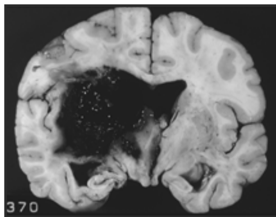
Early outcome following spontaneous ICH in adults:
risk factors and treatment effects



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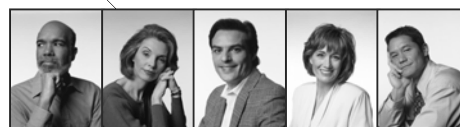
Stroke: the stats

- 3rd leading killer in U.S.
- 700,000 Americans suffer a stroke each year
- Stroke incidence will double by 2050



Stroke Can Strike Anyone!

Stroke Disables Millions

Number one cause of disability in America

3 million Americans live with disability from stroke

Two Types of Stroke

Ischemic
- 84% of all strokes
- Disruption of blood flow to brain

Hemorrhagic
- Less common, more deadly
- Rupture of a blood vessel
- Immediate and delayed damage to brain tissue

ICH: the stats

- 16% of cases presenting with acute neurologic deficit
- 12-15 cases per 100,000/yr
- Male : female ratio 1.5:1
- Age: >55 years

30-day mortality rate is 35-50%

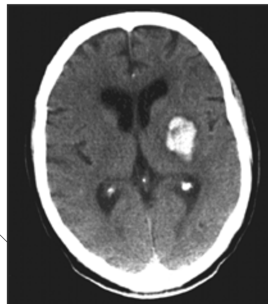
Etiologies

- Hypertension
- Amyloid angiopathy

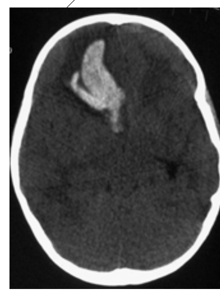
- Vascular anomaly
- Trauma
- Infection
- Tumor

“Typical” bleeds

- Evaluated with CT scan only
- Hypertensive: located in thalamus or basal ganglia, pons, cerebellum, brain stem or white matter, associated with hypertension
- Amyloid: lobar location in age > 60



“Atypical”



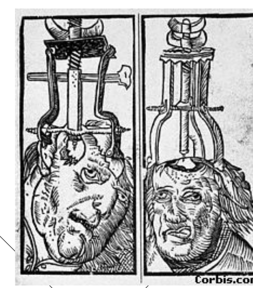
- Prompt further workup with MRI or angiography
- Associated subarachnoid hemorrhage, lobar location in age = 60, suspected structural abnormality

Clinical Presentation

- Headache
- Focal neurologic deficit
- Nausea, vomiting
- Coma
- Seizures
- Death

Management

- Supportive care
  - Strict blood pressure control
  - Correction of coagulopathy
- Ventriculostomy
- Surgical evacuation
- Stereotactic catheter placement and thrombolysis



What do we know?

- Able to predict mortality
  - Level of consciousness
  - Hematoma volume
- Mortality associated with cerebellar hemorrhage is greatly reduced with surgical intervention
  - >3cm, evidence of brain stem compression

What don’t we know?

- Very little about risk factors affecting <u>functional</u> outcome
- No evidence for effective surgical treatment outside of cerebellum

Previous studies: problems

- Many important variables not accounted for (DNR status, preadmission function)
- Selection bias: no adjustment for WHY some receive surgery and some do not
- Susceptibility bias: patients treated surgically probably do not have the same risk of poor outcome as those treated medically

Questions

- What risk factors are associated with mortality and poor functional outcome?
- Are there differences in covariates between those selected for surgical vs. medical treatment?
- After adjusting for selection bias, which treatment modality has a higher chance of improving outcome: surgical or medical?

Hypotheses:

- Outcome at time of discharge may be predicted by admission characteristics
- Surgical treatment will improve mortality and functional outcome in some patients with ICH

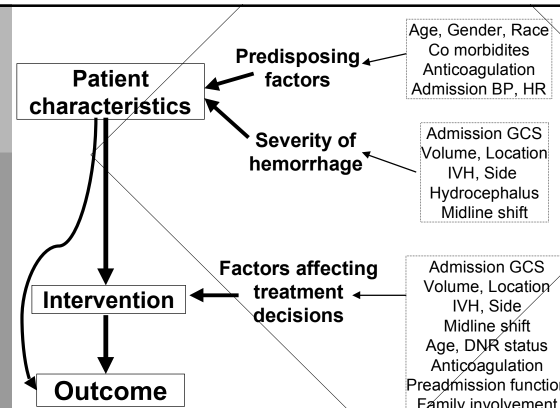
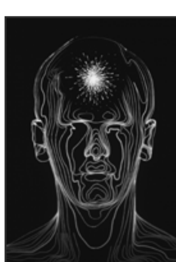


Figure 1

Aims

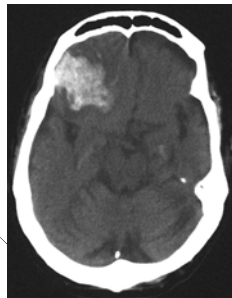
- To determine risk factors associated with death and poor outcome in patients with ICH
- To evaluate effectiveness of surgical treatment in patients matched on probability for surgical treatment



Study design

Design

- Retrospective cohort
- Chart review of 306 patients admitted with diagnosis of ICH



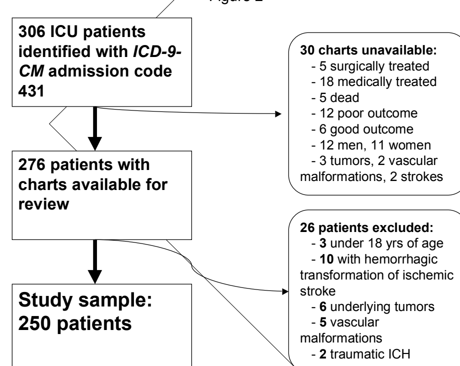
Inclusion criteria

- Spontaneous intraparenchymal ICH
- Adult (= 18y)
- Admitted to the neurosurgical ICU of University Hospitals of Cleveland between Jan.1, 1995 and Jan.1, 2002 (policy: all ICH admitted to neurosurgery service and observed for at least 24 h in ICU)
- CT scan results documented or actual CT available for review

Exclusion criteria

- History of recent trauma
- Evidence of tumor or vascular malformation (found during workup of “atypical” bleed)
- Hemorrhage secondary to treatment of ischemic stroke with thrombolytic (tPA)
- Chart unavailable for review

Figure 2



Unavailable charts Table 1

	% or Mean		
Variable	*Study sample (n=250)*	*Unavailable charts (n=23)*	*p-value*
Age	**68.0**	**66.6**	**0.63**
Gender			
Male	**50.8**	**52.2**	
Female	**49.2**	**47.8**	**0.90**
Intervention			
Medical	**89.6**	**78.3**	
Surgical	**10.4**	**21.7**	**0.21**
Side of hemorrhage			
Right	**47.6**	**34.8**	
Left	**52.4**	**65.2**	**0.34**
Location of hemorrhage			
Cerebellum	**7.6**	**4.3**	
Lobar	**34.8**	**39.1**	
Basal Ganglia	**49.2**	**47.8**	
Brainstem	**8.4**	**8.7**	**0.93**
Outcome			
Dead	**27.2**	**21.7**	
Poor	**39.2**	**52.2**	
Good	**33.6**	**26.1**	**0.48**

Selection of variables

- Panel of four neurosurgeons and neurocritical care specialists identified variables believed to be associated with outcome and selection of surgical treatment (Table 2)

Study variables – patient characteristics

- Age
- Gender
- Race
- Preadmission function
- Insurance status
- Documentation of PMHX
  - Diabetes
  - Cigarette use
  - EtOH abuse
  - CAD
  - Hypercholesterol
  - Hypertension
  - On warfarin

Study variables – admission characteristics

- DNR status
- Comfort measures
- Family involvement
- Time of admission
- MAP
- HR
- GCS

Study variables – radiographic findings

- Volume of hemorrhage
- Location of hemorrhage
  - Cerebellum
  - Lobar
  - Basal ganglia
  - Brainstem
- Side of hemorrhage
- IVH
- Hydrocephalus
- >2mm midline shift

Some specifics

- Admission GCS: either as recorded in history, or calculated from documented neurologic exam
- Clot volume calculated as (a*b*c)/2, either from CT scan directly or from dimensions recorded in chart
- Hydrocephalus determined from presence of temporal horns, rounded third ventricle, or enlarged lateral ventricles without evidence of generalized atrophy, or as recorded in chart
- Medical history as recorded in admission note

Outcome variables

- Level of function at time of discharge
  - Glasgow Outcome Scale
    - 1: dead
    - 2: vegetative state
    - 3: disabled, dependent for ADLs
    - 4: mildly disabled, independent for ADLs
    - 5: no disability
  - Dead = GOS 1
  - Poor outcome = GOS 2,3
  - Good outcome = GOS 4,5
- Secondary outcomes: length of stay, number of days in ICU

Why group this way?

- Dead is dead
- Only have early outcomes – tendency for GOS 2 to die, and for GOS 3,4 to either die or improve in longer-term study

Chart abstraction and data quality

- Single reviewer responsible for extraction of chart data using standardized form
- Second reviewer evaluated 10% of charts on five different variables to establish inter-observer agreement

Reviewers

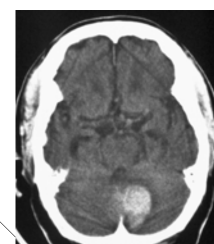
- Both senior neurosurgery residents at UH
- Chosen for familiarity with neurological grading scales as well as facility with radiographic interpretation

In General: Statistical Tests used – univariate analyses

- ANOVA, Wilcoxon rank-sum for continuous variables
- Chi-square or Fisher's exact for categorical variables

Regression analysis

- Logistic regression used to determine odds of death, then odds of poor outcome in survivors, based on admission characteristics



Regression Modeling

- Included all study variables (except comfort measure institution), including interaction terms: volume*location, age*insurance, DNR*race
- Used a backwards stepwise elimination procedure

Regression Modeling

- RR obtained by adjusting OR for outcome prevalence
- CI obtained by bootstrapping

Results

Inter-observer agreement
Table 3

Variable	r or kappa statistic
Volume of hemorrhage	(r) 0.9092
Admission GCS	(r) 0.9925
Length of stay	(r) 0.9432
IVH	(kappa) 0.8434
GOS	(wt kappa) 0.8030

Aim #1:

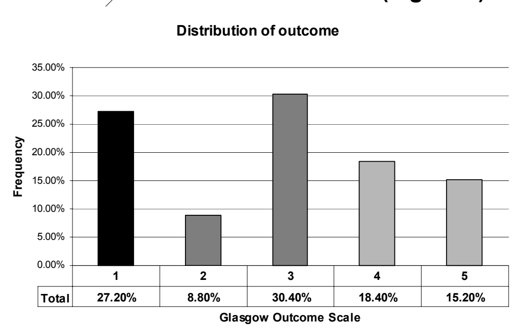
To determine risk factors associated with death and poor outcome in patients with ICH

Analysis of entire study sample (n=250)

Important descriptive statistics

- 224 (89.6%) treated medically
- 26 (10.4%) treated surgically
- 68 died
- 22 vegetative state
- 76 disabled, dependent
- 84 independent of ADLs

Important descriptive statistics: outcome (Figure 3)



Univariate analysis (Table 4)

	% or Mean				
	Dead (n=68)	*Poor (n=98)*	*Good (n=84)*	*Total*	*p-value*
Anticoagulation	26.5	5.1	21.4	16.4	0.0004*
DNR status	63.2	17.3	8.3	26.8	<0.0001*
Comfort measures	61.8	5.1	2.4	18.8	<0.0001*
Intervention					
Medical	92.7	85.7	91.7	89.6	
Surgical	7.3	14.3	8.33	10.4	0.27
Other					
Length of stay	4.7	11.4	5.2	7.5	<0.0001*
# ICU days	3.0	6.8	2.8	4.4	<0.0001*
Total N = 250	68 (27.2%)	98 (39.2%)	84 (33.6%)	250	

Univariate analysis (Table 4)

	% or Mean				
	Dead (n=68)	*Poor (n=98)*	*Good (n=84)*	*Total*	*p-value*
Location					
Cerebellum	0.0	5.1	16.7	7.6	
Lobar	36.8	34.7	33.3	39.1	
Basal Ganglia	47.0	55.1	44.1	49.2	
Brainstem	16.2	5.1	5.9	8.4	0.0007*
Volume (cc^3)	58.2	26.1	8.4	28.9	<0.0001*
Admission GCS	6.2	10.2	14.2	10.4	<0.0001*
IVH	70.6	40.8	17.9	41.2	<0.0001*
>2mm shift	45.6	21.7	4.8	22.4	<0.0001*
Hydrocephalus	51.5	25.5	17.9	30.0	<0.0001*
Total N = 250	68 (27.2%)	98 (39.2%)	84 (33.6%)	250	

Multivariate analysis

Outcome = Treatment + Covariates + error

Multivariate analysis – significant predictors of mortality (Table 5)

Relative risk of death (GOS 1), adjusted for covariates (c=0.927, Hosmer-Lemeshow GOF test p=0.11, n=250, n(dead)=68, *=significant at α=0.05)

Patient characteristics	RR	95% CI	p-value
Volume (cc^3)	1.016	[1.005, 1.030]	0.004*
GCS	0.808	[0.736, 0.888]	<0.0001*
IVH	1.577	[1.151, 1.891]	0.009*
Anticoagulation	1.718	[1.255, 2.045]	0.018*
DNR status	1.474	[1.354, 1.548]	<0.0001*
Surgical treatment	1.062	[0.183, 3.047]	0.916

Multivariate analysis – significant predictors of poor outcome in survivors (Table 6)

Relative risk of poor functional outcome in survivors (GOS 2-3), adjusted for covariates (c=0.900, Hosmer-Lemeshow GOF test p=0.11, n=172, n(poor)=98, *=significant at α=0.05)

Patient characteristics	RR	95% CI	p-value
Volume (cc^3)	1.036	[1.017, 1.056]	0.0002*
GCS	0.826	[0.693, 0.899]	<0.0001*
Anticoagulation	0.119	[0.017, 0.582]	0.005*
Age	1.017	[1.003, 1.034]	0.02*
Surgical treatment	0.611	[0.113, 1.644]	0.24

Conclusions: Outcome

- Five factors associated with mortality:
  - Early DNR status
  - Admission GCS
  - Volume of hematoma
  - Presence of IVH
  - Use of warfarin
- In addition, age associated with poor functional outcome in survivors

Limitations

- No accounting for treatment selection bias
- No blinding to outcome

Aim #2:

To evaluate effectiveness of surgical treatment

What was all this about potential bias in selection of treatment?

Univariate analysis – variables associated with surgical treatment (Table 7)

	% or Mean			
	Medical (n=224)	*Surgical (n=26)*	*Total*	*p-value*
Age (years)	**69.4**	**56.6**	**68.0**	**<0.0001***
Cigarette use	**5.8**	**9.2**	**7.2**	**0.012***
Hypertension	**74.6**	**53.9**	**72.4**	**0.02***
Uninsured	**7.1**	**19.2**	**8.4**	**0.04***
DNR status	**29.5**	**3.9**	**26.8**	**0.005***
Total N = 250	**224 (89.6%)**	**26 (10.4%)**	**250**	

Univariate analysis – variables associated with surgical treatment (Table 7)

	% or Mean			
	Medical (n=224)	*Surgical (n=26)*	*Total*	*p-value*
Location				
Cerebellum	**6.3**	**19.2**	**7.6**	
Lobar	**33.5**	**46.2**	**39.1**	
Basal Ganglia	**51.3**	**30.8**	**49.2**	
Brainstem	**8.9**	**3.8**	**8.4**	**0.03***
Volume (cc^3)	**27.3**	**42.5**	**28.9**	**0.04***
>2mm shift	**19.3**	**50.0**	**22.4**	**0.0004***
Other				
Length of stay	**7.2**	**10.6**	**7.5**	**0.02***
# ICU days	**4.2**	**6.2**	**4.4**	**0.08**
Outcome				
Dead	**28.1**	**19.2**	**27.2**	
Poor	**37.5**	**53.9**	**39.2**	
Good	**34.4**	**26.9**	**33.6**	**0.93**
Total N = 250	**224 (89.6%)**	**26 (10.4%)**	**250**	

OK, so there's bias

How did we adjust for it?

Propensity scores

Used to balance covariates (identify comparable medical and surgical patients) in order to determine effectiveness of treatment

Propensity score

- Logistic regression analysis, using treatment as outcome variable
- Adjust for all variables which may impact both outcome and selection of treatment (see Table 8)

Propensity score

- Propensity score is *predicted probability of surgical treatment given variables in the model*, ranges from 0 to 1
- Use as an adjustor in regression analysis, or as a means of matching similar patients

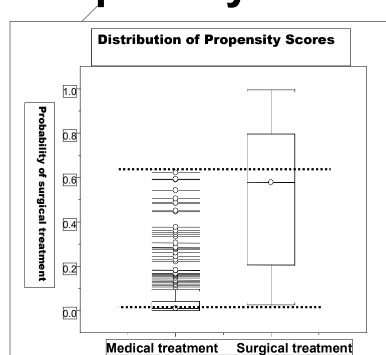
For example

- Patient age 45, with 45cc^3 hemorrhage in cerebellum region, GCS 8 may end up with PS=0.95
- Patient age 95, with 10 cc^3 hemorrhage in left thalamus, GCS 14 may end up with PS=0.03

Then what?

- Identify patients with similar PS
- These can be considered similar over the covariates in the PS model
- Patients with same PS who get different treatments can be considered “pseudorandomized”

Propensity score



How did we use the propensity score?

- Match one surgical patient to one medical patient, within ± 0.05 on propensity score (*matched subset*)
- Identify all medical and surgical patients within range of overlap, consider as patients in whom a decision needed to be made (*clinically-relevant subset*)

Why not use it simply to adjust for treatment?

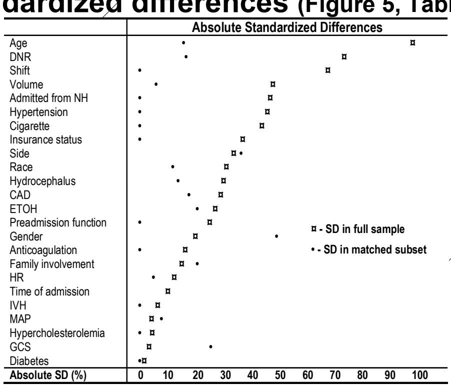
- c=0.935, excellent discrimination between surgical and medical patients – too little overlap to use as an adjustor variable in the model using the entire cohort

Matched analysis (n=36)

Matched analysis

- 18 / 26 surgical patients able to be matched one-to-one with medical patients on the propensity score within ± 0.05

Covariate balance: comparison of standardized differences (Figure 5, Table 9)



Matched sample: multivariate analysis

- No difference in mortality (RR=1.00 [0.329, 1.908]) or poor functional outcome (RR=1.27 [0.568, 1.620]) between medically- and surgically-treated groups

Matched sample: secondary outcomes

- LOS, number of days in ICU not significantly different in medically- and surgically-treated groups

	Medical (n=18)	*Surgical (n=18)*	*Total mean*	*p-value*
Length of stay	**8.8**	**10.5**	**9.6**	**0.48**
# ICU days	**5.8**	**6.2**	**6.0**	**0.82**

Conclusions: treatment effectiveness

- No difference in functional outcome, regardless of treatment strategy
- No difference in LOS, or number of days in an ICU in closely matched patients

Limitations

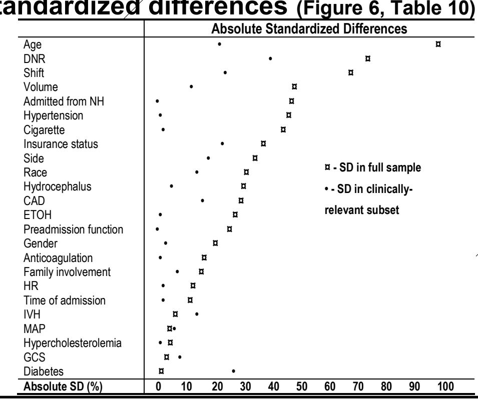
- SMALL SAMPLE SIZE!
- SMALL SAMPLE SIZE!
- SMALL SAMPLE SIZE!

Clinically-relevant subset (n=92)

Clinically-relevant subset

- 18 surgical patients had propensity scores which overlapped with 74 medical patients

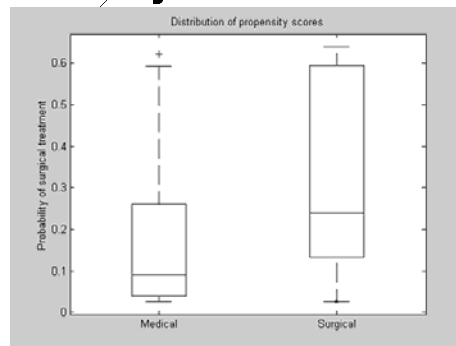
Covariate balance: comparison of standardized differences (Figure 6, Table 10)



Clinically-relevant subset: multivariate analysis

- Used similar outcome model as for entire cohort, but now used propensity score as an adjustor variable
- Outcome = Treatment + Propensity for surgery + Covariates + error

Propensity scores in clinically-relevant subset



Clinically-relevant subset: multivariate analysis – mortality (Table 11)

Patient characteristics	RR	95% CI	p-value
Surgical treatment	**1.64**	**[0.45, 2.99]**	**0.39**
Propensity for surgery	**0.695**	**[0.426, 1.068]**	**0.10**
Volume (cc^3)	**1.029**	**[1.013, 1.046]**	**0.0005***
GCS	**0.851**	**[0.743, 0.970]**	**0.015***
IVH	**1.57**	**[1.23, 1.68]**	**0.006***

Clinically-relevant subset: multivariate analysis – poor outcome (Table 12)

Patient characteristics	RR	95% CI	p-value
Surgical treatment	**0.132**	**[0.003, 1.09]**	**0.08**
Propensity for surgery	**0.999**	**[0.660, 1.306]**	**0.99**
Anticoagulation	**0.001**	**[<0.001, 0.24]**	**0.003***
Volume (cc^3)	**1.10**	**[1.04, 1.15]**	**0.0005***

Clinically-relevant subset: secondary outcomes

- Increased LOS and marginally significant increase in number of ICU days in surgically-treated group

	Medical (n=74)	*Surgical (n=18)*	*Total mean*	*p-value*
Length of stay	**7.0**	**10.5**	**7.7**	**0.02***
# ICU days	**4.8**	**6.2**	**5.1**	**0.09**

Conclusions: clinically-relevant subset

- No significant effect of surgical intervention on survival
- Trend towards protective effect of surgery on outcome in survivors
- Increased LOS, marginally-significant increase in number of days in the ICU in surgical patients

Limitations

- Again, not very big sample size
- Not as well-matched as n=36 sample
- Able to match about a third of our study sample – these results not really generalizable to most patients with ICH

What about the patients that couldn't be matched?

What can we say about them?

Patients unable to be matched on propensity score – "extreme" patients

- 8 surgical patients had propensity scores above 0.62
- 150 medical patients had propensity scores below 0.03

"Extreme" patients (Table 13)

	% or Mean			
	Medical (n=150)	*PS-Matched (n=92)*	*Surgical (n=8)*	*p-value*
Age (years)	**73.1**	**61.4**	**50.3**	**0.0006***
Cigarette use	**2.7**	**12.0**	**37.5**	**0.003***
Hypertension	**78.0**	**67.4**	**25.0**	**0.0007***
DNR status	**36.0**	**14.1**	**0.0**	**0.04***
Location				
Cerebellum	**3.3**	**14.1**	**12.5**	
Lobar	**30.0**	**40.2**	**62.5**	
Basal Ganglia	**56.7**	**39.1**	**25.0**	
Brainstem	**10.0**	**6.6**	**0.0**	**0.02***
Total N	**150**	**92**	**8**	

"Extreme" patients (Table 13)

	% or Mean			
	Medical (n=150)	*PS-Matched (n=92)*	*Surgical (n=8)*	*p-value*
Volume (cc^3)	**20.9**	**39.5**	**57.5**	**0.004***
>2mm shift	**12.1**	**35.9**	**62.5**	**<0.0001***
Hydrocephalus	**34.0**	**26.1**	**0.0**	**0.05***
Length of stay	**7.2**	**7.7**	**11**	**0.002***
# ICU days	**3.9**	**5.1**	**6**	**0.002***
Dead	**26.0**	**31.5**	**0.0**	
Poor	**38.0**	**39.1**	**62.5**	
Good	**36.0**	**29.4**	**37.5**	**0.33**
Total N	**150**	**92**	**8**	

What does it mean?

- Patients with high propensity for surgery are very different than those with low propensity, and different from patients we were able to match on PS
- The 8 surgical patients have no comparable medical counterparts – we can't say whether or not there might be a benefit in this subset

Surgical benefit?

- In the 8 surgical patients with high propensity for surgery, there are no deaths, but a disproportionate rate of poor outcome

Limitations

- "Propensity for DNR" not evaluated
- INR not recorded – paradoxical effect of warfarin
- Small sample, matching strategies bias towards null
- Underreporting in chart
- Potential for verification bias
- Single institution
- Amyloid vs. Hypertensive – fair to lump them together?
- Effect of ventriculostomy not considered

What comes after this study?

- Sensitivity analysis – hidden bias?
- Validate models on another set of patients
- Follow longer-term outcomes
- Larger scale, multi-center observational study
- RCT – medical vs. surgical management

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