Artzner Thierry (Orcid ID: 0000-0001-6077-5148)
Belli Luca Saverio (Orcid ID: 0000-0001-8714-2439)
Cortesi Paolo Angelo (Orcid ID: 0000-0001-5241-4473)
Trebicka Jonel (Orcid ID: 0000-0002-7028-3881)
Piano Salvatore (Orcid ID: 0000-0002-9356-5830)
Martini Silvia (Orcid ID: 0000-0002-9738-5538)
Faitot François (Orcid ID: 0000-0001-6514-0774)
MEUNIER Lucy (Orcid ID: 0000-0001-5697-286X)
Meszaros Magdalena (Orcid ID: 0000-0002-5569-7285)
Artzner Thierry (Orcid ID: 0000-0001-6077-5148)

Location and allocation: inequity of access to liver transplantation for patients with severe acute-on-chronic liver failure in Europe

Thierry Artzner[1*], William Bernal[2*], Luca S Belli[3*], Sara Conti[4,5], Paolo A Cortesi[4,5], Sophie-Caroline Sacleux[6], George-Philippe Pageaux[7], Sylvie Radenne[8], Jonel Trebicka[9,29], Javier Fernandez[10,27], Giovanni Perricone[3], Salvatore Piano[11], Silvio Nadalin[12], Maria C Morelli[13], Silvia Martini[14], Wojciech G Polak[15], Krzysztof Zieniewicz[16], Christian Toso[17], Marina Berenguer[18,19], Claudia Iegri[20], Federica Invernizzi[21], Riccardo Volpes[22], Vincent Karam[23], René Adam[23], François Faitot[24], Liane Rabinowich[2], Faouzi Saliba[6], Lucy Meunier[7], Mickael Lesurtel[25], Frank E Uschner[9], Baptiste Michard[24], Audrey Coilly[6], Magdalena Meszaros[7], Domitille Poinsot[8], Camille Besch[24], Andreas Schnitzbauer[9], Luciano G De Carlis[26,27], Roberto Fumagalli[28], Paolo Angeli[11], Vincente Arroyo[29], **Constantino Fondevila[30**], Christophe Duvoux[31**], Rajiv Jalan[29,32**]** for the ELITA/EF-CLIF working group: see list of collaborators.
**Joint first authors.* ***Joint senior authors.*

Affiliations

1. Service de Réanimation Médicale, Hôpital de Hautepierre, Strasbourg, France.
2. Liver Intensive Therapy Unit, Institute of Liver Studies, Kings College Hospital, London UK.
3. Hepatology and Gastroenterology Unit, ASST GOM Niguarda, Milan, Italy.
4. Value-Based Healthcare Unit, IRCCS Multi Medica, Sesto San Giovanni, Italy.
5. Research Centre on Public Health (CESP), University of Milan-Bicocca, Monza, Italy.
6. AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif; Unité INSERM 1193, Université Paris-Saclay, France.
7. Department of hepatogastroenterology, Hepatology and Liver Transplantation Unit, Saint Eloi Hospital, University of Montpellier, France.
8. Department of hepatogastroenterology, Hepatology and Liver Transplantation Unit, HCL Hopital de la Croix-Rousse, Lyon, France.
9. Translational Hepatology, Department of Internal Medicine, Goethe University, Frankfurt, Germany.
10. Liver ICU, Liver Unit, Institute of Digestive and Metabolic Diseases, Hospital Clinic, University of Barcelona, IDIBAPS and CIBERehd, Barcelona, Spain.
11. Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine, University of Padova.
12. Department of General, Visceral and Transplant Surgery, University Hospital Tübingen, Germany.
13. IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.
14. Gastro-hepatology Unit, Azienda Ospedaliera Universitaria, Città della Salute e della Scienza di Torino, University of Torino, Torino, Italy.

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15. Erasmus MC, Transplant Institute, University Medical Center Rotterdam Department of Surgery, Division of HPB and Transplant Surgery, Rotterdam, Rotterdam, the Netherland.
16. Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland.
17. Division of Abdominal Surgery, Department of Surgery, Geneva University Hospitals, Geneva, Switzerland.
18. Hepatology and Liver Transplantation Unit, Ciberehd
19. Faculty of Medicine, La Fe University Hospital, Valencia, Spain.
20. Gastroenterology Unit, Papa Giovanni XXIII Hospital, Bergamo, Italy.
21. Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Milan, Italy.
22. Hepatology and Gastroenterology Unit, ISMETT-IRCCS, Palermo, Italy.
23. European Liver Transplant Registry, Centre Hépatobiliaire Hôpital Universitaire Paul Brousse, Villejuif, France.
24. Service de Chirurgie Hépato-Biliaire et Transplantation Hépatique, Hôpital de Hautepierre, Strasbourg, France
25. Department of Digestive Surgery and Liver Transplantation, Croix Rousse Hospital, Hospices Civils de Lyon, University of Lyon I, Lyon, France.
26. General Surgery and Transplantation Unit, ASST GOM Niguarda, Milan, Italy.
27. School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy.
28. Department of Anesthesia, Critical Care, ASST GOM Niguarda, School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy.
29. European Foundation for the Study of Chronic Liver Failure (EF Clif), 08021 Barcelona, Spain.
30. HPB Surgery and Transplantation, Hospital Universitario La Paz, Madrid
31. Hôpital Henri Mondor, Service d'Hepatologie, Créteil, France.
32. Liver Failure Group, Institute for Liver and Digestive Health, UCL Medical School, London, UK.

List of collaborators

1- Hepatology and Gastroenterology Unit, ASST GOM Niguarda, Milan, Italy: Luca S Belli, Giovanni Perricone, Raffaella Viganò, Chiara Mazzarelli.
2- General Surgery and Abdominal Transplantation Unit, ASST GOM Niguarda, and School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy: Luciano G De Carlis, Andrea Lauterio, Alessandro Giacomoni.
3- Gastroenterology and Hepatology Unit, University of Milan, Milan, Italy: Federica Invernizzi, Francesca Donato, Pietro Lampertico.
4- Gastroenterology Unit, Papa Giovanni XXIII Hospital, Bergamo: Claudia Iegri, Luisa Pasulo, Stefano Fagiuoli.
5- Department of Surgery, Papa Giovanni XXIII Hospital, Bergamo, Italy: Michele Colledan.
6- IRCCS Azienda Ospedaliero-Universitaria di Bologna. Maria Cristina Morelli, Giovanni Vitale.
7- Liver Transplant Unit, Molinette Hospital, Turin, Italy: Silvia Martini, Antonio Ottobrelli
8- Liver Transplantation Center, Molinette Hospital, Turin, Italy: Damiano Patrono, Renato Romagnoli.
9- Hepatology and Gastroenterology Unit, ISMETT-IRCCS, Palermo, Italy: Riccardo Volpes, Ioannis Petridis.
10- Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine, University of Padova: Salvatore Piano, Paolo Angeli.
11- Hepatobiliary Surgery and Liver Transplant Center, University of Padova, Italy: Umberto Cillo.

12- Multivisceral Transplant Unit, Gastroenterology, University of Padova, Italy: Giacomo Germani, Patrizia Burra.
13- Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg: Philippe Bachellier, Francis Schneider, Vincent Castelain, Pietro Addeo, Mathilde Deridder
14- Hôpital Paul Brousse, Centre Hépato Biliaire, Villejuif, France: Sophie Caroline Sacleux Audrey Coilly, Saliba Faouzi, Rene Adam, Didier Samuel.
15- Hôpital Henri Mondor, Service d'Hepatologie, Créteil, France: Christophe Duvoux.
16- Department of hepatogastroenterology, Hepatology and Liver Transplantation Unit, HCL Hopital de la Croix-Rousse, Lyon, France: Sylvie Radenne, Mickael Lesurtel, Domitille Poinsot and Celine Guichon.
17- Department of hepatogastroenterology, Hepatology and Liver Transplantation Unit, Saint Eloi Hospital, University of Montpellier, France: George-Philippe Pageaux, Stéfanie Faure, Magdalena Meszaros, Lucy Meunier and Josè Ursic-Bedoya.
18- Hospital Clinic I Provincial de Barcelona, Spain: Costantino Fondevila, Jorde Colmenero, David Toapanta, María Hernández-Tejero.
19- Hepatology and Liver Transplantation Unit, Ciberehd, and Facultad de Medicina, La Fe University Hospital, Valencia, Spain: Marina Berenguer and Carmen Vinaixa.
20- Erasmus MC Transplant Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands, Department of Surgery: Wojciech G. Polak.
21- Erasmus MC Transplant Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands, Department of Gastroenterology and Hepatology: Caroline den Hoed.
22- Erasmus MC Transplant Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands, Department of Intensive Care: Jubi E. de Haan.
23- Dept. of General, Visceral and Transplant Surgery, University Hospital Tübingen, Germany: Silvio Nadalin, Andrea Della Penna.
24- Goethe University Frankfurt, Germany. Frank Erhard Uschner, Martin Welker, Andreas Schnitzbauer, Stefan Zeuzem, Wolf Bechstein, Jonel Trebicka.
25- Division of Abdominal Surgery, Department of Surgery, Geneva University Hospitals, Geneva, Switzerland: Christian Toso, Nicolas Goossens.
26- Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland: Joanna Raszeja-Wyszomirska, Krzysztof Zieniewicz.
27- Liver Intensive Therapy Unit, Institute of Liver Studies, Kings College Hospital, London UK: William Bernal, Liane Rabinovich.
28- Liver Failure Group, Institute for Liver and Digestive Health, UCL Medical School, London, UK: Dev Katarey, Banwari Agarwal, Rajiv Jalan.

Corresponding author
Dr Thierry Artzner
Service de Réanimation Médicale
Hôpital de Hautepierre, Strasbourg, France
Telephone + 33 388116768
E-mail: thierry.artzner@chru-strasbourg.fr

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Authors contributions

- Concept and design: LSB, CD, TA, WB and RJ.
- Collection of data: LSB, TA, WB, SCS, GPP, SR, JT, JF, GP, SA, SN, MCM, SM, WGP, KZ, CT, MB, CI, FI, RV, FF, LR, FS, LM, ML, FEU, CF, BM, AC, MM, and DM.
- Analysis and interpretation of data: SC, PC, LSB, GP, CD, TA, WB and RJ.
- Writing: TA, LSB, WB and RJ.

- Revision for important intellectual content and final approval of the version to be published: LSB, TA, WB, SC, PAC, SCS, GPP, SR, JT, JF, GP, SA, SN, MCM, SM, WGP, KZ, CT, MB, CI, FI, RV, FF, LR, FS, LM, ML, FEU, CF, BM, AC, MM, DM, PA, VK, RA, PA, VA and RJ.

Data availability statement:
The data that support the findings of this study are available from the corresponding author upon reasonable request

Conflict of interest statement:
No conflict of interest for this study.

Abbreviations

ACLF: Acute-on-chronic liver failure
DC: Decompensated cirrhosis
HCC: Hepatocellular carcinoma
ICU: Intensive care unit
LT: Liver transplant

Abstract

Background

There is growing evidence that liver transplantation (LT) is the most effective treatment for acute-on-chronic liver failure grade-3 (ACLF-3). This study examines whether and how this evidence translates into practice by analyzing the variability in intensive care unit (ICU) admissions, listing strategies and LT activity for ACLF-3 patients across transplant centers in Europe.

Methods

Consecutive patients who were admitted to the ICU with ACLF-3, whether or not they were listed and/or transplanted with ACLF-3 between 2018 and 2019 were included across 20 transplantation centers.

Results

351 patients with ACLF-3 were included: 33 had been listed prior to developing ACLF-3 and 318 had not been listed at the time of admission to the ICU. There was no correlation between the number of unlisted ACLF-3 patients admitted to the ICU and the number listed or transplanted whilst in ACLF-3 across centers. In contrast, there was a correlation between the number of patients listed and the number transplanted whilst in ACLF-3. 21% of patients who were listed whilst in ACLF-3 died on the waiting list or were delisted. The percentage of LT for ACLF-3 patients varied from 0%-29% of patients transplanted with decompensated cirrhosis across centers (average = 8%), with an I^2 index of 68% (95% CI: 49%-80%), showing substantial heterogeneity among centers.

The one-year survival for all patients with ACLF-3 was significantly higher in centers that listed and transplanted more ACLF-3 patients (>10 patients) than in centers that listed and transplanted fewer: respectively 36% vs. 20%, p = 0.012.

Conclusion

Patients with ACLF-3 face inequity of access to LT across Europe. Wait-listing strategies for ACLF-3 patients influence their access to LT and, ultimately, their survival.

Introduction

Liver transplantation (LT) is currently the most effective treatment available for selected critically ill cirrhotic patients with multiple organ failure. In the absence of LT, the 3-month mortality rate of patients with acute-on-chronic liver failure grade 3 (ACLF-3) has been reported to be as high as 80% (1). Several studies have now shown that access to LT may hugely improve the survival of these patients (2,3). While support for LT increases through the transplant community, in practice, utilization of LT for patients with ACLF-3 remains a frontier in transplantation, and continues to raise specific ethical and clinical questions (4).

Extending LT for patients with ACLF-3 potentially requires fundamental changes of intensive care unit (ICU) admission practices, listing strategies, surgical and anesthesiologic techniques and post-LT management. It also requires carefully balancing the individual benefit of LT for ACLF-3 patients against the collective utility of LT for the broader community of transplant candidates.

While previous registry or multicenter studies on LT for ACLF-3 patients have predominantly focused on post-LT *outcomes* among groups of transplant centers this report

focuses on variations of *practices* among individual transplant centers, offering an analytic panorama of the access to LT for ACLF-3 patients across Europe.

In particular, this study aims to describe variation in the access to three key steps of LT for ACLF-3 patients: ICU admission, listing, and transplantation. First, we investigate the issue of ICU access for patients with ACLF-3 and analyze the reasons for which some patients were admitted to the ICU but were not listed for LT. Second, we assess the relationship between listing strategies and LT activity. In particular, we determine the percentage of patients listed with ACLF-3 who actually went on to receive LT. Third, we assess the variability in LT activity for ACLF-3 across centers. Finally, we conduct a survival analysis of all ACLF-3 patients according to the inclination of centers to list ACLF-3 patients for LT.

Methods

Study Cohort

This study is a collaboration among the European Liver and Intestine Transplant Association (ELITA), the European Liver Transplant Registry (ELTR) and the European Foundation for the Study of Chronic Liver Failure (EF-CLIF). Twenty centers from 8 European countries participated in the study. Consecutive patients between January 1st 2018 and June 30th 2019 were retrospectively included if (i) they were admitted to the ICU with ACLF-3 or developed ACLF-3 3-7 days after admission to the ICU and/or if (ii) they were transplanted with ACLF-3. In parallel, total LT activity, LT activity for HCC and DC during the same period were recorded in each center.

Diagnostic criteria of ACLF and data collection

Diagnostic criteria of ACLF and its grades and data collection details have been described previously (5). The definition and grades of the CLIF-Consortium were strictly followed.

Ethical and regulatory approval

Data was collected in accordance with general data protection regulation, the European Union legislation and the ELTR privacy declaration. All procedures were followed in accordance with STROBE guidelines (6).

Statistical analysis

We assessed the correlation between the total number of patients transplanted in each center and the number of patients transplanted for HCC, DC and ACLF-3 by analyzing the Kendall tau correlation. The variability of ACLF-3 LT activity was represented through a forest plot, reporting center-specific estimates of proportion of LTs for ACLF-3 among LTs for DC in each center. Confidence intervals (CI) at a 95% level for the proportions were computed using the Clopper-Pearson method. The pooled estimate of the total proportion was obtained from a fixed-effects meta-analysis, based on generalized linear mixed-effects model. I^2, with its 95% confidence interval, and $\chi 2$, with correlated p-value, were reported as measures of heterogeneity among centers.

The relationship between the number of patients listed with ACLF-3 and the number of patients transplanted with ACLF-3 was also explored using the Kendall tau correlation coefficient, as was the relationship between the number of patients admitted to the ICU and the number of patients listed/transplanted with ACLF-3.

Overall one-year survival analysis from the time of ACLF-3 diagnosis was stratified according to the number of patients listed for LT with ACLF-3 over the study period in each center. Survival curves were computed using the Kaplan Meier method and compared with the log-rank test.

Centers were stratified into high- and low listing centers according to the number of patients that were listed over the study period. The cutoff was determined in order to minimize the difference in the number of patients in each group. When stratifying by high- and low-listing

centers, distribution of categorical variables were compared using the $\chi 2$ or Fisher's exact tests. All tests were two-sided and used a significance level of 0.05.

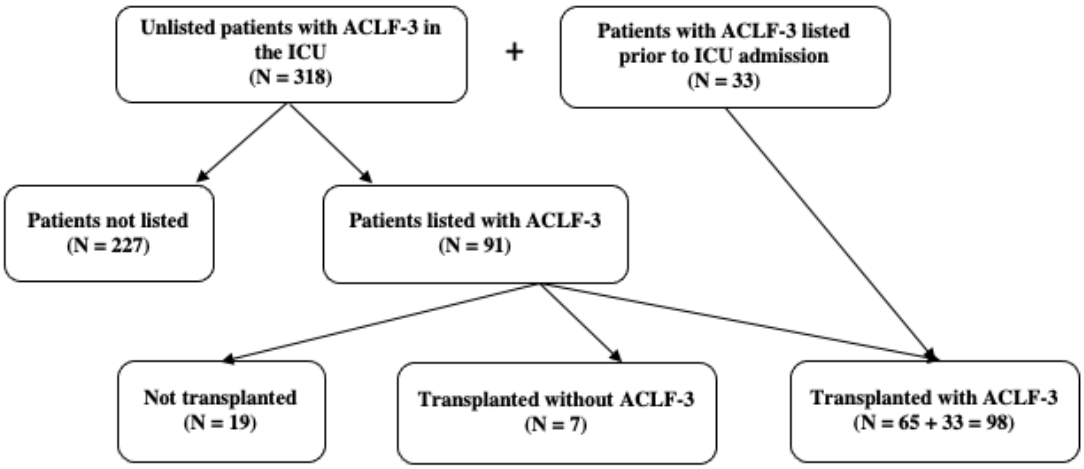
All statistical analyses were conducted using R version 4.0.2 (R Core Team, Vienna, Austria) with the specific packages ggplot2, survival, survminer, metafor, ggpubr and cowplot.

Results

Study population

351 patients with ACLF-3 were included (figure 1): 318 were not listed at the time of admission in ICU and 33 had already been listed prior to developing ACLF-3.

Figure 1. Study flowchart



Over the study period, a total of 2683 LTs were performed across the 20 centers (Table 1). 1226 LTs were performed for DC, 897 for HCC and 560 for other indications.

The four centers (FR1, FR2, FR3 and FR4) who transplanted the highest number of ACLF-3 patients (>10 over the study period) were also the centers who listed the most patients with ACLF-3: they were identified as "high listing/transplanting centers", as opposed to "low listing/transplanting centers" (UK1, UK2, ES1, NL1, DE1, IT1, IT2, IT3, IT4, IT5 and PL1). The 5 centers that did not provide data on the total number of patients admitted to the ICU with ACLF-3 were not included in the analyses comparing high and low listing/transplanting centers ES2, DE2, IT6, IT7, CH1). The full list of participating centers is provided in supplementary table 1.

Table 1. Transplantation activity, ICU admission of ACLF-3 patients and listing of ACLF-3 patients across centers

Center*	Total number of LTs	LT for decompensated cirrhosis	LT for hepatocellular carcinoma	LT for other indications	LT for ACLF-3	Unlisted patients admitted to the ICU with ACLF-3 (patients subsequently listed with ACLF-3, %)
FR1	250	100	76	75	12	62 (16, 26%)
FR2	120	69	39	12	20	47 (16, 34%)
FR3	107	55	28	24	12	24 (9, 38%)
FR4	136	92	36	8	16	23 (16, 70%)
UK1	310	160	70	70	6	42 (6, 14%)
UK2	185	115	33	37	0	16 (0, 0%)
ES1	112	51	32	29	1	28 (1, 4%)
ES2	117	50	54	13	0	NA[1] (0)
NL1	114	59	40	24	3	14 (3, 21%)
DE1	16	14	2	0	3	12 (1, 8%)
DE2	69	27	19	23	4	NA[1] (3)
IT1	121	33	68	20	6	9 (3, 33%)
IT2	76	38	34	4	2	7 (3, 43%)

IT3	142	56	65	21	0	7 (0, 0%)
IT4	164	68	84	12	2	6 (1, 17%)
IT5	81	36	30	15	3	5 (4, 80%)
IT6	114	53	34	27	2	NA[1] (2)
IT7	199	79	98	22	3	NA[1](2)
PL1	184	45	22	117	1	6 (2, 33%)
CH1	66	26	33	7	2	NA[1]
TOTAL	**2683**	**1226**	**897**	**560**	**98**	**318 (91)**

*** FR: France; UK: United Kingdom; ES: Spain; NL: Netherlands; DE: Germany; IT: Italy; PL: Poland; CH: Switzerland**

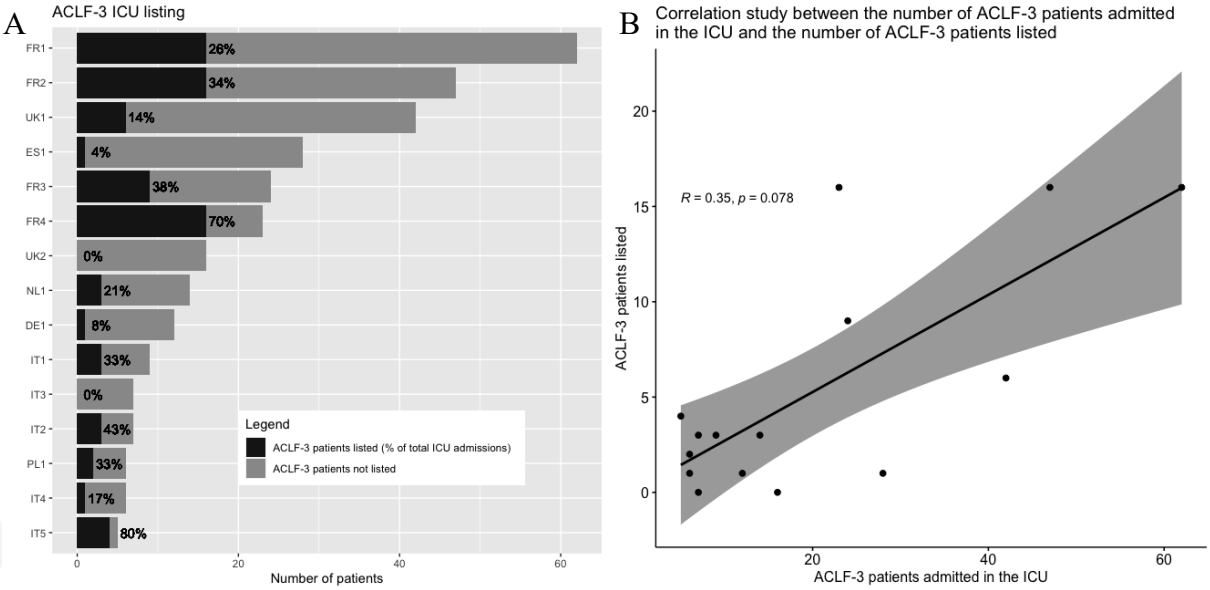
[1] 5 centers could not provide data on patients admitted to the ICU and not listed/transplanted

ICU admissions and access to the transplant list for ACLF-3 patients in Europe

The number of unlisted patients admitted to the ICU ranged from 5 to 62 across the cohort (table 1 and figure 2A). The number of patients listed with ACLF-3 from 0 to 16 across centers, with a proportion of patients listed to patients admitted to the ICU ranging from 0% to 80% (figure 2A).

There was no significant correlation between the number of patients admitted to the ICU and the number of patients listed with ACLF-3 (figure 2B) or those transplanted with ACLF-3 (supplementary figure 1).

Figure 2. ICU admission and listing of ACLF-3 patients*



* 5 centers did not provide data on patients admitted to the ICU and not listed/transplanted

Among the 227 patients who were admitted to the ICU with ACLF-3 but not listed, the most frequent reason for not listing was illness severity (88 patients, 39%) (table 2). Addiction issues (62 patients, 28%), comorbidities (30 patients, 13%) and uncontrolled bacterial infection (21 patients, 9%) were the other important causes (table 2).

When comparing "high" and "low" listing /transplanting centers, a significant difference was only observed for the illness severity criteria (31% vs. 46%, p=0.042).

Table 2. Main reason for not listing patients with ACLF-3 in the ICU

Main reason for not listing	Total[1] N = 227	High listing/transplanting centers[2] N = 99	Low listing/transplanting centers[2] N = 128	p-value
Illness severity, n (%)	88 (39%)	31 (31%)	57 (46%)	0.04
Addiction, n (%)	62 (28%)	32 (32%)	30 (24%)	0.14
Comorbidities, n (%)	30 (13%)	16 (16%)	14 (11%)	0.25
Uncontrolled bacterial infection, n (%)	21 (9%)	8 (8%)	13 (10%)	0.59
Other, n (%)	23 (10%)	12 (12%)	11 (8.8%)	0.38

[1]The main reason for not listing was not provided for 3 patients in the low listers group

[2] "High listing/transplanting centers": 4 centers who listed the most patients (and who were also the centers who transplanted more than 10 patients with ACFL3 over the study period). "Low listing/transplanting centers": the 11 other centers. N.B. The 4 centers that did not provide data on patients in the ICU with ACLF-3 who were not listed were not included in this analysis.

There were individual differences in the balance of the main reasons for not listing patients among centers (supplementary figure 2), with no clear pattern emerging.

In addition, the percentage of female patients not listed was not significantly different between the "high" and "low" listing /transplanting centers (27% vs. 29%, p = 0.79), as was the mean age of patients not listed (55 vs. 53 years, p = 0.14).

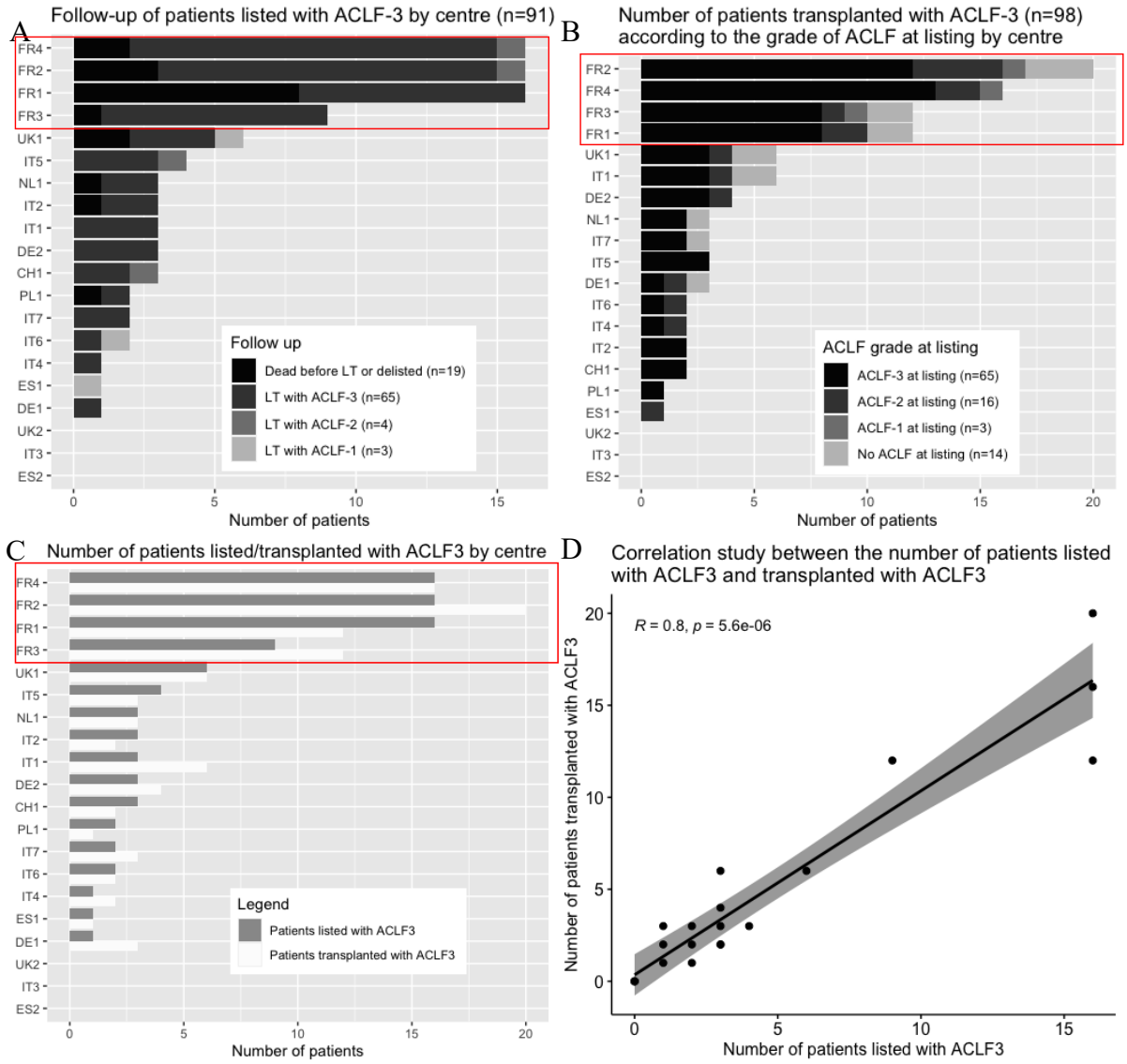
Relationship between listing and transplanting patients with ACLF-3

Among the 91 patients who were *listed* whilst in ACLF-3 (figure 3A), the majority (65 patients, 71%) were transplanted with ACLF-3 and 19 patients (21%) died or were delisted before LT (none of these 19 patients were alive one year after listing).

Among the 98 patients who were *transplanted* with ACLF-3 over the study period, 65 (66%) were also *listed* whilst in ACLF-3 (figure 3B). The make-up of the population of patients transplanted with ACLF-3 was similar across centers. In particular, among the centers that transplanted patients with ACLF-3, none of them restricted the access to LT for patients who had been listed prior to developing ACLF.

There was a significant correlation between listing and transplanting patients with ACLF-3 (correlation coefficient: 0.8, p<0.0001) (figure 3D). In particular, the 4 centers that transplanted the highest number of patients with ACLF-3 were also the centers that listed the highest number of patients with ACLF-3 (red box, figure 3A, 3B and 3C).

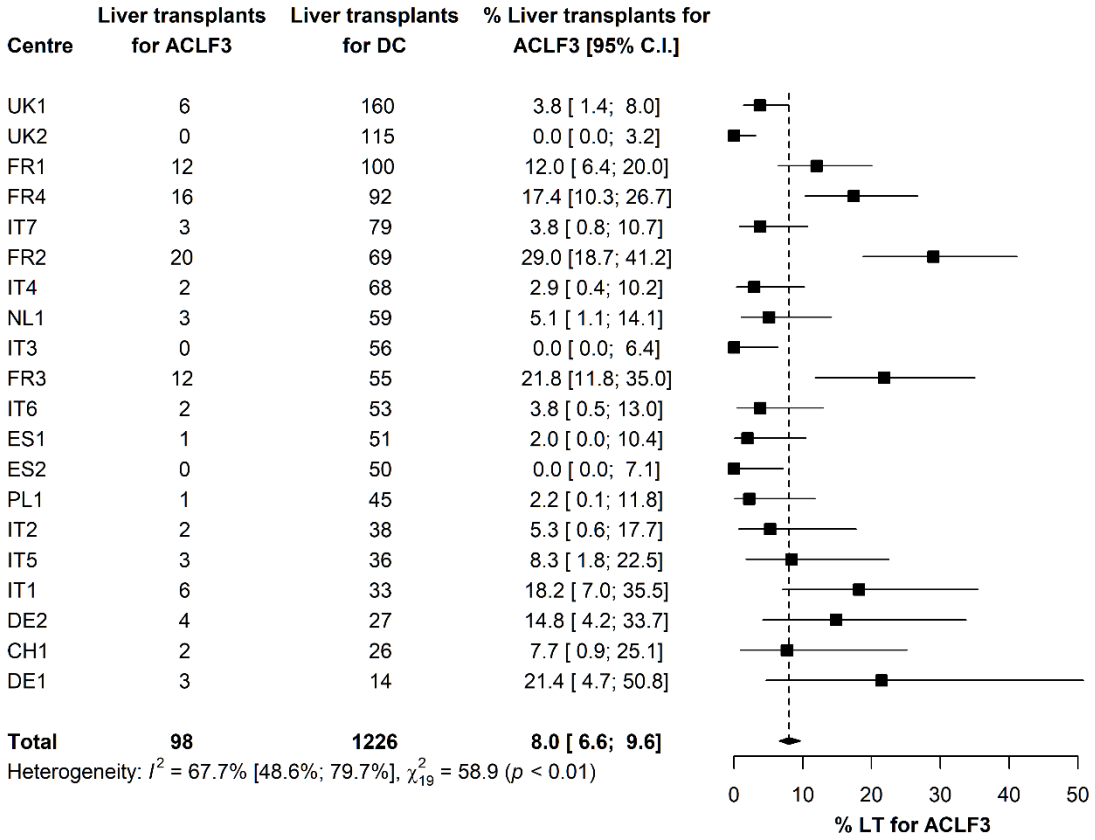
Figure 3. Listing and transplanting ACLF-3 patients



Variability of LT activity for patients with ACLF-3 across the cohort

On average, LT for ACLF-3 accounted for 8% of patients transplanted for decompensated cirrhosis in the study cohort. However, the number of LTs for ACLF-3 patients ranged from 0 (in three centers) to 20 patients across transplant centers, with percentages ranging from 0% to 29% (figure 4). The forest plot of LT activity for ACLF-3 shows consistent variation of such percentage among centers, with an I^2 of 67.7% (95% CI: 48.6%, 79.7%) showing substantial heterogeneity, confirmed by the $\chi 2$ (p-value<0.01).

Figure 4. Forest plot of the percentage of LT for ACLF-3 on LT for DC across the cohort



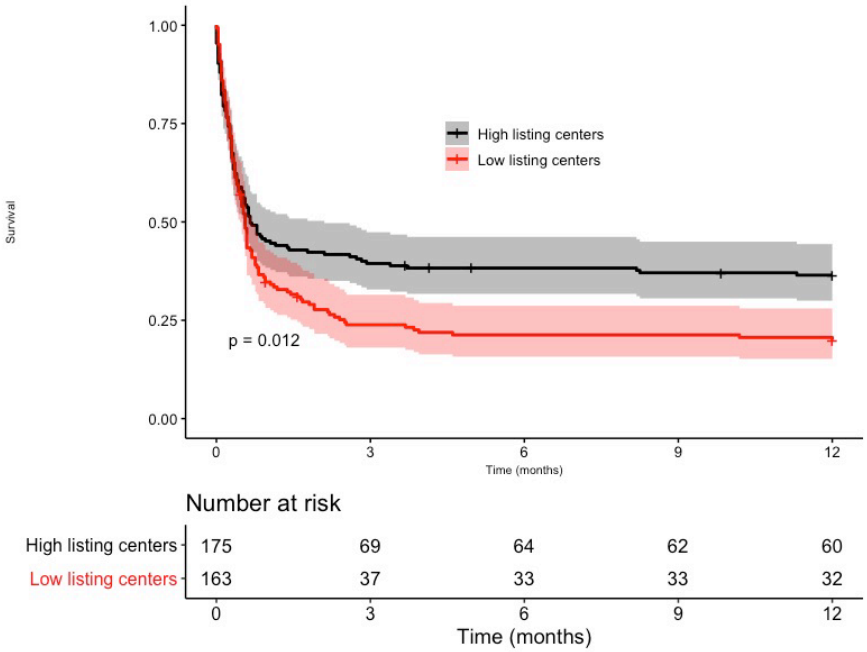
There was a significant correlation between the transplant volume of the LT center over the study period and both the number of LTs performed for HCC (correlation coefficient: 0.55, p = 0.00082) and for DC (correlation coefficient: 0.66, p < 0.0001) (supplementary figure 3A and 3B).

In contrast, there was no significant correlation between LT center transplant volume and the number of LTs performed for ACLF-3 (supplementary figure 3C) or between the number of LTs for decompensated cirrhosis and the number for ACLF-3 (supplementary figure 3D).

Analysis of overall survival depending on the type of center (high listing/transplanting vs. low)

One-year survival of the whole cohort (including patients admitted to the ICU but not listed, and all those listed and transplanted with ACLF-3)from the time of ACLF-3 diagnosis was significantly higher in the 4 centers that listed/transplanted the most patients in ACLF-3 when compared to the 11 other centers (respectively 36% vs 20%, p = 0.012).

Figure 5. Survival analysis depending on the type of center (high listing/transplanting vs. low)



On intention to transplant analysis for patients listed whilst in ACLF-3, the overall one-year survival was 64%, with no significant difference between high listing and low listing centers (respectively 71% vs. 60%, p = 0.25) (none of the patients listed whilst in ACLF-3 who were not transplanted survived one year).

Finally, the one-year survival of patients transplanted whilst in ACLF-3 was 79% with no significant difference between high listing and low listing centers (respectively 76% vs. 80%, p = 0.71)

Discussion

The results of this study reveal a substantial variability of liver transplantation activity for patients with ACLF-3 across European transplant centers. This is despite the observation that the overall one-year survival of ACLF-3 patients from the time of ACLF-3 diagnosis was significantly higher in centers that listed and transplanted more ACLF-3 patients than in centers that listed and transplanted fewer. It is important to note that there was no correlation between the number of patients transplanted with ACLF-3 and the volume of LTs performed by individual centers. In addition, the number of patients with ACLF-3 admitted in the ICU and the number of patients who were listed for LT with ACLF-3 was also unrelated. The main reason for not wait listing ACLF-3 patients differed between the two groups of "higher" and "lower" listing centers, with the low listing group more commonly citing illness severity as a reason for not listing patients with ACLF-3.

Taken together, the results of this study help clarify three key steps in the clinical management of patients with ACLF-3.

First, it shows that ICU admission practices of patients with ACLF-3 varies across centers but this does not correlate with their wait-listing strategies for LT. In particular, admitting higher numbers of unlisted ACLF-3 patients to the ICU did not translate into more wait-listing and greater access to LT for these patients.

Second, the attitude of the center toward wait listing patients with ACLF-3 was a key element that defined the variability of transplant activity for these patients across centers. In practice, this implies that a transplant program for patients with ACLF-3 may require listing patients who are too ill to be transplanted at the time of listing, optimizing their care in the ICU, and potentially transplanting them later, when a degree of improvement has occurred. It was therefore striking that the criteria that distinguished high and low listing centers as the principal reason for not listing patients with ACLF-3 in the ICU was illness severity, rather than comorbidities or addiction issues. There was a strong and significant correlation between wait-listing and LT whilst patients had ACLF-3. The majority (66%) of patients who were transplanted with ACLF-3 had been listed whilst they had ACLF-3 and only 14% of patients transplanted with ACLF-3 had been listed prior to developing ACLF (30% had been listed with ACLF-1 or 2). This finding implies that transplanting critically ill patients requires being able to fast-track the pre-LT assessment of patients who have often not been previously considered as LT candidates by the transplant team. It is a clinical challenge that requires obtaining medical and psychosocial background information about the patient and organizing multidisciplinary decision-making meetings with different team members rapidly on the basis of what may be limited or fragmentary information (when the patient is intubated, for example).

Third, the percentage of patients who were listed with ACLF-3 but died on the waiting list or were delisted was much lower (21%) than that reported in the literature, in particular in the UNOS database (7). The data suggests that this may be due to many ACLF-3 patients not being listed at all because they are thought to be too sick. In addition, it may suggest that in Europe, patients listed with ACLF-3 are less likely to need prioritization beyond the MELD score in order to have access to LT (the median time from listing to transplant was 5 days for patients listed with ACLF-3). In other words, variations in listing strategies for patients with ACLF-3 seems to be the main obstacle for their access to LT. Interestingly, the 4 centers that listed and transplanted most patients came from France, where there is no extra prioritization for patients with ACLF beyond the MELD score (this is also the case in the other countries included in this study) and where it has been shown that there are also important variations in access to LT for critically ill cirrhotic patients despite a single, centralized allocation algorithm (8). However,

whether lack of prioritization prevents patients with ACLF-3 from being listed is beyond the scope of this study.

The observation that the main difference between the low and the high volume centers was that the patients were thought to be too ill to undergo LT in the low volume centers suggests a lack of consensus defining which ACLF-3 patients should not be transplanted. It is therefore crucial to distinguish criteria that should be used to decide that a patient is too sick to be *listed* for LT (based chiefly on comorbidities) from criteria to decide that a patient is too sick to be *transplanted* at the time when an organ becomes available (figure 6). Granular studies have shown that respiratory failure, arterial lactate level, age, the TAM score,MDRO and fungal infections are useful criteria to judge whether a patient is too sick to be transplanted at the time of organ availability, based on poor post-LT survival (5,9–11). Without this appreciation and consensus, we risk transplanting too few patients with ACLF-3 or too many with poor outcomes thereby funneling scarce resources to patients with potentially unacceptably low post-LT survival rates.

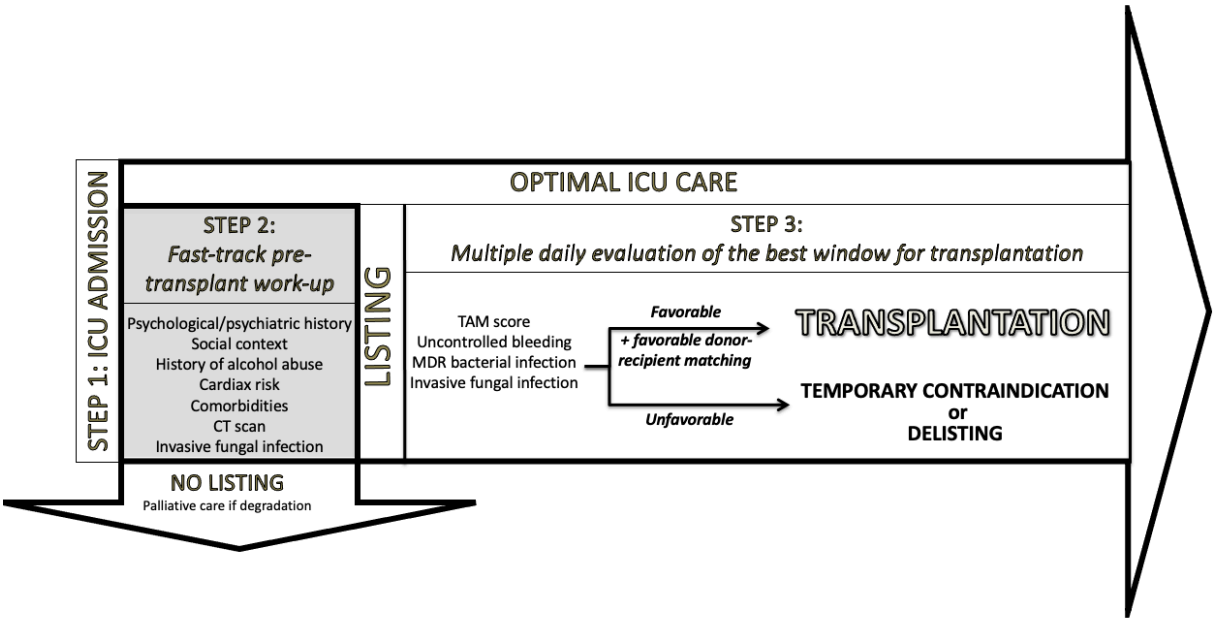
The variability of LT activity for ACLF-3 patients among European transplant centers described in this study highlights the inequity of access to LT for patients with ACLF-3. This variability among centers also reflects a lack of consensus among European transplant teams on this specific indication of LT. Such a lack of consensus is possibly due to the relative scarcity of prospectively collected data. While studies from the UNOS registry report >80% one-year post-LT survival rates for ACLF-3 patients (12), smaller case series studies report contrasting findings. Some, including the results from the current series, report similar post-LT survival (5,13), others report significantly poorer results (10,14). To date, only one registry study has reported on longer term survival (15). In addition to this relative scarcity of data, the variability of LT activity probably also relates to diverging views concerning the overall utilization of LT and its application to patients with DC. There are justifiable concerns that more widespread use of LT for patients with ACLF-3 could disadvantage cirrhotic candidates who were listed without ACLF with a "traditional" elective pre-LT assessment and more certainty of optimal outcomes.

The scope of this study is limited by its retrospective nature and by the limited number of patients included over selected centers in Europe. However, it uses granular data and reports exhaustively on all patients treated. The other major limitation is that we did not did not report on patients with ACLF-3 who did not have access to the ICU. To date, no study has been able to provide a consistent picture of this subgroup of critically ill cirrhotic patients who are denied access to the ICU and whose epidemiology remains hard to assess.

Conclusion

The results of this study highlight the inequity of access to LT that patients with ACLF-3 experience across European transplant centers. It underlines how listing strategies for ACLF-3 patients influence their access to LT and, ultimately, their survival. Finally, this study demonstrates the lack of practical consensus among European transplant teams on this specific indication of LT, highlighting the need for more prospective data defining the role of LT in ACLF-3.

Figure 6.



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