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Clinical paper

Hypoxic liver injury after in- and out-of-hospital cardiac arrest: Risk factors and neurological outcome

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Abstract

Background: Hypoxic liver injury (HLI) is a frequent and life-threatening complication in critically ill patients that occurs in up to ten percent of critically ill patients. However, there is a lack of data on HLI following cardiac arrest and its clinical implications on outcome. Aim of this study was to investigate incidence, outcome and functional outcome of patients with HLI after in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA).

Methods: We conducted an analysis of a cardiac arrest registry data over a 7-year period. All patients with non-traumatic OHCA and IHCA with return of spontaneous circulation (ROSC) treated at the emergency department of a tertiary care hospital were included in the study. HLI was defined according to established criteria. Predictors of HLI, occurrence, clinical and neurological outcome were assessed using multivariable regression.

Results: Out of 1068 patients after IHCA and OHCA with ROSC, 219 (21%) patients developed HLI. Rate of HLI did not differ significantly in IHCA and OHCA patients. Multivariate regression analysis identified time-to-ROSC [OR 1.18, 95% CI (1.01–1.38); $p < 0.05$], presence of cardiac failure [OR 2.57, 95% CI (1.65–4.01); $p < 0.001$] and Charlson comorbidity index [OR 0.83, 95% CI (0.72–0.95); $p < 0.01$] as independent predictors for occurrence of HLI. Good functional outcome was significantly lower in patients suffering from HLI after 28-days (35% vs. 48%, $p < 0.001$) and 1-year (34% vs. 44%, $p < 0.001$). Occurrence of HLI was associated with unfavourable neurological outcome [OR 1.74, 95% CI (1.16–2.61); $p < 0.01$] in multivariate regression analysis.

Conclusion: New onset of HLI is a frequent finding after IHCA and OHCA. HLI is associated with increased mortality, unfavourable neurological and overall outcome.

Keywords: Cardiac arrest, Hypoxic liver injury, Hypoxic hepatitis, Ischemic hepatitis, Shock liver, Acute liver failure, Multiple organ failure, Intensive care unit

Abbreviations: CA, Cardiac arrest; HLI, Hypoxic liver injury; ROSC, Return of spontaneous circulation; ICU, Intensive care unit; OHCA, Out-of-hospital cardiac arrest; IHCA, In-hospital cardiac arrest; TTM, Targeted temperature management; CPC, Cerebral performance categories; OPC, Overall performance categories; SOFA, Sequential organ failure assessment; SAPS, Simplified acute physiology score; CCI, Charlson comorbidity index.

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Background

Every year estimated 375,000–700,000 citizens are suffering sudden cardiac arrest (CA) in Europe and the USA.[1] Mortality rates, even in patients with return of spontaneous circulation (ROSC), after in-hospital-cardiac arrest (IHCA) or out-of-hospital cardiac arrest (OHCA) are high.[2] Mortality after CA is mainly triggered by post-CA shock and brain injury.[3] The post-CA ischemia and reperfusion injury can lead to the post-CA syndrome, involving multiple organs.[4,5] To date, only few studies addressed the topic of prognostic impact of organ damage after CA.[6–8] Incidence of liver failure after CA is currently poorly studied and was mainly described in studies addressing OHCA.[9–11]

Hypoxic liver injury (HLI), also known as shock liver, hypoxic hepatitis or ischemic hepatitis, is a life-threatening complication accompanying states of oxygen depletion in critically ill patients in the intensive care unit (ICU).[12] HLI can be found in up to 10% of patients admitted to medical ICU's and is associated with mortality rates of over 50%.[13,14] HLI is defined as sharp increase of aminotransferase levels in an acute setting of cardiac, septic or respiratory failure.[12]

In the present study we aimed to investigate the incidence, outcome and course of HLI in a large cohort of successfully resuscitated patients after IHCA or OHCA admitted to a critical care facility.

Methods

This study is based on a prospectively maintained registry at the emergency department (ED) of the Medical University of Vienna. All consecutive patients admitted to the ED (IHCA and non-traumatic OHCA) followed by ROSC, between January 2005 and January 2012, were included in the study. This study was approved by the local ethics committee (Medical University of Vienna, reference number EK-456/2005, extended by EK-1814/2012), informed consent was waived due to observational character of the study.

Cardiopulmonary resuscitation and post-CA care were performed in accordance to the European Resuscitation Council guidelines.[15–17] Data was collected prospectively according to Utstein-style guidelines. OHCA patients were treated by the Viennese two-tier EMS system, featured by an EMS-physician and paramedics, the EMS system was described previously in detail.[18] Survivors were followed prospectively for at least 1-year after CA for assessment of survival and neurological outcome. Cerebral function was assessed on admission and after 28-days and 1-year, by clinical visits, by physicians on-site or contacting the attending physician, the patients or the family directly by telephone. Cerebral Performance Categories (CPC) were used to assess neurological outcome. A CPC score of 1–2 was defined as favourable neurological outcome, whereas 3–5 as unfavourable. Post-CA shock was defined as need for continuous vasopressor therapy (epi-/norepinephrine) for >6 h after ROSC in order to maintain a mean arterial pressure above 65 mmHg despite adequate fluid administration.[3] Cardiac failure was defined as need for inotrope/vasopressor infusion (dobutamine, epi-/norepinephrine) during the first 72 h after CA.[7,9]

HLI was diagnosed according to well-established criteria: (a) setting of cardiac, circulatory or respiratory failure; (b) dramatic but transient elevation of aminotransferase levels to at least 20-fold the upper limit of normal; (c) exclusion of other putative causes of liver cell necrosis (viral-/drug-induced-hepatitis).[12] If these criteria were met, a histological confirmation was not required for diagnosis. All patients were screened for the presence of HLI by daily laboratory and clinical assessment, for 28-days after CA if available. Patients with criteria of HLI accompanying liver cirrhosis or other pre-existing liver diseases were not considered as HLI.

Severity of illness was evaluated by sequential organ failure assessment (SOFA)[19] and simplified acute physiology (SAPS II)[20] score. Charlson Comorbidity Index (CCI)[21] was calculated in all patients.

Statistical analysis

Data are presented as count and relative frequency or median and 25–75% interquartile range (IQR). We tabulated clinical variables according to presence of HLI, and used Chi-squared, Fisher exact or Mann–Whitney U test for hypothesis testing as appropriate. First, we assessed factors associated with the occurrence of HLI. We used multivariable-logistic-regression with HLI as the dependent variable and clinical variables as covariables. In a second step aiming at prognostic information of HLI we used multivariable-logistic-regression to estimate the effect of HLI on clinically important outcomes. The dependent variables were favourable neurological survival (best CPC 1 or 2; yes vs. no) or mortality at one year in separate models. We entered HLI as main covariable and age, sex, OHCA, witnessed-CA, resuscitation times, presence of shockable rhythm, cardiac cause of CA, mechanical ventilation, SOFA on admission, initiation of TTM, and CCI as other covariates to the model. In all models we tested for linear effects, first order interactions and model fit using the likelihood ratio test. Survival function estimates were calculated using the Kaplan–Meier Method and were compared by the log-rank test. We used a multivariable Cox proportional hazards model to estimate the effect of HLI on survival up to one year. Statistical analysis was conducted using Stata 14 (Stata Corp, College Station,TX) and IBM SPSS Statistics Version 24.0 (IBM Corp.,Armonk,NY). Generally, a p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

In total 1068 patients with ROSC after IHCA or OHCA were treated during the study period. The median age was 61 (50–72) years, 72% (n = 765) of patients were male. A normal cerebral performance (CPC 1/2) was observed in 98% (n = 1043) of patients prior CA. Seventy-five per-cent (n = 798) had OHCA, 86% (n = 921) CAs were witnessed. Initial cardiac rhythm was shockable (VT/VF) in 51% (n = 550) of all patients; defibrillation during CPR was performed in 60% (n = 646) of patients. Median witnessed no-flow, low-flow and time-to-ROSC was 0 (0–3), 13 (4–25) and 16 (5–30) min, respectively. Cause of CA was cardiac in 678 (63%) patients. TTM was performed in 62% (n = 666) of patients. Fifty-eight per cent (n = 616) suffered from post-CA shock, cardiac failure was observed in 74% (n = 794) patients. Intensive care unit stay was median 7 (1–15) days. See Table 1, Supp. Tables 3/4.

Characteristics of patients with hypoxic liver injury

Two-hundred nineteen patients (21%) developed HLI following CA. In the vast majority (n = 193, 88%), HLI occurred within 24 h after CA; 11 (5%) patients developed HLI within 24–48 h; 13 (6%) developed HLI

within 48 h–7 days. Two (1%) patients developed HLI within 7–14 days after CA. Duration of HLI > 24 h (i.e. duration of increasing aminotransferase levels) was observed in 114 (52%) patients (Fig. 2).

Patients with HLI were significantly younger ($p < 0.05$), CPC status prior CA was comparable in both groups. Patients with HLI had significantly longer low-flow and time-to-ROSC (both $p < 0.001$). Cause of CA was cardiac in most patients and initial rhythm was shockable, rates did not differ significantly between both groups. Cumulative used epinephrine was significantly higher in the group with HLI ($p < 0.001$). SOFA, SAPS II on admission as well as CCI were significantly higher in patients with HLI. Admission pH levels were significantly lower in patients with HLI (7.11 vs. 7.21, $p < 0.001$). Further, admission lactate was significantly higher in patients with HLI (10.25 vs. 6.7 mmol/l, $p < 0.001$). TTM was performed in 149 (68%) patients with HLI and in 517 (61%) without HLI. Incidence of rhabdomyolysis (CPK > 10,000U/l) was significantly higher in patients with HLI (13% vs. 4%, $p < 0.001$). Significantly higher rates of post-CA shock and cardiac failure were found in patients suffering from HLI. Multivariate regression analysis identified time-to-ROSC [OR 1.18, 95% CI (1.01–1.38); $p < 0.05$] and cardiac failure [OR 2.57, 95% CI (1.65–4.01); $p < 0.001$] as factors significantly associated with new-onset of HLI. CCI [OR 0.83, 95% CI (0.72–0.95); $p < 0.01$] was a protective factor (see Table 3). We observed similar rates of HLI in IHCA (19%, n = 51) and OHCA (21%, n = 168) ($p = 0.62$). Multivariate regression did not reveal an association with unfavourable neurological outcome regarding IHCA or OHCA. Further detailed information on HLI can be found in Tables 1–4.

Survival and functional outcome after cardiac arrest

We observed a significantly higher 28-day and 1-year mortality rate in patients suffering from HLI after CA compared to patients without HLI. Mortality was 57% vs. 39% after 28 days ($p < 0.001$) and 61% vs. 49% after 1-year ($p < 0.001$) in patients with and without HLI, respectively (See Fig.1).

Favourable neurological outcome (CPC I/II) was 35% after 28-days and 34% after 1-year in patients with HLI, compared to 48% after 28-days and 44% after 1 year in patients without HLI, respectively ($p < 0.001$ for all time points).

Sixty-five percent (n = 142) of patients with HLI had unfavourable neurological outcome (CPC III/IV) or died within 28 days. Patients with unfavourable 28-days outcome were significantly older, had a significant higher CCI and severity of illness compared to HLI-patients and favourable outcome. Resuscitation times were significantly longer in patients with 28 day unfavourable outcome (see Table 2). Initial rhythm was significantly less shockable in patients with HLI and unfavourable 28 day outcome. Patients with unfavourable 28 day outcome had a significantly higher rate of cardiac re-arrest after sustained ROSC (15% vs. 5%), post-CA shock (82% vs. 56%) and cardiac failure (93% vs. 75%) after CA. After adjustment for confounders, we observed that HLI was associated with unfavourable neurological outcome [OR 1.74, 95% CI (1.16–2.61); $p < 0.01$] and 1-year mortality [HR 1.29, 95% CI (1.16–2.61); $p < 0.05$]. For other factors associated with unfavourable neurological outcome or 1-year mortality see Supp. Tables 1 and 2.

Table 1 – Baseline characteristics of the study population at admission stratified according presence of hypoxic liver injury.

Variables	All patients (n = 1068)	Non-HLI (n = 849)	HLI (n = 219)	p value
Age, years (median; IQR)	61 (50–72)	62 (51–72)	57 (49–69)	< 0.05
Male (n, %)	765 (72)	606 (71)	159 (73)	0.72
Weight, kg (median; IQR)	80 (70–90)	80 (70–90)	80 (70–90)	0.89
Height, cm (median; IQR)	175 (168–180)	175 (168–180)	175 (165–180)	0.85
Before cardiac arrest				
- Normal cerebral performance (n, %)	1043 (98)	830 (98)	213 (97)	0.55
- Normal overall performance (n, %)	973 (91)	776 (91)	197 (90)	0.99
Witnessed ischemic time, min[a] (median; IQR)				
- No-flow	0 (0–3)	0 (0–3)	0 (0–2)	0.07
- Low-flow	13 (4–25)	12 (4–22)	18 (6.25–36)	<0.001
- Time to ROSC	16 (5–30)	15 (5–28)	20 (7.25–39.75)	<0.001
Cardiac cause (n, %)	678 (63)	536 (63)	142 (65)	0.64
Out of hospital (n, %)	798 (75)	630 (74)	168 (77)	0.45
Initial shockable (VT/VF) rhythm (n, %)	550 (51)	444 (52)	106 (48)	0.30
Defibrillation (n, %)	646 (60)	516 (61)	130 (59)	0.70
Epinephrine cumulative (mg) (median; IQR)	3 (1–4)	2 (1–4)	3 (2–6)	< 0.001
SOFA admission, pts (median; IQR)	9 (6–12)	9 (6–12)	11 (9–13)	< 0.001
SAPS II admission, pts (median; IQR)	80 (74–88)	80 (72–87)	81 (75–90)	< 0.05
Charlson comorbidity index, pts. (median; IQR)	1 (0–3)	1 (0–3)	1 (0–2)	< 0.01
Mechanical ventilation (n, %)	837 (78)	658 (78)	179 (82)	< 0.05
Admission - pH (arterial) - (median; IQR)	7.19 (7.03–7.29)	7.21 (7.06–7.3)	7.11 (6.96–7.23)	< 0.001
Admission - lactate (mmol/l) - (median; IQR)	7.4 (4.3–10.9)	6.7 (4–10.1)	10.25 (6.98–14.13)	< 0.001
Targeted temperature management (n, %)	666 (62)	517 (61)	149 (68)	0.05
Re-Arrest <2 h (n, %)	95 (9)	70 (8)	25 (11)	0.14
Post-CA shock (n, %)	616 (58)	456 (54)	160 (73)	< 0.001
Cardiac failure (n, %)	794 (74)	604 (71)	190 (87)	< 0.001

Abbreviations: ROSC, return of spontaneous circulation; VT, ventricular tachycardia; VF, ventricular fibrillation; mg, milligram; SOFA, sequential organ failure assessment; SAPS, simplified acute physiology score; CA, cardiac arrest.

[a] Data available in 921 patients.

Table 2 – Characteristics of patients with hypoxic liver injury stratified in 28-days favourable and 28-days unfavourable outcome.

Parameters	Overall (n = 219)	28-day favourable outcome (n = 77)	28-day unfavourable outcome (n = 142)	p value[a]
Age, years (median; IQR)	57 (49–69)	54 (46–63)	62 (50–72)	< 0.01
Male (n, %)	159 (73)	59 (77)	100 (70)	0.31
SOFA admission, pts (median; IQR)	11 (9–13)	9 (5–11)	11 (9–13)	< 0.001
SOFA 24 h, pts (median; IQR)	11 (9–13)	9 (5–11)	12 (11– 13.25)	< 0.01
SOFA 48 h, pts (median; IQR)	11 (9–13)	9.5 (5.75–12)	12 (11–14)	< 0.05
SAPS II admission, pts (median; IQR)	81 (75–90)	76 (72–82)	84 (78–93)	< 0.01
Charlson comorbidity index, pts. (median; IQR)	1 (0–2)	0 (0–2)	1 (0–2)	< 0.05
Admission - pH (arterial) - (median; IQR)	7.11 (6.96–7.23)	7.21 (7.12–7.32)	7.05 (6.92–7.19)	< 0.001
Admission - lactate (mmol/l) - (median; IQR)	10.25 (6.98–14.13)	7.3 (4.2–10.9)	12.1 (8.03–15)	< 0.001
Lactate after 24 h (mmol/l) - (median; IQR)	1.9 (1.3–4.13)	1.5 (1.1–2.5)	2.6 (1.4–5.23)	< 0.001
Lactate after 48 h (mmol/l) - (median; IQR)	1.6 (1.1–2.6)	1.4 (1–1.8)	1.9 (1.3– 3.1)	< 0.001
Witnessed ischemic time, min[b] (median; IQR)				
- No-flow	0 (0– 2)	0 (0–1)	0 (0– 4)	< 0.05
- Low-flow	18 (6.25–36)	13 (4.5–24)	23 (10–44.75)	< 0.01
- Time to ROSC	20 (7.25–39.75)	15 (4.5–26)	28 (10.5–52.5)	<0.001
Shockable (VT/VF) (n, %)	106 (49)	59 (77)	47 (33)	< 0.001
OHCA (n, %)	168 (77)	61 (79)	107 (76)	0.57
Defibrillation (n, %)	130 (59)	62 (81)	68 (48)	< 0.001
Targeted temperature management (n, %)	149 (68)	44 (57)	105 (73)	< 0.05
Mechanical ventilation (n, %)	179 (82)	50 (65)	129 (91)	< 0.001
Epinephrine cumulative (mg) (median; IQR)	3 (2–6)	2 (1–5.5)	4 (2–6)	0.05
Cardiac cause of CA (n, %)	142 (65)	63 (82)	79 (56)	< 0.001
Mean arterial pressure – admission (median; IQR)	73 (57–89.5)	78 (66–92)	68 (54–87)	< 0.05
Heart rate – admission (median; IQR)	100 (80–120)	90 (80–110)	100 (80–120)	0.26
Post-CA shock (n, %)	160 (73)	43 (56)	117 (82)	< 0.001
Cardiac failure (n, %)	190 (87)	58 (75)	132 (93)	< 0.001
Re-Arrest <2 h (n, %)	25 (11)	4 (5)	21 (15)	< 0.05
Cholestasis (n, %)	38 (17)	13 (17)	25 (18)	0.45

Abbreviations: SOFA, sequential organ failure assessment; SAPS, simplified acute physiology score; ROSC, return of spontaneous circulation; VT, ventricular tachycardia; VF, ventricular fibrillation; PEA, pulseless electric activity; OHCA, out-of-hospital cardiac arrest; CA, cardiac arrest; HLI, hypoxic liver injury.
[a] 28-days favourable outcome (CPC 1/2) vs.28-days unfavourable outcome (CPC 3/4 or mortality).
[b] Data available in 186 patients.

Sixty-nine (32%) patients showed a dramatic elevation of aminotransferase levels (HLI) at hospital admission. Of those with HLI on admission 71% didn`t survive 28-days and most of the survivors (78%) had unfavourable neurological 28-day-outcome. The rate of unfavourable outcome increased with the duration of HLI as illustrated in Fig.2. Overall, in 114 (52%) patients HLI lasted for more than 24 h (defined as duration of increasing aminotransferase levels); we observed a rate of unfavourable 28-day-outcome in 69% after 28-days in those patients. All patients with a HLI duration of >72 h had an unfavourable 28-days outcome.

Jaundice (defined as bilirubin ≥ 3 mg/dl) developed in 17% (n = 38) patients with HLI. Rate of jaundice was comparable in patients with and without unfavourable outcome after 28-days (p = 0.45) (see Table 2).

Table 3 – Logistic regression model for factors associated with occurrence of hypoxic liver injury.

Covariables	OR (95% CI)	p value
Age (years)	0.99 (0.98–1.01)	0.305
Gender (female vs. male)	0.92 (0.65–1.30)	0.653
Time-to-ROSC, *min* (quartiles)	1.18 (1.01–1.38)	< 0.05
1 – 4	0.95 (0.57– 1.56)	0.827
5 – 15	1.16 (0.71–1.89)	0.544
16 – 29	2.14 (1.36–3.37)	< 0.01
> 30	1.55 (0.91–2.62)	0.105
Charlson comorbidity index (per category[a])	0.83 (0.72–0.95)	< 0.01
CA witnessed (yes vs. no)	1.16 (0.67–2.02)	0.598
Cardiac cause of CA (yes vs. no)	1.12 (0.80–1.57)	0.519
Cardiac failure (yes vs. no)	2.57 (1.65–4.01)	< 0.001

Abbreviations: OR, multivariable adjusted odds ratio; CI confidence interval; CA, cardiac arrest.
[a] 0, 1, 2, 3–10, or missing.

Discussion

In this large prospective registry HLI was a frequent finding after IHCA and OHCA. Occurrence of HLI was significantly associated with unfavourable neurological outcome and mortality. To date, occurrence of organ failure after CA, especially liver failure has only been described in patients with OHCA. Our study is the first and by far largest study that investigated occurrence, neurological outcome and risk factors of HLI after IHCA and OHCA in a large cohort of successfully resuscitated patients.

Patients who initially survive CA enter the post-CA phase, which is characterised by systemic ischemia/reperfusion injury, involving

Table 4 – Regression models for factors associated with unfavourable neurological outcome and factors associated with 1-Year mortality.

Logistic regression model for factors associated with unfavourable neurological outcome

	Covariables	OR (95% CI)	p value
Unadjusted OR	Hypoxic liver injury (yes vs. no)	1.94 (1.44–2.64)	< 0.001
Multivariable adjusted OR[a]	Hypoxic liver injury (yes vs. no)	1.74 (1.16–2.61)	< 0.01

Cox regression model estimating factors associated with 1-Year mortality

	Covariables	HR (95% CI)	*p* value
Unadjusted HR	Hypoxic liver injury (yes vs no)	1.44 (1.19–1.75)	< 0.001
Multivariable adjusted HR[a]	Hypoxic liver injury (yes vs no)	1.29 (1.16–2.61)	< 0.05

Abbreviations: OR, odds ratio; CI, confidence interval.
[a] Adjusted for: age; gender; OHCA; witnessed CA; low-flow time; no-flow time; shockable rhythm; cardiac cause of CA; CCI, SOFA Score, TTM, mechanical Ventilation.

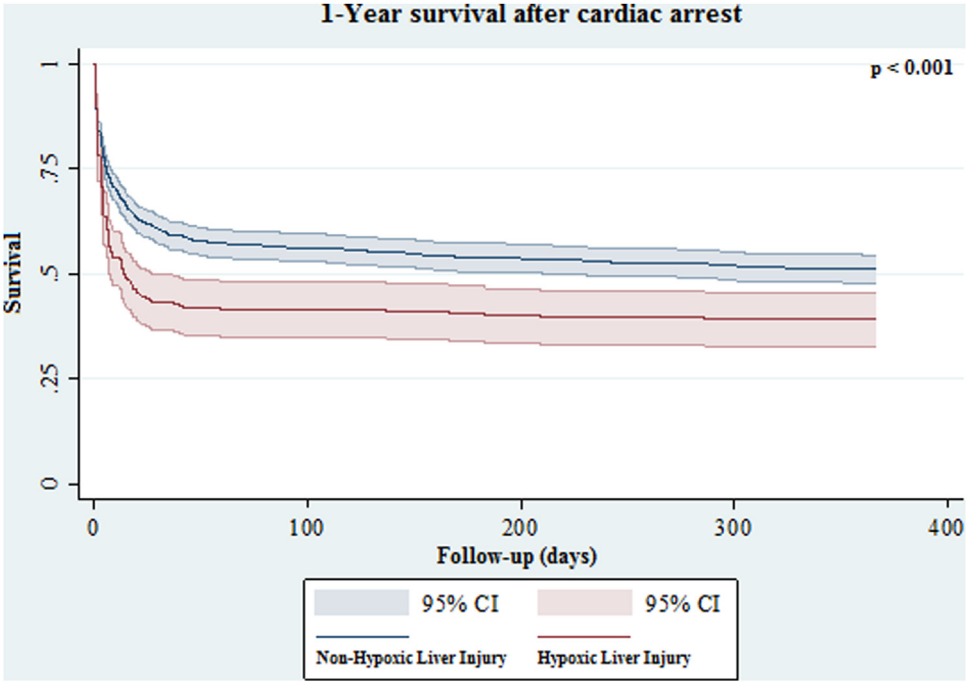

Fig. 1 – One-Year-Survival after ICU admission stratified according presence or absence of hypoxic liver injury estimated by Kaplan–Meier method.

multiple organs and termed the post-CA syndrome.[4] High morbidity and mortality after CA is mainly triggered by post-CA shock and brain injury.[3,4] Liver dysfunction after CA is currently poorly studied, data is only available in patients suffering from OHCA.[9,10] Furthermore, a recent study by our working-group showed that pre-existing cirrhosis was found to be strongly associated with unfavourable outcome in patients with CA.[11]

To date, only two studies evaluated the occurrence of HLI after CA in OHCA setting.[9,10] HLI occurred with a prevalence of 11.4%[9]–13.5%[10]. In contrast, we found an almost doubled prevalence of 21% in patients with IHCA and OHCA. Of interest, we observed similar rates of HLI in OHCA (21%) and IHCA (19%). The higher prevalence of HLI in our cohort may be the consequence of several factors. First, the two cited studies used different and less accurate diagnostic criteria for HLI. For example, Champigneulle et al. used only a rise of ALAT for diagnosis, without taking more sensitive ASAT into account.[9] In contrast, we used the widely accepted and well-established criteria of HLI in our cohort.[12,13,22–30] Second, the two studies only included HLI cases that developed within the first 72 h after CA.[9,10] However, we found that a relevant proportion of patients developed HLI 48 h after CA. Third, our study included all patients with ROSC admitted to our institution. Previous studies excluded patients who did not survive the first 24 h,[9,10] potentially contributing to an underrepresentation of HLI.

Cardiac failure was the strongest factor [OR 2.57; 95% CI 1.65–4.01] associated with occurrence of HLI in our cohort. Furthermore, time-to-ROSC as well as pre-arrest comorbidities were associated with occurrence of HLI. This is in accordance to previous studies,[9,10] where patients with HLI had a significant higher rate of cardiac failure

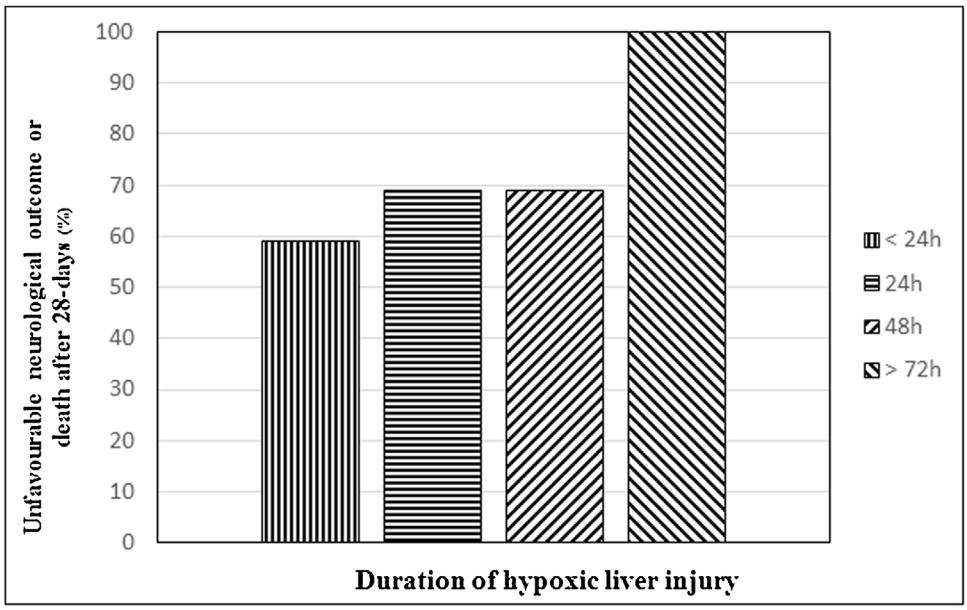

Fig. 2 – Duration of HLI and 28-days mortality or unfavourable neurological outcome.

and post-CA shock. Our findings are consistent with earlier studies on patients with HLI in the medical ICU, which found that more than 2/3 of patients had more than one factor contributing to the development of HLI.[22] Ischemia/reperfusion injury is a very important factor for development of HLI.[12] However, after CA ischemia/reperfusion response can lead to consecutive shock due to endothelial dysfunction and vasoplegia.[4] Differentiating between cardiac failure and shock due to CA ischemia/reperfusion response is difficult without echocardiographic data, which should be taken into account interpreting our results. Nevertheless, our data strongly supports the hypothesis that HLI after CA is a multifactorial triggered event.

Unfavourable outcome and mortality rates after 28-days were significantly higher in patients with HLI than compared to patients without HLI (65% vs. 52%), despite comparable CA characteristics and short no-flow times. Higher unfavourable outcome rates can be explained by significantly longer duration of resuscitation, accordingly higher lactate and lower pH levels on admission. Severe metabolic acidosis, as well as high lactate levels $>$ 10 mmol/l have been shown to be factors contributing to unfavourable outcome following CA and liver diseases.[31–33] Furthermore, we observed a significant higher rate of cardiac failure and post-CA shock in patients with HLI, which is in accordance to previous publications.[22,28,34] Further a significant higher rate of mechanical ventilation was observed in patients with HLI. Studies described decreased liver outflow and portal vein flow, whereas other clinical studies showed no effect in liver hemodynamics due to MV.[35,36] However, the effect of prolonged MV on liver hemodynamics is unknown and currently not well described in critical care setting. Nevertheless, pre-existing right ventricular dysfunction, which is common in patients with HLI,[22,37] could aggravate venous congestion and the susceptibility to occurrence of HLI. We observed a significantly higher severity of illness, expressed by SOFA and SAPS II on admission. Shockable rhythm and cardiac cause of cardiac arrest were revealed as factors improving outcome as illustrated in Supp. Table 1. Relatively low mortality and unfavourable outcome rates in the overall cohort can be explained by the solely inclusion of patients with ROSC in our study. Additionally, outcome rates were comparable to previous studies only including patients with ROSC.[38] Further, we observed a high rate of witnessed CA's and shockable rhythm.

Overall mortality in patients with HLI after 28-days was 57%. We observed distinct lower mortality rates compared to the two previous studies of HLI in OHCA where mortality rates were ranging from 75 to 86%.[9,10] Mortality rates in our cohort were comparable to previous studies in patients with HLI ranging from 56 to 70%.[13,14,22,27,34] The different mortality rates in our study as compared to the two other studies addressing HLI after CA seem to be a consequence of several circumstances. First, the two studies reported a lower rate of shockable rhythm ranging from 30 to 56%,[9,10] whereas our study observed 77% shockable rhythms in patients with HLI. Second, duration of resuscitation was shorter in our cohort.[9,10] Third, we observed a lower rate of post-CA shock, but similar rates of cardiac failure in patients with HLI compared to a previous study.[9] Regression analysis showed that HLI was significantly associated with 1-year mortality [HR 1.29, 95% CI (1.16–2.61); $p < 0.05$].

Organ failure after CA is a frequent finding and associated with poor neurological outcome after CA in previous studies.[6,8] Interestingly, one study did not find an association of liver failure and mortality.[8] However, only the SOFA sub-score liver – and not distinguished hepatic criteria of HLI as in our study – was used to identify liver failure, which likely contributes to an underrepresentation of liver failure. We observed a significant rise of bilirubin (defined as $\geq$ 3 mg/dl) in 17% of patients with HLI, rate of jaundice was similar in patients with or without unfavourable outcome after 28-days. This finding can be explained by high rate of early death in the unfavourable outcome group. Nevertheless, rate of jaundice was lower than previously observed in patients with HLI of a mixed medical ICU collective.[27] Patients can be affected by the post-CA syndrome, triggered by ischemia and reperfusion injury, which involves multiple organs. Different clinical patterns have been associated with worse outcome after CA like hypo- or hyperglycemia, hypo- and hyperoxaemia, hypotension, and acute kidney injury.[4,6,7,39] HLI in general is associated with worse outcomes in critically ill patients.[13,14,22,25–27,34,37,40] Recent studies showed that complications like hypoglycemia, hyperammonemia, respiratory

failure or acute kidney injury in patients with HLI are associated with increased mortality.[12,13,22,23,27,30] However, even though there is no specific treatment available, prevention of consecutive complications of central importance. Therefore, prevention of complications during the post-CA phase may be important in patients suffering from HLI.

This study has strengths and limitations. First, data are derived from a large prospective CA registry with uniform reporting (Utstein-style guidelines) and inclusion of all patients treated at a tertiary care hospital ED with IHCA and OHCA. However, our study was a post-hoc analysis of prospectively determined data. Second, we show results of a high volume cardiac arrest center highly experienced in CA management. Thus, our results are generally not transferable to other settings with less experience. Third, this study included solely patients with ROSC, which should be taken into account when interpreting our results. However, laboratory liver parameters, which are the keys to HLI diagnosis, are seldom determined in patients without ROSC. Fourth, residual confounding is a matter of concern and cannot be entirely excluded. Future studies should confirm these results, especially in IHCA setting.

In conclusion, this is the first study evaluating onset, risk factors, duration and outcome including functional outcome of HLI following IHCA and OHCA. HLI is a common and life-threatening complication in patients suffering CA and associated with mortality and unfavourable neurological outcome. HLI after CA develops due to multifactorial influences and is not triggered by duration of resuscitation alone.

Ethics approval and consent to participate

This study was based on a prospectively maintained registry at the Emergency Department of the Medical University of Vienna. This registry was approved by the ethics committee of the Medical University Vienna (reference number EK-456/2005, extended by EK-1814/2012), due to the observational character of the study informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets supporting the conclusions of this article are included within the article.

Competing interest

The authors declare that they have no competing interests.

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Authors' contributions

KR, FS, HH and VF participated in study conception and design. AOS, AN, TH, AD, PH, AMW, VF and KR were involved in acquisition of data. KR, VF, FS, and HH contributed to analysis and interpretation of data. KR drafted the manuscript. VF, AOS, FS and HH were involved in critical revision of the manuscript for important intellectual content. VF and FS participated in supervision. All authors reasd and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.02.038.

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