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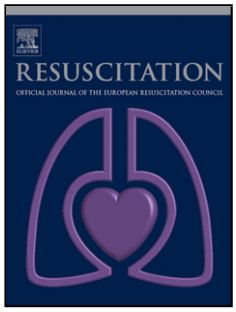

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The impact of diastolic blood pressure values on the neurological outcome of cardiac arrest patients

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Abstract

Aim: Which haemodynamic variable is the best predictor of neurological outcome remains unclear. We investigated the association of several haemodynamic variables with neurological outcome in CA patients.

Methods: Retrospective analysis of adult comatose survivors of CA admitted to the intensive care unit (ICU) of a University Hospital. Exclusion criteria were early death due to withdrawal of care, missing haemodynamic data and use of intra-aortic balloon pump or extracorporeal membrane oxygenation. We retrieved CA characteristics; lactate concentration and cardiovascular sequential organ failure assessment

(cSOFA) score on admission; systolic (SAP), diastolic (DAP), mean arterial pressure (MAP), and the use of vasopressors and inotropic agents during the first 6 hours of ICU stay. Unfavourable neurological outcome (UO) was defined as a 3-month cerebral performance category score of 3-5.

Results: Among the 170 patients (median age 63 years, 67% male, 60% out-of-hospital CA), 106 (63%) had UO. Admission lactate was higher in patients with UO than in those with favourable neurological outcome (4.0[2.4-7.3] vs. 2.5[1.4-6.0] mEq/L; p=0.003) as was the cSOFA (3[1-4] vs. 2[0-3]; p=0.007). The lowest DAP during the first 6 hours after ICU admission was significantly lower in patients with unfavourable neurological outcome, notably in patients with high cSOFA scores. In multivariable analysis, high adrenaline doses and the lowest value of DAP during the first 6 hours after ICU admission was significantly associated with unfavourable neurological outcome.

Conclusions: In CA patients admitted to the ICU, low DAP during the first 6 hours is an independent predictor of unfavourable neurological outcome at 3 months.

Keywords: cardiac arrest; haemodynamics; outcome; diastolic pressure

Introduction

Despite improvements in the early management of cardiac arrest (CA) over the last few decades, prognosis remains poor, with a small percentage of patients surviving to hospital admission and a high mortality rate.[1] Moreover, among comatose CA survivors, extensive brain damage remains a major concern and is responsible for almost two thirds of deaths or decisions to limit life-sustaining therapies in this patient population.[2] Although the majority of post-anoxic brain injury occurs at the moment of cessation of brain perfusion, secondary brain damage, including brain hypoperfusion and reperfusion injuries, may develop in these patients and may contribute to further reduce the likelihood of a favourable neurological recovery.[3]

As such, haemodynamic monitoring and therapeutic strategies should be considered in these patients to optimise the administration of inotropic and vasopressor agents and to maintain adequate cerebral perfusion pressure and oxygen delivery in the post-resuscitation phase. However, no randomised clinical studies have defined the optimal haemodynamic strategy to achieve these goals. Although current guidelines recommend that mean arterial pressure (MAP) should be titrated to values greater than 65 mmHg in such patients,[4] values should probably be individualised.[5] Indeed, the lower threshold of cerebral autoregulation is often shifted rightward in this setting, meaning that in some patients a MAP of 65 mmHg may still result in brain hypoperfusion and in large variation of cerebral blood flow.[6] Moreover, several studies have shown that a higher MAP (>80 mmHg) could be associated with better outcome and adequate cerebral oxygenation.[7,8] Unfortunately, this evidence remains weak due to the observational design of those studies and the limited number and heterogeneity of the patients included.

In the early phase after hospital admission, almost half CA survivors develop shock.[9] In the presence of shock (i.e.. need for vasopressor agents and signs of hypoperfusion), using vasopressor agents to achieve higher blood pressure targets may be detrimental despite the improvement in cerebral perfusion pressure, because of an increase in cardiac complications, such as arrhythmias, coronary ischaemia and heart failure, secondary to the increased afterload.[10] In the setting of cardiogenic shock, higher MAP, cardiac power index, and lower simplified acute physiology score II (SAPS II) were independently associated with better survival rates in one study,[11] whereas the minimum diastolic arterial pressure (DAP) in the first 6 hours was

independently associated with 28-day mortality in another study.[12]

We, therefore, designed this study to investigate the relationship between early haemodynamic variables and neurological outcome in comatose survivors after CA.

Methods

Study population

This retrospective study was performed in the 35-bed medico-surgical Department of Intensive Care of Erasme University Hospital (Brussels. Belgium). All consecutive patients admitted after in-hospital (IHCA) or out-of-hospital (OHCA) CA and surviving at least 24 hours were included in an institutional database. We analysed data from all patients admitted from January 2009 to January 2013 who: a) were comatose (Glasgow Coma Scale [GCS] < 9) on admission; and b) had haemodynamic variables available for the first 6 hours following admission. Exclusion criteria were age <18 years and treatment with intra-aortic balloon pump or extracorporeal membrane oxygenation (ECMO). The local Ethics Committee approved the study (P2017/264), but waived the need for informed consent because of the retrospective nature of the study.

Patient management

All comatose CA patients were treated with targeted temperature management (TTM; target body temperature: 32-34°C) for 24 hours, according to a standardised institutional protocol. Cooling was started immediately after hospital admission using a bolus of cold fluids (in general saline solutions, given as a dose of 10-30 ml/kg over 30 min, as determined by the attending physician) and a water-circulating blanket device (Medi-Therm II, Gaymar, USA). Sedation and analgesia consisted of midazolam and morphine, which were adjusted to obtain deep sedation; cisatracurium was administered as a bolus to control shivering in the induction phase and then given, if needed, by continuous infusion. Rewarming (<0.5°C/h) was achieved passively and sedation/analgesia was discontinued at normothermia (> 37°C). Patients were kept in a 30° semi-recumbent position; ventilation was set to target $PaCO_2$ between 35 and 45 mmHg and SpO_2 > 94%. Blood glucose was kept between 110 and 150 mg/dL using a local protocol for continuous insulin infusion; enteral nutrition was permitted from the early phase of TTM. Haemodynamic assessment consisted of either continuous measurement of cardiac output (PiCCO, Pulsion, Munich, Germany) or assessment of cardiac function by repeated trans-oesophageal and/or trans-thoracic echocardiography. MAP was maintained > 65-70 mmHg using volume resuscitation, dobutamine and/or noradrenaline, as needed.

Life-support therapies were maintained for at least 72 hours after arrest and the decision process for withdrawal of such therapies was interdisciplinary and based on a combination of clinical evaluation (i.e. persistent coma with absent motor response or posturing and absence of pupillary and corneal reflexes and/or status myoclonus), somatosensory evoked potentials (SSEPs; i.e. bilateral absence of the cortical N20 response) and electroencephalogram (EEG; i.e. presence of non-convulsive status epilepticus refractory to 3 anti-epileptic drugs and continuous sedation OR persistent "malignant patterns", which were burst-suppressed or suppressed background, at 48-72 hours).

Data collection

We collected demographic characteristics for all patients. CA data were also recorded (location, initial rhythm, cause of arrest, bystander cardiopulmonary resuscitation [CPR], time to return of spontaneous circulation [ROSC], drugs administered) as well as the use of vasopressors or inotropes during the ICU stay and lactate levels on admission. The modified sequential organ failure assessment (SOFA) score (mSOFA, excluding the neurological SOFA sub-score) and cardiac SOFA sub-score (cSOFA) on admission were also recorded. During the first 6 h after admission, systolic arterial pressure (SAP), DAP, MAP and pulse pressure (PP), the use of vasopressors and inotropes (from the patient data management system; PDMS, Picis Critical Care Manager, Picis Inc., Wakefield, USA), and the mSOFA and cSOFA scores were recorded hourly. The lowest values of SAP, MAP, and DAP during the first 6 hours after ICU admission and the highest cSOFA and mSOFA were noted for each patient.

Neurological function was assessed at 3 months after CA either from the medical files or by telephone call. The Cerebral Performance Category score (CPC: 1 = no or mild neurological disability, 2 = moderate neurological disability, 3 = severe neurological impairment, 4 = vegetative state, 5 = death) was used and neurological recovery was subsequently dichotomised as favourable (CPC 1 and 2) or unfavourable (UO, CPC 3–5)

Statistical analysis

Data were tested for normality and are presented as either median (interquartile range) or mean ± standard deviation. Categorical variables are presented as counts (%). Categorical variables were compared using the Fisher exact test or Chi-square test, as appropriate, while the Mann-Whitney U-test was used to compare continuous variables. Repeated measures ANOVA for group per time interaction and group and time comparisons with Bonferroni correction for *post hoc* analysis was used. Linear correlation was calculated using Spearman's correlation coefficient. To identify the haemodynamic variables independently associated with UO, a multivariable logistic regression analysis with UO as the dependent variable was performed in all patients; co-linearity between variables was excluded prior to modelling; only hemodynamic and demographic variables associated with UO ($p < 0.2$) on a univariate basis were introduced in the multivariable model (i.e.: age, gender, weight, liver cirrhosis, previous neurological disease, coronary artery disease, adrenaline dose, vasopressors on admission and at 6 hours, lactate on admission and at 6 hours, mSOFA and cSOFA on admission and the highest value over the first 6 hours, the lowest MAP, DAP and PP). Odds ratios (OR) with 95% confidence intervals (CI) were computed. After the multivariable analysis, the discriminative ability of the lowest DAP to predict unfavourable neurological outcome was evaluated using receiver operating characteristic (ROC) curves with the corresponding area under the curve (AUC) and related sensitivity and specificity. A p value <0.05 was considered statistically significant. All analyses were performed using SPSS 24.0 package.

RESULTS

Study population

During the study period, 221 patients were admitted after a CA; 11 died within 4 hours after hospital admission without invasive haemodynamic monitoring, 31 received IABP/ECMO on admission and 9 had missing haemodynamic data, leaving a total of 170 patients for analysis. Among these patients (median age 63 years, 66% male, 59% OHCA), 106 (63%) had an unfavourable neurological outcome at 3 months. Patients with UO were older and more likely to have previous neurological diseases and liver cirrhosis than those with a favourable outcome (Table 1). The characteristics of CA were also different between the two groups, with a lower proportion of witnessed CA and a higher incidence of non-shockable rhythm at presentation and of CA due to non-cardiac causes in patients with unfavourable neurological outcome compared to those with favourable outcomes (Table 1).

Haemodynamic variables

Admission lactate levels, cSOFA and mSOFA scores were higher in patients with UO than in those with favourable neurological outcomes (Table 1). Admission MAP was lower in patients with UO (91 [75-105] vs. 98 [83-112] mmHg; p=0.01), as was DAP (69 [58-84] vs. 78 [64-96] mmHg; p=0.003), whereas SAP and PP were similar between groups.

The lowest values of DAP and MAP during the first 6 hours after ICU admission were significantly lower in the patients with UO than in those with favourable neurological outcomes (Table 1). MAP was lower throughout the 6-h period after admission in patients with UO (Figure 1), but the difference was only statistically significant at 4 hours after admission. DAP was statistically significantly lower during the first 4 hours after admission in patients with UO compared to those with a favourable outcome (Figure 1). SAP was similar in the two groups over time. When differences in DAP were compared according to cSOFA scores, the differences in DAP over time in patients with UO and favourable outcomes were only statistically significant in patients with cardiovascular impairment (i.e. with a cSOFA ≥1; Figure 2); there were no differences in MAP or SAP overtime between groups in the same analysis (data not shown).

Multivariable analysis

In a multivariable logistic regression analysis, high adrenaline doses during CPR and the lowest value for DAP during the first 6 hours were independently associated with UO (Table 2). The lowest DAP values over the first 6 hours after ICU admission had an AUC of 0.65 [0.56-0.73; p=0.001] to predict unfavourable neurological outcome in this cohort (Figure 3). A DAP value ≤ 60 mmHg had a sensitivity of 61%, a specificity of 63%, a PPV of 70% and a NPV of 57% to predict unfavourable neurological outcome.

DISCUSSION

In the present study, we investigated which haemodynamic variables in the early phase after ICU admission were associated with long-term neurological outcome in patients admitted to the ICU after cardiac arrest. High admission lactate levels and cSOFA scores, and lower lowest MAP and DAP values during the 6 hours post-ICU admission were observed in patients with UO compared to those with favourable outcome. However, the lowest DAP value during the first six hours after ICU admission was the only haemodynamic parameter independently associated with unfavourable 3-month neurological outcome.

Monitoring of haemodynamic status of patients after CA represents a challenge for the intensivist, as he/she tries to prevent secondary brain damage, which may contribute to further compromise neurological recovery in this setting.[13] No randomised clinical studies are available to help define the optimal haemodynamic strategy to improve neurological outcome after CA, in particular because of the lack of specific goals or targets to individualise treatment.[14] Several studies showed that high lactate levels during the first few hours after ICU admission were predictors of mortality or unfavourable neurological outcome in CA patients.[15.16] Our results were consistent with these observations. Nevertheless, initial high lactate levels probably indicate a longer no/low-flow time during the resuscitation period and decreasing lactate levels are observed over time in both survivors and non-survivors.[16] Only one study has investigated the relationship between cSOFA and neurological recovery, Cour et al. showed that the cSOFA on admission was significantly lower in survivors than in non-survivors after out-of-hospital CA, although it was not independently associated with mortality at 28 days.[17] In our study, a considerable proportion of our cohort had had an IHCA (41%); the clinical condition of hospitalised patients pre-CA may worsen the baseline SOFA score and result in a higher use of vasopressors in this setting.

In the present study, the lowest DAP value during the first 6 hours after ICU admission was the only haemodynamic variable independently associated with an unfavourable 3-month outcome. A recent systematic review demonstrated that higher MAP was associated with improved neurologic outcomes in patients after CA.[18] However, there was considerable heterogeneity between studies in terms of inclusion criteria, targets of MAP and use of vasopressors, which complicated the identification of relevant therapeutic

goals in this setting. The current guidelines for post-resuscitation care recommend keeping MAP levels at least above 65 mmHg and close to the patient's usual value, in particular in patients with chronic hypertension, to avoid peripheral organ and cerebral hypoperfusion, although no indications about a potential role for DAP values was discussed.[4]

To the best of our knowledge, this is the first study to evaluate the impact of DAP on neurological outcome in adult patients resuscitated after CA. In a recent multicentric pediatric study (n=164), maintaining mean DBP ≥25 mm Hg in infants and ≥30 mm Hg in children ≥1 year of age was associated with improved survival and favorable neurological outcome.[19] The role of DAP has been gaining popularity as a potential index for therapy and prognosis during CPR and cardiogenic shock.[12,20] However, how DAP should be managed in CA patients remains to be better understood. First, DAP is a major determinant of coronary perfusion pressure, which is crucial to maintain adequate myocardial perfusion, either during CPR (to improve the efficacy of defibrillation) or in the post-resuscitation phase.[20] As such, one may argue that titrating an adequate DAP (i.e. at least 60 mmHg as suggested by our findings) should be considered as the main target in future studies evaluating different hemodynamic strategies in CA patients. It would be interesting also to evaluate whether DAP would result in a main determinant of cardiac and neurological function in CA due to coronary lesions only or if it would relevant also in other causes of arrest. More interestingly, DAP might also be used as a "safety end-point" in those CA patients receiving hypotensive drugs to reduce ventricular afterload in case of hypertension associated with acute myocardial ischemia. Second, the post-resuscitation syndrome is also characterized by a systemic ischemic/reperfusion response, inducing a "sepsis"-like status;[1] thus, DAP reflects the arterial tone and, in part, the arterial elastance and might be considered a useful marker of altered peripheral vascular response to endogenous and exogenous catecholamines. Third, severe bradycardia, cardiac valve dysfunction and heart failure could be common causes of reduced DAP, which could be used as a indicator of severe cardiac dysfunction in CA patients. As such, Rigamonti et al. showed the minimum value of DAP in the first hours after ICU admission was a significant risk factor for 28-day mortality in patients with cardiogenic shock.[12] Finally, low DAP may represent faulty of brain signaling (i.e. "neurally" mediated hypotension), which would then represent just a

marker of severe post-anoxic cerebral damage. Our data do not provide a definite answer to the role of DAP in the management of CA patients, neither on the impact of optimizing DAP on improved cardiac and neurological outcomes in these patients.

Interestingly, DAP was the strongest predictor of UO with all available hemodynamic variables. Bradycardia was reported as an independent predictor of favourable outcome in one study.[21] In another one, heart rate >93/min, cardiac index <2.5L/min.m^2 and lower average of MAP were independently associated with in-hospital mortality.[22] In a large cohort, high lactate concentrations on admission were also independently associated with UO after in-hospital and out-of-hospital CA.[23] Also, persistent systolic dysfunction on repeated echocardiography was observed in non-survivors after OHCA.[24] Finally, reduced oxygen consumption in the early phase after ROSC was associated with UO in a small recent prospective study.[25] These findings clearly underline the need for systematic report of several hemodynamic data in different cohorts in order to better understand which is the hemodynamic variable that might deserve a specific interest, either in terms of monitoring or as a target for therapeutic interventions, in CA patients.

Our study has some limitations. First, the accuracy of DAP to discriminate between unfavourable and favourable outcome was relatively weak, which would limit the use of a specific threshold in clinical practice; however, the same results have been found in previous studies focusing on MAP and it is plausible that several haemodynamic targets should be used in this setting. Second, the daily fluid management in this cohort was not specifically analysed, thus preventing any further analyses of the role of intravenous infusions and vasopressors on haemodynamic variables. Third, due to the retrospective design of the study, we could not exclude the presence of pressure artefacts affecting the arterial pressure waveform, which may occur in up to 30% of cardiovascular patients.[26] However, most artefacts are generally represented by "underdamping" of blood pressure, which notoriously affects mainly SBP (i.e. overestimation), whereas DAP is affected to a lesser extent. Also, time from ICU admission is an arbitrary administrative time and time from resuscitation would have been a more logical starting point for data collection. Fourth, we considered the lowest DAP value in our multivariable analysis; however, DAP corrected for a longer observation period (e.g. area under the curve of DAP below specific thresholds during the first day after admission) might have been

more informative. Fifth, we considered the severity of cardiovascular impairment based on predefined doses of vasopressors, according to cSOFA, while individual daily doses of these drugs could have been more precise to address the haemodynamic alterations in these patients. Finally, considering long-term neurological outcomes may mask the impact of haemodynamic therapies on early organ recovery and improvement in peripheral perfusion. Despite its limitation, DAP is an easy and immediate variable that is easily determined in every patient equipped with an invasive arterial pressure monitoring device and our results encourage further research on this topic.

In conclusion, among survivors admitted to the ICU after CA, high admission lactate levels, higher cSOFA levels and lower DAP values over the first six hours were associated with a unfavourable neurological outcome at 3 months; however, the lowest value of DAP in the first six hours after ICU admission was an independent predictive factor in these patients.

Author contributions: FA and FST conceived and designed the study; FA, FST and AMD selected the population. FA, FF, KD and AMD screened and collected data from the population; FST, SS and FF conducted the statistical analysis; FA, FST, JC, SS and JLV wrote the first draft of the manuscript; FST, JC, KD and JLV revised the text for intellectual content. All the authors read and approved the final text.

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Table 1. Characteristics of the study population and comparison between patients with favourable and unfavourable outcome. Data are presented as count (%) or median (IQRs).

	ALL PATIENTS (n=170)	FAVOURABLE OUTCOME (n=64)	UNFAVOURABLE OUTCOME (n=106)	*OR (95% CIs)*	*p value*
AGE, years	63 (52-76)	59 (51-71)	66 (53-78)	1.02 (0.21-0.87)	**0.03**
MALE, n (%)	113 (66)	49 (76)	64 (60)	1.02 (1.00-1.04)	**0.015**
WEIGHT, Kgs	76 (65-86)	78 (70-90)	75 (64-85)	0.98 (0.95-1.10)	0.06
ICU LENGTH OF STAY, days *	3 (2-6)	5 (3-8)	3 (2-5)		**<0.01**
COMORBIDITIES					
ARTERIAL HYPERTENSION, n (%)	70 (62)	25 (39)	45 (42)	0.98 (0.52-1.84)	0.74
HEART FAILURE, n (%)	36 (21)	13 (20)	23 (25)	0.91 (0.42-1.98)	0.7
CORONARY ARTERY DISEASE, n (%)	64 (38)	30 (46)	34 (36)	0.55 (0.29-1.03)	0.1
NEUROLOGICAL DISEASE, n (%)	30 (18)	6(9)	24 (23)	2.83 (1.09-7.36)	**0.03**
COPD/Asthma, n (%)	38 (22)	15 (23)	23 (22)	1.11 (0.52-2.31)	0.85
LIVER CIRRHOSIS, n (%)	8 (5)	0 (0)	8 (8)	5.14 (0.63-42.12)	**0.02**
DIABETES, n (%)	29 (17)	9 (14)	20 (19)	0.70 (0.30-1.66)	0.52
CHRONIC KIDNEY DISEASE, n (%)	28 (16)	8 (13)	20(19)	0.61 (0.25-1.49)	0.39
CARDIAC ARREST					
OUT OF HOSPITAL CA, n (%)	101 (59)	36 (56)	65 (61)	0.81 (0.43-1.52)	0.52
BYSTANDER CPR, n (%)	103 (61)	43 (67)	60 (57)	0.59 (0.31-1.14)	0.19
WITNESSED CA, n (%)	132 (78)	55 (86)	77 (72)	0.33 (0.13-0.80)	**0.015**

	TIME TO ROSC, min	15 (8-23)	13 (5-20)	15 (10-24)	1.01 (0.99-1.04)	0.12
	NON CARDIAC CAUSES, n (%)	63 (37)	10 (15)	53 (50)	5.40 (2.50-11.72)	**<0.01**
	NON SHOCKABLE RHYTHM, n (%)	100 (59)	20 (31)	80 (75)	6.30 (3.18-12.5)	**<0.01**
	ADRENALINE, mg	3 (2-5)	3 (1-5)	4 (2-6)	1.12 (1.00-1.26)	**0.03**
	ON ICU ADMISSION					
	VASOPRESSORS, n (%)	104 (61)	32 (50)	72 (68)	1.98 (0.98-3.59)	**0.03**
	DOBUTAMINE, n (%)	25 (15)	9 (14)	16 (15)	0.92 (0.38-2.23)	0.89
	LACTATE, mEq/L	3.8 (1.9-6.8)	2.5 (1.4-6.0)	4.4 (2.4-7.3)	1.12 (1.06-1.54)	**<0.01**
	CREATININE, mg/dL	1.1 (1.1-1.4)	1.1 (0.9-1.5)	1.1 (0.9-1.4)	1.04 (0.93-1.19)	0.94
	PaO_2, mmHg	129 (81-230)	150 (83-227)	125 (77-234)	1.08 (0.93-1.21)	0.62
	$PaCO_2$, mmHg	41 (35-50)	41 (36-50)	40 (34-50)	0.93 (0.89-1.09)	0.58
	pH	7.25 (7.19-7.30)	7.26 (7.20-7.30)	7.23 (7.18-7.32)	0.91 (0.84-1.08)	0.52
	mSOFA	5 (3-6)	4 (2-5)	5 (3-7)	1.14 (1.03-1.26)	**0.03**
	cSOFA	2 (0-4)	2 (0-3)	3 (1-4)	1.28 (1.06-1.54)	**<0.01**
	DURING THE FIRST 6 HOURS AFTER ICU ADMISSION					
	VASOPRESSORS, n (%)	109 (64)	34 (53)	75 (71)	2.07 (1.10-3.92)	**0.02**
	DOBUTAMINE, n (%)	78 (46)	29 (45)	49 (46)	0.96 (0.51-1.79)	1
	LACTATE, mEq/L	2.3 (1.3-4.4)	1.8 (1.1-3.2)	2.6 (1.8-4.8)	1.14 (1.03-1.26)	**<0.01**
	pH	7.35 (7.29-7.41)	7.35 (7.29-7.41)	7.35 (7.28-7.41)	0.98 (0.89-1.07)	0.78

	Highest mSOFA	5 (3-7)	4 (2-6)	5 (4-7)	1.45 (1.08-2.21)	**0.02**
	Highest cSOFA	2 (0-4)	2 (0-3)	3 (1-4)	1.23 (1.07-1.69)	**<0.01**
	CVVH, n (%)	17 (10)	7 (11)	10 (9)	1.18 (0.42-3.27)	0.79
	HYPOTHERMIA, n (%)	161 (95)	61 (94)	100 (95)	1.22 (0.29-5.05)	1
	Lowest SAP, mmHg (IQ)	102 (92-118)	107 (94-121)	100 (90-115)	1.09 (0.90-1.21)	0.29
	Lowest MAP, mmHg (IQ)	74 (68-85)	78 (71-88)	72 (71-88)	0.97 (0.95-0.99)	**0.02**
	Lowest DAP, mmHg (IQ)	58 (52-69)	63 (56-72)	56 (50-64)	0.96 (0.94-0.99)	**<0.01**
	Lowest PP, mmHg (IQ)	39 (29-49)	37 (27-47)	39 (30-50)	1.01 (0.99-1.03)	0.16

COPD = chronic obstructive pulmonary disease; CA = cardiac arrest; ROSC = return of spontaneous circulation; CPR = cardiopulmonary resuscitation; CVVH = continuous veno-venous haemofiltration; AKI = acute kidney injury; SOFA = sequential organ failure assessment score (highest during 6 h); cSOFA = cardiovascular sub score; mSOFA = modified SOFA (without neurological sub score); SAP = systolic arterial blood pressure; MAP = mean arterial blood pressure; DAP =diastolic arterial blood pressure; PP = pulse pressure

* not included in the multivariable analysis

Table 2. Multivariable analysis to identify independent predictors of unfavourable neurological outcome at 3 months.

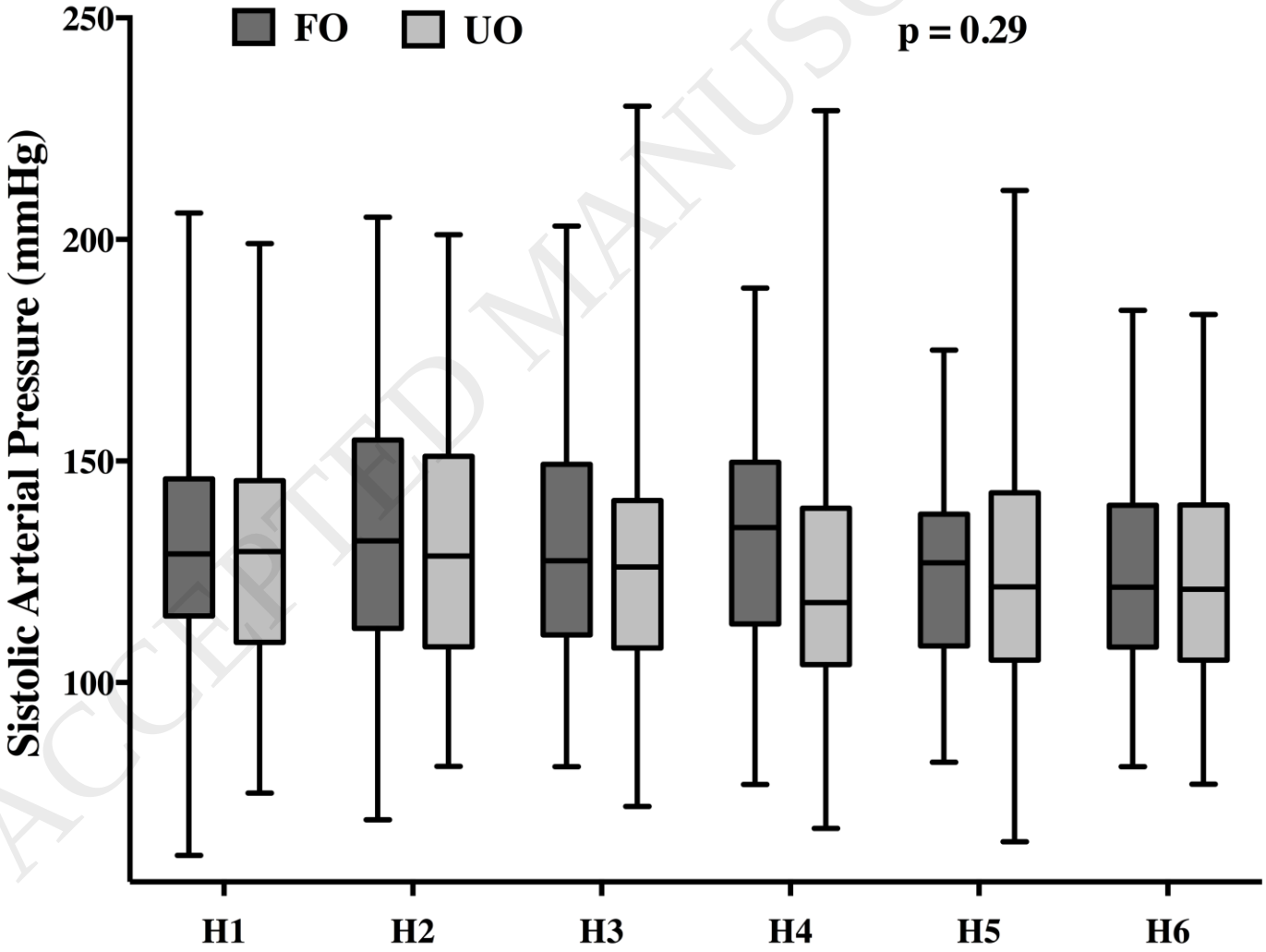
Variable	p value	OR	95% CI for OR	
			Lower	Upper
Age	0.101	1.024	0.995	1.054
Male Gender	0.130	0.519	0.222	1.213
Weight, Kgs	0.730	0.867	0.741	1.128
Coronary Artery Disease	0.076	0.479	0.213	1.081
Neurological Disease	0.077	2.598	0.902	7.481
Liver Cirrhosis	0.198	4.34	0.464	40.607
Bystander CPR	0.068	0.509	0.319	1.029
Non-cardiac causes	0.101	3.925	0.845	11.205
Non-shockable rhythm	0.083	4.429	0.908	14.133
Adrenaline, mg	0.016	1.158	1.027	1.306
Vasopressors on admission	0.088	3.416	0.901	9.355
Lactate on admission	0.061	1.505	0.955	1.987
Highest mSOFA	0.108	1.813	0.937	2.555
Highest cSOFA	0.229	0.064	1.258	0.987
Lowest MAP, mmHg	0.083	0.982	0.936	1.023
Lowest DAP, mmHg	0.003	0.956	0.930	0.986
Lowest PP, mmHg	0.085	0.894	0.815	1.193

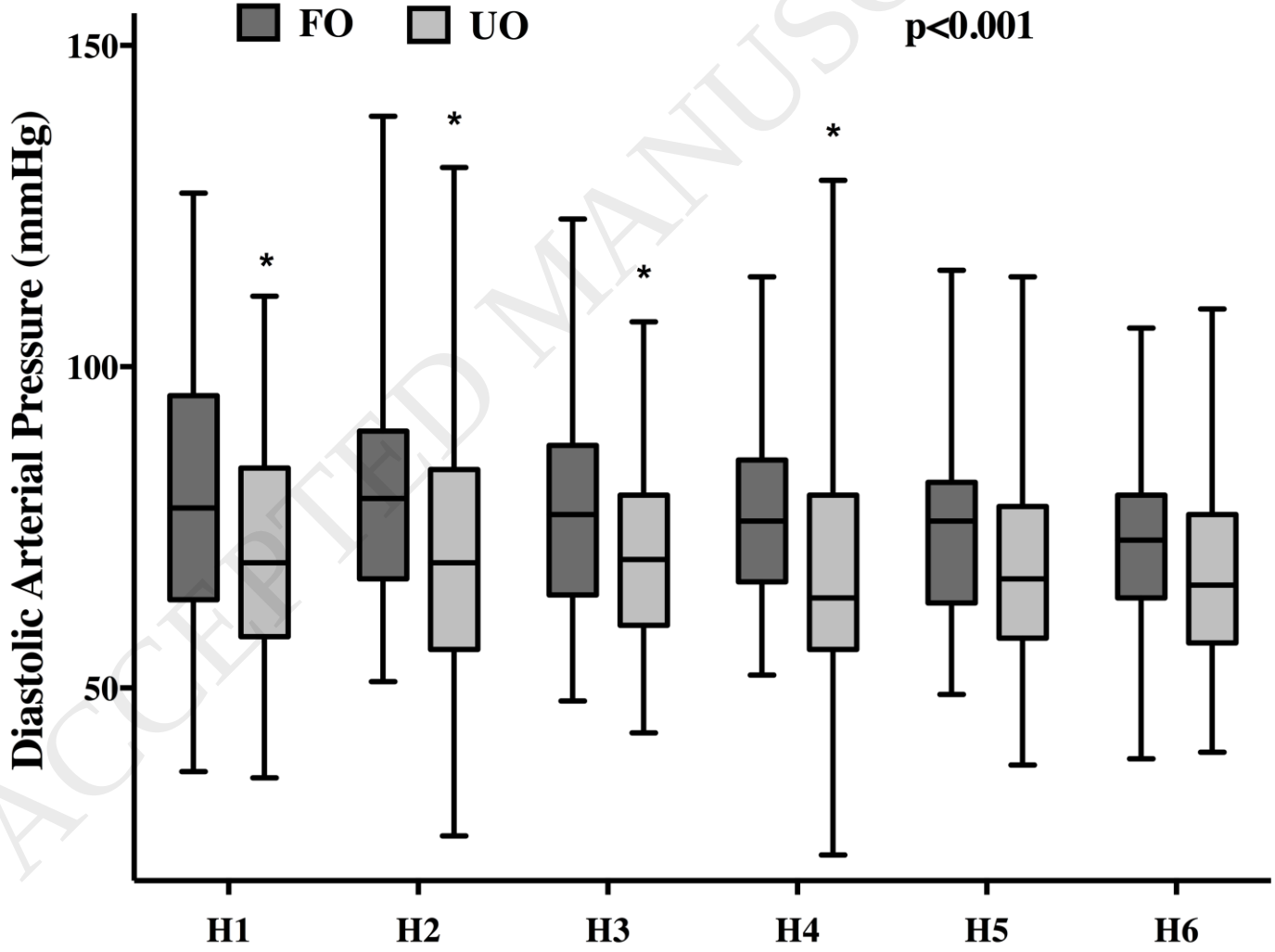
CPR = cardiopulmonary resuscitation; DAP = diastolic arterial pressure; mSOFA = modified Sequential Organ Failure Assessment score; cSOFA = cardiovascular Sequential Organ Failure Assessment score; MAP = mean arterial pressure; PP = pulse pressure

Hosmer and Lemeshow goodness-of-fit test chi-squared = 8.25 (p = 0.21). This model has a 65.1% correct classification (75.0% for unfavourable and 53.3% for favourable outcome).

Figure legends

Figure 1. Systolic (A), diastolic (B), and mean arterial pressure (C) in the first 6 hours after ICU admission. FO, favourable 3-month neurological outcome; UO, unfavourable 3-month neurological outcome. The results of the analysis of variance (ANOVA) analysis between groups are reported in the Figure. *p<0.05 between FO and PO patients in the *post hoc* analysis. ANOVA analyses for interaction and time are: p=0.34 and P=0.004 (systolic); p=0.65 and p<0.001 (diastolic); p=0.61 and p<0.001 (mean), respectively.





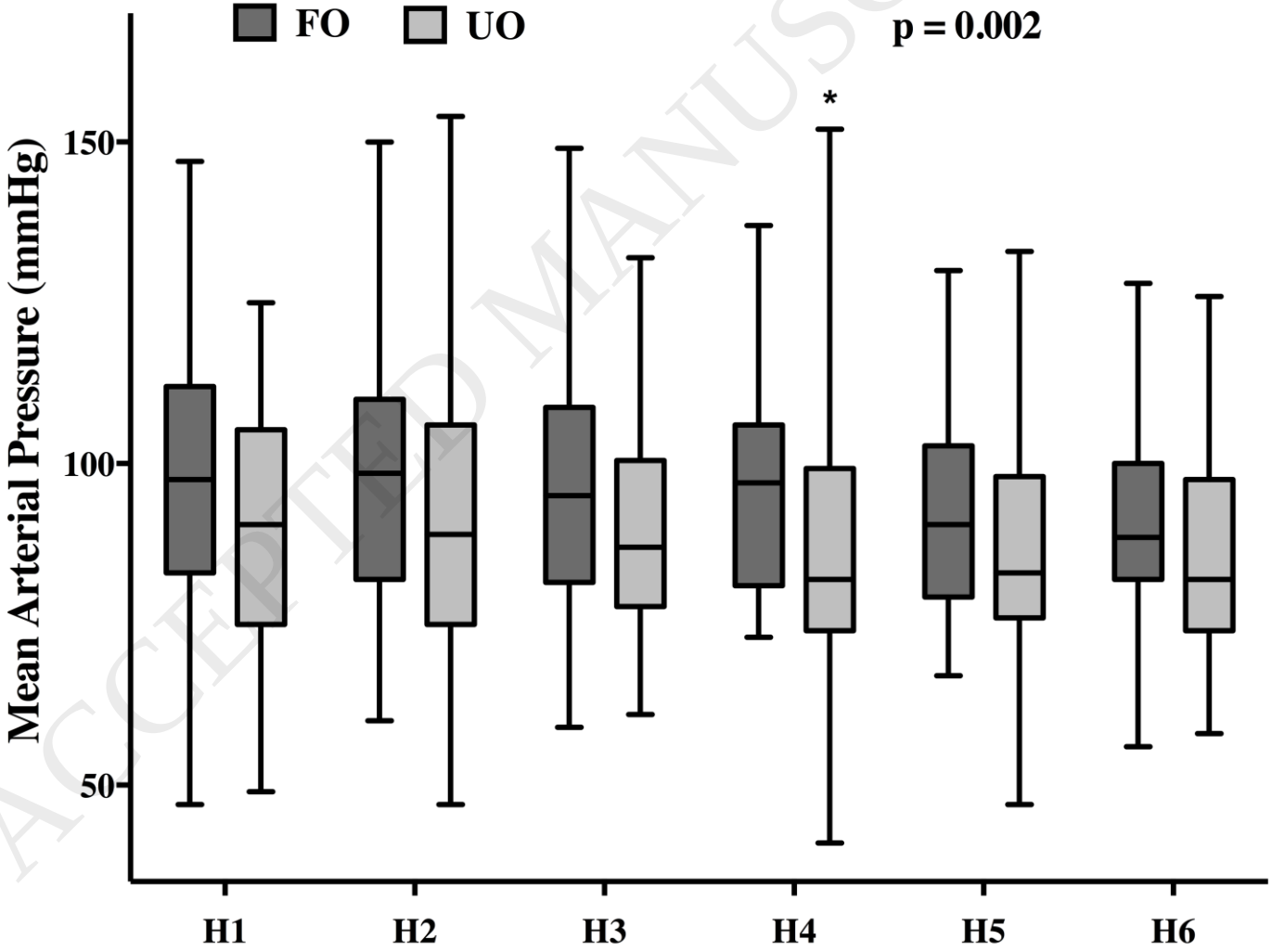
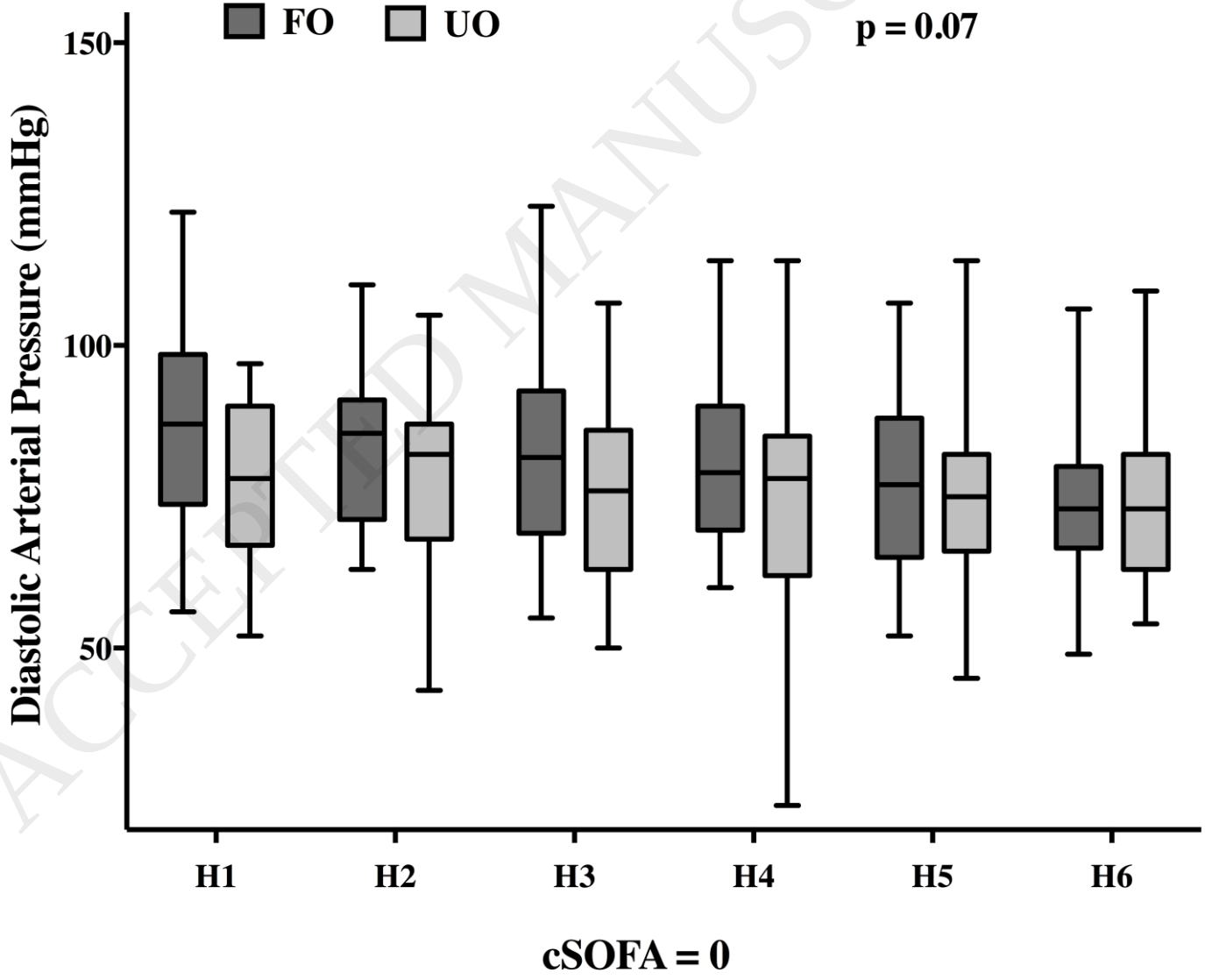
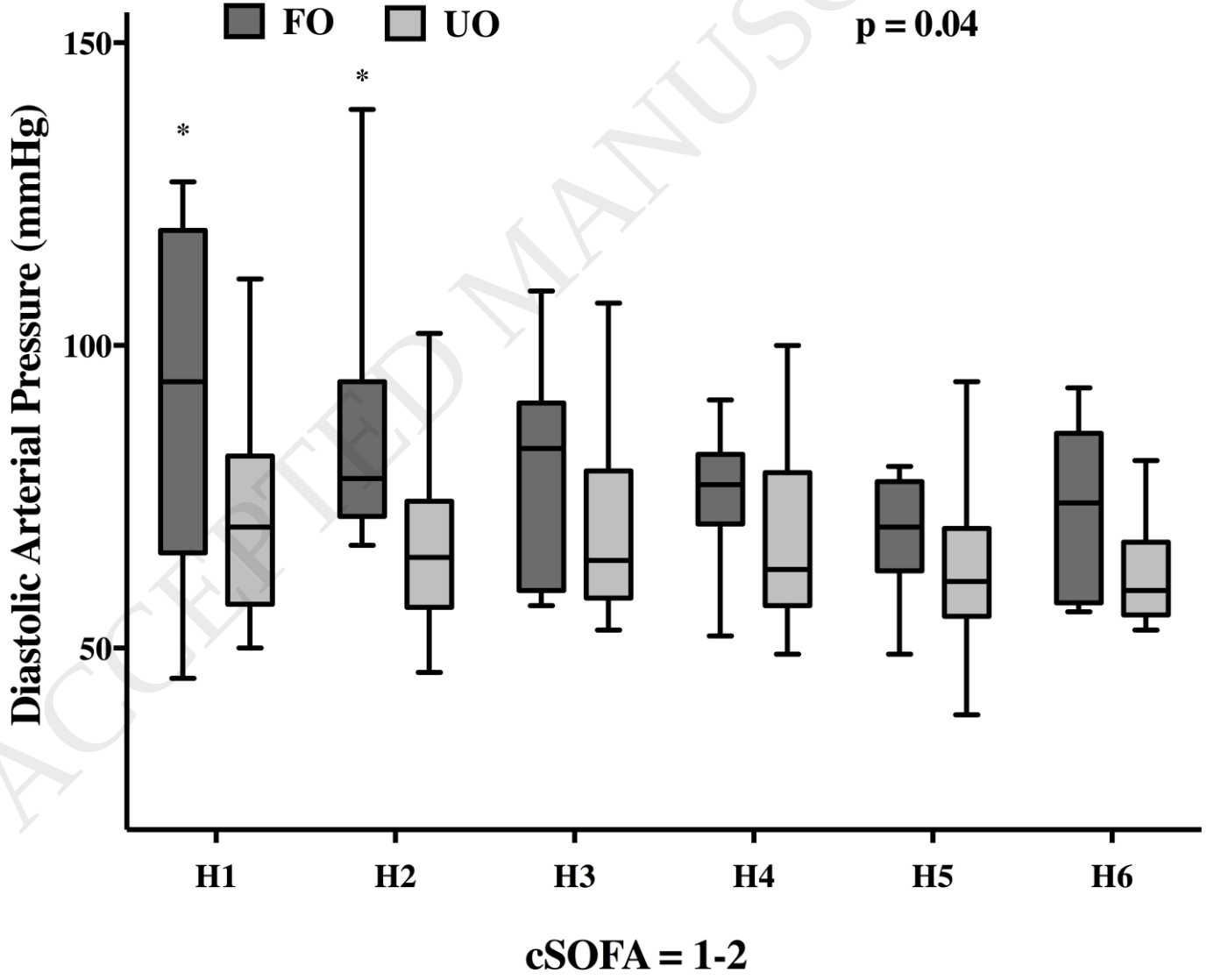


Figure 2. Diastolic arterial pressure in the first 6 hours after ICU admission, according to the cardiovascular sub-score of the sequential organ failure assessment (cSOFA) score. FO, favourable 3-month neurological outcome; UO, unfavourable 3-month neurological outcome. *p<0.05 between FO and PO patients in the *post hoc* analysis.





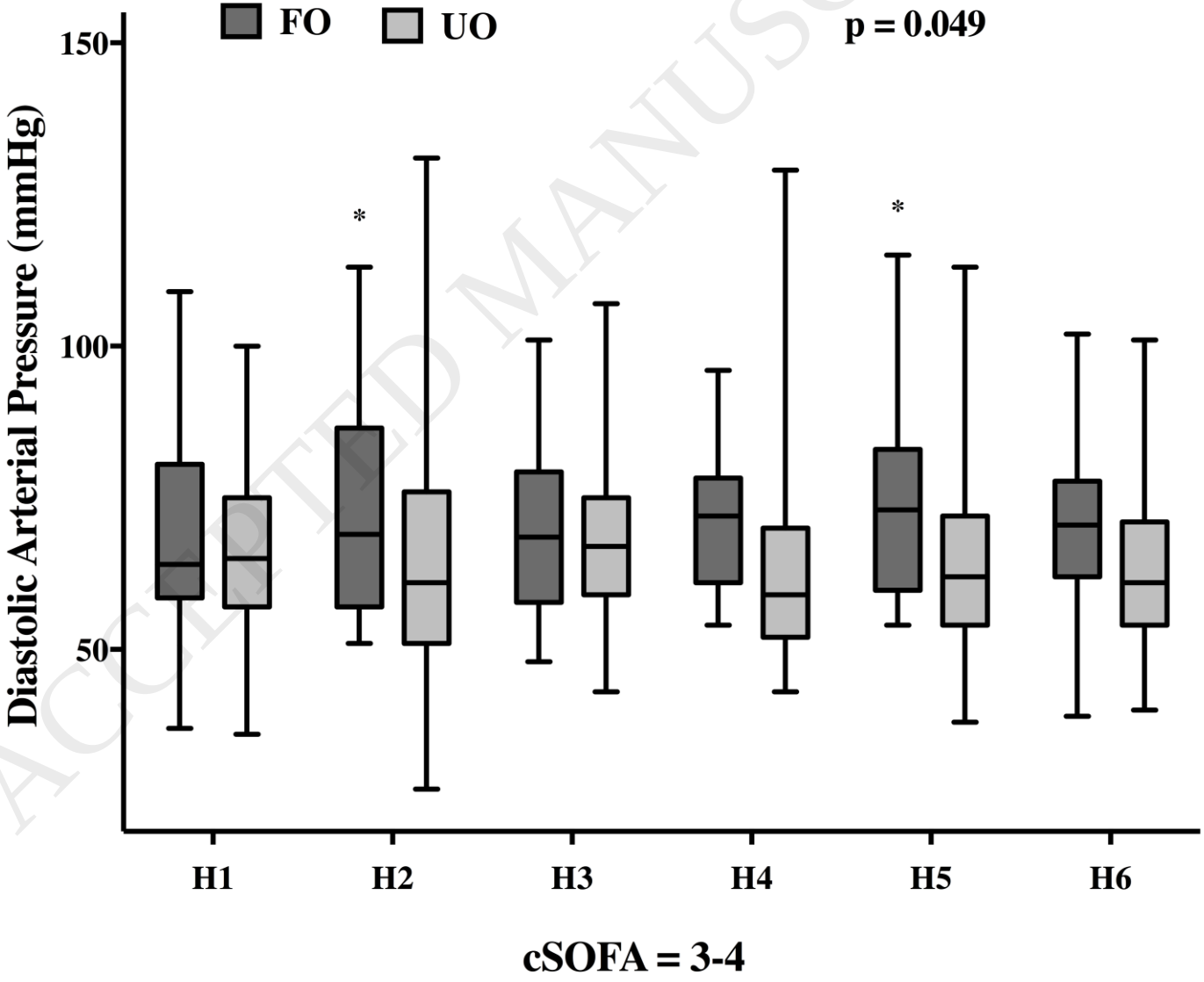


Figure 3. Receiver operating characteristic (ROC) curve showing the accuracy of the lowest value of diastolic arterial pressure (DAP) over the first 6 hours after ICU admission for predicting unfavourable neurological outcome at 3 months.