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Clinical paper

Intestinal injury in cardiac arrest is associated with multiple organ dysfunction: A prospective cohort study

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Abstract

Background: The impact of intestinal injury in cardiac arrest is not established. The first aim of this study was to assess associations between clinical characteristics in out-of-hospital cardiac arrest (OHCA) and a biomarker for intestinal injury, Intestinal Fatty Acid Binding Protein (IFABP). The second aim was to assess associations between IFABP and multiple organ dysfunction and 30-day mortality.

Methods: We measured plasma IFABP in 50 patients at admission to intensive care unit (ICU) after OHCA. Demographic and clinical variables were analysed by stratifying patients on median IFABP, and by linear regression. We compared Sequential Organ Failure Assessment (SOFA) score, haemodynamic variables, and clinical-chemistry tests at day two between the "high" and "low" IFABP groups. Logistic regression was applied to assess factors associated with 30-day mortality.

Results: Several markers of whole body ischaemia correlated with intestinal injury. Duration of arrest and lactate serum concentrations contributed to elevated IFABP in a multivariable model ($p < 0.01$ and $p = 0.04$, respectively). At day two, all seven patients who had died were in the "high" IFABP group, and all six patients who had been transferred to ward were in the "low" group. Of patients still treated in the ICU, the "high" group had higher total, renal and respiratory SOFA score ($p < 0.01$) and included all patients receiving inotropic drugs. IFABP predicted mortality (OR 16.9 per standard deviation increase, $p = 0.04$).

Conclusion: Cardiac arrest duration and lactate serum concentrations were risk factors for intestinal injury. High levels of IFABP at admission were associated with multiple organ dysfunction and mortality.

Trial registration: ClinicalTrials.gov: NCT02648061.

Keywords: Cardiac arrest, Intestinal ischaemia, Intestinal fatty acid binding protein, IFABP, Multiple organ dysfunction, Organ failure

Introduction

Organ dysfunction after out-of-hospital cardiac arrest (OHCA) is common and carries a high mortality rate.[1] The organ dysfunction is caused by whole-body ischaemia–reperfusion injury and include neurologic, circulatory and respiratory functions.[2] Ischaemia-reperfusion in OHCA may also injure the intestines, and both gastric regurgitation and early diarrhea after OHCA has been shown to predict poor neurological outcome.[3–5]

The most severe forms of intestinal ischaemia are termed ´non-occlusive mesenteric ischaemia´ (NOMI), a syndrome caused by hypoperfusion.[3] However, clinical findings, current clinical-chemistry tests, and computed tomography (CT) findings of NOMI are non-specific.[3] Novel biomarkers are emerging, and intestinal fatty acid binding protein (IFABP) is one of the most widely studied biomarkers for small bowel injury.[6] IFABP is a cytosolic protein of enterocytes and is released rapidly into the bloodstream if the mucosal tissue becomes ischaemic.[7–8] The incidences of NOMI after cardiac arrest have been reported to be low.[9–10] However, due to the diagnostic limitations, intestinal injury may be underreported. A higher incidence of intestinal injury after cardiac arrest is supported by an elevated level of IFABP in most of these patients.[11–12]

In two previous reports IFABP was associated with high doses of adrenaline (epinephrine) given during resuscitation, but not with time

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to ROSC.[11,13] Further, increases in IFABP were associated with higher mortality and poor neurological outcome.[11,13] These studies included patients with both in-hospital cardiac arrest (IHCA) and OHCA. The high levels of plasma IFABP at admission declined rapidly.[11] However, injured intestines may enhance bacterial translocation or release pro-inflammatory mediators, in addition to IFABP, contributing to subsequent and prolonged multiple organ dysfunction.[14]

Risk factors for intestinal injury, and the potential relation between intestinal injury and organ dysfunction are highlighted as research priorities by the European Society of Intensive Care Medicine.[15] Thus, the first aim of this study was to assess associations between OHCA characteristics and IFABP at admission. The second aim was to assess possible associations between IFABP at admission and organ dysfunctions and 30-day mortality.

Methods

Study design and setting

This is a post hoc analysis of a prospective cohort consisting of 50 consecutive patients with ROSC after OHCA admitted to the Intensive Care Unit (ICU) at St. Olav's University Hospital, Norway. The circulatory characteristics and trajectories, together with development of inflammatory biomarkers, have been published previously.[16–18] Patients were included between January 2016 and November 2017.

Participants

Both comatose and awake adult patients were assessed for eligibility. Exclusion criteria were age <18 years, transferal from other hospitals, assumed septic or anaphylactic aetiology, pregnancy, decision to limit life-sustaining therapy upon arrival, or the following before arrival in the ICU: cardiothoracic surgery, application of extracorporeal membranous oxygenation (ECMO) or a ventricular assist device (VAD).

Patients were followed from admission to a maximum of five days. The follow-up was terminated earlier if the patient died or was transferred to ward, extracorporeal membrane oxygenation or a ventricular assist device was applied, cardio-thoracic surgery was performed, or withdrawing of life-prolonging therapies was decided. Day one started the morning after admission at 06:00, and therefore the admission day ("day zero") had variable length.

Early management

The hospital's standard treatment of comatose patients was targeted temperature management at 36 °C for 24 hours. Percutaneous coronary intervention was performed if indicated. Patients with hypotension and/or clinical signs of hypoperfusion were treated with fluids, vasopressors and/or inotropic drug administration. Detailed information about the clinical care given has been published previously.[19]

Data sources and definitions

We obtained data according to the Utstein cardiac arrest template from the pre-hospital report.[20] Charlson Comorbidity Index was calculated and clinical information on assessment and treatment were gathered from the hospital record.[21] Arterial blood gas variables (pH, base deficit, and lactate) were obtained from the first sample after hospital admission. Circulatory shock in emergency room was defined as systolic blood pressure <90 mmHg *or* in need of fluids and/or vasopressors to maintain systolic blood pressure >90 mmHg.[22] We scored Glasgow Coma Scale at admission, Simplified Acute Physiology Score II (SAPS II) 24 hours after admission, and Sequential Organ Failure Assessment (SOFA) daily.[23–25]

A pulmonary artery catheter (Swan-Ganz CCOmbo, Edwards Lifesciences, USA) for continuous central haemodynamic measurements was inserted in all comatose patients who did not have contraindications. Medication and all haemodynamic variables were gathered from the electronic critical care information system (Picis CareSuite, Optum Inc., USA). The haemodynamic variables were cardiac output, proportion of patients receiving inotropic drugs (adrenaline, dobutamine, dopamine), dose of noradrenaline and amount of fluid infusion. Cardiac output and dose of noradrenaline reported are the mean value over the period starting 30 minutes before and ending 30 minutes after each blood sample collection. Amount of fluid infusion is the mean for the previous day.

Visceral organ function and injury were assessed by the clinical-chemistry tests alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, albumin (liver), lipase, amylase (pancreas), and creatinine (renal). In addition, platelets were registered for the SOFA score. We obtained cerebral performance category (CPC) at discharge and vital status after 30 days from the medical records.[26]

Blood sampling

Blood samples were drawn at inclusion and every morning during the ICU period. After gentle mixing, the blood samples were placed vertical for 30 minutes in ambient temperature and then centrifuged at 2200 *g* for 10 minutes. EDTA-plasma was frozen to −80 °C within 1 hour from sampling.

Levels of IFABP were measured in duplicate by enzyme immunoassays (EIA) using commercially available antibodies (Cat# DY3078, R&D Systems, Minneapolis, MN, USA) in a 384-format using a combination of a SELMA (Jena, Germany) pipetting robot and a BioTek (Winooski, VT, USA) dispenser/washer. Absorption was read at 450 nm with wavelength correction set to 540 nm using an ELISA plate reader (Bio-Rad, Hercules, CA, USA). Coefficients of variation were <10%. We measured IFABP in blood samples from 18 healthy subjects for reference.

Statistical analysis

Normal distributed data are presented as mean ± standard deviation (SD), otherwise median with first and third quartile (Q1–Q3) or proportions (%). We divided the population into "high" and "low" by the median value of the IFABP concentration at admission. The distribution of variables in the two groups were compared using Student t-test, chi-square test, Fisher exact test, and Wilcoxon rank-sum test, as appropriate.

First, we evaluated risk factors for intestinal injury by comparing the distributions of demographic, Utstein and clinical variables in the "high" and "low" IFABP groups. The same variables were then analysed in a linear regression model with admission IFABP as a continuous outcome variable. Due to concerns of non-linearity between IFABP and dose of adrenaline given, we stratified patients into three groups (no adrenaline, 1–2 mg and $\geq$ 3 mg adrenaline, respectively) and applied the multivariable regression model per category (with no adrenaline as the reference). The assumptions of linearity, homoscedasticity and collinearity in the model were met. Because of low sample size, we only included the three variables with the lowest p-values in univariate analyses in the multivariable model. These variables were judged to be clinically relevant.

Second, to assess organ dysfunction, we compared SOFA score, haemodynamic variables, and clinical-chemistry tests between the high and low IFABP group. Thirty-day mortality was evaluated in univariable logistic analyses. Because of the low sample size, we assessed the three variables with the lowest p-values in a multivariable model after confirming that they were clinically important.

Finally, we performed sensitivity analyses on the multivariable models by analysing all variables with $p < 0.1$ in univariable analyses independently and together, and by exchanging lactate for base deficit.

All tests were two-sided and statistical significance was defined as $p < 0.05$. Data were extracted with the software Matlab (Mathworks Inc., Natick, MA), and the statistical analyses were performed with Stata 17.0 (StataCorp LCC, Collage Station, TX). No adjustment for multiplicity were made.

Sample size

No formal sample size was calculated, as described in the protocol article for the main study.[19]

Ethics

The Regional Committee for Medical and Health Research Ethics, Central Norway Health Region (REK Midt, No. 2015/1807) approved the study. Participants or their proxies provided written consent. The study is registered in ClinicalTrials.gov (Identifier: NCT02648061).

Results

Among 65 consecutive patients assessed for eligibility, 15 patients were excluded. Seven patients due to immediate withdrawal of life-support, two had septic etiology, two patients were not in need of ICU admission, three patients received VAD or ECMO and one patient underwent immediate surgery. Fifty patients were included in the study.[18] Demographic data are provided in Table 1. Mean length of day zero was 11 hours. At start of day two, seven patients had died, all in the high IFABP group, and six patients had been transferred to ward, all in the low IFABP group (Fig. 1).

Plasma intestinal fatty acid binding protein (IFABP)

The mean IFABP level was 28.2 ng/mL (SD 12.9) at admission (Table 1). The levels declined rapidly, with low values by day two (Fig. 2). The mean IFABP in the 18 healthy controls was 1.2 ng/mL (data not shown).

Association between cardiac arrest and IFABP at admission

Patients in the high IFABP group had more often non-shockable initial rhythm, longer time to ROSC, higher doses of adrenaline, base deficit, and lactate, but lower pH (Table 1). Presumed non-cardiac etiology together with circulatory shock and comatose state in emergency room were also more frequent in the high IFABP group.

Table 1 – Characteristics on admission of successfully resuscitated OHCA patients.

	All (n = 50)	Low IFABP (n = 25)	High IFABP (n = 25)	p-value
Demographic				
Age	67 [54–76]	67 [54–73]	65 [52–76]	0.94
Sex, male	40 (80%)	22 (88%)	18 (72%)	0.29
Charlson Comorbidity Index	3 [2–4]	4 [2–5]	3 [1–4]	0.23
Prehospital Utstein variables				
Witnessed cardiac arrest	42 (84%)	22 (88%)	20 (80%)	0.70
Bystander CPR	44 (91.7%)	23 (100%)	21 (84%)	0.11
Time to ACLS (min)	10 [5–13]	9 [5–12]	10 [5–16]	0.47
Shockable initial rhythm	39 (78%)	24 (96%)	15 (60%)	0.005
Number of defibrillations	2 [1–4]	2 [1–3]	2 [0–4]	0.95
Adrenaline, total dose in mg	0 [0–2]	0 [0–0]	2 [1–3]	<0.001
Time to ROSC (min)	24 [14–32]	18 [10–28]	28 [20.5–35.5]	0.009
Presumed cardiac etiology	42 (84%)	24 (96%)	18 (72%)	0.05
At admission				
Circulatory shock in ER*	17 (36%)	4 (16%)	13 (52%)	0.02
Comatose at admission (GCS < 8)	42 (84%)	18 (72%)	24 (96%)	0.05
Initial pH	7.24 [7.09–7.28]	7.28 [7.25–7.31]	7.09 [7.02–7.24]	<0.001
Initial Base deficit	10.4 [6–13.8]	6.3 [3.4–10.4]	13.8 [8.7–17.5]	<0.001
Initial arterial lactate (mmol/L)	6.2 [3.1–9.6]	3.8 [2.1–6.6]	9.3 [5.2–12]	<0.001
SAPS II score	64 (53–73)	60.5 (41.5–69.5)	67 (58–75)	0.06
Creatinine (micromol/L)	96.4 (30.6)	96.4 (30.6)	101.4 (25.8)	0.57
IFABP (ng/mL)	28.2 (12.9)	18.3 (10.3)	38.2 (5.9)	NA
CPC 1–2 at discharge	31 (62%)	23 (92%)	8 (32%)	<0.001

Dichotomous variables are summarized as counts and percentages and compared by Fisher's exact test. Normal distributed variables are expressed as mean and standard deviation and compared by Student's T-Test. Other continuous variables and categorical variables are expressed as median and interquartile range (IQR) and compared by Wilcoxon rank-sum test.

*Shock defined as systolic blood pressure <90 mmHg *or* in need of fluids and/or vasopressors to maintain systolic blood pressure >90 mmHg.

OHCA: Out-of hospital cardiac arrest. CPR: Cardiopulmonary resuscitation. ACLS: Advanced cardiac life support. ROSC: Return of spontaneous circulation. ER: Emergency room. GCS: Glasgow Coma Scale. SAPS II: Simplified Acute Physiology Score II. IFABP: Intestinal Fatty Acid Binding Protein. CPC: Cerebral performance category.

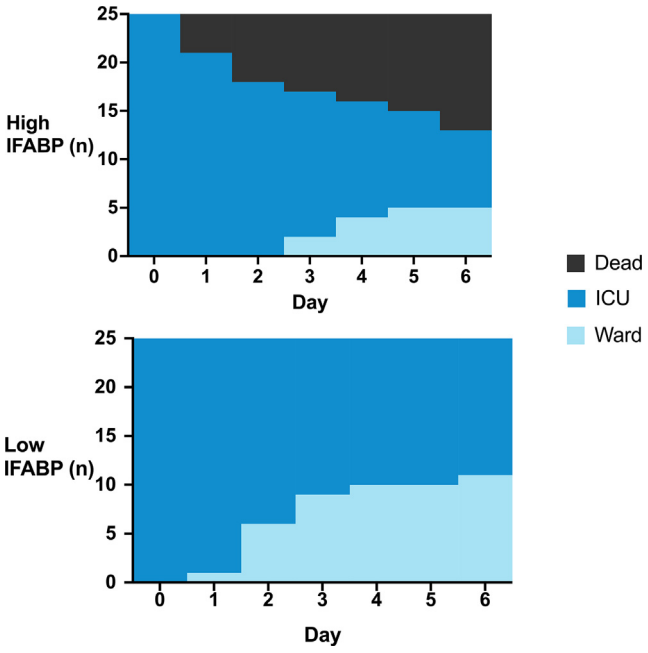

Fig. 1 – Status of patients at start of each day (0600 hours), day zero is of variable length. Only patients still treated in the ICU were included in the statistical analyses of organ dysfunction. IFABP: Intestinal Fatty Acid Binding Protein. ICU: Intensive Care Unit.

Evaluated as a continuous variable in univariable linear regression analyses, IFABP levels increased significantly with increasing time to advanced life support, time to ROSC, dose of adrenaline, higher Simplified Acute Physiology Score (SAPS) II score, pH, lactate, and base deficit. Also, circulatory shock and comatose state in emergency department were associated with higher IFABP levels (Supplementary Table 2).

In multivariable regression analysis IFABP increased significantly with longer times to ROSC and higher levels of lactate, but not with increasing dose of adrenaline (Table 2). For adrenaline, the rate of rise in IFABP was higher for patients given 1–2 mg adrenaline than for those receiving $\geq$ 3 mg, but with wide and overlapping confidence intervals (11.5, 95% CI 4.4–18.7, and 7.9, 95% CI 0.2–15.7, respectively). The results were not notably different in the sensitivity analyses (Supplementary Table 3).

Associations between IFABP at admission and organ dysfunction

At the start of day two, 37 patients were still treated in ICU and included in the analyses of organ dysfunctions. Total SOFA score and the sub-scores of renal and respiratory functions at day two were significantly higher in the high IFABP group (Supplementary Table 1).

Neither of the other SOFA sub-scores nor other clinical-chemistry tests differed between the two groups (Supplementary Table 1). However, all six patients receiving inotropic drugs were in the high IFABP group ($p = 0.009$, Supplementary Table 1). The evolution of organ dysfunction and support are shown in Fig. 2 and Supplementary Fig. 1.

IFABP at admission and mortality

Lactate and IFABP contributed significantly to 30-day mortality in the multivariable logistic analysis, but not non-shockable rhythm, as presented in Table 3. The odds ratio was 16.9 per standard deviation increase in IFABP ($p = 0.04$). The results were similar in the sensitivity analyses. Time to ROSC did neither contribute significantly nor alter the order of the other variables when added to the model (Supplementary Table 4).

Discussion

In this study time to ROSC and initial lactate concentrations after OHCA were significant risk factors for intestinal injury as reflected by IFABP at admission. High levels of IFABP were associated with multiple organ dysfunction at day two and increased mortality. Notably, at the start of day two, all patients who had died were in the high IFABP group, while all patients who had been transferred to ward were in the low IFABP group.

We found that several clinical markers of whole body ischaemia–reperfusion injury were associated with high IFABP levels. Multivariable analysis identified time to ROSC and lactate serum concentrations as significant predictors of IFABP levels. In contrast, the dose of adrenaline given during resuscitation did not contribute significantly to raised IFABP. The sensitivity analyses did not alter this finding. This result is contrary to two previous studies, which found that multiple doses of adrenaline, and not duration of cardiac arrest, were associated with higher IFABP levels.[11,13] Doses of adrenaline in the report by Krychtiuk et al. were comparable to our study and both studies had comparable eligibility criteria except for inclusion of both OHCA and IHCA patients.[11,13] IHCA represent a different population, which is more frequently witnessed by health professionals.[27] Indeed, Krychtiuk et al. found shorter time to ROSC and an initial median lactate value of only 1.9 mmol/l compared to 5.2 mmol/l in our cohort.[13] This may indicate higher load of ischaemia in our study which could contribute to more severe intestinal injury and higher IFABP levels. However, IFABP was measured by a different kit in our study making absolute values of IFABP, and thus severity of intestinal ischaemia, difficult to compare.[6]

Intuitively, it would be surprising if intestinal ischemic injury was not related to duration of cardiac arrest. In other studies of gastrointestinal injury after cardiac arrest, two of NOMI and two of endoscopic lesions, three out of four studies found an association with time to ROSC.[9–10,28–29] In multivariable analysis, cardiac arrest duration but not dose of adrenaline was associated with NOMI, but vice versa in a recent study of endoscopic lesions.[10,29] These results may reflect that time to ROSC and total dose of adrenaline are closely related and it will vary which of these factors that are identified in a multivariable analysis.

Organ dysfunction at day two occurred more frequently in the high IFABP group. To our knowledge, this is the first study of OHCA to show a correlation between intestinal injury and the degree of multiple organ dysfunction. In conditions other than OHCA, however, the association between IFABP and organ dysfunction has been reported previously.[30–33] We observed that patients with high IFABP had more frequent renal and respiratory organ dysfunction, but neither higher circulatory SOFA score nor higher dose of noradrenaline at day two. The incidences of circulatory dysfunction have been reported to be high following both NOMI and cardiac arrest.[2,34] Therefore, we would expect to find a difference in severity of circulatory dysfunction between the high and low IFABP group. Indeed, our findings do not exclude a correlation between high IFABP and circulatory dysfunction for several reasons. Firstly, all patients receiving

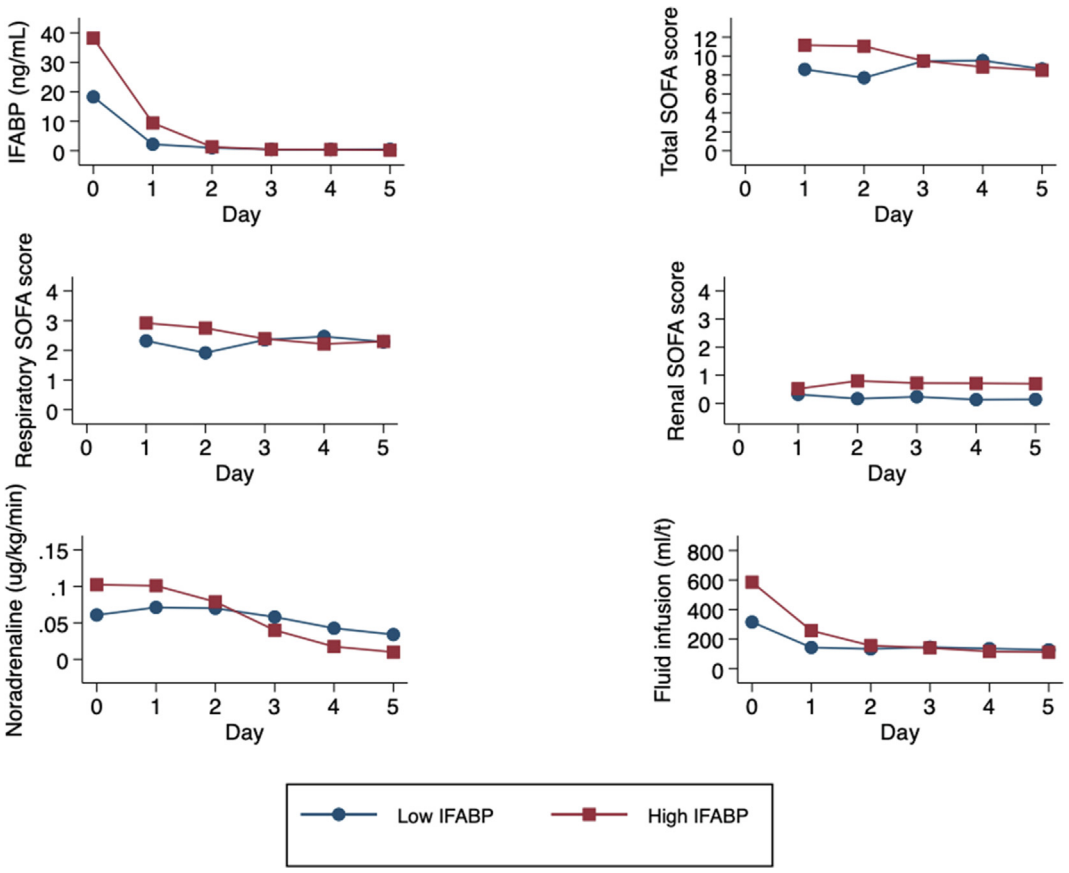

Fig. 2 – Evolution of IFABP and variables of organ dysfunction and support, displayed as means, first five days after admission. Day zero is of variable length. Only patients treated in the ICU at each time point are included in the figure. SOFA scores and fluid infusion are based on previous 24 hours. Dose of noradrenaline and IFABP are obtained at the time point given. Statistical tests were performed on day two only. IFABP: Intestinal Fatty Acid Binding Protein. SOFA: Sequential Organ Failure Assessment.

Table 2 – Factors associated with IFABP at admission in multivariable linear regression model.

Variable	Univariable		Multivariable Adjusted R^2 = 0.37		
	Unadjusted coefficient	95% CI	Adjusted Coefficient	95% CI	p-value
Time to ROSC (min)	0.52	0.33–0.71	0.35	0.11–0.59	0.006
Adrenaline (mg)	2.86	1.09–4.63	0.53	−1.32–2.37	0.57
Lactate (mmol/l)	1.26	0.51–2.00	0.76	0.03–1.49	0.04

IFABP: Intestinal Fatty Acid Binding Protein. ROSC: Return of spontaneous circulation.

inotropic drugs were in the high IFABP group. Secondly, the lack of an association with circulatory SOFA score may be due to many patients obtaining the highest score, which may be a type of ceiling effect. Finally, only patients still treated in the ICU were included in the statistical analysis of organ dysfunction. At the start of day two, thirteen patients had left the cohort. Of these, all patients with good outcomes were in the low IFABP group, and all the patients with poor outcomes were in the high IFABP group (Fig. 1). Clearly, this could have attenuated the differences in organ dysfunction between the two groups.

Whether intestinal injury, except in primary intestinal diseases, occurs in parallel with other organ dysfunctions or contributes to multiple organ dysfunction, has not been clarified.[15] This study was not designed to prove a contribution, but our findings do not exclude that important pathophysiological events could be mediated by the intestines, either through bacterial translocation or inflammatory cytokines.[14,35–38]

The association between IFABP and mortality in our study was convincing. Indeed, all twelve patients who died the first five days were in the high IFABP group (Fig. 1). This is in line with other

Table 3 – Factors associated with death within 30 days in logistic regression model.

	Univariable analysis			Multivariable analysis		
Variables	OR	95% CI	p-value	OR	95% CI	p-value
Lactate, per SD	7.15	2.43–21.00	<0.001	7.81	1.67–36.57	0.009
Non-shockable initial rhythm	20.57	3.62–116.83	0.001	18.05	0.91–359.22	0.06
IFABP at admission, per SD	12.23	2.46–60.76	0.002	16.90	1.10–261.27	0.04
Time to ROSC, per SD	2.49	1.18–5.27	0.02			
SAPS II, per unit	1.05	1.00–1.09	0.03			
Time to ACLS, per SD	1.84	0.99–3.43	0.05			
Shock in emergency room*	2.78	0.80–9.61	0.11			
Dose of adrenaline, per mg	1.22	0.90–1.66	0.19			
Bystander CPR	0.47	0.06–3.66	0.47			

OR: Odds ratio, CI: Confidence interval, SD: Standard Deviation, IFABP: Intestinal fatty acid binding protein, ROSC: Return of spontaneous circulation, SAPS II: Simplified Acute Physiology Score II, ACLS: Advanced cardiac life support, CPR: Cardiopulmonary resuscitation.

*Shock defined as systolic blood pressure <90 mmHg *or* in need of fluids and/or vasopressors to maintain systolic blood pressure >90 mmHg.

reports, where gastrointestinal injury regardless of diagnostic modality is consistently associated with poor outcome after cardiac arrest.[4,9–11,13,28–29] IFABP, in specific, has been shown to predict mortality in a variety of patient populations, including trauma, sepsis, acute heart failure and in unselected critically ill patients.[30–31,39–42]

The present study has several limitations. Firstly, it is a small single-center study, although patients were consecutively included and with a diversity in severity reflecting the OHCA population. Secondly, IFABP is a novel biomarker and the validity in the cardiac arrest population has not yet been established. Thirdly, plasma IFABP is renally excreted and has short half-life.[43] Even if blood samples were obtained shortly after hospital admission, both time from ROSC to admission and from admission to blood sampling may have influenced the observations. Fourthly, the selection of variables may not have been optimal to capture the potential multiple organ dysfunction following intestinal injury. Finally, we divided our cohort in two based on low and high IFABP levels. It is important to state that also patients in the low IFABP group had IFABP levels much higher than healthy volunteers. Thus, the comparison in our study is not between intestinal uninjured versus injured patients, but more likely between two stages of intestinal injury.

Conclusion

We found that cardiac arrest duration and lactate were significant risk factors for intestinal injury at admission. High levels of plasma IFABP at admission were associated with multiple organ dysfunction and high mortality.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Conflict of interest

Author BF has received PhD-funding by the Norwegian Air Ambulance Foundation. All other authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Bjørn Hoftun Farbu: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Project administration. **Halvor Langeland:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Thor Ueland:** Formal analysis, Writing – review & editing. **Annika E. Michelsen:** Formal analysis, Writing – review & editing. **Andreas Jørstad Krüger:** Conceptualization, Methodology, Writing – original draft, Supervision. **Pål Klepstad:** Conceptualization, Methodology, Investigation, Writing – original draft. **Trond Nordseth:** Formal analysis, Methodology, Writing – review & editing, Supervision.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109748.

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