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Original Research Article

Safety and efficacy of stereotactic aspiration with fibrinolysis for deep-seated spontaneous intracerebral hemorrhages: A single-center experience

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ABSTRACT

Objective: The aim of this study was to evaluate feasibility and safety of stereotactic aspiration with fibrinolysis of deep-seated intracerebral hemorrhages (ICH).

Materials and methods: From March 1995 until December 2016, 58 adult patients (34 men and 24 women; mean age of 56.8 ± 11.8 years) presenting with deep-seated spontaneous supratentorial ICH were treated using a minimally invasive technique. Intracerebral hematomas were aspirated until obvious resistance to free-hand suction and subsequent clot fibrinolysis was done using either streptokinase or recombinant tissue-type plasminogen activator. CT scans were performed at intervals ranging from 24 to 72 h. At discharge, functional outcomes were evaluated using the Glasgow outcome scale (GOS). The 30-day mortality rate was evaluated in all patients.

Results: The average ICH volume on initial CT scan was 34.7 ± 11.1 cm^3 (range, 20–90 cm^3). Mean residual hematoma volume after the treatment was 8.0 ± 5.1 cm^3 (range, 3–32 cm^3). There was statistically significant reduction of ICH volume after the treatment ($P < 0.001$). Median ICH reduction rate was 5 cm^3/d (range, 1.5–16.0 cm^3/d) and 17.2%/d (range, 5.27–40.0%/d). Median discharge GOS score was 3 (range, 1–4). Six (10.9%) patients died during the 30-day follow-up period. Treatment related complications were observed in three (5.5%) patients. In two patients asymptomatic increase of ICH volume occurred and one patient was diagnosed with CNS infection.

Conclusions: Stereotactic clot aspiration with subsequent fibrinolytic therapy is safe and feasible treatment procedure associated with significant hematoma resolution rates and acceptable patient outcomes.

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1. Introduction

Non-traumatic intracerebral hemorrhage (ICH) is the second commonest type of stroke with annual incidence rate ranging from 10 to 30 cases per 100,000 population [1]. The incidence rate of spontaneous ICH is constantly growing due to aging population, and increasing use of anticoagulant and thrombolytic therapies [2]. Intracerebral hemorrhage is the most devastating type of all strokes that is associated with the highest mortality, morbidity and disability rates [3,4]. Estimated 1-year survival of ICH victims is approximately 46%, while 5-year survival reaches only 29% [5].

The optimal treatment strategy of ICH remains controversial. The Surgical Trial in Intracerebral Hemorrhage (STICH) trial compared early surgery with optimal medical therapy for treatment of spontaneous ICH [6] and did not find overall benefit from early surgery when compared with conservative treatment. However, a subgroup analysis showed that patients with superficial ICHs may benefit from early surgery [6]. Consequentially, a subsequent STICH-II trial compared early surgery with conservative treatment for superficial spontaneous supratentorial ICH, but also showed no significant outcome differences at 6 months between the two treatment groups [7]. The main reason for lack of benefit from surgical clot removal could be attributed to additional damage to healthy brain overlying the hematoma caused by the surgical intervention [8] because surgical approach of deep-seated lesions necessitates dissection of white matter tracts and brain retraction, both of which can increase risk for postoperative venous infarction, cerebral edema and seizures [9].

To overcome surgery-related brain damage, minimally invasive techniques for deep-seated ICH removal have been developed and are becoming increasingly used [10]. The most commonly employed minimally invasive treatment modalities include stereotactic aspiration and endoscopic ICH evacuation with or without intra-clot fibrinolysis. An increasing body of evidence suggests that minimally invasive techniques of deep-seated spontaneous ICH removal are associated with adequate clot removal, lower surgery-related morbidity and improved patient outcomes [11,12]. Further studies investigating the safety and optimal protocols of minimally invasive ICH removal techniques are warranted.

The aim of this study was to evaluate feasibility and safety of stereotactic aspiration with fibrinolysis of deep-seated ICHs.

2. Materials and methods

2.1. Patients

From March 1995 until December 2016, 74 patients presenting with spontaneous supratentorial ICH were treated using a minimally invasive technique at the Neurosurgery Department of the Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania. The study inclusion criteria were deep-seated subcortical ICH located in the basal ganglia or thalamus; and ICH volume ranging from 10 to 100 cm^3. The study exclusion criteria were patient age of less than 18 years; secondary ICH due to trauma or tumor; underlying vascular abnormalities (arteriovenous malformation or cerebral aneurysm); and infratentorial or brainstem ICH extension. A total of 58 (34 men and 24 women) patients meeting the study criteria were selected for the present report. The patients' age ranged from 18 to 84 years with a mean age of 56.8 ± 11.8 years. The study was approved by the institutional review board.

2.2. Diagnostic evaluations

On admission, all patients were evaluated for level of consciousness (Glasgow coma scale or GCS [13]), neurological deficits and timing of symptom onset, and underwent non-enhanced brain computed tomography (CT) scanning. After surgery, patients were followed daily for adverse events. At discharge, functional outcomes were evaluated using the Glasgow outcome scale or GOS [14]. The 30-day mortality rate was evaluated in all patients.

Volume of ICH was calculated using the ABC/2 method [15], where A is the largest diameter of the hematoma on axial CT cuts, B is the diameter of the hematoma perpendicular to A line on the same cut, and C is the number of CT slices in which hematoma is visible multiplied by the slice thickness in centimeters. Presence of intraventricular hemorrhage, acute hydrocephalus and midline shift were also recorded. Digital subtraction angiography or CT angiography were performed in selected cases where vessel malformation or an aneurysm rupture were suspected.

2.3. Treatment protocol

In the operating room, following skin incision, burr hole and dural opening, the ventricular catheter was stereotactically placed using the Leksell stereotactic frame. The goal of the insertion was to center the catheter along the long axis of the clot. Special attention was paid to avoid eloquent brain areas. Following catheter placement, the hematoma was carefully aspirated using syringe until obvious resistance to free-hand suction. When no more blood could be withdrawn, the hematoma cavity was thoroughly rinsed with isotonic saline, until the saline fluid was clear. In three cases, more than 80% of the hematoma volume was successfully aspirated, therefore procedure was finished and subsequent clot fibrinolysis was not performed. In the remaining 55 cases, the catheter was left in the hematoma cavity and skin incision was closed. After the surgery, a CT scan was performed for assessment of catheter placement. Usually one catheter was left in the hematoma cavity; however, under certain circumstances (i.e. large hematoma) two catheters were used.

After the surgery, patients were transported to neurosurgery intensive care unit and clot fibrinolysis and drainage were performed immediately at the bedside using sterile techniques. Fibrinolytics were selected based on hospital availability. In 45 cases fibrinolysis was done using streptokinase and in 10 cases recombinant tissue-type plasminogen activator (rt-PA) was used. After fibrinolytic injection, the drainage system was closed and left for 1 h to allow fibrinolytic-ICH interaction. After 1 h the system was opened to allow hematoma drainage. Fibrinolytic dose and injection interval varied case by case, and was based on hematoma volume reduction rate. A single

streptokinase dose varied from 2500 to 10,000 units and rt-PA dose, from 4 to 10 mg.

During fibrinolytic therapy period, CT scans were performed in all patients at intervals ranging from 24 to 72 h or in cases of clinical deterioration. Reduction of hematoma volume and presence of re-bleeding were assessed on follow-up CT scans. Fibrinolysis was completed when hematoma volume reduced by 80%. After the final fibrinolytic injection, the catheter was left in place for additional 48 h to allow drainage of residual blood and was removed.

2.4. *Outcome assessment*

Discharge functional outcomes were evaluated using the GOS scale. Good outcome was defined as GOS scores of 4 (moderate disability) and 5 (low disability), and poor outcome, as GOS scores ranging from 3 (severe disability) to 1 (death).

Thirty-day mortality rates were assessed in all patients. In order to compare our 30-day mortality rate with other investigator data, we used the ICH grading scale proposed by Hemphill et al. [16]. The ICH score was calculated by evaluating five components: (1) initial GCS score (from 3 to 4, 2 points; from 5 to 12, 1 point; and from 13 to 15, 0 points); (2) age (≥80 years, 1 point or <80 years, 0 points), (3) ICH localization (infratentorial, 1 point; supratentorial, 0 points), (4) ICH volume (≥30 cm^3, 1 point or <30 cm^3, 0 points); and (5) presence of intraventricular hemorrhage (yes, 1 point; or no, 0 points). The total ICH score is the sum of these points, with a higher score indicating a worse prognosis.

Complications were analyzed in all patients. Re-bleeding and CNS infection were considered as fibrinolysis related complications.

2.5. *Statistical analysis*

Data were analyzed with the Statistical Package for the Social Sciences (SPSS) 22.0. *P* values of <0.05 were considered to be statistically significant. Continuous variables are presented as mean ± standard deviation (range) and categorical data as number (percentage).

First, we investigated the association of ICH volume with admission GCS score and gender by using the independent-sample *t* test and Pearson correlation analysis. By using independent-sample *t* test we compared the volume of blood aspirated in patients who subsequently received intra-clot fibrinolysis therapy vs. patients who did not. Next, we compared initial and final ICH volumes (in cm^3) by using paired samples *t*-test. By using independent-sample *t* test, Chi-squared test and Mann–Whitney *U* test we evaluated the association of discharge outcome (favorable vs. unfavorable) and the 30-day mortality rate with patients' age (in years), admission GCS score, initial ICH volume (in cm^3), presence of intraventricular hemorrhage, acute hydrocephalus and midline shift on admission CT scan, GCS at completion of ICH fibrinolysis, ICH reduction (%), and ICH score.

3. Results

Demographic and clinical characteristics at baseline are shown in Table 1. The mean GCS score on arrival was 10.3 ± 3.0 (range, 4–15). Nineteen (32.8%) patients had a GCS score between 4 and 8; 19 (32.8%) patients, between 9 and 12; and 20 (34.5%) patients, between 13 and 15. All patients presented with hemiparesis or hemiplegia, and 36 (62.1%) patients had aphasia. The majority (82.8%) of hematomas were located in the basal ganglia (putamen and/or caudate nucleus) and half of hematomas were located in the left hemisphere. Intraventricular extension was present in 48% of patients and occlusive hydrocephalus was present in 16% of patients. Midline shift on the CT scan was recorded in 60% of patients with an average shift of 0.7 ± 0.3 cm (range, 0.2–1.2 cm). The average ICH volume on the initial CT scan was 34.7 ± 11.1 cm^3 (range, 20–90 cm^3). Mean time from stroke onset to the start of hematoma aspiration was 97 h, with 25 (43.1%) patients having the procedure initiated within 72 h after the stroke onset. The median ICH score was 2 (range, 0–4).

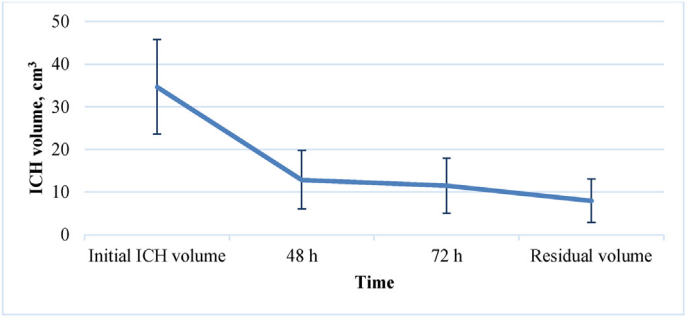
Table 1 – Baseline demographic and clinical data of the study patients.

Variable	Value
Age, years, mean ± SD	56.8 ± 11.8
Sex	
Male	34 (58.6)
Female	24 (41.4)
Glasgow coma scale	
Score, mean ± SD	10.3 (3.0)
Score between 4 and 8	19 (32.8)
Score between 9 and 12	19 (32.8)
Score between 13 and 15	20 (34.5)
Clinical presentation	
Hemiparesis or hemiplegia	58 (100)
Aphasia	36 (62.1)
Location of intracerebral hemorrhage	
Putamen and/or caudate nucleus)	48 (82.8)
Thalamus	10 (17.2)
Side of intracerebral hemorrhage	
Left hemisphere	29 (50.0)
Right hemisphere	29 (50.0)
Presence of intraventricular hemorrhage	28 (48.3)
Presence of occlusive hydrocephalus	9 (15.5)
Presence of midline shift	35 (60.3)
ICH score, median (range)	2 (0–4)

Values are number (percentage) unless otherwise indicated.
ICH, intracerebral hemorrhage.

Mean ICH volume was larger in patients with GCS score of 3–8, compared to patients with GCS score of 9–15 (40.7 ± 15.0 cm^3 vs. 31.9 ± 7.4 cm^3; $P = 0.005$). There was a correlation between GCS score on arrival and ICH volume ($r = -0.262$; $P = 0.051$). Mean hematoma volume was larger in female patients relative to male patients (39.0 ± 14.8 cm^3 and 31.7 ± 6.1 cm^3, respectively, $P = 0.033$).

Three (5.2%) patients received ICH aspiration without subsequent fibrinolysis. In the fibrinolysis group, 13.1 ± 5.7 cm^3 (or 38.8 ± 15.7% of the initial ICH volume) of blood was aspirated during the catheter placement surgery when compared to the 21.7 ± 7.2 cm^3 (or 81.7 ± 20.2% of the initial ICH volume) in the group without fibrinolysis ($P = 0.017$). In 42 (76.4%) patients evacuation and drainage of ICH was done using one catheter, and in the remaining 13 (23.6%) cases two catheters were used.



ICH – intracerebral hemorrhage
Error bars represent standard deviation

Fig. 1 – Change of ICH volume during the treatment ($P < 0.001$).

Median duration of ICH fibrinolytic treatment was 2 days (range, 1–6 days) and the catheter for ICH drainage was left in ICH bed for a median of 5 days (range, 2–11 days). Mean residual hematoma volume after the treatment was 8.0 ± 5.1 cm^3 (range, 3–32 cm^3). This means that hematoma volume reduction ranged from 39% to 92%, with a mean reduction of 76.6 ± 11.2% when compared to initial ICH volume. There was statistically significant reduction of ICH volume after the treatment ($P < 0.001$). Median ICH reduction rate was 5 cm^3/d (range, 1.5–16.0 cm^3/d) and 17.2%/d (range, 5.27–40.0%/d). Fig. 1 shows ICH volume reduction during fibrinolysis. There were no statistically significant differences ($P = 0.347$) in hematoma reduction rate as a function of fibrinolytic used (rt-PA or streptokinase).

Median GCS score at the end of fibrinolytic therapy was 14 (range, 3–15) and median GCS score at the time of discharge was 15 (range, 3–15). Median discharge GOS score was 3 (range, 1–4) and the majority ($N = 40$; 72.7%) of patients had unfavorable outcome. Among patients with initial GCS score of 3–8, only one (5.3%) patient had favorable outcome, among patients with initial GCS score of 9–12, 4 (23.5%) had favorable outcome, and among patients with GCS score of 13–15, 10 (52.6%) patients had favorable outcome ($P = 0.004$). Six (10.9%) patients died during the 30-day follow-up period after the stroke. All deaths occurred after completion of fibrinolytic treatment. Patients who died during the 30-day follow-up period, relative to patients who were alive, were significantly older ($P < 0.001$), had lower GCS score at admission ($P < 0.001$) and upon completion of fibrinolysis therapy ($P = 0.003$), were more likely to have acute hydrocephalus ($P = 0.049$) (Table 2). Patients with unfavorable discharge outcome, compared to patients with favorable outcome, had lower GCS score at admission ($P = 0.001$) and upon completion of fibrinolysis therapy ($P < 0.001$), had higher ICH score ($P = 0.004$) (Table 3).

Treatment related complications were observed in three (5.5%) patients. In two patients asymptomatic increase of ICH volume occurred and one patient was diagnosed with CNS infection. The latter patient had the catheter inserted for 6 days and meningitis was diagnosed after the catheter removal. All 3 patients, who suffered from treatment-related complications were alive at 30 days after the stroke; however, all of them had unfavorable discharge outcomes.

4. Discussion

Our study findings suggest that in patients with spontaneous supratentorial deep-seated ICH, stereotactic clot aspiration with subsequent fibrinolytic therapy is safe and feasible treatment procedure that is associated with significant hematoma resolution rate and acceptable 30-day mortality rate.

Minimally invasive surgery plus rt-PA for intracerebral hemorrhage evacuation (MISTIE) trial is the most comprehensive

Table 2 – Comparison of clinical and radiological findings between dead and alive patients, who underwent fibrinolytic therapy, at 30 days.

Variable	Dead patients ($n = 6$)	Alive patients ($n = 49$)	P value
Age, years	66.0 ± 2.8	56.1 ± 12.2	<0.001
Admission GCS score	8.0 ± 1.3	10.5 ± 3.1	<0.001
Initial ICH volume (cm^3)	40.7 ± 24.9	34.5 ± 8.3	0.204
Intraventricular hemorrhage, n (%)	5 (83.3)	23 (46.9)	0.193
Acute hydrocephalus, n (%)	3 (50.0)	6 (12.2)	0.049
Midline shift, n (%)	4 (66.7)	30 (61.2)	1.000
GCS score at completion of ICH fibrinolysis	9.5 ± 3.2	13.3 ± 2.8	0.003
Reduction of ICH (%)	79.2 ± 9.2	76.3 ± 11.5	0.590
ICH score, median (range)	2.5 (2–3)	2.0 (0–4)	0.092

Values are mean ± standard deviation unless otherwise indicated.
GCS, Glasgow coma scale; ICH, intracerebral hemorrhage.

Table 3 – Comparison of clinical and radiological data between patients, who underwent fibrinolytic therapy, with favorable and unfavorable discharge outcomes.

Variable	Unfavorable outcome ($n = 40$)	Favorable outcome ($n = 15$)	P value
Age, years	58.3 ± 10.9	54.1 ± 14.4	0.251
Admission GCS score	9.4 ± 2.9	12.4 ± 2.2	0.001
Initial ICH volume (cm^3)	36.5 ± 12.4	31.9 ± 6.4	0.188
Intraventricular hemorrhage, n (%)	23 (57.5)	5 (33.3)	0.138
Acute hydrocephalus, n (%)	9 (22.5)	0 (0%)	0.052
Midline shift, n (%)	25 (62.5)	9 (60.0)	1
GCS score at completion of ICH fibrinolysis	12.3 ± 3.3	14.6 ± 0.8	<0.001
Reduction of ICH (%)	76.0 ± 11.6	78.2 ± 10.1	0.522
ICH score, median (range)	2 (0–4)	1 (0–3)	0.004

Values are mean ± standard deviation unless otherwise indicated.
GCS, Glasgow coma scale; ICH, intracerebral hemorrhage.

study exploring [11,12,17] minimally invasive treatment of spontaneous supratentorial ICH, therefore differences between our protocol and the MISTIE study protocols should be noted. Firstly, in our study the time from stroke onset until the start of the treatment was longer, whereas in the MISTIE trial the eligibility window was only 48 h. Since optimal time window for surgical treatment of spontaneous ICH remains unclear, our findings suggest that it could be clinically useful to evacuate hematoma beyond the 48 h window. Treatment related variables, such as surgical technique, thrombolytic agents and thrombolytic dosage, were also different; however, the clot removal rate was similar in our study and the MISTIE trial. In the MISTIE trial reduction of hematoma size in rt-PA group was 57% versus 5% in the standard medical care group; however, faster lysis of ICH did not result in better clinical outcomes. As a result, phase III MISTIE trial that aims to include 500 is ongoing. Investigators hypothesize, that by removing the blood clot faster, injury to the brain will be reduced and the patient's long-term prognosis will improve.

The major benefits of clot removal are lowering of intracranial pressure, reduced likelihood of brain edema formation, improved cerebral perfusion, and prevention of ICH enlargement and secondary brain injury by cytotoxic clot degradation components [18,19]. However, the clinical value of surgical ICH removal via craniotomy remains controversial. The major advantage of minimally invasive surgery is clot removal with minimal damage of uninjured brain damage [18]. Therefore, minimally invasive techniques should be considered as a treatment option in patients with spontaneous ICH. Chen et al. assessed effectiveness and safety of stereotactic aspiration plus subsequent fibrinolysis in 105 patients with thalamic ICHs [20]. They found that 30-day mortality rate in the conservative group was significantly higher than in the aspiration group (28.3% vs. 11.2%). Furthermore, at 90 days after stroke aspiration group patients had better functional outcomes when compared to conservative group (51.1% vs. 30.0%). Our results showed similar 30-day mortality rate, suggesting that stereotactic clot aspiration and fibrinolysis is safe for treatment of deep-seated spontaneous ICH.

We found that the 30-day mortality rate was lower in our cohort relative to previous studies in patients presenting with ICH score of 2 (Fig. 2) [16,21–23]. It is important to note that in these studies, the vast majority of ICH patients were treated conservatively (range from 78% to 95%) and none of the patients had minimally invasive treatment. These findings suggest that minimally invasive treatment may be superior to conservative management in reducing mortality rate for patients with ICH.

As expected older patients were more likely to have lethal consequences after ICH and lower ICH resolution rate was

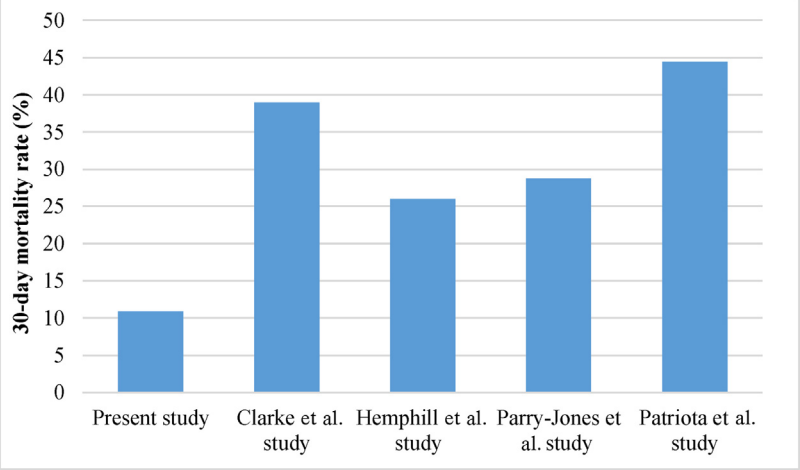


Fig. 2 – 30-day mortality rates in the present study compared to ICH grade 2 30-day mortality rate in Clarke et al. study (2004) [22], Hemphill et al. study (2001) [16], Parry-Jones et al. study (2013) [21], Patriota et al. study (2009) [23].

associated with more advanced age. Selection of the optimal ICH treatment method in elderly patients is challenging because open craniotomy with ICH removal is associated with higher complications rate in elderly patients [24]. The major limitation of conservative ICH treatment in elderly patients is slower natural lysis of ICH that may be associated with decreasing potency of fibrinolytic system with advancing age, particularly with the increased levels of plasminogen activator inhibitor-1 (PAI 1) [25,26]. Larger studies investigating safety and efficacy of minimally invasive ICH evacuation techniques in elderly patients are encouraged.

The overall complication rate in our study was 5.5%, with one patient developing CNS infection and two patients experiencing asymptomatic re-bleeding. All patients who experienced adverse events were alive at 30-days. These adverse events were within safety limits and similar rates of adverse events following minimally invasive ICH removal with fibrinolysis were reported by majority of other investigators (range from 7% to 9%) [20,27–29]. Only MISTIE investigators found increased risk of asymptomatic bleeding in rt-PA group compared to standard medical care (22.2% vs. 7.1%) [12].

This study has several limitations. Firstly, due to observational study design we were unable to compare minimally invasive treatment with other treatment methods of ICH. However, comparison of 30-days mortality rates with expected mortality rates based on the ICH score in other studies suggests that the survival rate after minimally invasive treatment was higher than expected. Randomized studies comparing the efficacy of minimally invasive ICH treatment with other treatment modalities are warranted. Furthermore, long-term functional outcomes were not evaluated; thus, we are unable to investigate recovery trajectories and long-term outcomes following minimally invasive ICH removal.

5. Conclusions

Stereotactic clot aspiration with subsequent fibrinolytic therapy is a safe and feasible treatment procedure associated with significant hematoma resolution rates and acceptable patient outcomes. Randomized controlled studies comparing the clinical efficacy of minimally invasive techniques with other treatment options for deep-seated ICHs are needed.

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No funding was received for this research.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study (or their next of kin) for the use of collected data for research purposes.

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