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TITLE PAGE

Diagnostic accuracy of a revised computed tomography angiography score for brain death confirmation, combining supra-tentorial arteries and infra-tentorial veins

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MANUSCRIPT

ABSTRACT

Purpose: The 4-point score is the corner stone of brain death (BD) confirmation using computed tomography angiography (CTA). We hypothesized that considering the superior petrosal veins (SPVs) may improve CTA diagnosis performance in BD setting. We aimed at comparing the diagnosis performance of three revised CTA scores including SPVs and the 4-point score in the confirmation of BD.

Methods: In this retrospective study, 69 consecutive adult-patients admitted in a French University Hospital meeting clinical brain death criteria and receiving at least one CTA were included. CTA images were reviewed by two blinded neuroradiologists. A first analysis compared the 4-point score, considered as the reference and three non-opacification scores: a “Toulouse score” including SPVs and middle cerebral arteries, a “venous score” including SPVs and internal cerebral veins and a “7-score” including all these vessels and the basilar artery. Psychometric tools, observer agreement and misclassification rates were assessed. A second analysis considered clinical examination as the reference.

Results: Brain death was confirmed by the 4-score in 59 cases (89.4%). When compared to the 4-score, the Toulouse score displayed a 100% positive predictive value, a substantial observer agreement (0.77 [0.53; 1]) and the least misclassification rate (3.03%). Results were similar in the craniectomy subgroup. The Toulouse score was the only revised test that combined a sensitivity close to that of the 4-score (86.4% [75.7; 93.6] and 89.4% [79.4; 95.6], p-value < 0.001, respectively) and a substantial observer agreement.

Conclusions: A score including SPVs and middle cerebral arteries is a valid method for BD confirmation using CTA even in patients receiving craniectomy.

Keywords: Brain death; Computed tomography angiography; Data accuracy; Psychometrics.

INTRODUCTION

Brain death (BD) is defined as the irreversible cessation of the functions of the entire brain including the cerebellum and brainstem. Its diagnosis relies on clinical examination [1,2]. Ancillary tests are needed in case of confounding factors or if patient state precludes full brainstem examination [1]. In half of European countries [3], it is mandatory to confirm clinical BD by ancillary tests before organ donation. Since it has been proposed by Dupas *et al.* [4], computed tomography angiography (CTA), a widely available technique, has become the preferred ancillary test used in France [5] and elsewhere [6]. According to the recommended 4-point score [7], diagnosis of cerebral circulatory arrest (CCA) relies on non-opacification of the cortical segment of both middle cerebral arteries (MCA) and both internal cerebral veins (ICV).

CTA sensitivity ranges between 65 and 100% depending on the gold standard used [6–13] which means preserved filling of supratentorial vessels in patients with nonviable brainstem injuries [2]. These false negative results imply damaging consequences : prolonged intensive care unit care and psychological burden for the next of kin [14,15], graft quality impairment [16], decreased conversion rate to organ donation [17,18], haemodynamic instability [19] and increased costs [2]. BD confirmation using CTA has been challenged in case of anoxic encephalopathy [2] or in case of discrepancies regarding compartmentalisation of intracranial pressure like in patients with decompressive craniectomy [20] or ventricular drainage [21]. The 4-point score is also challenged in primary brainstem injuries while supra-tentorial circulation is transiently preserved [22]. These conditions may account for up to 20% of patients [12].

To address this issue, Welshehold *et al.* [12] have called for CTA evaluation of the posterior circulation and Marchand *et al.* [19] have proposed a revised score consisting of the non-opacification of both ICVs and both superior petrosal veins (SPV) since SPVs receive the largest number of veins from the brainstem [19]. Considering clinical examination as the reference, Marchand *et al.* [19] reported a 95% sensitivity compared to 88% for this revised score and the 4-point score, respectively. We therefore hypothesized that considering infra-tentorial veins may increase diagnosis accuracy. Thus, the primary objective was to compare the diagnosis performance of three revised CTA scores including SPVs and the 4-point score in the diagnosis of BD. The secondary objective was to perform this comparison using clinical examination as the reference.

MATERIALS AND METHODS

Trial design

This retrospective study included prospectively collected data of four intensive care units of a French University Hospital.

Ethics and legal

The study protocol was approved by the local Ethical Committee of the Toulouse University Hospital (approval 04-1115) and by the French national commission for data protection and privacy (Commission Nationale de l'Informatique et des Libertés, approval DR 2016-096). The local ethical committee waived the need for next of kin consent. We anonymized data before statistical analysis.

Participants

Consecutive patients were included between January 2016 and February 2017 if the following criteria were present : age of 18 years or more, coverage by French public health insurance, clinical brainstem examination consistent with BD diagnosis in accordance with international guidelines [23], performance of at least one CTA during BD confirmation procedure. Exclusion criteria were renal failure (defined as serum level creatinine of $133 \mu\text{mol.L}^{-1}$ [24] or more), severe liver failure (defined as International Normalized Ratio of more than 1.5 associated with elevated bilirubin level), pregnancy and post-partum period.

Management of brain death including imaging

Our management policy of at-risk for BD or brain-dead patients has been described elsewhere [25]. Briefly, patients at-risk for BD were subjected to a clinical examination by a nurse at least every two hours (including the Glasgow Coma Scale [GCS], assessment of pupil diameter and their reactivity, urine output). The intensive care physician was alerted in case of modification of these parameters in order to perform immediately a full neurological examination including brainstem assessment. After the exclusion of confounding factors (e.g., temperature $< 35^{\circ}\text{C}$, sedation, metabolic disorders) patients were diagnosed clinically-brain-dead when all the following criteria were fulfilled [1]: a GCS of 3 and a cessation of all brainstem reflexes including spontaneous ventilation assessed by the apnea testing. When clinical examination could not be completed (facial damage, hypoxemia precluding apnea testing), the decision to perform CTA and its timing was left to the physician's discretion. Transcranial Doppler was possible as an adjunct for decision-making [26]. We used a triple phase CTA and standardized data acquisition as recommended by the French Society of Neuroradiology [27]. Three scans were acquired every 20 seconds for 60 seconds. The first enhanced acquisition was used to evaluate the contrast enhancement of the extracranial vessels, in order to

demonstrate intravenous contrast medium administration (Iomeprol; concentration 400 mg / mL; volume: 90-120 mL). We used the last one to assess intracranial vessels opacification. All CTA studies were prospectively interpreted by the neuroradiologist on-call using the 4-point score [19] and were retrospectively reviewed by two other radiologists for the need of this study (ZM and MP). Reviewers were blinded to the results of the other reviewer's interpretation. They were also blinded to patient medical conditions and to the result of the first interpretation.

Test methods

We assessed the opacification of the seven following vessels for each CTA: cortical segment of the MCA on both sides, SPV on both sides, ICV on both sides and the basilar artery. We evaluated three revised CTA scores.

- The first one consisted of two supra-tentorial arteries (MCA on both sides) and two infra-tentorial veins (SPV on both sides). We named it the "Toulouse score".
- The second was the revised score investigated by Marchand *et al.* from Rennes University Hospital [19] including the two SPVs and the two ICVs. We termed it the "Venous score".
- We called the third score the "7-point score" which consisted of three arteries (MCA on both sides and basilar artery) and four veins (SPV on both sides and ICV on both sides).

Each vessel was considered as an item of the score and was associated to one point if opacified and zero if not. We summed the items to yield an "opacification score" [7]. The reference standard was a 4-point score value equal to zero in patients meeting all clinical BD criteria, following the design of a recent similar study assessing computed tomography perfusion performance [6]. The CTA was "positive" and thus confirming BD if the 4-point was equal to zero and "negative" if not, defining conclusive and inconclusive subgroups, respectively. We have chosen to compare performance of the three scores to the 4-point score upfront because we wanted to perform both the reference standard and the index tests at the same time warranting that there was neither clinical intervention, nor change in blood pressure or intracranial pressure overtime that may confound accuracy assessment [25,28,29]. The electroencephalogram was not considered because it has been associated with a risk of false positive [30,31] and false negative [32] results.

Other collected data

We collected from medical records and patient charts baseline patient characteristics, cause for intensive care unit admission, mechanism and location of baseline injury, decompressive craniectomy status, full brainstem assessment, BD management, final neuroradiologist interpretation.

Statistical analysis

The unknown diagnosis performance variance precluded sample size determination. It was determined on the basis of similar existing studies which have included between 30 and 105 CTAs [6,7,12,19,21,22,28]. We also considered a sample size superior to thirty to allow parametric tests. We reported categorical variables as absolute frequencies and proportions and continuous variables as medians and interquartile ranges (IQR, 25-75th percentile). We used Fisher's exact test and Mann-Whitney test for comparisons between two groups. A p-value below 0.05 was considered for statistical significance. The diagnosis performance of each index test was estimated using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, Youden's index and inter-observer agreement, considering the 4-score as the reference. We used discriminant linear analysis to compute misclassification rate associated with each score. We used the Fisher exact test to compare the sensitivity of each new CTA score and the 4-score in the diagnosis of BD. An index test was considered as "positive" if no vessel was opacified and "negative" if at least one vessel was opacified. Confidence intervals for sensitivity, specificity and accuracy were "exact" Clopper-Pearson confidence intervals [33]. Confidence intervals for the likelihood ratios and the predictive values used respectively the "Log method" and the standard logit confidence intervals [34]. Unweighted Cohen Kappa expressed inter-observer agreement. Indeterminate index test or reference standard results were excluded as were missing data. We reported the results derived from only one reviewer's interpretation (e.g., rater 1), otherwise indicated. The results pertaining to the second reviewer were captured by a high Cohen Kappa. We performed a second analysis considering the clinical diagnosis as the reference. Data were analysed using R software (version 3.3.1, 2016-06-21, R Development Core Team 2008, Vienna, Austria, <http://www.R-project.org>).

RESULTS

Participants

Seventy-six patients who have undergone 76 CTAs were considered for inclusion, of whom 10 cases (13.2%) were excluded. The reference standard and the index tests were performed in 66 cases/CTAs (86.8%). The reasons for exclusion were impossibility to extract brain imaging from server (6 cases), failure of apnea test (3 cases) and metal artefacts precluding interpretation (1 case). A true positive CTA was present in 59 cases (89.4%), leaving 7 cases (10.6%) in the inconclusive (10.6%) according to rater 1 (Figure 1).

The median age was 59.5 years [42.3; 70] and the baseline injury was supra-tentorial in 56 cases (84.8%) and infra-tentorial in 10 cases (15.2%). The median time between clinical BD diagnosis and CTA performance was 7.1 hours [5.4; 9.3]. Fifteen patients (22.7%) received decompressive craniectomy. The most frequent admission reason was traumatic brain injury, which accounted for 27 cases (40.9%). Seven patients (10.6%) suffered from anoxic encephalopathy (Table 1).

There were significantly more patients with craniectomy in the inconclusive subgroup than in the conclusive subgroup (respectively 5 out of 7 [71.4%] versus 10 out of 59 [16.9%], p -value = 0.005). There was no significant difference between these subgroups regarding age, time between clinical diagnosis and CTA performance, proportion of infra-tentorial injury and mechanism of injury (Table 2).

Tests results when considering the 4-score as the reference

SPVs were observed in all patients despite intracranial hypertension (Figure 2). In the overall cohort, 3 out of 4 scores exhibited substantial inter-observer agreement: the 4-point score (0.77 [0.53; 1]), the Toulouse score (0.77 [0.53; 1]) and the 7-point score (0.74 [0.6; 0.9]). The sensitivity of all index tests differed significantly from that of the 4-score. The Toulouse score was associated with the highest PPV (100%). It also yielded the highest levels of specificity (100% [63.1; 100]); accuracy (97% [89.5; 99.6]) and the highest Youden's index (0.97). The 7-point score yielded the highest NPV (88.2% [65.4; 96.8]) but did not reach the performance of the Toulouse score when considering the specificity, the accuracy and the Youden's index (Table 3 and Figure 3).

In patients receiving craniectomy, 3 out of 4 scores exhibited substantial inter-observer agreement: the 4-point score (0.73 [0.39; 1]), the Toulouse score (0.86 [0.6; 1]) and the 7-point score (0.7 [0.3; 1]). The Toulouse score and the 7-point score yielded the highest PPV (100%) and specificity (100% [47.8; 100]). The Toulouse score yielded the highest NPV (83.3% [43.8; 97]) as well as the best accuracy (93.3% [68.1; 100]) and the best Youden's index (0.9). The Toulouse score was associated with the least misclassification rate both in the overall cohort (3.03%) and in patients receiving craniectomy (6.67%) (Table 4 and Figure 4).

Tests results when considering clinical examination as the reference

In the overall cohort, the sensitivity of the venous-score was the highest and differed significantly from that of the 4-score (92.4 [83.2; 97.5] vs. 89.4% [79.4; 95.6], respectively, p-value = 0.007). The venous score displayed the highest sensitivity in the craniectomy subgroup but the difference with the 4-score failed to reach statistical significance (80% [51.9; 95.7] versus 66.7 [38.4; 88.2], p-value = 0.24) (Table S1 in the Supplementary Appendix).

Based upon the worst performance reported either by anyone of the raters, non-opacification of both SPVs was observed in 62 cases (93.9%) in the overall cohort. Both SPVs were non-opacified in at least 5 out of 7 cases (71.4%) in the inconclusive subgroup and in at least 13 out of 15 cases (86.7%) in the craniectomy subgroup. Non-opacification of ICVs was observed in 64 cases (97%) in the overall cohort, in 5 cases (71.4%) in the inconclusive subgroup in 14 cases (93.3%) in the craniectomy subgroup (Table S2 and Figure S1 in the Supplementary Appendix).

DISCUSSION

Our main result is that a score based on supra-tentorial arteries (cortical segment of MCA on both sides) and infra-tentorial veins (SPV on both sides) performed very well for BD confirmation even in the presence of decompressive craniectomy. Hence, the Toulouse score yielded a 100% PPV when compared to the 4-score, which means that all patients diagnosed as brain-dead by the Toulouse score had this diagnosis confirmed by the reference, even in the craniectomy subgroup. It was also associated with a substantial observer agreement and the least misclassification rate among the index tests both in the overall cohort (3.03%) and in patients receiving craniectomy (6.67%). The 7-score provided an advantage over the Toulouse score regarding NPV but did not perform alike regarding other criteria and is less feasible owing to a greater number of items than the Toulouse score. When compared to clinical examination, a score combining both SPVs and both ICVs, namely the venous score, yielded the highest sensitivity (92.4% [83.2; 97.5]) among all tests including the standard (89.4% [79.4; 95.6]) but this seeming advantage was neutralized by a weaker observer agreement than the Toulouse score. Moreover, the SPVs and the ICVs were non-opacified in merely the same manner (93.9% vs. 97%, respectively).

We could not demonstrate an advantage of the Toulouse score over the 4-score since we considered the 4-score as the reference. We could not compute specificity when considering clinical examination as the reference since we did not include any comatose patient not meeting clinical BD criteria. Though, this scenario may never be encountered clinically because clinical BD criteria are the trigger for ancillary tests. The timing of CTA varied among patients owing to the retrospective design, the fact that may have confounded sensitivity when considering clinical examination as the standard. However, CTA timing varied among close boundaries (median time, 7.1h [5.4; 9.3]) and was not associated with inconclusive results. Our results need to be confirmed because of the relatively small - although similar to existing studies - size of both the overall cohort and the craniectomy subgroup (15 patients). We provided here detailed data to compute variance of each psychometric tool and hence size determination of further studies. The varying SPVs positions and the fact that SPVs could exhibit hypoplasia or lack of visibility may preclude their widespread use especially by non-specialist radiologists. Yet, Marchand et al. [19] showed in 43 control patients constant visibility of SPVs, the fact that we also noticed but this result may have been influenced by the small sample size. Eventually, the low rate of exclusion (e.g., 13.2%) and the fact that all patients had complete brainstem examination including apnea testing may have contributed to reduce the selection bias and to guarantee the homogeneity of prospectively-entered data. However, one should keep in mind that in a trauma centre, some patients may have facial trauma precluding pupil's examination and therefore complete brainstem evaluation.

We gave here evidence to support the noninferiority of the Toulouse score when compared to the 4-score, based upon a 100% PPV, a misclassification rate of 3.03% in the overall cohort and a

substantial observer agreement. When considering clinical diagnosis as the reference, the sensitivity of the Toulouse score and the 4-score were nearly the same (e.g., 86.4% [75.7; 93.6] and 89.4% [79.4; 95.6], respectively) and much more importantly had their confidence intervals overlapping suggesting close performance. Moreover, the Toulouse score was the only test that combined a high level of sensitivity and a substantial observer agreement. Marchand *et al.* [19] reported a 95.2% SPVs' non-opacification rate (4 cases with persistent opacification out of 83 cases) which is consistent with our findings (e.g., 93.9%). Our venous score displayed a 92.4% sensitivity [83.2; 97.5] which is close to the 95% sensitivity cited by Marchand *et al.* [19]. In the available literature, CTA studies were reviewed by two [7,12,19] or three radiologists [5] but observer agreement has never been computed except in the study by MacDonald *et al.* [22] who considered clinical examination as the standard and reported a Cohen Kappa value of 1 (confidence interval not provided) versus 0.77 [0.53 ; 1] in our study. We therefore have confirmed here that CTA provides at least a substantial observer agreement. We found a sensitivity of 89.4% [79.4 ; 95.6] which is higher than the reported sensitivity of 59.1% by MacDonald *et al.* [22]. This difference may be explained by a higher median time between clinical BD and CTA in our study (7.1 h [5.4; 9.3]) than in the study by MacDonald *et al.* (2.5 h) given that CTA sensitivity increases over time [25,28,29]. Welschehold *et al.* [21] has reported sensitivity and specificity in a prospective cohort included 30 cases. Recently, Garret *et al.* [35] has studied CTA performance using clinical criteria alone or clinical criteria and cerebral angiography as reference standard to compute sensitivity, specificity, PPV and NPV of CTA. Our study dissented from this latter since we used a different reference standard. Moreover, the present study includes a larger cohort and a more extended psychometric assessment than Garret *et al.* [36]. The other strength of our study is that the reference standard and the index tests were performed at the same time ruling out the potential effect of time on vessels filling. Another valuable aspect in the design was that each radiologist was blinded to patient clinical state and to the other radiologist's interpretation. This was not performed in comparable study previously published [13]. Finally, we confirmed here that CTA lacks sensitivity in BD confirmation [37], the fact that justifies recent assessment of other ancillary tests like magnetic resonance imaging [38] and computed tomography perfusion.

These results and the fact that SPVs draw off blood from the brainstem provide rationale for a further prospective comparison of the diagnosis performance of the Toulouse score and the 4-score. Our results may add some arguments to consider infra-tentorial veins non-opacification as an adjunct to the diagnosis especially in conditions like decompressive craniectomy, ventricular drains, or skull defect. These latter may stand for a large proportion of patients in an expert trauma center.

CONCLUSION

Within the limitation of a retrospective study, we demonstrated the noninferiority of a revised score including supra-tentorial arteries and infra-tentorial veins opacification on CTA for BD confirmation when considering the 4-score as the reference. The proposed Toulouse score displayed strong diagnosis performance even in the presence of decompressive craniectomy, paving the way toward considering SPVs for BD confirmation using CTA.

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REFERENCES

- [1] E.F.M. Wijndicks, P.N. Varelas, G.S. Gronserth, D.M. Greer, Evidence-based guideline update: determining brain death in adults: report of the quality standards subcommittee of the American Academy of Neurology, *Neurol.* 74. 8 (2010) 1911–1914.
- [2] E.F.M. Wijndicks, The case against confirmatory tests for determining brain death in adults, *Neurology.* 75 (2010) 77–83.
- [3] G. Citerio, I.A. Crippa, A. Bronco, A. Vargiolu, M. Smith, Variability in Brain Death Determination in Europe: Looking for a Solution, *Neurocrit. Care.* 21 (2014) 376–382.
- [4] B. Dupas, M. Gayet-Delacroix, D. Villers, D. Antonioli, M.F. Veccherini, J.P. Soullou, Diagnosis of brain death using two-phase spiral CT., *AJNR. Am. J. Neuroradiol.* 19 (1998) 641–7.
- [5] J.C. Orban, E. Ferret, P. Jambou, C. Ichai, Confirmation of brain death diagnosis: A study on French practice, *Anaesthesia, Crit. Care Pain Med.* 34 (2015) 145–150.
- [6] M. Sawicki, J. Sołek-Pastuszka, K. Chamier-Cienińska, A. Walecka, J. Walecki, R. Bohatyrewicz, Computed Tomography Perfusion is a Useful Adjunct to Computed Tomography Angiography in the Diagnosis of Brain Death, *Clin. Neuroradiol.* (2017) 1–8.
- [7] E. Frampas, M. Videcoq, E. De Kerviler, F. Ricolfi, V. Kuoch, F. Mourey, A. Tenailon, B. Dupas, CT angiography for brain death diagnosis, *Am. J. Neuroradiol.* 30 (2009) 1566–1570.
- [8] R. Bohatyrewicz, M. Sawicki, A. Walecka, J. Walecki, O. Rowinski, A. Bohatyrewicz, Z. Czajkowski, A. Krzyształowski, J. Solek-Pastuszka, M. Zukowski, E. Marzec-Lewenstein, M. Wojtaszek, Computed tomographic angiography and perfusion in the diagnosis of brain death, *Transplant. Proc.* 42 (2010) 3941–3946.
- [9] D. Escudero, J. Otero, L. Marqués, D. Parra, J.A. Gonzalo, G.M. Albaiceta, L. Cofiño, A. Blanco, P. Vega, E. Murias, Á. Meilan, R.L. Roger, F. Taboada, Diagnosing brain death by CT perfusion and multislice CT angiography, *Neurocrit. Care.* 11 (2009) 261–271.
- [10] X. Leclerc, C.A. Taschner, A. Vidal, G. Strecker, J. Savage, J.Y. Gauvrit, J.P. Pruvo, The role of spiral CT for the assessment of the intracranial circulation in suspected brain-death, *J. Neuroradiol.* 33 (2006) 90–95.
- [11] A. Rieke, B. Regli, H.P. Mattle, C. Brekenfeld, J. Gralla, G. Schroth, C. Ozdoba, Computed tomography angiography (CTA) to prove circulatory arrest for the diagnosis of brain death in the context of organ transplantation, *Swiss Med. Wkly.* 141 (2011).
- [12] S. Welschehold, T. Kerz, S. Boor, K. Reuland, F. Thömke, A. Reuland, C. Beyer, W. Wagner,

- W. Müller-Forell, A. Giese, Detection of intracranial circulatory arrest in brain death using cranial CT-angiography, *Eur. J. Neurol.* 20 (2013) 173–179.
- [13] S. Brasil, E. Bor-Seng-Shu, M. De-Lima-Oliveira, M. K. Azevedo, M. J. Teixeira, L. Bernardo, W. M. Bernardo, Role of computed tomography angiography and perfusion tomography in diagnosing brain death: A systematic review, *J. Neuroradiol.* 43 (2016) 133–140.
- [14] E. Azoulay, F. Pochard, N. Kentish-Barnes, S. Chevret, J. Aboab, C. Adrie, D. Annane, G. Bleichner, P.E. Bollaert, M. Darmon, T. Fassier, R. Galliot, M. Garrouste-Orgeas, C. Goulenok, D. Goldgran-Toledano, J. Hayon, M. Jourdain, M. Kaidomar, C. Laplace, J. Larché, J. Liotier, L. Papazian, C. Poisson, J. Reignier, F. Saidi, B. Schlemmer, Risk of post-traumatic stress symptoms in family members of intensive care unit patients, *Am. J. Respir. Crit. Care Med.* 171 (2005) 987–994.
- [15] I. Fukunishi, Y. Kita, W. Paris, S. Mitchell, B. Nour, Relationship between posttraumatic stress disorder and emotional conditions in families of the cadaveric donor population, *Transplant. Proc.* 35 (2003) 295.
- [16] H. Belzberg, W.C. Shoemaker, C.C.J. Wo, T.P. Nicholls, A.B.C. Dang, V. Zelman, J.P. Gruen, T. V Berne, D. Demetriades, Hemodynamic and oxygen transport patterns after head trauma and brain death: implications for management of the organ donor, *J. Trauma.* 63 (2007) 1032–1042.
- [17] D. Lustbader, D. O'Hara, E.F.M. Wijidicks, L. MacLean, W. Tajik, A. Ying, E. Berg, M. Goldstein, Second brain death examination may negatively affect organ donation, *Neurology.* 76 (2011) 119–124.
- [18] K. Inaba, B.C. Branco, L. Lam, A. Salim, P. Talving, D. Plurad, D.J. Green, D. Demetriades, Organ donation and time to procurement: late is not too late., *J. Trauma.* 68 (2010) 1362–6.
- [19] A.J. Marchand, P. Seguin, Y. Malledant, M. Taleb, H. Raoult, J.Y. Gouvrit, E. Wijidicks, P. Varelas, G. Gronseth, D. Greer, D. Hwang, E. Gilmore, D. Greer, T. Nakagawa, S. Ashwal, M. Mathur, M. Mysore, J. Link, M. Schaefer, M. Lang, A. Sherrington, M. Smith, K. Busl, D. Greer, S. Welschehold, S. Boor, K. Reuland, F. Thomke, T. Kerz, A. Reuland, B. Dupas, M. Gayet-Delacroix, D. Villers, D. Antonioli, M. Veccherini, J. Soullillou, L. Monteiro, C. Bollen, A. Huffelen, R. Ackerstaff, N. Jansen, A. Vught, J. Harding, B. Chatterton, O. Heiskanen, K. Jones, P. Barnes, G. Boulard, P. Guiot, T. Pottecher, A. Tenailon, G. Citerio, I. Crippa, A. Bronco, A. Vargiolu, M. Smith, E. Frampas, M. Videcoq, E. Kerviler, F. Ricolfi, V. Kuoch, F. Mourey, M. Sawicki, R. Bohatyrewicz, K. Safranow, A. Walecka, J. Walecki, O. Rowinski, J. Shankar, R. Vandorpe, T. Taylor, R. Dineen, D. Gardiner, C. Buss, A. Howatson, N. Pace, M. Braum, X. Ducrocq, J. Huot, G. Audibert, R. Anxionnat, L. Picard, R. Kotloff, S. Blosser, G.

- Fulda, D. Malinoski, V. Ahya, L. Angel, X. Leclerc, T. Matsushima, A. Rhoton, E. Oliveira, D. Peace, N. Tanriover, H. Abe, A. Rhoton, M. Kawashima, G. Sanus, Z. Akar, A. Rhoton, G. Young, D. Lee, C. Quesnel, J. Fulgencio, C. Adrie, B. Marro, L. Payen, N. Lembert, B. Asgeirsson, P. Grande, A. Joffe, A. Joffe, N. Anton, D. Escudero, J. Otero, L. Marques, D. Parra, J. Gonzalo, G. Albaiceta, E. Vicenzini, S. Pro, F. Randi, P. Pulitano, G. Spadetta, M. Rocco, A. Hansen, P. Lavin, E. Moody, M. Sandler, E. Wijdicks, M. Ebinger, J. Fiebach, H. Audebert, Revised CT angiography venous score with consideration of infratentorial circulation value for diagnosing brain death, *Ann. Intensive Care*. 6 (2016) 88.
- [20] F. Frisardi, M. Stefanini, S. Natoli, V. Cama, G. Loreni, F. Di Giuliano, D. Fiume, C. Leonardis, M. Dauri, A.F. Sabato, G. Simonetti, F. Leonardis, Decompressive craniectomy may cause diagnostic challenges to assess brain death by computed tomography angiography, *Minerva Anestesiol.* 80 (2014) 113–118.
- [21] S. Welschehold, T. Kerz, S. Boor, K. Reuland, F. Thömke, A. Reuland, C. Beyer, C. Tschan, W. Wagner, W. Müller-Forell, A. Giese, Computed tomographic angiography as a useful adjunct in the diagnosis of brain death., *J. Trauma Acute Care Surg.* 74 (2013) 1279–85.
- [22] D. MacDonald, B. Stewart-Perrin, J.J.S. Shankar, The Role of Neuroimaging in the Determination of Brain Death, *J. Neuroimaging.* 28 (2018) 374–379.
- [23] E.F.M. Wijdicks, D.M. Greer, Evidence-based guideline update : Determining brain death in adults Report of the Quality Standards Subcommittee of the American Academy of Neurology, *Am. Acad. Neurol.* 74 (2010) 1911–1918.
- [24] T.H. Lee, E.R. Marcantonio, C.M. Mangione, E.J. Thomas, C.A. Polanczyk, E.F. Cook, D.J. Sugarbaker, M.C. Donaldson, R. Poss, K.K.L. Ho, L.E. Ludwig, A. Pedan, L. Goldman, Derivation and Prospective Validation of a Simple Index for Prediction of Cardiac Risk of Major Noncardiac Surgery, *Circulation.* 100 (1999) 1043 LP – 1049.
- [25] L. Kerhuel, M. Srairi, G. Georget, F. Bonneville, S. Mrozek, N. Mayeur, L. Lonjaret, S. Sacrista, N. Hermant, F. Marhar, F. Gaussiat, T. Abaziou, D. Osinski, B. LE Gaillard, R. Menut, C. Larcher, O. Fourcade, T. Geeraerts, The optimal time between clinical brain death diagnosis and confirmation using CT angiography: a retrospective study., *Minerva Anestesiol.* 82 (2016) 1180–1188.
- [26] J.-C. Orban, A. El-Mahjoub, L. Rami, P. Jambou, C. Ichai, Transcranial Doppler shortens the time between clinical brain death and angiographic confirmation: a randomized trial., *Transplantation.* 94 (2012) 585–8.
- [27] Société française de radiologie, Agence de la biomédecine, Recommandations sur les critères

- diagnostiques de la mort encéphalique par la technique d'angiographe cérébral, *J. Neuroradiol.* 38 (2011) 36–39.
- [28] M. Sawicki, R. Bohatyrewicz, A. Walecka, J. Sołek-Pastuszka, O. Rowiński, J. Walecki, CT Angiography in the Diagnosis of Brain Death., *Pol. J. Radiol.* 79 (2014) 417–21.
- [29] W.M. Flowers, B.R. Patel, Persistence of cerebral blood flow after brain death., *South. Med. J.* 93 (2000) 364–70.
- [30] J.G. Heckmann, C.J.G. Lang, M. Pfau, B. Neundörfer, Electroencephalographic silence with preserved but reduced cortical brain perfusion., *Eur. J. Emerg. Med.* 10 (2003) 241–3.
- [31] T. Rimmelé, S. Malhière, A. Ben Cheikh, E. Boselli, M. Bret, C.-E. Ber, P. Petit, B. Allaouchiche, [The electroencephalogram is not an adequate test to confirm the diagnosis of brain death]., *Can. J. Anaesth.* 54 (2007) 652–6.
- [32] J.R. Hughes, Limitations of the EEG in coma and brain death, *Ann N Y Acad Sci.* 315 (1978) 121–136.
- [33] M.C. Somerville, R.S. Brown, Exact likelihood ratio and score confidence intervals for the binomial proportion., *Pharm. Stat.* 12 (n.d.) 120–8.
- [34] N.D. Mercaldo, K.F. Lau, X.H. Zhou, Confidence intervals for predictive values with an emphasis to case-control studies., *Stat. Med.* 26 (2007) 2170–83.
- [35] M.P. Garrett, R.W. Williamson, M.A. Bohl, C.R. Bird, N. Theodore, Computed tomography angiography as a confirmatory test for the diagnosis of brain death, (2017) 1–6.
- [36] E.F.M. Wijdicks, A.A. Rabinstein, E.M. Manno, J.D. Atkinson, Pronouncing brain death: Contemporary practice and safety of the apnea test., *Neurology.* 71 (2008) 1240–4.
- [37] M.P. Garrett, R.W. Williamson, M.A. Bohl, C.R. Bird, N. Theodore, Computed tomography angiography as a confirmatory test for the diagnosis of brain death., *J. Neurosurg.* (2017) 1–6.
- [38] M.E. Peckham, J.S. Anderson, U.A. Rassner, L.M. Shah, P.J. Hinckley, A. de Havenon, S.-E. Kim, J.S. McNally, Low b-value diffusion weighted imaging is promising in the diagnosis of brain death and hypoxic-ischemic injury secondary to cardiopulmonary arrest, *Crit. Care.* 22 (2018) 165.

Figure 1: Flow diagram.

Results are pertaining to rater 1's assessment. The "new" CTA scores were the following index tests: the Toulouse score, the Venous score and the 7-point score. Abbreviation: CTAs: computed tomography angiographies.

Figure 2: CT angiography in two patients meeting clinical brain death criteria.

Panel A: Non-opacification of superior petrosal veins in a patient with decompressive craniectomy. The right perimesencephalic hyperdensity is due to a subarachnoid hemorrhage already present on the non-contrast-enhanced phase. Panel B: Opacification of cortical segment of the right middle cerebral artery (white arrow) in the same patient. Panel C: Opacification of the right and left superior petrosal veins (white arrows) in another patient. The veins are captured on two different slides because they exhibit an asymmetry.

Figure 3: Diagnosis performance of radiological scores in the overall cohort (n= 66 cases) when considering the 4-score as the reference.

Results are pertaining to the same rater except unweighted Cohen Kappa by definition. White lines indicate confidence intervals.

Figure 4: Diagnosis performance of radiological scores in the craniectomy subgroup when considering the 4-score as the reference (n= 15 cases).

Results are pertaining to rater 1's reviewing except unweighted Cohen Kappa by definition. White lines indicate confidence intervals. *Confidence interval is not shown because of negative inferior confidence boundary owing to the fact that observed agreement is inferior to chance agreement.

Characteristics	Observed data
Age, year, median [IQR]	59.5 [42.3 ; 70]
SAPS 2, median [interval]*	66 [38 ; 95]
Sex ratio (Male/Female)	1.2
Mechanism of injury, n (%)	
Traumatic brain injury	27 (40.9)
Aneurysmal subarachnoid haemorrhage	14 (21.2)
Intracranial haemorrhage	13 (19.7)
Anoxic encephalopathy	7 (10.6)
Ischemic stroke	3 (4.5)
Central nervous system infection	2 (3)
Location of baseline injury, n (%)	
Supra-tentorial	56 (84.8)
Infra-tentorial	10 (15.2)
Decompressive craniectomy, n (%)	15 (22.7)
Time from clinical BD to CTA performance, hour, median [IQR]**	7.1 [5.4 ; 9.3]
Facility, n (%)*	
Neurosurgical ICU	49 (75.4)
General ICU	16 (24.6)

Table 1: Demographics and clinical characteristics (n= 66 cases, otherwise indicated).

Categorical variables are reported as absolute frequency (proportions) and continuous variables as median [interquartile range, 25-75th percentile].* One case excluded because of missing data. ** Three cases excluded because of lack of either time of apnea testing or time of imaging performance. Abbreviations: IQR: interquartile range, BD: brain death, CTA: computed tomography angiography, AT: apnea testing, ICU: intensive care unit, SAPS 2: Simplified Acute Physiology Score 2.

Variables	Conclusive subgroup n= 59	Inconclusive subgroup n= 7	p-value
Age, median [IQR]	61 [43 ; 70.5]	47 [26 ; 59]	0.08*
Decompressive craniectomy, n (%)	10 (16.9)	5 (71.4)	0.005**
Time between clinical BD and CTA, hour [IQR]	7.1 [5.4 ; 9]	13.7 [6.8 ; 21.2]	0.095*
Infra-tentorial location of baseline injury, n (%)	9 (15.3)	1 (14.3)	1**
Mechanism of injury, n (%) ^o			0.70**
Traumatic brain injury	24 (40.7)	3 (42.9)	
Aneurysmal subarachnoid haemorrhage	12 (20.3)	2 (28.6)	
Intracranial haemorrhage	12 (20.3)	1 (14.3)	
Anoxic encephalopathy	7 (11.9)	0 (0)	
Ischemic stroke	2 (3.4)	1 (14.3)	
Central nervous system infection	2 (3.4)	0 ()	

Table 2: Comparison between the conclusive and the inconclusive subgroup (n = 66 cases). Results are pertaining to rater 1's interpretation. The computed tomography angiography was considered as "positive" and confirming BD if the 4-point non-opacification score was equal to zero and "negative" if not, defining conclusive and inconclusive subgroups, respectively. Categorical variables are reported as absolute frequency (proportions). Continuous variables are reported as medians [interquartile range, 25-75th percentile] Abbreviations: IQR: interquartile range, BD: brain death, CTA: computed tomography angiography. *Mann-Whitney test, **Fisher's Exact test for count data? ^oSum of percentage exceed 100% in the inconclusive subgroup owing to rounding.

Psychometric tools	Toulouse score	Venous score	7-point score
Sensitivity, % [CI]	96.7 [82.3 ; 99.6]	96.7 [88.3 ; 99.6]	95.7 [85.2 ; 99.5]
Specificity, % [CI]	100 [63.1 ; 100]	50 [9.9 ; 81.6]	75 [51 ; 91.3]
PPV, % [CI]	100	93.4 [88.2 ; 96.4]	89.8 [80.4 ; 95]
NPV, % [CI]	77.8 [47.3 ; 93.2]	60 [23.1 ; 88.2]	88.2 [65.4 ; 96.8]
Accuracy, % [CI]	97 [89.5 ; 99.6]	90.9 [81.3 ; 96.6]	89.4 [79.4 ; 95.6]
Youden's index	0.97	0.47	0.71
Unweighted Cohen Kappa [CI]	0.77 [0.53 ; 1]	0.55 [0.1 ; 1]	0.74 [0.6 ; 0.9]
Positive likelihood ratio	N/A	1.69 [0.9 ; 3.2]	3.83 [1.8 ; 8.2]
Negative likelihood ratio	0.03 [0.01 ; 0.13]	0.08	0.06 [0.01 ; 0.2]
Misclassification rate, %	3.03	9.09	15.15

Table 3: Diagnosis performance of radiological scores when considering the 4-score as the reference (n= 66 patients). Results are pertaining to rater 1's reviewing except unweighted Cohen Kappa by definition. We used linear discriminant analysis to compute misclassification rate. Abbreviations: CI: confidence interval, %: percent, N/A: not applicable owing to the division by zero.

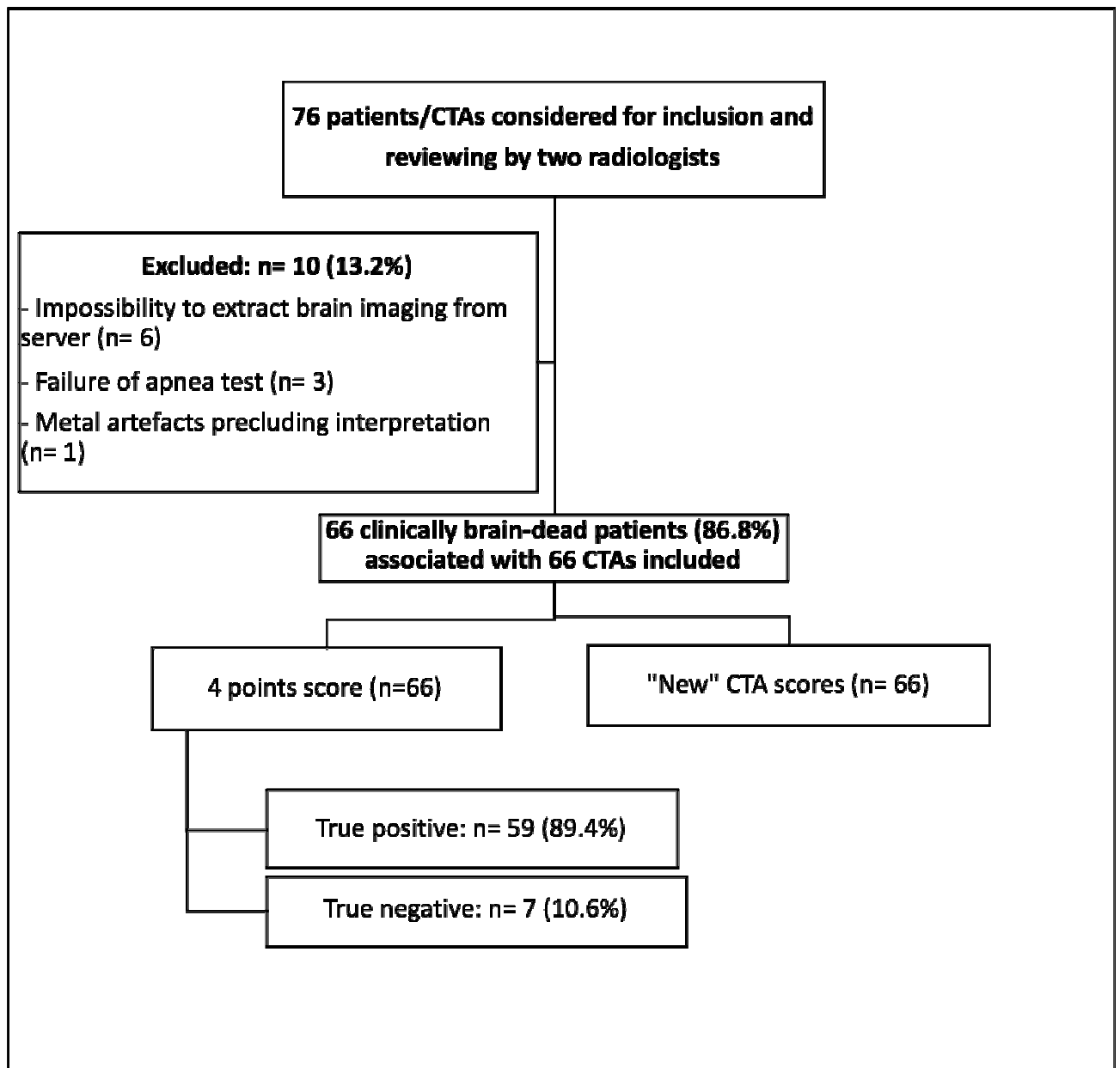


Figure 1: Flow diagram.

Results are pertaining to rater 1's assessment. The "new" CTA scores were the following index tests: the Toulouse score, the Venous score and the 7-point score. Abbreviation: CTAs: computed tomography angiographies.

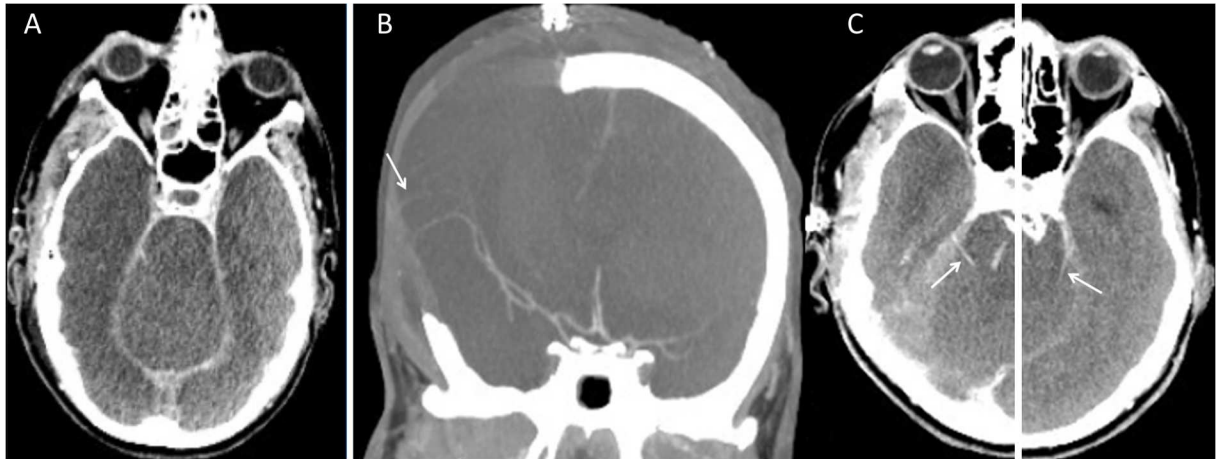


Figure 2: CT angiography in two patients meeting clinical brain death criteria.

Panel A: Non-opacification of superior petrosal veins in a patient with decompressive craniectomy. The right perimesencephalic hyperdensity is due to a subarachnoid hemorrhage already present on the non-contrast-enhanced phase. Panel B: Opacification of cortical segment of the right middle cerebral artery (white arrow) in the same patient. Panel C: Opacification of the right and left superior petrosal veins (white arrows) in another patient. The veins are captured on two different slides because they exhibit an asymmetry.



Figure 3: Diagnosis performance of radiological scores in the overall cohort (n= 66 cases) when considering the 4-score as the reference. Results are pertaining to the same rater except unweighted Cohen Kappa by definition. White lines indicate confidence intervals.

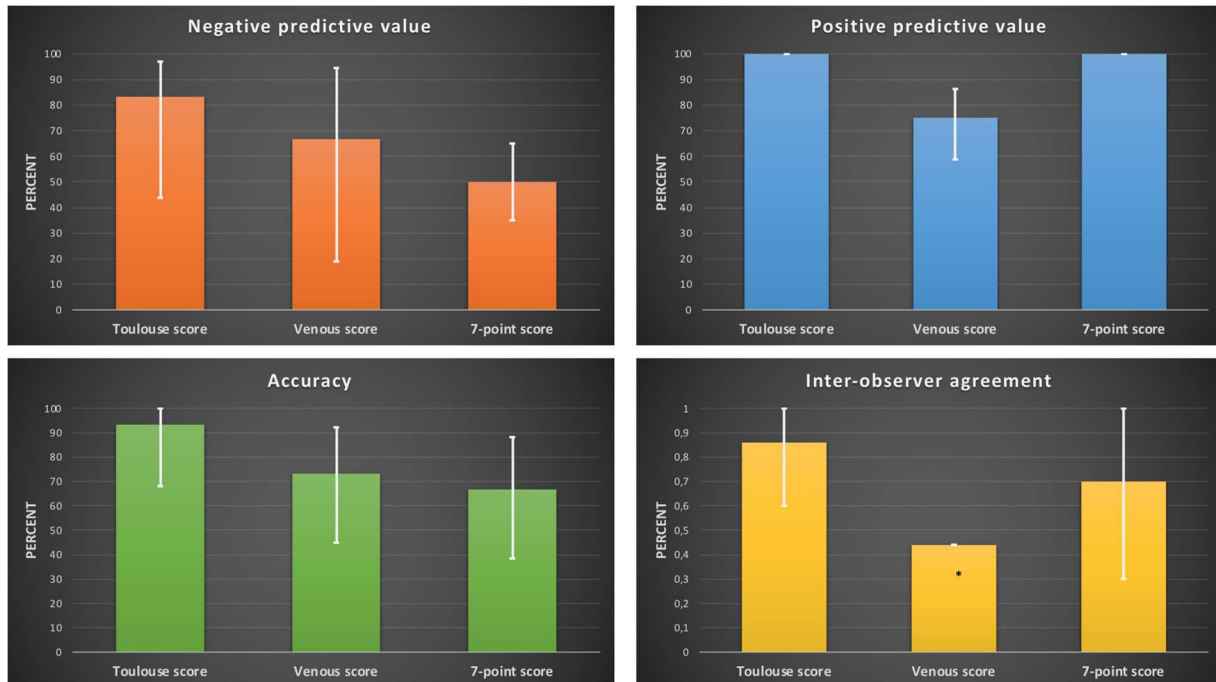


Figure 4: Diagnosis performance of radiological scores in the craniectomy subgroup when considering the 4-score as the reference (n= 15 cases). Results are pertaining to rater 1's reviewing except unweighted Cohen Kappa by definition. White lines indicate confidence intervals. *Confidence interval is not shown because of negative inferior confidence boundary owing to the fact that observed agreement is inferior to chance agreement.