Therapeutic plasma exchange in acute liver failure

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Abstract

Background: Multi-organ dysfunction in acute liver failure (ALF) has been attributed to a systemic inflammatory response directly triggered by the injured liver. High-volume therapeutic plasma exchange (HV-TPE) has been demonstrated in a large randomized controlled trial to improve survival. Here, we investigated if a more cost-/resource effective low-volume (LV) TPE strategy might have comparable beneficial effects.

Methods: This retrospective study evaluated the effect of LV-TPE on remote organ failure, hemodynamical and biochemical parameters as well as on survival in patients with ALF. Twenty patients treated with LV-TPE in addition to standard medical therapy (SMT) were identified and 1:1 matched to a historical ALF cohort treated with SMT only. Clinical and biochemical parameters were recorded at admission to the intensive care unit and the following 7 days after LV-TPE.

Results: Mean arterial pressure increased following first LV-TPE treatments (d0: 68 [61-75] mm Hg vs d7: 88 [79-98] mm Hg, \( P = .003 \)) and norepinephrine dose was reduced (d0: 0.264 [0.051-0.906] \( \mu \)g/kg/min vs d3: 0 [0-0.024] \( \mu \)g/kg/min, \( P = .016 \)). Multi-organ dysfunction was significantly diminished following LV-TPE (CLIF-SOFA d0: 17 [13-20] vs d7: 7 [3-11], \( P = .001 \)). Thirty-day in-hospital survival was 65% in the LV-TPE cohort and 50% in the SMT cohort (Hazard-ratio for TPE: 0.637; 95% CI: 0.238-1.706, \( P = .369 \)).

Abbreviations: ACLF, acute on chronic liver failure; ALF, acute liver failure; CLIF-OF, chronic liver failure-organ failure score; CLIF-SOFA, chronic liver failure-sequential organ failure assessment score; DAMPs, damage associated molecular patterns; FFP, fresh frozen plasma; HE, hepatic encephalopathy; HV-TPE, high-volume therapeutic plasma exchange; IBW, ideal body weight; INR, international normalized ratio; LV-TPE, low-volume therapeutic plasma exchange; MAP, mean arterial pressure; NE, norepinephrine; PCM, paracetamol; PDMS, patient data monitoring system; RRT, renal replacement therapy; SMT, standard medical therapy; SOFA, sequential organ failure assessment; TPE, therapeutic plasma exchange; TRALI, transfusion-related acute lung injury.
Conclusions: Patients treated with LV-TPE showed improved surrogate parameters comparable with the effects reported with HV-TPE. These data need to be interpreted with caution due to their retrospective character. Future controlled studies are highly desirable.

KEYWORDS
acute liver failure, liver transplantation, plasma exchange

1 INTRODUCTION

It has been proposed that the predominant mechanism responsible for the development of multi-organ failure (MOF) and hepatic encephalopathy (HE) in acute liver failure (ALF) patients is an overwhelming systemic immune response triggered by the release of proinflammatory cytokines and damage-associated molecular patterns (DAMPs) due to acute and often massive necrosis of hepatocytes. In line with this hypothesis, several studies have shown that the presence of a systemic inflammatory response syndrome is associated with a worsening of HE and a particularly poor prognosis in ALF. Extracorporeal removal of excess circulating proinflammatory molecules might be a therapeutic option.

In this context, therapeutic plasma exchange (TPE) has shown beneficial effects. It combines two treatment principles in a single intervention: (a) replacement of the excretory and metabolic functions of the failing liver via supplementation of the lacking proteins and (b) removal of deleterious DAMPs and cytokines thus modulating the pathological overwhelming immune response that counts responsible for the associated MOF. Various case series and uncontrolled studies have shown that TPE is safe in patients with ALF and can significantly reduce both the concentration of ammonia and the grade of HE as well as improvements in hemodynamics. A more recently published prospective multicenter randomized controlled trial (RCT) by Larsen et al in which 182 ALF patients received either standard medical therapy (SMT) or SMT plus high-volume therapeutic plasma exchange (HV-TPE) demonstrated that HV-TPE did not only improve hemodynamic and biochemical parameters but also overall hospital survival in patients with ALF by approximately 10%. This landmark work was the first RCT to show a survival benefit in the medical treatment of patients with ALF. HV-TPE was defined herein as TPE with donor plasma at 15% of ideal body weight (IBW), or 8 to 12 L in each approximately 9-hour treatment sessions on three consecutive days. As stated by the authors, the dose of TPE had been chosen arbitrarily, and both lower as well as higher doses could have had the same beneficial effects.

In our hospital, we have performed TPE since 2013 in patients with ALF. However, in contrast to Larsen et al we have employed a low-volume TPE (LV-TPE) approach consisting of a TPE volume of approximately 3 to 4 L per session (eg, 12 units of fresh frozen plasma [FFP]) per day until clinical improvement or until liver transplantation. A similar protocol has successfully been used at our institution in other hyperinflammatory diseases causing MOF, for example, the treatment of severe septic shock. A lower incidence of transfusion-related complications such as transfusion-related acute lung injury (TRALI) and a shorter discontinuation of continuous renal replacement therapy (RRT) could be hypothesized as additional advantages of such a LV-TPE regimen.

Current guidelines of the American Society of Apheresis (ASFA) give a strong grade 1A/III recommendation for HV-TPE but only a weak grade 2B/III recommendation for the use of any non-HV-TPE in ALF given the lack of robust data for a LV-TPE approach.

Here, we retrospectively analyzed the effect of a LV-TPE strategy on organ failure, hemodynamics, and biochemical parameters as well as on survival in patients with ALF. We additionally compared survival of those patients with a matched historical cohort of patients with ALF receiving SMT only.

2 METHODS

2.1 Study population

This was a retrospective single-center study performed in a tertiary care hospital from July 2013 to May 2018. We screened intensive care patients, admitted with hepatic failure (DRG coding number K72.0) to our medical intensive care unit (ICU), who were receiving TPE (German OPS code 8-820). Patients with acute on chronic liver failure (ACLF) and with secondary ALF due to other critical illnesses such as septic or cardiogenic shock were excluded from the analysis. Patients with primary ALF following the definition suggested by the European Association for the Study of the Liver (EASL) Clinical Practical Guidelines on the management of ALF (severe acute liver injury as
indicated by the presence of both coagulopathy [INR. 1.5] and HE without preexisting chronic liver disease) were finally enrolled into the analysis. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2 | Intervention—TPE

Vascular access was established by venous insertion of an 11-French two-lumen hemodialysis catheter.

Procedural characteristics of LV-TPE treatment are demonstrated in Table 1. LV-TPE was performed daily against a fixed dose of replacement fluid of 12 units FFP for all patients. Only plasma and no albumin was used as replacement fluid. Treatment duration was about 2 hours and LV-TPE was performed on all consecutive days since diagnosis of ALF until clinical recovery or liver transplantation. Therefore number of performed LV-TPE treatments varied between patients from 1 to 11 treatment sessions. Anti-coagulation during LV-TPE was achieved by regional citrate infusion. Post filter calcium concentration was checked about 15 minutes after starting treatment and then every 8 hours as regulated by a local protocol at our institution. Citrate flow rate was adjusted to target post filter ionized calcium concentrations of 0.5 to 0.6 mmOL/L. Additionally systemic blood gas analysis was performed every 2 to 4 hours to exclude electrolyte and acid-base dysbalances. Seventy-five percent of patients received no more than three TPE treatments. Median treatment time was 110 (93-114) min. Given the fixed dose of 12 units of FFP in all treatments, median exchanged plasma volume was 3.1 L (3-3.6), corresponding to 5.3 (4.9-6.1) % of patients' individual IBW. As the number of performed treatment sessions varied substantially between individual patients so did the total exchanged plasma volume. Median volume was 6.6 L, which corresponded to about 12% of IBW. In patients with acute kidney injury, continuous hemodialysis was interrupted for the duration of LV-TPE.

2.3 | Data collection

All personal patient data were anonymized before further analysis. Data were collected using electronic medical records including the patient data monitoring system (PDMS) m.life (Version 10.5.0.71, medisite GmbH, Berlin, Germany). Sequential organ failure assessment (SOFA) scores were calculated according to the description by Vincent et al. Organ failure was defined as an organ specific SOFA score of equal or greater than two. Additional, more liver specific organ failure scores were used: the chronic liver failure-SOFA (CLIF-SOFA) score as described by Moreau et al and the CLIF-organ failure (CLIF-OF) score as described and Jalan et al, respectively. CLIF-SOFA and CLIF-OF scores were primarily validated for patients with ACLF and not ALF. However, since they

| Category                     | Median (interquartile range)/No (%) |
|------------------------------|-------------------------------------|
| Device                       | Spectra Optia                       |
| Version                      | -                                   |
| Manufacturer                 | Terumo BCT Inc., Lakewood, California|
| Anticoagulant: citrate, dextrose solution A (ACD-A)—no (%) | 20 (100) |
| AC ratio                     | 10 to 1                             |
| Plasma volume treated        | Fixed dose of 12 units of fresh frozen plasma |
| Replacement fluid            | 100% fresh frozen plasma            |
| Number and frequency of procedures |                                      |
| TPE number—no (%)            | 1× 4 (20)                           |
|                              | 2× 7 (35)                           |
|                              | 3× 4 (20)                           |
|                              | 4× 1 (5)                            |
|                              | 5× 1 (5)                            |
|                              | 9× 1 (5)                            |
|                              | 10× 1 (5)                           |
|                              | 11× 1 (5)                           |
| Frequency                    | Daily                               |
| Blood flow—mL/min            | 50 (44.8-58)                        |
| Singular treatment           |                                      |
| Time of treatment—min        | 110 (93-114)                        |
| Number of plasma units       | 12 (12-12)                          |
| Max. volume of plasma exchange—L | 3.13 (3-3.599)                     |
| Max. volume of plasma exchange—% of IBW | 5.3 (4.9-6.1)                  |
| Cumulative of all treatments |                                      |
| Volume of plasma exchange—L | 6.603 (5.076-11.848)               |
| Volume of plasma exchange—% of IBW | 11.7 (8.5-19.8)             |

Note: Description of number of performed treatments, choice of anticoagulation and blood flow as well as plasma volume exchanged in singular and cumulative treatment sessions. Values are presented as median (25%-75% interquartile range) or (if categorical) as numbers and percentages. Abbreviations: FFP, fresh frozen plasma; IBW, ideal body weight; LV-TPE, low-volume therapeutic plasma exchange.
are, especially in terms of the subcategories hepatic failure/bilirubin and neurologic failure/HE, more liver specific than the regular SOFA score, they are used also in patients with ALF as seen in the original publication describing use of HV-TPE in ALF by Larsen et al.9 Clinical and biochemical parameters were recorded at day 0, 1, 3, and 7 with day 0 indicating the day of first TPE session.

2.4 | Matching with historic cohort receiving SMT only

The cohort of patients with ALF receiving LV-TPE was matched 1:1 to a historical cohort treated at the same ICU with SMT only.17 Patients were matched for the following demographic and clinical characteristics: age, gender, BMI, etiology of ALF, onset of ALF (acute/hyperacute vs subacute), grade of HE (grade I/II vs grade III/IV), need for invasive ventilation, oxygenation index, need of vasopressor therapy, vasopressor dose, INR, lactate concentration, SOFA score, CLIF-SOFA score, and CLIF-OF score.

Since July 2013 we are routinely using LV-TPE for all patients with ALF. All patients of the historic control cohort treated at the same ICU were treated (without TPE) before July 2013. Therefore no decision was made to treat or not treat patients with TPE at the same time period.

2.5 | Statistical analysis

We used GraphPad Prism (Version 6.0, GraphPad Software, La Jolla, California) and IBM SPSS Statistics (Version 25.0, IBM Corp., Armonk, New York) for data analysis and graph generation. Categorical variables are shown as numbers (n) and percentages (%). Continuous variables are shown as median and 25% to 75% quartiles, unless indicated otherwise. Variables were checked for normal distribution using the D’Agostino-Pearson omnibus normality test and the Shapiro-Wilk normality test. For comparisons, Chi-squared test, Mann-Whitney U test, Wilcoxon matched-pairs signed rank test, and two-sided paired t test were used accordingly. Univariate logistic regressions were conducted. Survival was analyzed for the whole cohort and for subgroups using Kaplan-Meier graphs and the Log-rank test. All reported P-values are two-sided unless indicated otherwise; P-values <.05 were considered statistically significant.

3 | RESULTS

3.1 | Cohort characterization

From July 2013 to May 2018, a total of 77 patients were admitted with ALF to our ICU and received LV-TPE. Thirteen patients with ACLF and 44 patients with secondary ALF due to other critical illnesses such as septic shock were excluded from the analysis. Finally, 20 patients with primary ALF were enrolled into the retrospective analysis. To compare survival a historical group of additional 20 patients receiving SMT only was matched in a 1:1 fashion as described previously. A flow chart in accordance to the consort statement is shown as Figure 1. Demographic and clinical details are summarized in Table 2.

Seventy-five percent of the patients in the LV-TPE cohort were female, and the median (interquartile range) age was 35 (26-52) years. The vast majority of patients had high grade HE at admission to the ICU with grade III and IV HE counting for 75% of cases. Acute kidney injury with need for RRT was present in 85% of the patients at inclusion. Sixty percent of patients were in shock reflected by the need of vasopressor therapy with norepinephrine and a median lactate concentration of 5.3 (3.1-10.6). Median SOFA, CLIF-SOFA, and CLIF-OF scores were 15 (9-20), 17 (13-20), and 12 (9-13), respectively.

The matched SMT cohort was comparable in most demographic and clinical characteristics at inclusion—including age, gender, BMI, etiology of ALF, onset of ALF (acute/hyperacute vs subacute), grade of HE (grade I/II vs grade III/IV) as well as the proportions for need of invasive ventilation and vasopressor therapy. Additionally, both oxygenation index, vasopressor dosage, INR, ALT, ammonia- and lactate concentration as well as SOFA, CLIF-SOFA, and CLIF-OF scores were 15 (9-20), 17 (13-20), and 12 (9-13), respectively.

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| Category                          | Median (interquartile range)/no (%) | All (n = 40) | LV-TPE (n = 20) | SMT (n = 20) | P  |
|----------------------------------|-------------------------------------|-------------|----------------|-------------|----|
| Age—y                            | 36 (28-48)                          | 35 (26-52)  | 37 (30-46)     | .876        |
| Sex—no (%)                       |                                     |             |                |             |    |
| Male                             | 8 (20)                              | 5 (25)      | 4 (20)         | 1.0         |
| Female                           | 32 (80)                             | 15 (75)     | 16 (80)        |             |
| Weight—kg                        | 70 (60-80)                          | 70 (58-83)  | 70 (60-75)     | .325        |
| Height—cm                        | 170 (165-170)                       | 169 (165-170)| 170 (160-170) | .707        |
| BMI—kg/m²                        | 24.2 (22.3-27.7)                    | 24.2 (22.4-29.3)| 24.2 (22.1-27.7)| .503    |
| ALF onset—no (%)                 |                                     |             |                |             |    |
| Hyperacute                       | 21 (52.5)                           | 12 (60)     | 9 (45)         | .342        |
| Acute                            | 11 (27.5)                           | 4 (20)      | 7 (35)         | .288        |
| Subacute                         | 8 (20)                              | 4 (20)      | 4 (20)         | 1.0         |
| ALF etiology—no (%)              |                                     |             |                |             |    |
| PCM                              | 4 (10)                              | 2 (10)      | 2 (10)         | 1.0         |
| Toxic                            | 16 (40)                             | 8 (40)      | 8 (40)         | 1.0         |
| Viral                            | 5 (12.5)                            | 2 (10)      | 3 (15)         | .633        |
| Ischemic                         | 3 (7.5)                             | 2 (10)      | 1 (5)          | .548        |
| Wilson's disease                 | 2 (5)                               | 1 (5)       | 1 (5)          | 1.0         |
| AIH                              | 2 (5)                               | 1 (5)       | 1 (5)          | 1.0         |
| Others                           | 5 (12.5)                            | 3 (15)      | 2 (10)         | .633        |
| Unknown                          | 3 (7.5)                             | 1 (5)       | 2 (10)         | .548        |
| Additional infection suspected—no (%) | 7 (17.5)                           | 5 (25)      | 2 (10)         | .212        |
| Hepatic encephalopathy—no (%)    |                                     |             |                |             |    |
| I                                | 2 (5)                               | 0 (0)       | 2 (10)         | .147        |
| II                               | 8 (20)                              | 5 (25)      | 4 (20)         | 1.0         |
| III                              | 7 (17.5)                            | 3 (15)      | 2 (10)         | .212        |
| IV                               | 23 (57.5)                           | 12 (60)     | 12 (60)        | .749        |
| pO2/FiO2 Oxygenation index        | 357 (188-429)                       | 334 (152-530) | 360 (250-394) | .883        |
| pCO2—mm Hg                       | 35 (30-43)                          | 39 (29-44)  | 34 (30-38)     | .207        |
| Invasive ventilation—no (%)      | 25 (62.5)                           | 12 (60)     | 13 (65)        | .744        |
| Vasopressor therapy—no (%)       | 19 (47.5)                           | 9 (45)      | 10 (50)        | .752        |
| Vasopressor dose—µg/kg/min        | 0.278 (0.178-0.556)                 | 0.3 (0.103-1.256)| 0.267 (0.198-0.730) | .365    |
| Renal replacement therapy—no (%) | 31 (77.5)                           | 17 (85)     | 14 (70)        | .465        |
| Listed for liver transplant—no (%)| 16 (40)                             | 8 (40)      | 8 (40)         | 1.0         |
| Lab                              |                                     |             |                |             |    |
| Bilirubin—µmol/L                 | 228 (81-380)                        | 87 (41-347) | 276 (142-448)  | .077        |
| INR                              | 2.04 (1.71-3.34)                    | 1.9 (1.7-2.8)| 2.12 (1.71-3.48)| .244        |
| ALT—IU/mL                        | 3496 (195-4108)                     | 1624 (240-4019)| 1237 (135-4108) | .957        |
| Lactate—µmol/L                   | 5.3 (2.7-10)                        | 5.3 (3.1-10.6)| 5.0 (2.5-9.9)  | .602        |
| Ammonia—µmol/L                   | 82 (58-146)                         | 92 (72-141) | 68 (53-150)    | .344        |
| SOFA score—points                | 15 (9-19)                           | 15 (9-20)   | 14 (8-19)      | .835        |
| CLIF-SOFA score—points           | 17 (12-20)                          | 17 (13-20)  | 17 (12-20)     | .917        |
| CLIF-OF score—points             | 12 (9-13)                           | 12 (9-13)   | 12 (9-13)      | .899        |
cohort (276 vs 87 μmol/L, \( P = .077 \)), although the variance of bilirubin baseline values was wide in both cohorts.

### 3.2 Feasibility and tolerability of LV-TPE

Low volume TPE treatment was feasible and well tolerated. It could easily be integrated in every day critical care routine as it tied the required specialized dialysis personal for no longer than 2 hours. No patient experienced severe side effects such as anaphylactic reaction or TRALI. Citrate was used safely in all patients as anticoagulant. No serious electrolyte or acid-base disturbances occurred in the patients investigated in this study.

#### 3.2.1 Effects of LV-TPE on organ dysfunction, hemodynamics, and biochemical parameters

Figure 2 shows clinically relevant parameters during the disease course following LV-TPE (with day 0 indicating baseline values before first LV-TPE treatment). Mean arterial pressure (MAP) increased early and steadily following first LV-TPE treatments (at d0: 68 [61-75] mm Hg vs d7: 88 [79-98] mm Hg, \( P = .003 \); Figure 2A). At the same time, the dose of norepinephrine was significantly reduced (d0: 0.264 [0.051-0.906] μg/kg/min vs d3: 0 [0-0.024] μg/kg/min, \( P = .016 \); Figure 2B). Lactate concentrations were also reduced (d0: 5.3 [3.1-10.6] mmol/L vs d7: 1.1 [0.9-1.6] mmol/L, \( P < .001 \); Figure 2C). Median Glasgow coma scale increased from 3 to 7.5 to 12 and 15 on days 0, 1, 3, and 7, respectively (Figure 2D). At the same time, median blood ammonia concentrations declined steadily from 91.5 (71.8-140.8) μmol/L at d0 to 38 (30.8-53.3) μmol/L (\( P = .037 \); Figure 2E). Coagulation was improved as indicated by a reduction of INR (d0: 1.9 [1.7-2.8] vs d7: 1.1 [1.1-1.4], \( P = .009 \); Figure 2F). LV-TPE was accompanied by a reversible decline in thrombocyte count (d0: 80 [44-133] 106/μL vs d1: 52 [31-92] 106/μL, \( P = .005 \) vs d7: 70 [47-109] 106/μL, \( P = .349 \); Figure 2G). ALT concentrations steadily decreased across the observation period.
the observation period (Figure 2I,J). Bilirubin and creatinine concentrations mainly remained unchanged during the LV-TPE treatment period (Figure 2K,L).

The effect of LV-TPE on organ dysfunction was assessed by established general and liver specific scores of organ dysfunction, namely the SOFA score as well as the CLIF-SOFA and CLIF-OF score, respectively. Median SOFA scores declined from 15 to 13 to 11 and 8 on days 0, 1, 3, and 7, respectively (P = .002 for d0 vs d7; Figure 3A). Additionally, both CLIF-SOFA and CLIF-OF scores demonstrated a steady decline that was significant at all-time points post TPE (for CLIF-SOFA d0: 17 [13-20] vs d7: 7 [3-11], P = .001; Figure 3B and for CLIF-OF d0: 17 [13-20] vs 8 [6-9]; Figure 3C).

**3.2.2 | Survival**

The overall 30-day in-hospital survival was 65% in the LV-TPE cohort and 50% in the matched SMT cohort (Hazard-ratio for TPE: 0.637; 95% CI: 0.238-1.706, P = .369; Figure 4A). Both in the LV-TPE group and in the SMT group, eight patients (40%) were listed for liver transplantation. Seven patients (35%) in the LV-TPE group and five patients (25%) in the matched SMT group eventually received a liver transplant. In patients undergoing liver transplantation, all survived in the SMT group while one died in the LV-TPE group (P = .398). In patients who were not receiving a liver transplantation, 54% survived in the LV-TPE group and 33% in the SMT group (Hazard-ratio for TPE: 0.639; 95% CI: 0.226-1.807, P = .398; Figure 4B).

**4 | DISCUSSION**

This retrospective single-center explorative cohort study examined the hypothesis that a LV-TPE might have comparable beneficial effects on organ failure, hemodynamic, biochemical parameters, and survival in patients with ALF as it has recently been shown for a HV-TPE regimen.9

First, our data show that LV-TPE was feasible and apparently less burdensome than the HV-approach. The LV-TPE...
remains the gold standard in critical care treatment of ALF until now.18 It is worthwhile mentioning that the discontinuation time of RRT for the LV-TPE (same catheter used) is relatively brief.

Second, LV-TPE was apparently well tolerated. We did not see any adverse events such as hypotension, allergic reaction, or TRALI in response to treatment. One could speculate that the exchange of only 3 to 3.5 L of plasma in each treatment compared to 9 to 12 L as described with HV-TPE might lead to reduced rates of pulmonary edema and TRALI. Larsen et al did report on one case of TRALI. The median oxygenation indices declined constantly from 306 to 258 under HV-TPE. In our study, oxygenation index increased slightly from 334 at baseline to 445 mm Hg on day 7. In contrast, following HV-TPE, a transient increase of pCO₂ not seen in the control group was observed. As with HV-TPE, we recognized a transient and modest decrease in thrombocyte count that was reversible at later time points. Comparable to HV-TPE, coagulation was improved by LV-TPE indicated by a stepwise normalization of INR.

Importantly, hemodynamic improvement indicated by increased MAP alongside with a reduction of vasopressor requirement could be seen under LV-TPE. All these effects were comparable to those seen with HV-TPE and hemodynamic improvement has been postulated by Larsen et al as one of the most important effects of TPE as it is the basis for stabilization of organ dysfunction in ALF. As a possible indicator of improved hepatic lactate clearance and/or microcirculation, lactate concentrations were also reduced.

Hepatic encephalopathy improved and a constant and significant reduction of ammonia blood concentrations—the same effect as described in relation to HV-TPE was observed. In contrast to Larsen’s study, intracranial pressure (ICP) was not recorded, since we do not routinely assess ICP in ALF patients.

Most importantly, multi-organ dysfunction as the main determinant of mortality in ALF could be effectively improved. This was indicated by a reduction in both the general SOFA score as well as of the (by the CLIF-consortium suggested) more liver disease specific organ failure scores CLIF-SOFA and CLIF-OF. Indeed, all scores could be reduced to approximately 50% of baseline values. This effect was even more pronounced as seen in HV-TPE although baseline SOFA (15 vs 13) and CLIF-SOFA (17 vs 16) scores were comparable in our study with the Larsen cohort.

We observed better survival rates in patients receiving LV-TPE compared to the matched cohort with SMT only (65% vs 50%, HR 0.64), although this did not reach statistical significance due to the rather small sample size. Larsen et al observed overall survival of 59% in the HV-TPE compared to 48% in the control group (HR 0.56). This survival benefit was exclusively due to patients not receiving liver transplantation. This observation reinforces the hypothesis that TPE might provide a time frame in which hepatic dysfunction might be reversed and liver function may recover.

Although the LV-TPE cohort in this study was comparable in many demographic and clinical characteristics with the cohort investigated by Larsen et al, important discrepancies between the two are of notice thus limiting comparability of both investigations.

The higher proportion of sub-ALF in our treatment group compared to the Danish cohort (20% vs 5%) as well as the surprisingly high proportion of AKI (85% vs 47%) underlines the high morbidity of our patient cohort. In addition, paracetamol (PCM) was responsible for 58% of ALF cases in the Larsen series compared to 33% in ours. The predominance of PCM-associated ALF in the Larsen cohort has been criticized by others, although Larsen et al argued that the observed effects of HV-TPE were comparable between PCM and other causes of ALF.20 We believe it is a strength of this study to represent more cases of drug-induced and subacute ALF as these conditions have been associated with particularly poor outcomes.21

The presence of high grade (stage III and IV) HE at baseline was comparable with 83% in the Larsen collective and 75% in this study as was the requirement of vasopressor therapy with 51% and 45%, respectively. Median dose of vasopressor therapy was also comparable with 0.4 and 0.3 μg/kg/min, respectively. Overall organ dysfunction at baseline as indicated by SOFA and CLIF-SOFA Score were, as mentioned above, estimated within comparable range.

Our study has important limitations—mostly its retrospective nature and the small sample size. Although the historical cohort was not perfectly matched in all relevant clinical characteristics, the grade of multi-organ dysfunction as indicated by equal SOFA, CLIF-SOFA, and CLIF-OF scores, was identical. In fact, this was the pivotal requisition we sought to fulfill by matching as multi-organ dysfunction likely constitutes the most important influence parameter of mortality in patients with ALF.1 Given the lack of a randomized control group, all positive effects observed during the course of LV-TPE might not be related to the intervention. Additionally, also we did not recognize severe side effects of the vascular access and LV-TPE procedure, minor side effects, not being reported in the notes, cannot be excluded completely. This study does not seek to challenge the work by Larsen et al as this remains the only prospective randomized investigation demonstrating a survival benefit in patients with ALF. The HV-TPE protocol continues to represent the gold standard in critical care treatment of ALF until further prospective randomized studies using different TPE regimens are able to show noninferiority results.
In conclusion, with the caveats of a retrospective, single-center study, our data show that patients treated with LV-TPE showed improved hemodynamics and reduced organ dysfunction comparable with the effects reported previously with HV-TPE. Future controlled studies investigating LV-TPE vs HV-TPE strategies in ALF are highly desirable.

ETHICS STATEMENT

The need for ethical approval was waived due to retrospective nature of analysis. All data were anonymized before analysis. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

CONFLICT OF INTEREST

The authors declare that they have no competing interest.

AUTHOR CONTRIBUTIONS

K.S. collected clinical data from the PDMS and generated the figures for publication. K.S., J.H., A.S., M.B., O.W., and S.D. recruited patients. K.S., M.M., M.H., M.B., and S.D. interpreted data, wrote the manuscript, and calculated statistics. S.D. and M.B. had the original idea for this study. All authors read and approved the final manuscript.

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