to the existing models aiming to find the most effective predictor (34-37).

Limitations to the study

Inclusion of patients in this study was dependent of identifying the correct diagnosis in the ICU, based on the three sources discussed in method. Reviewing the medical records of each case revealed that some patients had more ICU stays due to their liver failure than the number of stays registered in the database, suggesting that other patients relevant for the study might have been missed when identifying patients for this study. This in addition to the limitations arising from source data mentioned in the methods section. The patients who were not included due to different diagnosis coding could have affected the outcomes. In what direction the correct coding would affect the results is hard to predict since transplantation, type of liver failure, and sex status is unknown in these cases. They could have increased the sample size and thereby the sizes of subgroups. Lacking consistency in comorbidity registration in Melior, there is a likelihood of missing data, particularly before the upgrade in 2014.

Renal replacement therapy, or mechanical ventilation was an inclusion criterion in this study. Yet in a previous study following up on the CANONIC study of ACLF patients, only 40% and 28%, were on dialysis or a mechanical ventilation, respectively (26), suggesting that the present study had narrower inclusion criteria and a higher morbidity among the patients. The lack of possibility to calculate scores such as ACLF and MELD-score in the material in this study makes comparison to other studies hard and further makes it hard to adjust for level of disease.

Clinical implications

This study aimed to evaluate the survival in severe liver failure requiring intensive care with and without transplantation and found that the survival in ACLF patients is low both in transplanted and non-transplanted patients in relation to other studies of ACLF patients. ACLF patients in this study have a worse prognosis than those in other studies, contributing to our knowledge by revealing a need for further research to understand why and identify possible ways to improve it.

The analysis of the patients' demographic characteristics and distribution of different types of liver failure, as well as the finding that alcohol use is still a large problem for survival, both short-term and long-term, gives us a better understanding about the population and suggest how we might be able to improve outcomes by identifying some for secondary prevention or identifying patients in potential need of transplantation earlier by using different scoring methods and/or interventions at an earlier stage.

Comparing survival has shown that transplanted patients have the best long-term survival, making transplantation a treatment to continue to consider in the future. Acute liver failure patients in this study have a similar survival as those in the literature, confirming that the treatment strategy in these patients at the general ICU at Sahlgrenska is efficient.
Insights into the need for correct diagnosis coding, the need to review the current use of prognostic scoring, and a larger prospective multicentre study involving early collection of ACLF-grading and HE in all cases, have all been obtained from this study.

Conclusion

The high mortality of transplanted and non-transplanted ACLF patients in this study point to the need to consider earlier investigations and evaluations for transplant along with grading of ACLF assessing the reasons behind non-transplantations in order to increase the overall survival of patients with severe liver failure.
Grading of ACLF and hepatic encephalopathy together with a standard documentation, give a base for better prognosis estimation and future studies.

Populärvetenskaplig sammanfattning

Titel: Utvärdering av överlevnad efter allvarlig leversvikt med och utan levertransplantation
Författare: Zanna Boström, Examensarbete, Läkarprogrammet vid Sahlgrenska akademin

Levern som organ reglerar flera system i kroppen så som rening av blodet, bildande av blodstillande ämnen (koagulation) och ämnesomsättningen. Om leverns funktion sviktar uppkommer symtom som gulsot, mental påverkan och försämrad koagulation. Svikten kan vara akut, utan tidigare leversjukdom, eller akut-på-kronisk om patienten har en tidigare leversjukdom.
Allvarlig leversvikt behandlas oftast på en intensivvårdsavdelning då patienterna är mycket sjuka och dödligheten är hög. Intensivvården strävar efter att reversera skador så som förgiftningar och behandla uppkomna symtom så som organsvikt genom exempelvis respiratorvård och dialys. Medicinsk behandling, som ovan, kan få leversvikten att bli bättre. För vissa patienter är medicinsk behandling inte tillräckligt och då är levertransplantation den sista livräddande behandlingen.

Syftet med den här studien var att kartlägga överlevnaden efter leversvikt med och utan transplantation samt i relation till akut eller kronisk leversvikt och kön, vid centrala intensivvårdsavdelningen (CIVA) på Sahlgrenska sjukhuset.
Studien undersökte medicinsk dokumentation om vuxna intensivvårdspatienter med allvarlig leversvikt som vårdats på CIVA under perioden januari 2010 till september 2020.

Studien visar att patienter som transplanterats har en högre överlevnad än de som inte transplanterats. Vidare visar den att patienter med akut-på-kronisk leversvikt har en sämre överlevnad än förväntat, både med och utan transplantation.

Studien bidrar till en ökad förståelse kring överlevnaden efter allvarlig leversvikt med och utan transplantation. Det är av stor vikt att se över handläggning av patienter med akut-på-kronisk leversvikt för att se huruvida ändringar i handläggandet kan höja överlevnaden.

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Appendix

Explanation for Table 3

Other cardiovascular diseases include heart failure, coronary artery disease, atrium flutter, heart infarction, carotid stenosis, aortic stenosis, vaule operation, hypertrophic cardiomyopathy, pulmonal hypertension and previous deep venous thrombosis (DVT).
Other metabolic diseases include obesities with or without gastric bypass, hyperlipidaemia and the metabolic syndrome.
Neurologic diseases include TIA, cerebral haemorrhage or infarction, cortical injuries due to alcohol and epilepsy.
Respiratory diseases include chronic obstructive pulmonary disease (COPD), fibrosis, asthma, unspecified obstructive disease, tuberculosis, hydrothorax, sleep apnea and lung fibrosis.
GI-tract diseases include ulcerous colitis with and without stoma, Crohns disease, stoma after radiation damage, herniated umbilical hernia, gallstone, sclerotic cholangitis, splenomegaly, ulceration in the ventriculi or duodenum, herniated ventriculi, chronic pancreatitis, polypys in the colon, atrophic gastritis and cholecystitis.
Psychiatric diseases include depression, anxiety, ADHD, personality disorders, schizophrenia, bipolar disorder, obsessive compulsive disorder and suicide attempts.
Malignant diseases include non metastasized cancer with a low long-term mortality or a history of cancer: urinary bladder cancer, gallbladder cancer, kidney cancer, ovary cancer, malignant melanoma, follicular and non-Hodgkins lymphoma.
Viral hepatitis includes hepatitis A/B/C/D and/or combinations.
Renal diseases include hydronephrosis, IgA-nefrit, kidney stones and polycystic kidney disease with kidney transplantation.
Other diseases include polymyalgia rheumatica (PMR), rheumatoid arthritis; hypo- and hyperthyroidism; spinal stenosis, disc herniation and spondyl-compression.
Previous abdominal surgeries include appendectomy, cholecystectomy, hysterectomy due to myoma, gastric by-pass and small intestine and colon resection.