RESEARCH ARTICLE

Effect of Onset-to-Admission Time and Care Bundle Achievement on Functional Outcomes in Patients With ICH

A Population-Based Study

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Abstract

Background and Objectives

Intracerebral hemorrhage (ICH) remains a leading cause of morbidity and mortality, with limited effective treatments. Early implementation of a care bundle protocol (CBP) within 6 hours of symptom onset has been shown to improve functional outcomes, although its effect beyond this time frame remains unclear. We assessed the impact of onset-to-admission (OTA) time and CBP achievement on functional outcome and mortality in patients with acute spontaneous ICH.

Methods

We conducted a population-based study of a prospective cohort of consecutive patients diagnosed with acute spontaneous ICH between 2020 and 2022 in Catalonia, Spain. Inclusion criteria were patients aged 18 years or older, OTA time <24 hours, and a baseline modified Rankin Scale (mRS) score ≤3. CBP achievement was defined as attaining control in the first 24 hours of blood pressure (<140/90 mm Hg), glycemia (<150 mg/dL), body temperature (<37.5°C), and blood oxygen saturation (>92%) and, if required, anticoagulation reversal. The primary outcome was the proportion of patients with a favorable functional outcome, defined as mRS score ≤3 at 3-month follow-up. The effects of OTA time and CBP achievement on outcomes were evaluated using multivariable logistic regression. Potential interaction between OTA time and CBP achievement was assessed using the likelihood ratio test.

Results

A total of 1,821 patients were included (mean age 70.3 ± 14.1 years, 37.7% women). CBP was achieved in 27.7% of patients. Shorter OTA time was independently associated with poorer functional outcome (adjusted odds ratio $[aOR]_{x1h}$ 1.04, 95% CI 1.02–1.06). CBP achievement was associated with a higher probability of favorable outcome at 3 months (aOR 1.66, 95% CI 1.29–2.15). An interaction between OTA time and CBP achievement was observed (p = 0.016), indicating greater CBP benefits for earlier admission. This interaction was evident up to 13.8 hours after symptom onset, with the CBP benefit concentrated in the first 8 hours.

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Supplementary Material

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Glossary

aOR = adjusted OR; **CBP** = care bundle protocol; **CSC** = comprehensive stroke center; **GCS** = Glasgow Coma Scale; **ICH** = intracerebral hemorrhage; **IVH** = intraventricular hemorrhage; **KPI** = key performance indicator; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **OTA** = onset-to-admission; **PSC** = primary stroke center; **TSC** = telestroke center; **WoC** = withdrawal of care.

Discussion

Our findings highlight the importance of timely CBP application to improve functional outcome in patients with ICH, even beyond the first 6 hours after symptom onset. While earlier intervention remains ideal, our results support expanding CBP implementation and promoting "Code ICH" initiatives to enhance patient outcomes in stroke care systems.

Trial Registration Information

Multicentre Registry of Patients With Spontaneous Acute Intracerebral Hemorrhage in Catalonia (HIC-CAT). ClinicalTrials.gov ID: NCT03956485. Registration submission: May 2019. First patient enrolled March 2020.

Classification of Evidence

This study provides Class III evidence that in patients with acute ICH, achievement of a standardized CBP is associated with better functional outcomes at 3 months.

Introduction

With nearly 3.5 million new cases worldwide each year, intracerebral hemorrhage (ICH) remains the type of stroke with the highest morbidity and mortality rates.[1] This scenario has remained unchanged for decades, likely due to a lack of effective treatments.[2]

Despite previous inconsistent findings in patients with ICH,[3,4] the INTERACT3 trial[5] demonstrated that implementing a care bundle protocol (CBP) in the first 6 hours after symptom onset—early control of high blood pressure and management of hyperglycemia, fever, and abnormal coagulation—significantly improves functional outcomes in patients with acute spontaneous ICH. Furthermore, the INTERACT4 trial[6] underscored the benefits of early intervention in patients with ICH, showing that lowering prehospital blood pressure is associated with better outcomes. Together, these findings highlight the critical role of timely medical management in ICH.[7]

A shorter time from symptom onset to hospital admission is also known to be an independent factor of hematoma expansion[8,9] and poorer outcomes,[10] likely reflecting the dynamic phase of early-stage active bleeding and the greater clinical severity of these patients. The fact that the "Code ICH" initiative[7,11]—based on INTERACT3 results—currently emphasizes treatment within the first 6 hours after symptom onset could inadvertently perpetuate therapeutic nihilism in the management of patients presenting beyond this time frame.[12] While CBP has also shown some benefits in reducing mortality in acute patients,[13] data on its implementation and effect on functional outcomes at extended time intervals remain scarce. Nevertheless, reducing onset-to-admission (OTA) time should stand as a primary goal for stroke code programs, facilitating faster diagnosis and tailored management. Given the findings of recent trials,[5,6] we wonder whether time could emerge as a new ally in acute ICH, or whether it remains a challenge to overcome.

Our aims with this population-based study were as follows: (1) to ascertain whether a reduced OTA time is associated with better functional outcomes in patients with acute spontaneous ICH who achieve CBP within the first 24 hours; (2) to assess CBP achievement according to OTA time; and (3) to explore whether the benefits of CBP for functional outcomes are influenced by OTA time.

Methods

Study Design and Population

We conducted an observational, multicenter study using a prospective population-based cohort of patients consecutively diagnosed with acute spontaneous ICH over a 2-year period (from March 2020 to March 2022) in Catalonia, Spain (HIC-CAT study).[14]

The HIC-CAT study included all patients aged 18 years or older diagnosed with spontaneous ICH in Catalan public hospitals with stroke care capacity. Based on stroke resources, participating hospitals—all audited by the Catalan Agency for Health Quality and Assessment—were classified as comprehensive stroke centers (CSCs, n = 9), primary stroke centers (PSCs, n = 5), and telestroke centers (TSCs, n = 14). CSCs met structural, staffing, and diagnostic criteria for 24/7 specialized care in ICH, including neurosurgery on-site, while PSCs lacked neurosurgical capacity and TSCs relied on remote neurology support. More details on the Catalan Stroke

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System and hospital organization are provided in the main HIC-CAT report.[14] Although no unified protocol for ICH management existed, centers adhered to available European Stroke Organization[15] and American Heart Association[16] guidelines. During the study period, each center followed its usual care pathway for patients with ICH. In general, blood pressure was managed with the goal of achieving values <140/90 mm Hg, typically using intravenous antihypertensive agents. Anticoagulation reversal was performed based on the type of anticoagulant used, with centers having access to prothrombin complex concentrate, vitamin K, and idarucizumab, among other options. For patients on vitamin K antagonists, reversal was indicated for an international normalized ratio above 1.3. All centers had access to neurosurgical consultation, either on-site or remote. Prehospital blood pressure management was not routinely implemented and only applied in selected hypertensive emergencies managed by advanced life support units.

Some patients were transferred between hospitals, but all were included in the analysis; time intervals were calculated from symptom onset to arrival at the first hospital, which marked the beginning of acute care.

Standard Protocol Approvals, Registrations, and Patient Consents

The HIC-CAT (ClinicalTrials.gov identifier: NCT03956485) study was approved by the ethics committee of Hospital de la Santa Creu i Sant Pau as the sponsoring center (IIBSP-HIC-2019-22) and locally by each participating center. Patients or their legal representatives provided informed consent to participation. In some hospitals, ethics committees required consent only for stroke survivors and for authorization of the 3-month follow-up assessments through telephone interview.

Inclusion and Exclusion Criteria

For this post hoc analysis, we included patients aged 18 years or older diagnosed with spontaneous ICH in the emergency departments of all Catalan public hospitals with stroke care capacity. Exclusion criteria were patients with OTA time ≥24 hours and those with a baseline modified Rankin Scale (mRS) score >3. Patients lacking critical data on time metrics or follow-up were also excluded (Figure 1). The reporting of this study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[17]

Study Variables

As described in the main HIC-CAT report,[14] the following variables were collected for all patients: (1) demographics: age and sex; (2) medical history: baseline mRS score, vascular risk factors, and use of antithrombotic agents; (3) logistics and time metrics: type of stroke center, OTA time, and admission-to-neuroimaging time; (4) clinical and radiologic findings on admission: NIH Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS) scores, ICH volume, location (lobar, deep, or infratentorial), and presence of an intraventricular hemorrhage (IVH) component; (5) treatment targets at 24 hours: blood pressure, glycemia, body temperature, blood oxygen saturation, and anticoagulation reversal; (6) neurosurgery consultation and intervention; (7) in-hospital complications; and (8) 3-month functional outcome and mortality. Hemorrhage volume was quantified using the ABC/2 formula or planimetry on CT, according to the usual local neuroradiology protocol.

Symptom onset was determined using the last-time-seen-well approach, classifying patients into 2 groups: those with a known onset time and those with wake-up strokes or unknown onset. The OTA time, defined as the time from symptom onset to first hospital admission, was analyzed both as a continuous variable and across categorized time frames (<2, 4, 6, 8, 10, 12, and 24 hours).

CBP achievement was defined as meeting, at any time within the first 24 hours, all prespecified goals as follows: (1) blood pressure <140/90 mm Hg; (2) glycemia <150 mg/dL; (3) body temperature <37.5°C; (4) blood oxygen saturation >92%; and (5) anticoagulation reversal if required.[13,15,16] To assess outcomes, any prespecified goal for which data were missing was considered as not achieved.

Primary and Secondary Outcomes

Our primary outcome was the proportion of patients achieving a favorable (mRS scores 0–3) vs unfavorable (mRS scores 4–6) functional outcome at 3 months. The secondary outcome was 3-month mortality. Outcomes were centrally assessed by blinded certified evaluators using a validated methodology.[18]

Statistical Analysis

Continuous descriptive variables were reported as means and SDs and, if not normally distributed (as tested by histograms or the Shapiro-Wilk normality test), as medians and interquartile ranges. Categorical variables were expressed as counts and percentages. Bivariable analyses comparing groups were performed using the Student t test or the Mann-Whitney U test (when a nonparametric test was required) for continuous variables and the χ^2 test for categorical variables.

The primary outcome was analyzed using logistic regression, calculating unadjusted odds ratio (OR) and adjusted OR (aOR) values with their 95% CIs. Adjustment variables were selected as follows: starting with a maximal model that included CBP achievement and all variables that were statistically significant ($p < 0.05$) in the univariable analysis (divided by 2 subgroups: 3-month mRS score ≤3 and 3-month mRS score >3), we performed permutations and combinations of all possible models. The best model was selected, ensuring good model fit and parsimony, according to the area under the curve and Akaike information criterion scores. The final model was adjusted for age, baseline mRS score, NIHSS score on admission, ICH volume, IVH component, and infratentorial location (all well-known predictors of ICH outcomes).[16] A collinearity analysis was performed among these adjustment variables,

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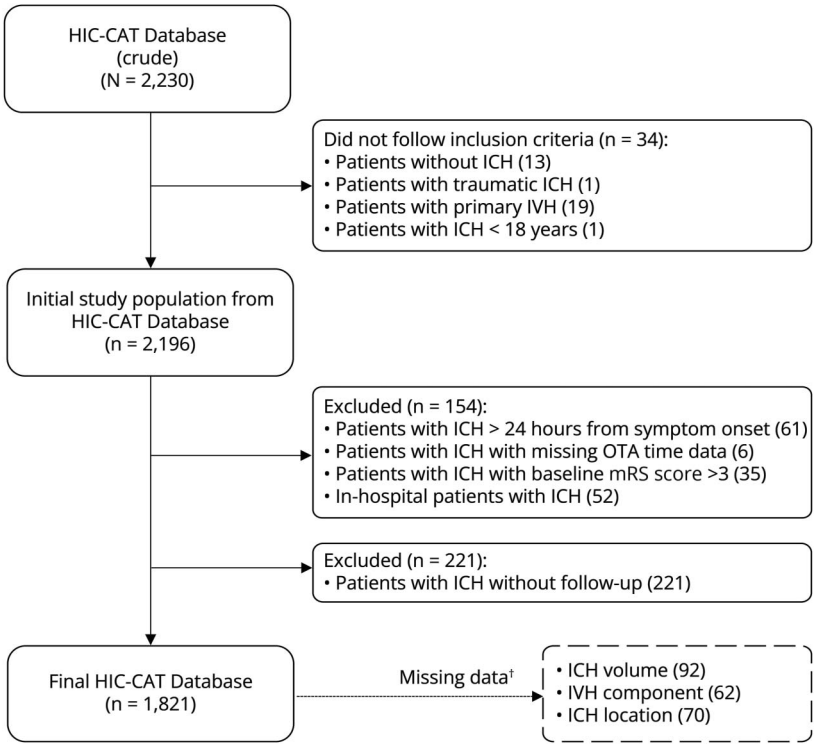
Figure 1 Study Flowchart Showing the Inclusion and Exclusion of Patients From the HIC-CAT Database



HIC-CAT = Registry of Patients with Spontaneous Acute Intracerebral Hemorrhage in Catalonia; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; OTA = onset-to-admission. †Data for key variables missing from the final HIC-CAT database. Following a complete-case analysis approach and given the low proportion of missing data, these patients (n = 101, 5.5%) were excluded from the multivariable analysis.

confirming the absence of collinearity. Following a complete-case analysis approach and given the low proportion of missing data (<10%), patients whose data for key adjustment variables were missing were excluded from the analysis.

We performed an exploratory mediation analysis to assess the effect of each CBP component on the primary outcome.

Interaction between CBP achievement and OTA time was tested using a likelihood ratio test. A binomial logistic regression model was developed to predict the 3-month favorable functional outcome, explained by CBP achievement (binary variable), OTA time (continuous variable), and the interaction of the 2 variables in our data set. Predictions were obtained in the same sample on the link scale, and the inverse logit transformation was applied to derive predicted probabilities with 95% CI. The CI for each group (CBP achievement no vs yes) was compared at corresponding time points to assess overlap. The association of CBP achievement with the 3-month favorable functional outcome was further studied in 2-hour OTA interval windows and adjusted by the same variables of the final model to assess the CBP effects over time.

A similar approach was used for the secondary outcome, with the final multivariable logistic regression model adjusted for the same variables as the primary outcome. The interaction between CBP achievement and OTA time for 3-month mortality was assessed using the same methodology.

Sensitivity analyses were conducted for primary and secondary outcomes, excluding patients with unknown symptom onset, active anticoagulation treatment, and withdrawal of care (WoC) within the first 24 hours. We also evaluated CBP achievement and functional outcomes based on the type of center providing initial medical care, categorized as either a CSC or PSC/TSC.

Statistical significance for all analyses was set at $p < 0.05$ (2-sided). All analyses were performed using Stata version 17 (StataCorp, College Station, TX). Forest plots and interaction figure between CBP achievement and OTA interval were plotted using R version 4.3.2 (RStudio, Boston, MA).

Data Availability

Anonymized data not published within this article may be shared on reasonable request to any qualified investigator.

Results

A total of 1,821 patients were included in this study (Figure 1). The mean age was 70.3 ± 14.1 years, and 37.7% (n = 687) were women. Symptom onset was known for 66.2% of patients (n = 1,205), and the median OTA time was 95 (58–186) minutes. The median baseline NIHSS score was 13 (5–21), the median hematoma volume was 17.5 (5.8–45) mL, and IVH was present in 38.6% of patients (n = 703) (eTable 1).

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The CBP goals were achieved by 27.7% of patients (n = 504), a proportion that increased to 31.8% after excluding those with WoC within the first 24 hours (20.9%, n = 355). Achievement of each prespecified CBP goal was as follows: body temperature, 91.9%; blood oxygen saturation, 91.3%; glycemia, 79.2%; anticoagulation reversal (if required), 77.5%; and blood pressure, 50.6%.

Influence of OTA Time on Functional Outcome and Mortality

Table 1 provides patient characteristics according to OTA time, stratified by OTA ≤6 hours (n = 1,294, 71.1%) and >6 hours (n = 527, 28.9%). Patients admitted within the first 6 hours were younger; had a better baseline mRS score, a higher NIHSS score, and blood pressure on admission; and were more likely to have deep ICH.

Patients with a favorable outcome (mRS scores 0–3) at 3 months (eTable 1) were more likely to achieve the CBP goals and had longer OTA time. Table 2 provides variables independently associated with a favorable outcome in the multivariable analysis, along with their strength of association. A shorter OTA time was associated with an unfavorable outcome (aOR_{x1h} 1.04, 95% CI 1.02–1.06), a finding that remained consistent in sensitivity analyses evaluating patients with known (aOR_{x1h} 1.09, 95% CI 1.05–1.14) and unknown (aOR_{x1h} 1.06, 95% CI 1.02–1.10) symptom onset. In addition, a shorter OTA time was independently associated with higher 3-month mortality (aOR_{x1h} 0.98, 95% CI 0.95–0.99). After excluding patients with WoC within the first 24 hours, the association between shorter OTA time and unfavorable functional outcome (mRS score >3) persisted, but the association with 3-month mortality was no longer statistically significant (aOR_{x1h} 0.98, 95% CI 0.96–1.01, $p = 0.226$).

Effect of CBP Achievement on Functional Outcome and Mortality

Table 3 summarizes the characteristics of patients according to CBP achievement. Patients who achieved the CBP goals were younger, had a lower NIHSS score on admission, and were more likely to arrive at a CSC. The CBP goals were met by 342 patients (26.4%) with an OTA ≤6 hours and by 162 patients (30.7%) with an OTA >6 hours ($p = 0.062$).

For the entire cohort, CBP achievement was independently associated with a favorable outcome (aOR 1.66, 95% CI 1.29–2.15) (Table 2). For patients with known symptom onset, this association persisted (aOR 1.98, 95% CI 1.44–2.73). However, for patients with unknown symptom onset, CBP achievement was only associated with favorable outcomes in patients not taking previous anticoagulation therapy (n = 430, 76.5%; aOR 1.89, 95%CI 1.07–3.33).

In an exploratory analysis, we assessed the individual contribution of each CBP component on the primary outcome, and the results are presented in eTable 2. It is important to note that the greatest effect size was shown for oxygen saturation and glycemia control.

Regarding the type of stroke center providing initial medical care, 31.3% of patients arriving at a CSC achieved the CBP goals, compared with 20.3% of patients arriving at a PSC/TSC ($p < 0.001$). Using the same model as for the primary outcome and after adjusting for confounders, initial care at a CSC was associated with higher odds of meeting the CBP goals (aOR 1.97, 95% CI 1.55–2.52). Nevertheless, stroke center type did not independently affect the 3-month mRS outcome (aOR 0.85, 95% CI 0.66–1.10, $p = 0.211$). Regarding acute ICH care, 388 patients (22.2%) were not admitted to any specialized critical care unit (stroke unit or intensive care unit). This proportion was higher among patients initially admitted to PSCs/TSCs (33%) compared with those admitted to CSCs (17.2%, $p < 0.001$). Of those admitted to a specialized unit, 31.6% achieved CBP goals, compared with 18.3% among patients who were not ($p < 0.001$). These differences remained significant after excluding WoC cases.

Hematoma expansion within the first 72 hours was observed in 256 patients (14.06%). In a sensitivity analysis including hematoma expansion in the multivariable model, both OTA time and CBP achievement remained independently associated with the 3-month functional outcome.

Concerning 3-month mortality, CBP achievement was associated with reduced risk of death, although this did not reach statistical significance (aOR 0.78, 95% CI 0.60–1.01, $p = 0.061$). This was consistent among patients with known symptom onset (aOR 0.73, 95% CI 0.52–1.03, $p = 0.070$) and significant in patients with unknown onset not taking anticoagulation therapy (n = 430, 76.5%; aOR 0.48, 95% CI 0.27–0.85). After excluding WoC cases, the association between CBP achievement and mortality remained nonsignificant (aOR 0.79, 95% CI 0.59–1.06, $p = 0.112$).

Interaction Between OTA Time and CBP Achievement

An interaction was observed between OTA time and CBP achievement in the adjusted logistic regression model for the 3-month functional outcome ($p = 0.016$), indicating that earlier arrival enhanced the effect of CBP. This interaction persisted up to 13.8 hours after symptom onset (Figure 2). When included in the adjusted model, CBP achievement had a stronger impact on the probability of a favorable functional outcome (aOR 1.97, 95% CI 1.47–2.63). This effect was consistent across all time frames and particularly pronounced in patients admitted within the first 12 hours (aOR 2.08, 95% CI 1.49–2.89). Notably, this association was primarily driven by early arrivals because adjusted sensitivity analyses showed significant effects only for the <2, 2–4, 4–6, and 6–8 hour intervals (Figure 3).

Regarding 3-month mortality, no interaction was observed between OTA time and CBP achievement in the adjusted model ($p = 0.901$). Likewise, sensitivity analyses across different time frames revealed no association.

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Table 1 Patients Characteristics Stratified by OTA Time

Variables	All (n = 1,821)	OTA time ≤6 h (n = 1,294)	OTA time >6 h (n = 527)	*p* Value
Age, y, mean (SD) [n = 1,821]	70 (14)	69 (14)	73 (13)	<0.001
Women, n (%) [n = 1,819]	687 (37.8)	476 (36.8)	211 (40.0)	0.202
Baseline mRS score, median (IQR) [n = 1,821]	0 (0–1)	0 (0–1)	0 (0–2)	<0.001
Unknown ICH onset time, n (%) [n = 1,821]	616 (33.8)	227 (17.6)	389 (73.8)	<0.001
Admission-to-CT, min, median (IQR) [n = 1,821]	25 (15–45)	22 (14–37)	34 (20–97)	<0.001
Initial admission to CSC, n (%) [n = 1,821]	1,219 (66.9)	867 (67.0)	352 (66.8)	0.932
Interhospital transfer, n (%) [n = 1,821]	302 (16.6)	198 (15.3)	104 (19.7)	0.021
GCS score, median (IQR) [n = 1,716]	15 (11–15)	14 (10–15)	15 (13–15)	<0.001
NIHSS score, median (IQR) [n = 1,821]	13 (5–21)	14 (6–22)	9 (4–19)	<0.001
ICH volume, mL, median (IQR) [n = 1,729]	18 (6–45)	18 (6–45)	16 (5–43)	0.284
IVH component, n (%) [n = 1,759]	703 (40.0)	513 (41.1)	190 (37.2)	0.127
Blood pressure on admission, mm Hg, median (IQR)				
Systolic [n = 1,607]	165 (143–190)	167 (145–192)	160 (140–182)	<0.001
Diastolic [n = 1,585]	89 (77–100)	90 (78–103)	85 (75–98)	<0.001
Body temperature, °C, median (IQR) [n = 1,109]	36 (35.9–36.5)	36.0 (35.9–36.4)	36.1 (36.0–36.5)	<0.001
O_2 pulse oximetry, %, median (IQR) [n = 1,220]	97 (95–99)	97 (95–99)	97 (95–99)	0.822
Medical history, n (%)				
Hypertension [n = 1,654]	1,233 (74.5)	886 (75.7)	347 (71.8)	0.105
Diabetes mellitus [n = 1,662]	416 (25.0)	289 (24.5)	127 (26.3)	0.446
Previous ischemic stroke [n = 1,618]	197 (12.2)	135 (11.8)	62 (13.1)	0.474
Previous ICH [n = 1,563]	114 (7.3)	70 (6.4)	44 (9.5)	0.032
Ischemic heart disease [n = 1,664]	181 (10.9)	113 (9.6)	68 (14.1)	0.007
Antiplatelet use [n = 1,596]	348 (21.8)	247 (21.9)	101 (21.6)	0.912
Oral anticoagulant use [n = 1,674]	322 (19.2)	214 (18.0)	108 (22.2)	0.047
ICH etiology, n (%) [n = 1,705]				<0.001
Hypertension	956 (56.1)	720 (59.7)	236 (47.4)	
Amyloid angiopathy	247 (14.5)	148 (12.3)	99 (19.9)	
Oral anticoagulants	170 (10.0)	114 (9.4)	56 (11.2)	
Malformation	77 (4.5)	55 (4.6)	22 (4.4)	
Other	75 (4.4)	46 (3.8)	29 (5.8)	
Unknown	180 (10.6)	124 (10.3)	56 (11.2)	
Location, n (%) [n = 1,751]				<0.001
Deep (hemisphere)	906 (51.7)	684 (55.0)	222 (43.7)	
Lobar (hemisphere)	655 (37.1)	426 (34.3)	229 (45.1)	
Infratentorial	190 (10.9)	133 (10.7)	57 (11.2)	
CBP achievement, n (%)				
Full achievement [n = 1,821]	504 (27.7)	342 (26.4)	162 (30.7)	0.062
Glycemia <150 mg/dL 0–24 h [n = 1,271]	1,007 (79.2)	714 (79.6)	293 (78.3)	0.615

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Table 1 Patients Characteristics Stratified by OTA Time *(continued)*

Variables	All (n = 1,821)	OTA time ≤6 h (n = 1,294)	OTA time >6 h (n = 527)	*p* Value
Body temperature <37.5°C 0–24 h [n = 1,363]	1,252 (91.9)	887 (92.5)	365 (90.3)	0.186
O_2 pulse oximetry >92% 0–24 h [n = 1,368]	1,249 (91.3)	869 (90.4)	380 (93.4)	0.078
Blood pressure <140/90 mm Hg 0–24 h [n = 1,420]	719 (50.6)	486 (48.7)	233 (55.2)	0.025
Blood pressure medication first 24 h [n = 1,508]	1,144 (75.9)	811 (76.7)	333 (73.8)	0.230
Anticoagulation reversal [n = 320]	248 (77.5)	163 (76.9)	85 (78.7)	0.713
Any neurosurgery,[a] n (%) [n = 707]	170 (24.0)	131 (25.1)	39 (21.0)	0.253
Hematoma evacuation	93 (13.1)	71 (13.6)	22 (11.8)	0.539
Decompressive craniectomy	60 (9.0)	46 (9.4)	14 (7.8)	0.332
External ventricular drainage	107 (15.1)	83 (15.9)	24 (12.9)	0.530
Mechanical ventilation, n (%) [n = 1,558]	321 (21.1)	93 (18.8)	236 (22.2)	0.131
Stroke unit admission, n (%) [n = 1,744]	1,098 (63.0)	745 (60.3)	353 (69.5)	<0.001
ICU admission, n (%) [n = 1,737]	391 (22.5)	317 (25.8)	74 (14.6)	<0.001
WoC <24 h, n (%) [n = 1,695]	355 (20.9)	257 (21.4)	98 (19.8)	0.456

Abbreviations: CBP = care bundle protocol; CSC = comprehensive stroke center; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; ICU = intensive care unit; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OTA = onset-to-admission; WoC = withdrawal of care.
[a] Any neurosurgery: external ventricular drainage, decompressive craniectomy, and/or hematoma evacuation.

Effect of OTA Time in Patients Who Achieved Care Bundle Goals

For the patients who achieved CBP goals (n = 504, 27.7%), Table 4 summarizes details of the multivariable analysis of variables independently associated with a favorable 3-month functional outcome, along with their strength of association. A shorter OTA time was no longer associated with unfavorable outcome (aOR_{x1h} 1.01, 95% CI 0.97–1.05, $p = 0.570$), nor with greater 3-month mortality (aOR_{x1h} 0.98, 95% CI 0.94–1.03, $p = 0.430$).

Table 2 Multivariable Logistic Regression Analysis for Variables Associated With Favorable Outcomes (mRS Score ≤3) at 3 Months

Variables	aOR	95% CI	*p* Value
Age, y	0.96	0.95–0.97	<0.001
Baseline mRS score	0.67	0.58–0.76	<0.001
NIHSS score on admission	0.1	0.89–0.92	<0.001
ICH volume on admission, mL	0.99	0.98–0.99	<0.001
IVH component on admission	0.64	0.49–0.84	0.001
Infratentorial location	0.62	0.48–0.92	0.019
OTA time, h	1.04	1.02–1.06	0.001
CBP achievement[a]	1.66	1.29–2.15	<0.001

Abbreviations: aOR = adjusted odds ratio; CBP = care bundle protocol; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OTA = onset-to-admission.
[a] CBP achievement is defined as control, in the first 24 hours according to prespecified goals, of blood pressure, glycemia, body temperature, and blood oxygen saturation and anticoagulation reversal if required. aOR >1 indicates increased odds of a favorable outcome (mRS score ≤3 at 3 months).

Classification of Evidence

This study provides Class III evidence that in patients with acute ICH, achievement of a standardized CBP is associated with better functional outcomes at 3 months.

Discussion

Our population-based study of patients with spontaneous ICH highlights the positive effect of CBP implementation in the first 24 hours after symptom onset on functional outcomes. CBP achievement in this time frame was independently associated with better functional outcomes at 3 months. The interaction observed between CBP achievement and OTA time emphasizes that the CBP benefits are greater the sooner the patients reach the hospital, supporting the need for timely CBP application.

Compared with the INTERACT3 trial, our study presents notable differences. In INTERACT3, only 0.9% of patients were on oral anticoagulants and 10.4% had diabetes, whereas in our cohort, these figures reached 19.2% and 25%, respectively, indicating a population with greater clinical complexity and higher risk of poor outcomes. In addition, our

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Table 3 Patient Characteristics Stratified by CBP Achievement

Variables	All (n = 1,821)	CBP achieved (n = 504)	CBP not achieved (n = 1,217)	*p* Value
Age, y, mean (SD) [n = 1,821]	70 (14)	68 (15)	71 (14)	<0.001
Women, n (%) [n = 1,819]	687 (37.8)	187 (37.1)	500 (38.0)	0.717
Baseline mRS score, median (IQR) [n = 1,821]	0 (0–1)	0 (0–1)	0 (0–1)	0.518
Unknown ICH onset time, n (%) [n = 1,821]	616 (33.8)	146 (32.9)	450 (34.1)	0.285
Onset-to-admission, min, median (IQR) [n = 1,821]	145 (71–442)	173 (75–493)	132 (69–414)	0.025
Admission-to-CT, min, median (IQR) [n = 1,821]	25 (15–45)	25 (15–52)	24 (15–43)	0.095
Initial admission to CSC, n (%) [n = 1,821]	1,219 (66.9)	382 (75.8)	837 (63.6)	<0.001
Interhospital transfer, n (%) [n = 1,821]	302 (16.6)	78 (15.5)	224 (17.0)	0.432
GCS score, median (IQR) [n = 1,716]	15 (11–15)	15 (13–15)	14 (9–15)	<0.001
NIHSS score, median (IQR) [n = 1,821]	13 (5–21)	9 (4–17)	15 (6–22)	<0.001
ICH volume, mL, median (IQR) [n = 1,729]	18 (6–45)	13 (5–30)	20 (6–56)	<0.001
IVH component, n (%) [n = 1,759]	703 (40.0)	155 (30.8)	548 (43.6)	<0.001
Blood pressure on admission, mm Hg, median (IQR)				
Systolic [n = 1,607]	165 (143–190)	154 (136–176)	170 (148–194)	<0.001
Diastolic [n = 1,585]	89 (77–100)	90 (78–104)	84 (74–95)	<0.001
Body temperature, °C, median (IQR) [n = 1,109]	36 (35.9–36.5)	36 (36.0–36.5)	36 (35.8–36.4)	0.027
O_2 pulse oximetry, %, median (IQR) [n = 1,220]	97 (95–99)	97 (95–99)	97 (96–99)	0.110
Medical history, n (%)				
Hypertension [n = 1,654]	1,233 (74.5)	330 (67.1)	903 (77.7)	<0.001
Diabetes mellitus [n = 1,662]	416 (25.0)	94 (19.0)	322 (27.6)	<0.001
Previous ischemic stroke [n = 1,618]	197 (12.2)	60 (12.1)	137 (12.2)	0.981
Previous ICH [n = 1,563]	114 (7.3)	44 (8.9)	70 (6.5)	0.089
Ischemic heart disease [n = 1,664]	181 (10.9)	48 (9.67)	133 (11.4)	0.314
Antiplatelet use [n = 1,596]	348 (21.8)	101 (20.5)	247 (22.4)	0.394
Oral anticoagulant use [n = 1,674]	322 (19.2)	79 (15.7)	243 (20.8)	0.016
ICH etiology, n (%) [n = 1,705]				<0.001
Hypertension	956 (56.1)	262 (52.0)	694 (57.8)	
Amyloid angiopathy	247 (14.5)	90 (17.9)	157 (13.1)	
Oral anticoagulants	170 (10.0)	25 (5.0)	145 (12.1)	
Malformation	77 (4.5)	34 (6.7)	43 (3.6)	
Other	75 (4.4)	27 (5.4)	48 (4.0)	
Unknown	180 (10.6)	66 (13.1)	114 (9.5)	
Location, n (%) [n = 1,751]				0.186
Deep (hemisphere)	906 (51.7)	253 (50.2)	623 (52.4)	
Lobar (hemisphere)	655 (37.1)	198 (39.3)	457 (36.6)	
Infratentorial	190 (10.9)	53 (10.5)	137 (11.0)	
Any neurosurgery,[a] n (%) [n = 707]	170 (24.0)	57 (32.2)	113 (21.4)	0.004
Hematoma evacuation	93 (13.1)	35 (19.7)	58 (10.9)	0.003

Continued

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Table 3 Patient Characteristics Stratified by CBP Achievement *(continued)*

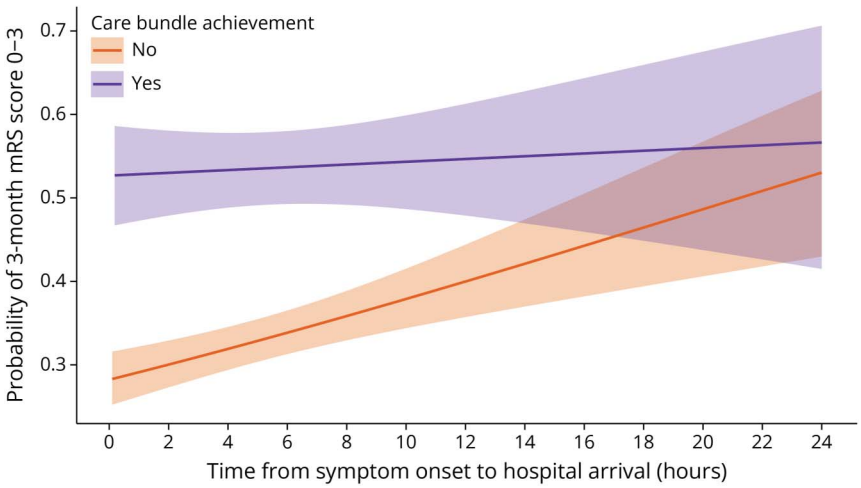
Variables	All (n = 1,821)	CBP achieved (n = 504)	CBP not achieved (n = 1,217)	*p* Value
Decompressive craniectomy	60 (9.0)	26 (14.7)	34 (6.9)	0.002
External ventricular drainage	107 (15.1)	34 (19.1)	73 (13.8)	0.084
Stroke unit admission, n (%) [n = 1,744]	1,098 (63.0)	367 (73.4)	731 (58.8)	<0.001
ICU admission, n (%) [n = 1,737]	391 (22.5)	93 (18.7)	298 (24.1)	0.015
WoC <24 h, n (%) [n = 1,695]	355 (20.9)	38 (7.5)	317 (26.6)	<0.001

Abbreviations: CBP = care bundle protocol; CSC = comprehensive stroke center; GCS = Glasgow Coma Scale; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; ICU = intensive care unit; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; WoC = withdrawal of care.
[a] Any neurosurgery: external ventricular drainage, decompressive craniectomy, and/or hematoma evacuation.

CBP included oxygen saturation as a predefined target from the acute phase, reflecting a broader physiologic optimization strategy. Structural and systemic differences between settings also warrant consideration. While INTERACT3 was conducted primarily in low and middle-income countries and implemented CBP in hospitals without previous standardized protocols, our study took place in Catalonia (Spain), a high-income region with a mature, integrated stroke network. Although no unified ICH-specific protocol was in place across centers, all adhered to international guidelines[15,16] and CBP targets were clearly defined. Despite these favorable conditions, only 27.7% of patients achieved full CBP implementation in our cohort. Similar challenges have been reported in other high-income countries, such as Germany and Italy, where real-world data reveal persistent barriers to implementing CBP targets, even in well-resourced environments.[19,20] Nevertheless, our findings are consistent with those of INTERACT3 in demonstrating the benefit of CBP implementation. The fact that CBP goal achievement remained independently associated with favorable outcomes, even in a high-income and real-world setting, reinforces the generalizability of their results. It is important to note that our experience highlights that having access to protocols is not sufficient; alignment with emerging high-quality evidence, sustained clinical adherence, and the adoption of key performance indicators (KPIs) are essential to translate protocolized care into improved outcomes.

Shorter times to ICH diagnosis or admission have traditionally been associated with poorer outcomes.[8-10] Of interest, in our study, the prognostic impact of a shorter OTA time was mitigated when CBP was achieved. In essence, CBP achievement seems to counteract the negative effect of early hospital admission, demonstrating the transformative potential of early intervention in acute ICH management. This finding, which challenges the conventional understanding of time in ICH prognosis,[10] suggests that timely CBP application could alter the natural course of the disease and become a cornerstone of effective management. Early and systematic implementation of these measures could optimize outcomes, regardless of patient-specific characteristics.[21,22]

Figure 2 Interaction Between OTA Time and CBP Achievement



Predicted probability of favorable outcome (mRS 0–3) according to OTA time, stratified by CBP achievement status. CBP = care bundle protocol; mRS = modified Rankin Scale; OTA = onset-to-admission.

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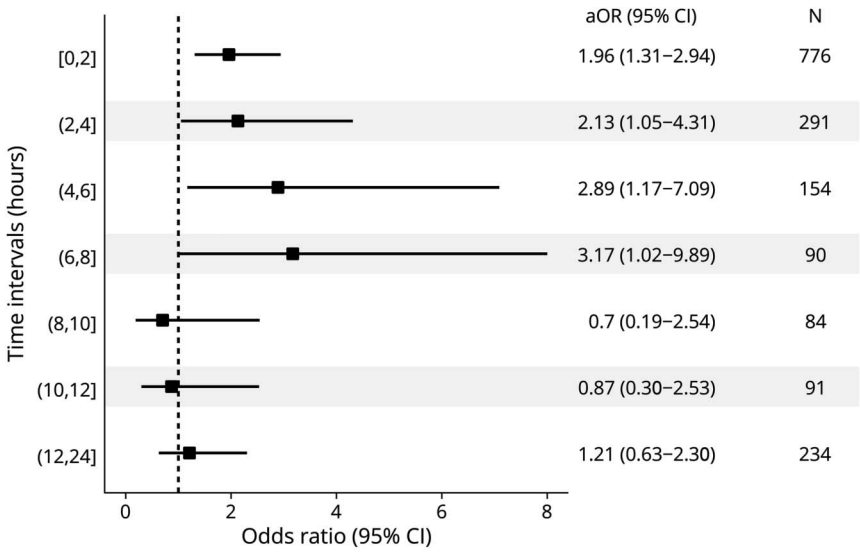
Figure 3 Forest Plot Showing the Effect of CBP Achievement on 3-Month Functional Outcome (mRS 0–3), Stratified by Time Intervals



The model was adjusted for age (years), baseline mRS score, NIHSS score on admission, ICH volume (milliliters), presence of IVH, and infratentorial location. aOR >1 indicates increased odds of favorable outcome (mRS 0–3 at 3 months). aOR = adjusted odds ratio; CBP = care bundle protocol; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.

In our cohort, the CBP effect persisted for up to 14 hours and, after adjustment for covariates, was particularly evident in the first 8 hours. Although our data may suggest that CBP efficacy diminishes beyond this time frame, it is important to note that CBP does not become entirely ineffective, merely that the effect is substantially reduced. A larger sample for the 8–24-hour window is needed to further clarify these results. Given these findings, we align with calls for the establishment of a "Code ICH."[7,11] However, we advocate for a time window extending beyond the first 6 hours reported by the INTERACT3 trial,[5] recommending a window encompassing the first 24 hours, as already implemented in acute ischemic stroke protocols. Our results not only underscore the importance of early intervention but also reinforce the pivotal role of CBP implementation in all acute ICH cases where timely intervention is feasible.

Table 4 Multivariable Logistic Regression Analysis for Variables Associated With a Favorable Outcomes (mRS Score ≤3) at 3 Months in Patients Who Achieved CBP Goals (n = 504)

Variables	aOR	95% CI	*p* Value
Age, y	0.96	0.94–0.97	<0.001
Baseline mRS score	0.61	0.48–0.77	<0.001
NIHSS score on admission	0.91	0.88–0.93	<0.001
ICH volume on admission, mL	0.98	0.97–0.99	<0.001
IVH component on admission	0.63	0.39–1.03	0.065
Infratentorial location	0.60	0.29–1.24	0.167
OTA time, h	1.01	0.97–1.05	0.570

Abbreviations: aOR = adjusted odds ratio; CBP = care bundle protocol; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; OTA = onset-to-admission. aOR >1 indicates increased odds of favorable outcome (mRS score ≤3 at 3 months).

Such an approach would facilitate early recognition, rapid transport, and prompt initiation of CBP at any available hospital, without waiting for specialized care at a CSC, where surgical interventions may be considered.[23] However, in our cohort study that included all types of stroke centers in Catalonia, achieving CBP was challenging because only 27.7% met all prespecified CBP goals. Leaving aside the potential impact of a longstanding therapeutic nihilism regarding ICH, this low rate may be partially explained by (1) the underutilization of specialized critical care units (up to 22.2% of patients did not receive this care) and (2) limited motivation for rapid and sustained control of CBP parameters at the time of the HIC-CAT study because recruitment for this study took place before the INTERACT3 and INTERACT4 trials had consistently demonstrated the positive effect of medical treatment on functional outcomes. Nevertheless, it is important to note that, even in those trials and in other observational studies, many patients failed to meet CBP goals (particularly regarding blood pressure).[5,6,21]

In addition, although CBP was originally designed and tested as an all-or-none strategy in the INTERACT3 trial, our post hoc exploratory analysis suggests that certain components may contribute more strongly to its impact. In our cohort, this was driven by oxygen saturation and glycemic control. Notably, the effect on functional outcome was significant when at least 4 of the 5 CBP targets were achieved, suggesting a cumulative and potentially synergistic effect. These findings reinforce the rationale behind bundled care strategies, where

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the combined implementation of multiple interventions likely drives the overall benefit. Furthermore, when we assessed whether the effects of OTA time and CBP were mediated solely through the prevention of hematoma expansion, both variables remained independently associated with functional outcomes. This suggests that early arrival may influence prognosis through multiple pathways: not only by increasing the risk of hematoma growth but also by contributing to other early complications.[24] Similarly, the protective effect of CBP likely extends beyond hematoma stabilization alone.

While the center type did not significantly affect prognosis, as already reported in the main HIC-CAT report,[14] CBP achievement was lower for PSCs/TSCs (20.3%) compared with CSCs (31.3%), underlining the importance of establishing well-coordinated care networks to enable CBP implementation across all hospitals. Mobile stroke units could provide earlier treatment for patients in remote areas lacking rapid hospital access, but they are unaffordable for many stroke care systems.[25] As for other strategies, such as direct transport to a CSC, these have shown no benefit for patients with ICH and may even cause harm.[24,26] Given the low technical requirements of CBP measures, allocating adequate resources, providing continuous training, and conducting regular re-evaluations of KPIs could improve adherence in centers where stroke physicians are not continuously available. This approach aligns with emerging evidence of the effectiveness of early intervention and emphasizes the need for enhanced prehospital and interhospital coordination to minimize treatment delays.[6,24] Ensuring timely access to any center that applies CBP should remain a priority until more effective prehospital solutions, such as blood-based biomarkers or other novel technologies, allow for the identification of patients with ICH, enabling CBP implementation even in the ambulance.

The main strengths of this study lie in its large population-based sample, providing a real-world perspective on current ICH management within an experienced stroke network, and the fact that reliability was ensured by central blind assessment of functional outcomes by qualified evaluators. However, several limitations are acknowledged. As happens with all observational studies, there is a potential for reporting bias and unmeasured confounding, particularly regarding factors excluded from analysis that may affect patient outcomes. In particular, disentangling the effects of OTA and CBP achievement from underlying disease severity is inherently difficult because both variables may reflect aspects of initial clinical status. Despite our efforts to adjust for relevant covariates, residual confounding cannot be excluded. "Owing to missing follow-up and core clinical variables, 221 patients (10.1%) could not be included in the central registry database, limiting our ability to assess potential selection bias."

In addition, although the study was based on prospectively collected data, the specific analyses assessing the effect of OTA time and CBP achievement on outcomes were post hoc in nature. As such, the findings should be interpreted with appropriate caution. Nevertheless, the prospective and consecutive enrollment of patients to some extent mitigates this limitation. In addition, stroke care organizations can vary significantly across regions, and consequently, our findings specific to the Catalan health care system cannot be considered generalizable to areas where prehospital, PSC/TSC, and CSC systems are not well integrated. Another limitation is that, although the participating centers adhered to clinical guidelines and documented CBP achievement, CBP was implemented in each center according to local adaptations that were not specifically recorded or prespecified. As a result, and because treatment goals were not among the primary objectives of the HIC-CAT study, CBP timing, implementation method, and consistency in achieving goals remain unknown and this variability may have influenced outcomes. Neurosurgical consultation—although available and performed in selected cases—was not included as a core component of the CBP because vascular neurologists filtered the need for referral based on clinical and radiologic criteria. While this reflects the structure of our stroke network, it differs from broader CBP definitions such as those used in INTERACT3 and may limit comparability across settings. The specific timing and reasons for WoC were also not assessed. Moreover, while our overall sample size was robust, the number of patients in the 8–24-hour window may have been insufficient to detect subtle differences in CBP efficacy during this period. Finally, the study focused on functional outcomes at 3 months and, therefore, may not capture the long-term consequences of ICH.

In patients with ICH admitted within the first 24 hours after symptom onset, achieving CBP goals is associated with better outcomes, particularly among those treated within the first 8 hours. Notably, CBP achievement seems to mitigate the poorer outcomes typically associated with early hospital arrival, highlighting the transformative potential of a "Code ICH" initiative to improve the natural course of the disease, even in high-income countries. Future research should aim to optimize these strategies and assess their applicability across diverse health care systems, while integrating these protocols into ongoing studies on acute spontaneous ICH to promote a comprehensive approach to care.

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Author Contributions

Á. Lambea-Gil: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. J. Marti-Fabregas: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept

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or design. P. Cardona: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Rodriguez-Luna: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Millán: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Amaro: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Prats-Sanchez: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. Y. Silva: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Seró: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Rodriguez-Campello: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D. Cánovas: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Martinez-Domeño: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Guasch-Jiménez: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. G. Ezcurra-Díaz: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Carcel-Marquez: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. I. Fernandez-Cadenas: drafting/revision of the manuscript for content, including medical writing for content. N. Pérez De La Ossa: drafting/revision of the manuscript for content, including medical writing for content. S. Abilleira: drafting/revision of the manuscript for content, including medical writing for content. M. Salvat-Plana: drafting/revision of the manuscript for content, including medical writing for content. O. Fagundez: drafting/revision of the manuscript for content, including medical writing for content. P. Camps-Renom: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. A. Ramos-Pachón: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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