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ABSTRACT

BACKGROUND AND PURPOSE: Baseline CTP sometimes overestimates the size of the infarct core ("ghost core" phenomenon). We investigated how often CTP overestimates infarct core compared with 24-hour imaging, and aimed to characterize the patient subgroup in whom a ghost core is most likely to occur.

MATERIALS AND METHODS: Data are from the randomized controlled ESCAPE-NA1 trial, in which patients with acute ischemic stroke undergoing endovascular treatment were randomized to intravenous nerinetide or placebo. Patients with available baseline CTP and 24-hour follow-up imaging were included in the analysis. Ghost infarct core was defined as CTP core volume minus 24-hour infarct volume > 10 mL). Clinical characteristics of patients with versus without ghost core were compared. Associations of ghost core and clinical characteristics were assessed by using multivariable logistic regression.

RESULTS: A total of 421 of 1105 patients (38.1%) were included in the analysis. Forty-seven (11.2%) had a ghost core > 10 mL, with a median ghost infarct volume of 13.4 mL (interquartile range 7.6–26.8). Young patient age, complete recanalization, short last known well to CT times, and possibly male sex were associated with ghost infarct core.

CONCLUSIONS: CTP ghost core occurred in ~1 of 10 patients, indicating that CTP frequently overestimates the infarct core size at baseline, particularly in young patients with complete recanalization and short ischemia duration.

ABBREVIATIONS: AIS = acute ischemic stroke; eTICI = expanded TICI; EVT = endovascular treatment; LVO = large vessel occlusion; rCBF = relative CBF

Endovascular treatment (EVT), the current standard of care for acute ischemic stroke (AIS) due to large vessel occlusion (LVO), improves clinical outcomes through reperfusion of ischemic tissue, which stops the progression from ischemia to infarction.[1-5] Based on our current understanding, if the entire ischemic area is irreversibly damaged (ie, there is only infarct "core," with no penumbra left), EVT is likely to be futile.

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Different imaging modalities allow us to estimate the size of the ischemic core; perhaps the most widely used is CTP.[4,6] In CTP, the brain is repeatedly imaged (over 45–90 seconds) after intravenous injection of a bolus of iodinated contrast. These repeated measurements are then used to derive time to maximum, relative CBF (rCBF), and CBV maps. The most commonly used threshold to identify infarct "core" is rCBF <30%.[3,4,7] Thresholded CTP maps sometimes overestimate the size of the infarct core: a phenomenon that is colloquially known as "ghost core," occurring in 16%–38% of patients.[8,9] This overestimation of initial infarct size on CTP can cause several problems, including inaccurate outcome prognostication and erroneous treatment decisions.[9] Therefore, it is of interest to quantify the prevalence of the ghost core phenomenon.

In this post hoc analysis of the randomized controlled ESCAPE-NA1 trial, we therefore assessed the prevalence of the ghost core phenomenon and assessed its associations with patient characteristics and clinical outcomes.

MATERIALS AND METHODS

Study Sample

This study is a post hoc analysis of the Safety and Efficacy of Nerinetide in Subjects Undergoing Endovascular Thrombectomy

for Stroke, or ESCAPE-NA1, trial (clinicaltrials.gov: NCT02930018), a double-blind, multicenter randomized controlled trial that evaluated the efficacy of nerinetide in patients with AIS who underwent EVT.[10] Patients were randomly allocated to either receive intravenous nerinetide versus placebo in addition to best medical management. Inclusion criteria were as follows: presence of a LVO, moderate to good collateral circulation, an ASPECTS of 5 or greater, age of at least 18 years, NIHSS of >5, functional independence before the stroke (Barthel index >90), and time since last known well <12 hours. The study was approved by the ethics committee of the University of Calgary and at each participating site. Informed consent was obtained from participants, legally authorized representatives, or via 2-physician consent, depending on national laws and regulations.

Imaging Acquisition

The ESCAPE-NA1 protocol mandated at minimum a noncontrast head CT and a multiphase CT angiography at baseline and either NCCT or diffusion-weighted MR imaging at 24 hours. Perfusion imaging was performed when part of clinical routine at each respective site, but not mandated by the trial, and therefore only available in a subset of patients. We only included patients with available CT perfusion imaging in the analysis. Perfusion source images, when available, were processed by using RAPID perfusion software version 5.2.2 (iSchemaView) to generate standard rCBF <30% volumes.

Imaging Analysis

All imaging was assessed by a central imaging core lab that was blinded to treatment allocation and clinical outcomes (Online Supplemental Data). Disagreement between 2 readers was solved by a senior neuroradiologist (M.G.; 24 years of experience). Core lab members were blinded to clinical outcomes. During baseline imaging assessment, core lab members were also blinded to 24-hour follow-up imaging. Time intervals between baseline and follow-up imaging readout sessions were ≥4 weeks.

Noncontrast CT and CT Angiography. ASPECTS score was assessed on baseline NCCT. Occlusion location on multiphase CT angiography was reported as either terminal internal carotid artery or M1 segment of the MCA.

CT Perfusion. All output DICOMs were converted to NIfTI by using dcm2niix (http://www.github.com/rordenlab/dcm2niix), and then underwent automated segmentation by using color-based thresholding in Python version 3.10 (http://www.python.org). Segmentation volumes for each threshold were extracted by using 3DSlicer version 5.0.2 (http://www.slicer.org). Key Python functions necessary for reproduction of feature extraction and processing are detailed on Github (https://github.com/naterex23/RAPID_Perfusion_Processing).

Angiography. Expanded TICI score (eTICI) was assessed on the final intracranial DSA run. Successful reperfusion was defined as eTICI 2b–3 (ie, >50% reperfusion of the target territory) and near-complete reperfusion as eTICI 2c–3 (ie, >90% reperfusion of the target territory).

24-Hour Imaging. Final infarct volumes were manually segmented for all patients with follow-up imaging (either NCCT or diffusion-weighted MR imaging) through manual planimetric measurements on axial NCCT or diffusion-weighted MRI follow-up imaging by using the open source software ITK snap (http://www.itksnap.org).

Outcomes of Interest

The primary outcome of this study was CTP ghost core. Because small ghost core volumes could be artificial related to CTP postprocessing or variability in manual infarct segmentations, we opted to define ghost core as ghost core volume >10 mL, that is, final infarct volume at 24 hour – rCBF <30% volume at baseline < −10 mL (motivated by a previous publication by Boned et al).[8]

In a secondary analysis, we further assessed the association of ghost core with clinical outcomes, as measured by the mRS at 90 days, which was assessed by blinded assessors who were unaware of the patients' treatment allocation.

Statistical Analysis

Prevalence of ghost core, patient baseline characteristics, and clinical outcomes in patients with versus without ghost core were described as counts and percentages for categoric variables and median and interquartile ranges for continuous variables. Baseline and treatment characteristics and clinical outcomes were compared between patients with versus without CTP ghost core.

The relationship between ghost infarct core and clinical outcome was modelled in an exploratory approach by using ordinal logistic regression. We adjusted the model for the following prespecified variables: patient age, baseline NIHSS, alteplase treatment, nerinetide treatment, reperfusion status (final eTICI), and final infarct volume. Furthermore, variables for which associations were seen in univariable analysis were included as adjustment factors. No imputation was performed for missing data because missing data were minimal. The analyses were performed separately for both "any ghost core" and "ghost core >10 mL" as a dependent variable.

All statistical tests were 2-sided and conventional levels of significance (alpha = 0.05) were used for interpretation. All analysis was performed by using Stata 17 (StataCorp).

RESULTS

Of the 1105 patients enrolled in ESCAPE-NA1, 421 had available CTP and 24-hour follow-up imaging and were included in the analysis. Their baseline characteristics are shown in the Online Supplemental Data. Forty-seven of 421 (11.2%) had a ghost core (defined as ghost core volume >10 mL). The median CTP ghost infarct volume was 13.4 mL (IQR 7.6–26.8) (Fig 1). In the early time window, a ghost core >10 mL was seen in 39/311 (12.5%) patients. In the late time window, a ghost core >10 mL was seen in 8/109 (7.3%) patients. When comparing patients with CT versus MRI 24-hour imaging, a ghost core >10 mL was seen in 23/224 (10.3%) patients with 24-hour CT and 24/197 (12.2%) patients with 24-hour MR imaging ($P = .540$).

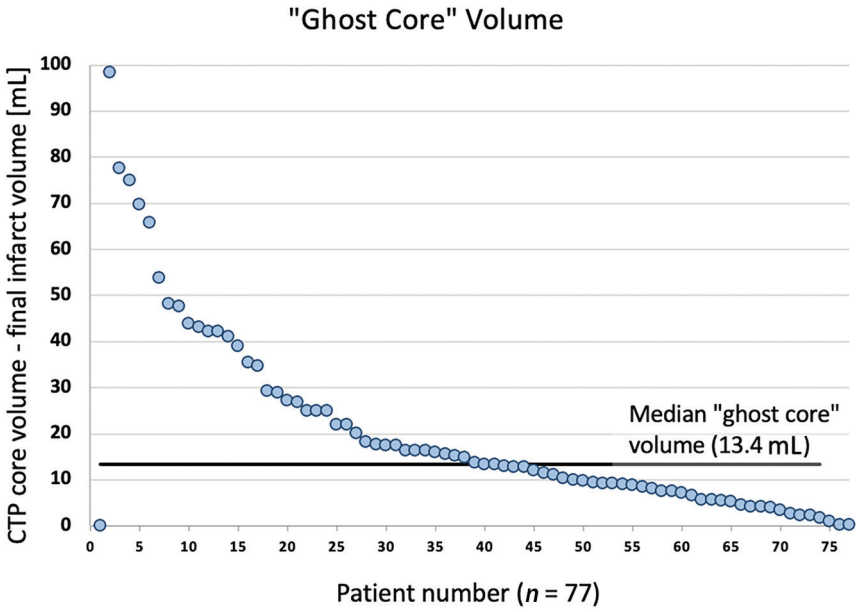

FIG 1. "Ghost core" infarct volumes (baseline CTP core volume – 24-hour infarct volume) in the 77 patients who had a baseline CTP rCBF >30% volume that was larger than 24-hour final infarct volume. To be considered a "ghost core" in the current analysis, this difference in volumes had to be >10 mL. Individual patient (*blue dot*). Median "ghost core" volume was 0.4 mL (*black horizontal line*).

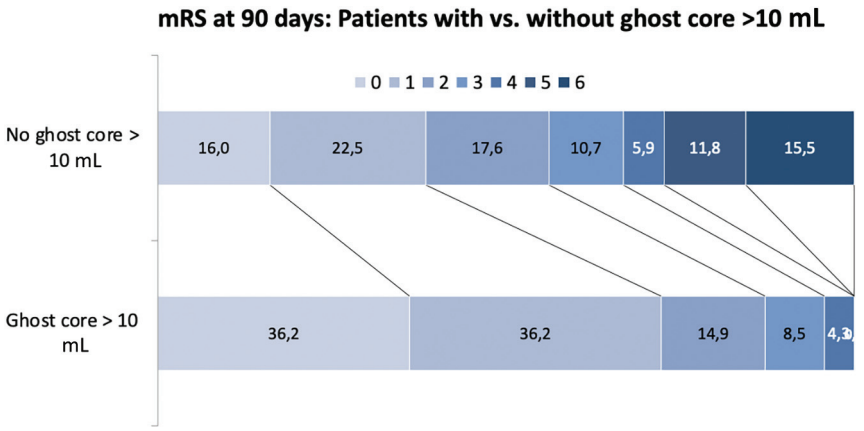

FIG 2. mRS at 90 days in patients with and without ghost infarct core >10 mL (ie, CBF <30% infarct core at baseline minus infarct volume at 24 hours >10 mL). mRS categories are shown in ascending order from left to right. Note that 4.3%, 0% and 0% patients achieved mRS 4, 5 and 6 respectively in the lower bar.

Association of Baseline and Treatment Variables with Ghost Infarct Core

Patients with ghost core were younger, more often male, had better collateral status, a higher proportion of eTICI 2b/3, and shorter last known well–to-CT times (Online Supplemental Data).

In the adjusted analysis, variables that significantly differed between patients with and without ghost core >10 mL were included in a binary logistic regression model with ghost core >10 mL as a dependent variable. Young patient age (adjusted OR 0.83 per 5-year increase [95% CI, 0.74–0.93]), male sex (adjusted OR 1.08 [95% CI, 1.06–4.09]), final eTICI (adjusted OR 1.51 [95% CI, 1.10–2.08]), and last known well–to-CT time (adjusted OR 0.97 per 10-min increase [95% CI, 0.95–0.996]) were associated with ghost core.

Association of Ghost Infarct Core with Clinical Outcomes

The median mRS in patients with ghost core >10 mL was 1 (IQR 0–2) versus 2 (IQR 1–5) in those without ghost core ($P < .001$) (Fig 2). Forty-one of 47 (87.2%) patients with versus 210/374 (56.2%) patients without ghost core >10 mL achieved a good outcome at 90 days ($P < .001$).

After adjusting for baseline and treatment variables, including final infarct volume, ghost core >10 mL was associated with ordinal mRS (adjusted common OR 0.52 [95% CI 0.28–0.95]).

DISCUSSION

A ghost core, that is, an overestimation of the infarct size on baseline CTP compared with 24-hour imaging >10 mL, was seen in ~1 of 10 patients. The median ghost core volume was 13 mL. Patients with ghost core were younger, more often male, and had better recanalization status at the end of the EVT procedure and shorter last known well–to-CT times.

Recent randomized controlled trials have shown that EVT is safe and effective even in patients with very large infarcts.[11-13] The implication is that estimating the core infarct by using CTP may not be required for endovascular treatment decision-making. However, it is not yet clear that the benefit of EVT observed in these large core EVT trials will be maintained outside the clinical trial setting, and physicians are often still hesitate to proceed with EVT when a large core is seen on baseline imaging.[14] In some patients, the ghost core phenomenon may be a contributing reason for the observation of benefit in these trials. Furthermore, current North American and European guidelines recommend perfusion imaging for treatment decision-making in patients with AIS only for patients presenting beyond 6 hours from last known well, but not for those presenting within 6 hours.[2,5] In clinical practice, however, a single stroke imaging protocol is often used for the early and late time window for the sake of simplicity, and this protocol often includes CTP. This means that CTP information is routinely available to physicians in many centers, and therefore invariably taken into account during treatment decision making. CTP overestimation of core volume could influence prognostication, in discussion with family members and possibly result in denial of treatment for a patient who might still benefit from reperfusion.[9] For these reasons, understanding ghost core is essential for the neuroradiologist.

Brain tissue tolerance to ischemia is time-dependent: when ischemia duration is short, much lower cerebral blood flow can be tolerated compared with longer ischemia durations. This was proved as early as 1981, when Jones et al[15] used macaques ischemic stroke models to show that CBF thresholds for infarction were much lower when ischemia duration was short, whereas at longer ischemia durations, infarction already occurred at a higher CBF. This has subsequently been confirmed in human patients with acute ischemic stroke.[16] CTP core thresholds as they are used in clinical practice for AIS imaging today are not time-dependent, and likely represent "average" thresholds that may be accurate in the middle range of ischemia duration. At very short ischemia durations, however, brain tissue can tolerate CBF impairments that are more severe than the commonly used core thresholds.

The current study confirms that the imprecision surrounding the CTP "core" concept is indeed clinically relevant: baseline CTP overestimated infarct volumes compared with 24-hour imaging in >10% of patients, which is roughly similar to previous studies.[8,9] The median ghost core volume was 13 mL; in one-fourth of the patients with ghost core, it exceeded 26 mL. It is not surprising that the use of a single rCBF dichotomy does not adequately delineate infarct core from penumbra, given that ischemia tolerance of brain tissue has been shown to depend on numerous factors, including tissue and cell type,[17] duration of ischemia, and patient age.[18]

The fact that younger patient age was positively associated with ghost infarct core is in line with previous literature, which describes an accelerated ischemic tissue-to-infarct conversion speed in older patients.[18] Furthermore, the age-related decrease in responsivity of the cerebral microvasculature and decrease in cerebral vessel attenuation likely contributes to a reduced recovery potential of ischemic tissue in elderly patients,[19] and may therefore also lead to a reduced prevalence of ghost infarct core.

Previous studies have shown an association of ghost core and poor collateral status.[20] Conversely, we found a significant positive association with better collateral status, but only in the unadjusted analysis. After adjusting for patient baseline factors, no signification association was seen anymore. There are 2 possible explanations for this: first, the ESCAPE-NA1 study included only patients with moderate-to-good collaterals. This preselection of patients may have confounded the results and precluded detection of a significant effect in the multivariable analysis. Second, the decrease in cerebrovascular capacity, and therefore also collateral status, with patient age suggests some degree of multicollinearity of patient age and collateral status. This may be the reason why, after adjusting for patient age, no independent effect of collateral status was observed anymore.

There is robust evidence that ghost core occurs more often in patients with short onset-to-imaging times.[20] Our findings support these previous observations when analyzing the entire patient sample that also included late time window patients. We deliberately refrained from analyzing patient subgroups stratified by ischemia duration due to the relatively small number of patients in these subgroups. Hence, we cannot comment on potential heterogeneity of the effect of onset-to-imaging times within these subgroups.

While the association of ghost core with better recanalization status has been previously described[9] and seems intuitively logical, we do not have a clear explanation for the observed difference in ghost core prevalence between men and women, and suspect that this effect, which was small in magnitude, may have been artificial.

Limitations

This study has several limitations. First, we batch processed perfusion studies from multiple sites with different sequence acquisition settings and CT machines through the RAPID software algorithm, which has introduced some heterogeneity in our data. Second, we defined CTP infarct core as rCBF <30%, which is the most commonly used threshold, and the results would have looked different if another core threshold had been used. Third, most of the patient population included in this study presented within 6 hours from onset and therefore did not meet guideline-based recommendations for CTP imaging, the latter being restricted to late window patients. Our study included only 109 late window patients, a group that was deemed too small for subgroup analysis, and thus limiting the generalizability of our results to late window patients. However, this simply reflects clinical reality, because CTP was part of the acute stroke imaging protocol in many participating sites, irrespective of the time of patient presentation. Fourth, follow-up infarct volumes were assessed at ~24 hours, but in some patients, but these measurements may not represent final infarct volumes, because infarcts can continue to grow after 24 hours.[21] Fifth, there is a possibility that intravenous thrombolysis treatment may have influenced the occurrence of ghost infarct core in our study and our study was powered to detect such an effect. Lastly, the ESCAPE-NA1 trial had rather stringent eligibility criteria, and our results may therefore not be generalizable to the general EVT population.

CONCLUSIONS

Baseline CTP overestimated the infarct size in 1 of 10 patients compared with 24-hour imaging, particularly in young patients with complete recanalization and short ischemia duration.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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