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DISSERTATION

Outcome Prediction after Cardiac Arrest using Automated Assessment of Brain Computed Tomography

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Abstract

After cardiac arrest (CA) and successful resuscitation, many patients suffer from severe hypoxic-ischemic encephalopathy (HIE). Prognostication of long-term neurological outcome is therefore an important step in deciding on therapeutic goals. Brain computed tomography (CT) is recommended by guidelines as part of a multimodal diagnostic pathway including serum biomarkers, clinical and electrophysiologic tests. The Gray-White-Matter Ratio (GWR) derived from CT quantifies global brain edema in patients with hypoxic-ischemic encephalopathy (HIE). Most studies report on GWR determined by a (neuro-)radiologist, a potential source of inter-rater variability.

We evaluated brain CT as a prognostic tool in three separate studies: (I) We retrospectively examined the relationship between CT timing and GWR to identify the optimal timepoint and threshold with the best prognostic performance. (II) We developed a method to automatically quantify regional radiodensity changes by co-registration of individual head CT images with a brain atlas, identified the regions with best prognostic performance in a derivation cohort and validated the results in a validation cohort. (III) We histopathologically examined postmortem brain autopsies to assess if exams and cutoffs used for prognostication accurately reflect the underlying pathologies. Neurologic outcome was evaluated using the Cerebral Performance Scale (CPC) at ICU/hospital discharge, dichotomized in good (CPC 1-3) and poor (CPC 4-5) outcome.

Results: Among 195 patients in the first study, no patient with good outcome patient had a (manually determined) GWR <1.10. Sensitivity for poor outcome prediction (unresponsive wakefulness syndrome or death) by GWR increased from 12% within the first 6 hours to 48% using CTs obtained later than 24 hours after CA. For automated assessment we evaluated 516 CTs from two cohorts with a total of 433 patients. In all gray matter regions radiodensity (in Hounsfield Units; HU) was significantly lower in poor outcome patients. Automated GWR at the basal ganglia level (GWR_si) had the best prognostic performance of all examined parameters. Consistently, sensitivity increased within the first 72 hours after CA. Autopsy revealed severe histopathological HIE in all patients with a GWR <1.10 and some patients with normal GWR values.

Conclusion: Outcome prediction using brain CTs is most accurate using CTs performed later than 24 hours after CA. Automated assessment of GWR is a promising new tool for quantifying changes after CA. A cut-off <1.10 in both manually and automatically determined GWR predicted poor outcome with high specificity and low-to-moderate sensitivity and correlated highly with histopathological severe HIE in brain autopsy.

Abstrakt

Die neurologische Prognoseabschätzung nach kardiopulmonaler Reanimation ist ein medizinisch und ethisch herausfordernder Schritt in der Therapieplanung von Patienten nach Herzstillstand. Als Teil eines multimodalen diagnostischen Konzepts wird die zerebrale Bildgebung, insbesondere die Computertomographie empfohlen, wobei der ideale Zeitpunkt für die Durchführung dieser bisher unklar ist. Ein bereits etablierter Parameter zur Quantifizierung des globalen Hirnödems als Zeichen für hypoxisch-ischämische Enzephalopathie (HIE) ist die „Gray-White-Matter Ratio“ (GWR). Sie wird üblicherweise manuell von einem (Neuro)-Radiologen bestimmt, was das Problem der Inter-Rater-Variabilität mit sich bringt. Wir untersuchten zunächst an einer Registerkohorte den Zusammenhang zwischen Zeit und GWR-Veränderungen um den Zeitpunkt und Grenzwert mit der besten prognostischen Aussagekraft der Bildgebung zu identifizieren.

Daraufhin entwickelten wir für eine zweite Studie eine Methode, um die radiologischen Veränderungen in CTs automatisiert zu erfassen, verwendeten diese, um daraus den aussagekräftigsten prognostischen Parameter zu eruieren und validierten diesen an einer weiteren Kohorte.

In einer multizentrischen Studie untersuchten wir schließlich retrospektiv in den histopathologisch aufgearbeiteten Gehirnen verstorbener Patienten den Schweregrad des hypoxischen Hirnschadens unter einem bestimmen GWR-Grenzwert.

Wir erfassten das neurologische Outcome mit der Cerebral Performance Category (CPC) Skala bei Entlassung von der Intensivstation bzw. aus dem Krankenhaus, dichotomisiert in gutes (CPC 1-3) und schlechtes Outcome (CPC 4-5).

Ergebnisse: Aus den in der ersten Studie eingeschlossenen 195 Patienten hatten kein Patient mit gutem Outcome eine (manuell bestimmte) GWR < 1.10. Die Sensitivität zur Vorhersage eines schlechten neurologischen Outcomes stieg von 12% bei CTs aus den ersten 6 Stunden nach Herzstillstand auf 48% für CTs, die später als 24 Stunden durchgeführt wurden. In die automatisierte Auswertung wurden 516 CTs von 433 Patienten eingeschlossen. In allen Regionen der grauen Substanz, insbesondere den Basalganglien war die Röntgendichte (in Hounsfield Units HU) bei Patienten mit schlechtem Outcome signifikant niedriger, in der weißen Substanz zeigte sich dies nicht. Die beste Vorhersagekraft hatte eine automatisierte GWR auf Ebene der Basalganglien (GWR_si). Auch hier stieg die Sensitivität innerhalb der ersten 72 Stunden deutlich an. Unter dem Grenzwert <1.10 für die automatisierte GWR_si fand sich auch in der Validationskohorte kein Patient mit gutem neurologischem Outcome.

In der Autopsiestudie hatten alle Patienten mit einer (manuellen) GWR <1.10 histopathologisch eine schwere hypoxische Enzephalopathie. Auch einige Patienten mit normalen GWR-Werten hatten Zeichen eines hypoxischen Hirnschadens.

Schlussfolgerung: Zur Prognose nach Reanimation sind CTs am aussagekräftigsten, wenn sie später als 24 Stunden nach Herzstillstand gemacht werden. Die automatisierte Analyse von CTs ist eine neue, Rater-unabhängige Methode, um die GWR zu bestimmen. Ein Cut-off von <1.10 war in der manuellen und automatisierten Auswertung sowie histopathologisch ein robuster Parameter für ein schlechtes neurologisches Outcome (Tod oder minimaler Bewusstseinszustand).

1. Introduction

Cardiac arrest (CA) is one of the major causes of death worldwide (Berdowski et al., 2010, Virani et al., 2020). In Germany, cardiopulmonary resuscitation (CPR) in out-of-hospital CA (OHCA) was performed in 62.6 per 100,000 inhabitants in 2019 (Fischer et al., 2020). Although the rate of bystander-CPR and the quality and accessibility of ICU treatment increases, OHCA survival rates are still relatively low such as 4.9% - 10.4% in a recent French report (Luc et al., 2018). Survivors of CA often develop hypoxic-ischemic encephalopathy (HIE) causing permanent disabling symptoms from cognitive and movement disorders to severe impairments of consciousness, most frequently unresponsive wakefulness syndrome (UWS) (Neumar et al., 2008, Grasner et al., 2016). If treatment is continued, patients may survive in UWS for many years. In Germany and many other countries, any treatment requires consent by the patient. If a patient cannot consent, treating physicians are obliged to determine the patients will. Frequently, patients have written advanced directives or authorized persons who decide on their behalf. In case of severe permanent brain injury, directives and representatives of the patient frequently express their will to withdraw intensive care.

Prognostication of neurological outcome is therefore essential and requires multimodal diagnostics at different time points after CA as clinical examination alone is not accurate enough. Physicians performing neuroprognostication might be in a quandary because the level of certainty needed for withdrawal of life sustaining therapy (WLST) has not been agreed upon. Although physicians have expressed a need for false-positive rates less than 0.1% in prediction of poor neurological outcome in a recent survey, no diagnostic test or a combination of multiple tests has shown such an accuracy so far (Steinberg et al., 2019). In clinical reality on the other hand, WLST is frequently performed as early as within the first 72h after cardiac arrest (Elmer et al., 2016). At that point, acute therapy such as targeted temperature management (TTM) and cardiac recompensation might not even be completed and sedatives might still be in effect. This sequence might lead to a self-fulfilling prophecy, a bias affecting previous neuroprognostication studies upon which current clinical practice and guidelines are based.

Currently, a combination of repeated clinical examination, electroencephalography (EEG), serum neuron-specific enolase (NSE), somatosensory evoked potentials (SSEP) and brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) is recommended (Nolan et al., 2021).

Brain CT has been shown to predict poor outcome when the differentiation of gray and white matter is diminished and brain edema is present (Lopez Soto et al., 2019). Optimal timing for CT imaging is unclear. Some authors suggest early imaging within hours (Yanagawa et al., 2005), others within days after cardiac arrest (Moseby-Knappe et al., 2017). To quantify changes after CA in brain CT, the Gray-White matter ratio (GWR) can be calculated (Na et al., 2018) by manually measuring the radiodensity in different regions-of-interest (ROI). Both qualitative interpretation and ROI placement are susceptible to inter-rater variability, which can lead to misjudgement (Caraganis et al., 2020). Automated analysis of brain CTs is a rater-independent alternative and different approaches such as atlas analysis, region growing and machine learning have been demonstrated in other neurological diseases such as stroke (Gillebert et al., 2014, Nagel et al., 2019) and intracerebral hemorrhage (Sharrock et al., 2021). Few studies with a limited number of patients have shown promising results using semi-automated/automated CT analysis in CA patients (Hanning et al., 2016, Wu et al., 2011), but included mostly CTs obtained within the first hours after CA.

In this thesis, I evaluated different aspects of brain CT in neuroprognostication after cardiac arrest. The main study of the thesis was on automated determination of the gray-white matter ratio. I contributed to two further studies, the first one evaluating the effect of timing of brain CT on the prognostic performance of manually determined GWR and the second one evaluating (among many other aspects) the relationship between GWR and severity of histopathological brain damage in post-mortem human brain tissue.

2. Methods

2.1 Patients

Approval for our studies was given by the local ethics committee. Patients were retrospectively identified from our prospectively maintained cardiac arrest database at the *Berlin Circulatory Arrest Center* from 2010 to 2016 (study 1) and December 2005 to July 2019 (study 2). For study 2, we used patients until October 2016 as derivation cohort, followed by a validation cohort from 2016 to July 2019.

Patients were treated with targeted temperature management (TTM) according to current guidelines at 33° for 24 hours (Nolan et al., 2021, Nolan et al., 2015). We used the Cerebral Performance Category Scale (CPC) (Phelps et al., 2013) at ICU discharge (study 1 and 3) and hospital discharge (study 2), respectively. The scale ranges from CPC 1 (good cerebral performance) to CPC 5 (death/brain death) and includes UWS (CPC 4), a frequent outcome in CA patients as separate category. Dichotomization in "good" (CPC 1-3) and "poor" (CPC 4-5) outcome included CPC 3 (severe cerebral disability) in the first category because of the potential for further improvement in rehabilitation.

Neuroprognostication was assessed using a multimodal diagnostic approach (Leithner et al., 2012, Nolan et al., 2021) including repeated clinical examination, electroencephalography (EEG), neuron-specific enolase (NSE) serum concentration, somatosensory evoked potentials (SSEP) and imaging. Only if results of prognostic test were congruent, poor prognosis was assumed; a prognostic statement was never made before the third day after CA and considerably later in most cases.

2.2 Brain Autopsy and HIE

To investigate the extent of histopathological brain damage in study 3, we retrospectively identified patients from three Charité hospitals in Berlin (Germany), Århus University Hospital (Denmark) and Skåne University Hospital Lund (Sweden) between 2003 and 2015 with brain CTs after CA who underwent postmortem brain autopsies. Formaldehyde-fixed and hematoxylin-eosin-stained regional brain slices (neocortex, hippocampus, cerebellum, mesecephalon, medulla oblongata, pons) were microscopically rated using the selective eosinophilic neuronal death (SEND) classification (Bjorklund et al., 2014). Other than necrosis, which involves all cell types, SEND appears after reperfusion as result of successful resuscitation and underlying selective ischemic vulnerability. If neuronal death

was more than 30 % (SEND >1) in any region, we dichotomized patients as “severe HIE”, otherwise as “no/mild HIE”.

2.3 CT Acquisition

CTs were mostly requested by treating physicians to exclude intracranial causes for CA or to assess consequential brain damage. The majority of CT scans were acquired on Scanners manufactured by GE Healthcare (Little Chalfont, UK), some on scanners Toshiba Medical (Ōtawara, Japan), Philips Medical Systems (Eindhoven, Netherlands) and Siemens Medical Solutions (Erlangen, Germany) with a a peak kilovoltage (kVp) of 120. Axial 5mm slice reconstructions of non-contrast CTs were used. Results were checked for inter-scanner-variability (supplement of study 2).

2.4 Manual GWR Calculation

In study 1 and 3, GWR was determined manually by neurologists with experience in post-CA imaging using 16 circular 0.1cm^2 regions-of-interest (ROIs) as previously established (Scheel et al., 2013). Raters were blinded to clinical information.

2.5 Automated Deconstruction of CTs/Automated GWR Determination

In study 2, images were gantry tilt-corrected and converted from DICOM into the NIfTI-Format using the *dcm2niix* script (Li et al., 2016). Images were linearly and non-linearly registered to a freely available CT-template in MNI-152 standard space (Rorden et al., 2012) using *FLIRT* and *FNIRT* from the *FMRIB Software Library* (FSL Version 5.0.9, *Analysis Group, FMRIB, Oxford, UK*) (Jenkinson et al., 2012). Images were excluded if they had confounding factors for automated analysis (intracerebral hemorrhage, hydrocephalus and shunt artifacts, severe motion artifacts, large old ischemic lesions, postcontrast images, calcification of the basal ganglia or acquisition with peak kilovoltage 100 kVP).

We used gray matter maps from the *Harvard-Oxford subcortical structural atlas* (Desikan et al., 2006) thresholded at 60% tissue probability and binary white matter region maps from the *ICBM-DTI-81 white-matter labels atlas* (Mori et al., 2008). We checked success of co-registration prior to data analysis and blinded to clinical information.

Brain segmentation was performed by using the inverse non-linear transformation-fields to transform the specific brain component maps from standard space into the individual CT-spaces (Kemmling et al., 2012). Mean HU were calculated using *FSL* per region and weighted by tissue probability. Three different GWRs were calculated: *GWR_cort (cortical)*

$= \frac{Cortex}{White\ Matter}$, $GWR\_bg\ (basal\ ganglia) = \frac{Pallidum+Thalamus+Caudate+Putamen/4}{PLIC+ALIC+RLIC/3}$ and $GWR\_si\ (simple) = \frac{Putamen}{PLIC}$ (PLIC – Posterior limb of the internal capsule, ALIC – Anterior limb of the internal capsule, RLIC – Retrolenticular limb of the internal capsule).

2.6 Statistical Analysis

For statistical analysis, we used *RStudio* (Version 1.0.136, RStudio, Inc., Boston, MA), for data visualization the *ggplot2* (Wickham, 2009) and *ggpubr* packages and for ROC calculation the *pROC* package (Robin et al., 2011). For the description of clinical baseline data, we used numbers and percentages or medians and interquartile ranges (IQR) as appropriate. HUs and GWRs were compared using a Mann-Whitney-U (MWU)-test between patients with good and poor outcome and using a Wilcoxon-Test between early and late CTs in patients with follow-up CTs. Sensitivities and specificities of outcome prediction were calculated with 95% confidence intervals (CI) using the Wilson-Score method.

3. Results

3.1 Timing of CT after CA

In study 1 (Streitberger et al., 2019), we investigated manually determined GWR (16 ROIs) in 245 CTs of 195 CA patients. In poor outcome patients, *GWR_man* decreased significantly over time. Sensitivity for poor outcome prediction at 100% Specificity and a cutoff of <1.10 was 17% for CTs within 6 hours after CA and increased to 39% for CTs taken later than 24h. Mean *GWR_man* was higher in patients with OHCA (79% of the study population) than in-hospital cardiac arrest (IHCA). The *time to achieve return of spontaneous circulation* (tROSC) did not significantly influence GWR values.

3.2 Automated Assessment of Brain CTs and Clinical Outcome

In study 2 (Kenda et al., 2021), 516 CTs of 433 patients (eighty-nine percent of available CTs) were eligible for automated analysis. In both cohorts (derivation [n=309] and validation [n=207]), most patients were male and suffered an OHCA. Leading causes for CA were cardiac in 46% and respiratory in 28%. At hospital discharge, 151 (35%) of patients had a good (CPC 1–3) and 282 (65%) a poor neurologic outcome (CPC 4-5). Poor outcome patients less commonly had a shockable rhythm, median tROSC was longer.

We first investigated images of the derivation cohort (309 CTs of 262 CA survivors) for regional variations in radiodensity (HU). Poor outcome patients had significantly lower radiodensities in the whole brain and all gray matter regions (Cortex, Putamen, Pallidum, Thalamus, Caudate) whereas no difference was observed in white matter regions. Therefore, GWRs were lower in poor outcome patients and outcome prediction was possible using gray matter HUs and GWRs. The area under the curve (AUC) of the receiver operating characteristics (ROC) curve for these parameters steadily increased over the first 120 hours after CA up to 0.86 (95%-CI; 0.80-0.93).

Sensitivity for poor outcome prediction at 100% specificity was best using automated GWR_si (Putamen/PLIC). For a >1.10 cutoff, sensitivity increased from 20% for CTs obtained within the first 24 hours after CA to 49% for CTs taken later than 24 hours after CA. Using this threshold on the validation cohort (209 CTs of 171 CA survivors), performance was similar: At 100% specificity, sensitivity increased from 13% to 39%. The lowest measured automated GWR_si in a good outcome survivor in this study was 1.11.

In a subgroup of patients with two consecutive CTs (both early and late, *n=83*), we found highly significant decreases of radiodensity over time in patients with poor outcome in

almost all investigated brain regions, including white matter regions. There were no significant changes in radiodensity over time in good outcome patients.

3.3 Histopathological Severity of HIE and GWR

In study 3 (Endisch et al., 2020), we investigated one hundred and twenty-two patients from three centers with CTs and postmortem brain autopsies after CA. Severe HIE was present in 60%, no/mild HIE in 40%. The extend of HIE increased with decreasing GWR values. All patients with a (manually determined) GWR <1.10 had severe HIE, the majority even near-total cortical and hippocampal neuronal death. Few patients with a GWR >1.3 had severe HIE. The lowest measured GWR for a patient with no/mild HIE was 1.13.

4. Discussion

The main findings of this thesis are:

1) Patients with poor neurologic outcome after cardiac arrest have significantly lower radiodensity in gray matter regions, especially basal ganglia. This effect increases over time.
2) Automated Gray-White Matter ratio at the basal ganglia level is a promising and rater-independent tool for prediction of poor neurological outcome after cardiac arrest.
3) Prognostic performance and sensitivity are considerably higher for brain CTs performed later than 24 hours and may be best at 72–120 hours after CA.
4) A cut-off <1.10 in both manually and automatically determined GWR at the basal ganglia level predicted poor outcome with high specificity and low to moderate sensitivity.
5) Postmortem brain tissue demonstrated severe histopathological neuronal damage in patients with GWR <1.10.

4.1 Brain Radiodensity After CA

In a single-center derivation/validation-cohort study, we analyzed the largest number of CTs *(n=533)* after cardiac arrest so far (study 2). Poor outcome patients exhibited significantly lower radiodensities in gray matter areas than good outcome patients, as previously observed (Wu et al., 2011). Radiodensity measured by CT changes linearly with the fraction of tissue water content (Broocks et al., 2018). Selective water uptake in hypoxia-vulnerable neurons after neuronal injury and consequent tissue edema leading to neuronal death is a likely explanation suggested by various imaging and animal studies (Selip et al., 2012, Luigetti et al., 2012, Hogler et al., 2010). We observed the largest differences of radiodensity between good and poor outcome patients in basal ganglia areas such as putamen and caudate nucleus. The cortical changes we measured were less extensive in contrast to previous MRI- and autopsy studies showing similar selective vulnerability, especially in neocortical areas (Horn and Schlote, 1992). Automated determination of cortical radiodensity might underestimate these changes due to partial volume effects, errors in co-registration and artifacts in voxels close to the skull. Future studies could try to increase CT acquisition quality as well as the co-registration algorithm, especially for cortical brain areas.

We studied 83 patients with follow-up CTs (one early CT within 24 hours and one late CT later than 24 hours after CA) and also detected radiodensity changes in white matter regions of patients with poor outcome. These changes were considerably smaller than the changes in gray matter areas. Delayed structural changes in the white matter due to axonal damage have been suggested in advanced diffusion imaging MRI studies and might account for our observations (van der Eerden et al., 2014, Velly et al., 2018). As good outcome patients had no changes of radiodensity in follow-up CTs in any brain region, our data indicates that a short transient global brain hypoxia with no or very limited neuronal damage and general ICU therapy per se do not relevantly affect brain radiodensity.

In conclusion, radiodensity decreases predominantly, but not exclusively, in gray matter regions in patients with poor neurological outcome (severe hypoxic-ischemic encephalopathy) after cardiac arrest. Determined by automated co-registration with a brain atlas, the changes are largest in basal ganglia structures. Water uptake /edema following neuronal death is the likely explanation. The changes increase over time after CA, are more pronounced later than 24 hours as compared to within 24 hours after CA and are not observed in good outcome patients (with no or only mild hypoxic-ischemic encephalopathy).

4.2 GWR for Prediction of Poor Neurological Outcome in CA Patients

GWRs can be obtained using a variety of ROIs from superficial and deep brain structures (Lopez Soto et al., 2019). In study 1, we used 16 manually placed ROIs in 8 regions (Scheel et al., 2013). Another study by our group compared this approach to a simplified version using only 4 ROIs in 2 regions (Putamen and PLIC) and found a non-inferior prognostic performance (Gentsch et al., 2015).

For our automated study, we used different combinations of regions to find the GWR with the best prognostic ability. In contrast to standard-sized circular and binary ROIs in manually determined GWR, the ROIs used here were derived from brain atlases, probabilistic – meaning that the HU of individual voxels were weighted by tissue probability – and varied in size and shape (examples in Figure 1, Kenda et al. 2021). Because HU in PLIC were stable across outcome and timing and changed the most in basal ganglia, performance was best for both GWRs at the basal ganglia level: *GWR_bg* and *GWR_si*. The latter exceeded in specificity, likely because it only used two central regions instead of seven, some of which closer to the (hypodense) ventricles, affecting measurements more if ROIs are misaligned.

Automated *GWR_si* predicted poor outcome with an AUC of 0.79/0.86 (derivation/validation) for early and 0.86/0.81 for late CTs. Sensitivity (49% derivation/38%

validation) was comparable to other modalities used for prognostication, such as SSEP, EEG or NSE (Westhall et al., 2016, Streitberger et al., 2017, Endisch et al., 2015). Our results confirm the results of previous, manual ROI studies (Na et al., 2018) indicating a consistent underlying pathophysiology.

4.3 Timing of CTs

Most CT studies so far have focused on early CTs (within 6 or 24 hours after CA) and found heterogeneous results with low to moderate sensitivity and mixed prognostic performance leading some authors even to the conclusion that CT cannot be used for outcome prediction (Hong et al., 2019, Sandroni et al., 2020). A large international prospective study using qualitative assessment by an expert neuroradiologist noticed an increase in sensitivity for poor outcome prediction from 14% to 57% within 24h for patients with radiologically diagnosed "generalized brain edema" (Moseby-Knappe et al., 2017). The increase in sensitivity in both our manual and automated study was comparable. However, in another study, interobserver agreement on CTs findings in qualitative assessment (i.e. absence or presence of HIE) was poor to moderate and varied widely between physicians, specialties and centers. Using first a manual and then an automated quantitative approach, we aimed to minimize this variability.

In our studies, as mentioned above, radiodensity for gray matter regions decreased in poor outcome patients, so did GWR. This difference became more pronounced over time, especially within the first 24 hours suggesting an ongoing effect within hours and days after CA. Our subgroup analysis in study 2 *(n=70)* suggests CTs might have the best prognostic capability between 72–120 hours after CA (supplementary material of Kenda et al. 2021). Even after 120 hours up until 240 hours after CA, prognostic performance stayed at a high level, indicating lasting effects on brain tissue as seen in ischemic stroke (Schwamm et al., 1998, Broocks et al., 2018).

Future studies should further evaluate post-CA CTs at later time points, repeated CTs and comment on reversible CT changes in CA survivors of patients with neurologic recovery. Serial CTs would also allow for quantification of water uptake, which could better establish thresholds for reversibility of brain damage due to edema as already demonstrated in stroke patients (Minnerup et al., 2016).

4.4 Cutoffs and Pitfalls using GWR

In none of our studies, we saw good outcome patients (CPC 1-3) with a GWR <1.10. Severe histopathological HIE was not only found in all patients under this cutoff, but also a relevant proportion of patients within the reference range, implying relevant neuronal damage undetectable by GWR. Severe HIE was rarely found in patients with GWR >1.3, indicating a possible upper cutoff for the detection of HIE and a role in good outcome prediction, respectively. As CPC 5 (death) partially includes death by causes other than HIE (i.e. sepsis, multiorgan failure, re-arrest), we find several patients with GWR >1.3 in our CT studies. Thus, using a multiparameter approach for prognostication is even more relevant.

If GWR is used in the clinical routine, the way of its acquisition and calculation should be taken into consideration. A previous pilot study that automatically assessed GWR in 84 patients with early CTs using masks of the whole white and gray matter found a similarly high ROC-performance but low sensitivity and non-maximal specificity at a cutoff different from ours (<1.04) (Hanning et al., 2016). Other studies - mainly retrospective single-center - used different combinations of ROIs and reported cut-offs between 1.10 and 1.24 (Na et al., 2018). This underlines the importance of method-specific, arguably even center-specific cutoffs until a standardized protocol has been established.

There have been reports of patients with selective bilateral basal ganglia lesions following whole brain hypoxia having good long-term outcome despite movement disorders (Wallays et al., 1995, Scheibe et al., 2020). The exact frequency of this phenomenon is currently unknown and seems more prominent in MRI (Ghasemi et al., 2018). Selective basal ganglia lesions without changes in the cortex should be considered when assessing GWR.

4.5 Limitations

Outcome assessment was performed at hospital or ICU discharge, respectively. Thus, subsequent neurological recovery is possible. We included CPC 3 patients in the good outcome group to avoid overly pessimistic prognosis based on our cohorts. Furthermore, selection bias must be considered because CT was not acquired in all CA patients.

Even though automated assessment minimizes rater-depended variability, there are rater-independent factors affecting quantification such as scanners, acquisition parameters, postprocessing protocols and artefacts. To exclude CTs with apparent artefacts that bias quantification, some degree of expertise is still needed (graphical examples given in supplement of study 2, Kenda et al. 2021). We tried to harmonize CT acquisition but used

different scanners by various manufacturers due to the multi-site structure of our ER, ICU and radiology department. Generally, CT provides a more standardized protocol than MRI as HU are always calibrated to the radiodensity of water (HU=0). Even though significant inter-scanner variability has been described in a small study of CA patients, GWR seemed to equalize most of it (Oh et al., 2019). In our study, Hounsfield Units were evenly distributed with a tendency to lower mean Hounsfield Units for two scanners (Supplementary material of study 2, Kenda et al. 2021). Future studies should standardize every aspect of CT acquisition and postprocessing and systematically investigate inter-scanner variability in diseased patients and healthy controls.

As mentioned in the introduction, early WLST and self-fulfilling prophecy due to presumed poor neurological outcome is an omnipresent and relevant problem in the field that cannot be fully excluded in our study. Nevertheless, in a long-term follow-up study, we did not find a single patient with neurological improvement who was discharged in a minimally conscious state (after a median ICU time of 27 days) and poor prognostic parameters (Petzinka et al., 2018). Furthermore, study 3 also illustrates a high correlation of the other diagnostics used for outcome prediction and histopathological HIE, further supporting the current guidelines. Due to religious and ethical beliefs, social conventions and different healthcare systems or laws, WLST is performed at different rates across countries and regions (Steinberg et al., 2021, Mohiuddin et al., 2020, El Jawiche et al., 2020). A recent Italian prospective multicentre study without WLST confirmed 100% (95%-CI; 97-100%) specificity for poor outcome prediction with the multimodal diagnostic approach including GWR (Scarpino et al., 2019). Further studying prognostication algorithms in cohorts where WLST is infrequently done is ethically and financially challenging but essential for advancing the field.

5. Conclusion

Automated assessment of Gray-White Matter Ratio from brain CTs is a novel and promising, rater independent tool for quantifying changes in brain CTs after CA. Outcome prediction is most accurate using imaging obtained later than 24 hours after cardiac arrest and might be best between 72-120 hours. A GWR threshold of <1.10 in both manually and automatically determined GWR at the basal ganglia level predicted poor outcome with high specificity and moderate sensitivity and correlated with histopathological severity HIE in brain autopsy. Performance was not unlike other diagnostic tools used in the field. Cut-offs used for prediction should be method- and scanner-specific until a standardized protocol for CT quantification has been established. To minimize the risk of falsely predicting poor outcome and self-fulfilling prophecy, a multiparameter approach should always be used before deciding on continuation or withdrawal of life sustaining therapy.

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Statutory Declaration

"I, Martin Kenda, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic "Outcome Prediction after Cardiac Arrest using Automated Assessment of Brain Computed Tomography", independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

_____	_____
Date	Signature of doctoral candidate

Declaration of contribution to the publications

Study 1

Timing of brain computed tomography and accuracy of outcome prediction after cardiac arrest
Kaspar J. Streitberger, Christian Endisch, Christoph J. Ploner, Robert Stevens, Michael Scheel, **Martin Kenda**, Christian Storm, Christoph Leithner
Resuscitation 2019; 145: 8-14.

Impact Factor: 4.215

(ranked 7th/36 journals in the Journal Citation Report 2019 "Critical Care Medicine")

Contributions: Critical discussion and revision of manuscript together with other coauthors.

Study 2

Automated Assessment of Brain Computed Tomography after Cardiac Arrest – an observational derivation/validation Cohort Study
Martin Kenda, Michael Scheel, André Kemmling, Noelle Aalberts, Christopher Guettler, Kaspar J. Streitberger, Christian Storm, Christoph J. Ploner, Christoph Leithner
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Contributions: Independent data collection from database established by Christian Storm. Collecting follow-up data together with Noelle Aalberts. Development of automated quantification method together with André Kemmling, optimization and testing under the supervision of Michael Scheel. Independed radiolgical data analysis, statistical analysis and creation of all figures and tables, manuscript as well as extensive supplementary material needed for revision. Data interpretation and discussion with the help of Christoph Leithner. Critical revision of manuscript together with other coauthors.

Study 3

Hypoxic-ischemic encephalopathy evaluated by brain autopsy and neuroprognostication after cardiac arrest

Christian Endisch, Erik Westhall, **Martin Kenda**, Kaspar J. Streitberger, Hans Kirkegaard, Werner Stenzel, Christian Storm, Christoph J. Ploner, Tobias Cronberg, Hans Friberg, Elisabet Englund, Christoph Leithner

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Awarded with "Paper of the Month 07/2020" by the Center for Stroke Research Berlin

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Contributions: Collection, analysis, and rating of brain CTs in Berlin and Lund. Interpretation of CT and histopathology data with Christian Endisch. Revision of manuscript together with other coauthors.

Study 1

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CV

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List of peer-review publications

Automated assessment of brain computed tomography after cardiac arrest – an observational derivation/validation cohort study
Martin Kenda, Michael Scheel, André Kemmling, Noelle Aalberts, Christopher Guettler, Kaspar J. Streitberger, Christian Storm, Christoph J. Ploner, Christoph Leithner

Crit. Care Med. 2021; doi: 10.1097/CCM.0000000000005198
Impact Factor: 7.598
(ranked 5th/36 journals in the Journal Citation Report 2020 "Critical Care Medicine")

Hypoxic-ischemic encephalopathy evaluated by brain autopsy and neuroprognostication after cardiac arrest
Christian Endisch, Erik Westhall, Martin Kenda, Kaspar J. Streitberger, Hans Kirkegaard, Werner Stenzel, Christian Storm, Christoph J. Ploner, Tobias Cronberg, Hans Friberg, Elisabet Englund, Christoph Leithner,

JAMA Neurol 2020; doi:10.1001/jamaneurol.2020.2340
Impact Factor: 18.302
(ranked 4th/208 journals in the Journal Citation Report 2020 "Clinical Neurology")

Timing of brain computed tomography and accuracy of outcome prediction after cardiac arrest
Kaspar J. Streitberger, Christian Endisch, Christoph J. Ploner, Robert Stevens, Michael Scheel, Martin Kenda, Christian Storm, Christoph Leithner,

Resuscitation 2019; 145: 8-14.
Impact Factor: 4.215
(ranked 7th/36 journals in the Journal Citation Report 2019 "Critical Care Medicine")

Poster presentations

Preliminary Analysis: Quantification of regional brain water uptake after cardiac arrest using computed tomography
4th International Symposium on Post Cardiac Arrest, Lund, Sweden (May 2019)

Talks

Outcome prediction in post cardiac arrest patients using automated assessment of Gray-White Matter Ratio (GWR) in brain computed tomography.
36th Arbeitstagung NeuroIntensivMedizin (ANIM), Berlin, Germany (January 2019)

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