

Supplementary material*Sembill et al.*

Hematoma enlargement characteristics in deep vs lobar intracerebral hemorrhage

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e-Table 1. Clinical characteristics of patients with deep vs lobar ICH

| Characteristics | Deep (n=1106) | Lobar (n=848) | p-value |
|--|------------------|------------------|--------------------|
| Age† (yrs) | 74 (67-80) | 76 (70-81) | <0.001 |
| Sex* (♀) | 425 (38.1%) | 372 (43.9%) | 0.02 ^e |
| Pre-mRS† ^a | 0 (0-1) | 0 (0-2) | 0.06 |
| Prior medical history | | | |
| Hypertension* | 984 (89.0%) | 720 (84.9%) | 0.008 ^e |
| Diabetes Mellitus* | 341 (30.8%) | 246 (29.0%) | 0.38 |
| Prior ischemic stroke or TIA* | 292 (26.4%) | 192 (22.6%) | 0.06 |
| Prior ICH or major bleeding* | 82 (7.4%) | 102 (12.0%) | <0.001 |
| Congestive heart failure* | 186 (16.8%) | 137 (16.2%) | 0.70 |
| Renal insufficiency* | 241 (21.8%) | 172 (20.3%) | 0.42 |
| Antiplatelet use* | 179 (16.2%) | 174 (20.5%) | 0.01 ^e |
| Vitamin K Antagonist use* | 681 (61.8%) | 505 (59.6%) | 0.37 |
| NOAC use* | 69 (6.2%) | 38 (4.5%) | 0.09 |
| On admission status | | | |
| Glasgow coma scale† ^d | 13 (11-15) | 14 (12-15) | <0.001 |
| ICH Score† ^e | 1 (0-2) | 1 (0-2) | 0.08 |
| Systolic blood pressure† (mmHg) | 170 (150-190) | 162 (145-181) | <0.001 |
| Imaging | | | |
| Symptom onset – first imaging, min | 156 (85-364) | 291 (140-740) | <0.001 |
| Symptom onset – second imaging, h | 24 (13-36) | 29 (17-52) | <0.001 |
| ICH volume† (cm ³) | 9.4 (3.9-18.3) | 19.5 (7.0-38.7) | <0.001 |
| Intraventricular hemorrhage* | 540 (48.8%) | 240 (28.3%) | <0.001 |
| Reversal treatment (OAC patients, n=1293) | | | |
| Any reversal treatment* | 725/750 (96.7%) | 513/543 (94.5%) | 0.05 |
| Admission – reversal, min | 95 (60-162) | 107 (66-206) | 0.007 ^e |
| PCC* | 656/750 (87.5%) | 445/543 (82.0%) | 0.006 ^e |
| FFP* | 32/750 (4.3%) | 41/543 (7.6%) | 0.01 ^e |
| Konakion* | 601/750 (80.1%) | 429/543 (79.0%) | 0.62 |
| Coagulation parameters (OAC patients, n=1293) | | | |
| INR on admission† | 2.50 (2.06-3.10) | 2.60 (2.09-3.40) | 0.01 ^e |
| 1 st INR after reversal† ^g | 1.26 (1.15-1.43) | 1.30 (1.17-1.56) | <0.001 |
| Length of stay (d) ‡ | 13 (8-19) | 10 (7-15) | <0.001 |

* n (%); † median (Interquartile range, 25th-75th percentile)

Abbreviations: d, days; FFP, Fresh frozen plasma; h, hours; ICH, intracerebral hemorrhage; INR, international normalized ratio; m, minutes; NOAC, Non-vitamin K antagonist oral anticoagulants; OAC, Oral anticoagulant; PCC, prothrombin complex concentrate; TIA, transient ischemic attack; yrs, years.

^a modified Rankin Scale, range 0-6, from no disability to death; ^b Glasgow coma scale, range 3-15, from coma to alertness. ^c ICH score, range 0-6, from low to high short-term mortality risk. ^d First value of in-hospital monitoring after reversal treatment, if appropriate. ^e Not significant after performance of Holm's sequential Bonferroni correction.

e-Table 2. Clinical characteristics of patients with vs without hematoma enlargement

| Characteristics | Non-OAC-ICH (n=661) | | | OAC-ICH (n=1293) | | |
|--|---------------------------------|-----------------------------|--------------------|---------------------------------|------------------------------|--------------------|
| | No hematoma enlargement (n=586) | Hematoma enlargement (n=75) | p-value | No hematoma enlargement (n=828) | Hematoma enlargement (n=465) | p-value |
| Age† (yrs) | 72 (63-79) | 72 (57-79) | 0.48 | 76 (71-81) | 76 (70-81) | 0.04 ^e |
| Sex* (♀) | 254 (43.3%) | 36 (48.0%) | 0.44 | 336 (40.6%) | 167 (35.9%) | 0.10 |
| Pre-mRS† ^a | 1 (0-2) | 1 (0-2) | 0.32 | 0 (0-2) | 0 (0-1) | 0.31 |
| <u>Prior medical history</u> | | | | | | |
| Hypertension* | 505 (86.2%) | 62 (82.7%) | 0.41 | 731 (88.3%) | 406 (87.3%) | 0.60 |
| Diabetes Mellitus* | 152 (25.9%) | 21 (28.0%) | 0.70 | 282 (34.1%) | 132 (28.4%) | 0.04 ^e |
| Prior ischemic stroke or TIA* | 107 (18.3%) | 10 (13.3%) | 0.29 | 234 (28.3%) | 133 (28.6%) | 0.89 |
| Prior ICH or major bleeding* | 73 (12.5%) | 4 (5.3%) | 0.07 | 66 (8.0%) | 41 (8.8%) | 0.60 |
| Congestive heart failure* | 66 (11.3%) | 10 (13.3%) | 0.60 | 165 (19.9%) | 82 (17.6%) | 0.31 |
| Renal insufficiency* | 69 (11.8%) | 11 (14.7%) | 0.47 | 205 (24.8%) | 128 (27.5%) | 0.28 |
| Antiplatelet use* | 196 (33.4%) | 25 (33.3%) | 1.00 | 82 (9.9%) | 50 (10.8%) | 0.63 |
| <u>On admission status</u> | | | | | | |
| Glasgow coma scale† ^b | 13 (11-15) | 13 (8-15) | 0.06 | 14 (12-15) | 13 (11-15) | <0.001 |
| ICH Score† ^c | 1 (0-2) | 1 (1-2) | 0.03 ^e | 1 (0-2) | 1 (0-2) | 0.03 ^e |
| Systolic blood pressure† (mmHg) | 169 (149-189) | 170 (155-197) | 0.26 | 164 (145-183) | 169 (148-191) | 0.05 ^e |
| <u>Imaging</u> | | | | | | |
| Symptom onset – first imaging† (min) | 332 (156-833) | 217 (112-502) | 0.009 ^e | 163 (88-393) | 118 (80-256) | <0.001 |
| Symptom onset – second imaging† (h) | 31 (21-50) | 25 (17-43) | 0.009 ^e | 23 (12-36) | 19 (9-31) | 0.001 |
| ICH volume† (mL) | 11.6 (4.2-27.4) | 13.5 (3.8-29.1) | 0.77 | 10.9 (4.9-24.0) | 14.2 (5.3-35.6) | <0.001 |
| Intraventricular hemorrhage* | 258 (44.0%) | 44 (58.7%) | 0.02 ^e | 317 (38.3%) | 161 (34.6%) | 0.19 |
| <u>Coagulation parameters (VKA patients)</u> | | | | | | |
| INR on admission† | N/A | N/A | N/A | 2.56 (2.13-3.20) | 2.70 (2.25-3.40) | 0.004 ^e |
| 1 st INR after reversal† ^d | N/A | N/A | N/A | 1.26 (1.16-1.46) | 1.34 (1.19-1.58) | <0.001 |

* n (%); † median (Interquartile range, 25th-75th percentile)

Abbreviations: h, hours; ICH, intracerebral hemorrhage; INR, international normalized ratio; m, minutes; N/A, not applicable; OAC, Oral anticoagulant; TIA, transient ischemic attack; VKA, vitamin K antagonists; yrs, years.

^a modified Rankin Scale, range 0-6, from no disability to death; ^b Glasgow coma scale, range 3-15, from coma to alertness. ^c ICH score, range 0-6, from low to high short-term mortality risk. ^d First value of in-hospital monitoring after reversal treatment, if appropriate. ^e Not significant after performance of Holm's sequential Bonferroni correction.

e-Table 3. Clinical characteristics of patients with deep vs lobar ICH after propensity score matching

| Characteristics | Non-OAC-ICH (n=270) | | | OAC-ICH (n=314) | | |
|--------------------------------------|---------------------|-----------------|-------------------|-----------------|-----------------|---------|
| | Deep (n=135) | Lobar (n=135) | p-value | Deep (n=157) | Lobar (n=157) | p-value |
| Age† (yrs) | 70 (60-79) | 73 (65-78) | 0.10 | 77 (70-83) | 75 (70-81) | 0.27 |
| Sex* (♀) | 62 (45.9%) | 72 (53.3%) | 0.22 | 60 (38.2%) | 58 (36.9%) | 0.82 |
| Pre-mRS† ^a | 1 (0-2) | 1 (0-2) | 0.42 | 0 (0-1) | 0 (0-1) | 0.88 |
| <u>Prior medical history</u> | | | | | | |
| Hypertension* | 121 (89.6%) | 107 (79.3%) | 0.02 ^e | 142 (90.4%) | 136 (86.6%) | 0.29 |
| Diabetes Mellitus* | 46 (34.1%) | 34 (25.2%) | 0.11 | 54 (34.4%) | 50 (31.8%) | 0.63 |
| Prior ischemic stroke or TIA* | 30 (22.2%) | 27 (20.0%) | 0.66 | 56 (35.7%) | 49 (31.2%) | 0.40 |
| Prior ICH or major bleeding* | 14 (10.4%) | 13 (9.6%) | 0.84 | 15 (9.6%) | 14 (8.9%) | 0.84 |
| Congestive heart failure* | 17 (12.6%) | 9 (6.7%) | 0.10 | 19 (12.1%) | 29 (18.5%) | 0.12 |
| Renal insufficiency* | 19 (14.1%) | 8 (5.9%) | 0.03 ^e | 39 (24.8%) | 42 (26.8%) | 0.70 |
| Antiplatelet use* | 39 (28.9%) | 50 (37.0%) | 0.15 | 22 (14.0%) | 12 (7.6%) | 0.07 |
| Vitamin K Antagonist use* | N/A | N/A | N/A | 142 (90.4%) | 141 (89.8%) | 0.84 |
| NOAC use* | | | | 15 (9.6%) | 16 (10.2%) | |
| <u>On admission status</u> | | | | | | |
| Glasgow coma scale† ^b | 13 (11-15) | 14 (11-15) | 0.56 | 14 (12-15) | 14 (12-15) | 0.83 |
| ICH Score† ^c | 1 (1-2) | 1 (0-2) | <0.001 | 1 (0-2) | 1 (0-2) | 0.35 |
| Systolic blood pressure† (mmHg) | 169 (148-190) | 170 (150-186) | 0.91 | 170 (140-187) | 164 (150-187) | 0.97 |
| <u>Imaging</u> | | | | | | |
| Symptom onset – first imaging† (min) | 280 (11-538) | 289 (155-502) | 0.94 | 139 (85-282) | 143 (87-257) | 0.86 |
| Symptom onset – second imaging† (h) | 30 (22-43) | 29 (19-41) | 0.39 | 23 (10-36) | 23 (11-33) | 0.91 |
| ICH volume† (mL) | 10.7 (3.4-24.3) | 12.8 (4.2-25.2) | 0.60 | 11.7 (4.6-22.4) | 10.9 (4.6-24.4) | 0.96 |
| Intraventricular hemorrhage* | 86 (63.7%) | 33 (24.4%) | <0.001 | 60 (38.2%) | 27 (17.2%) | <0.001 |
| <u>Reversal treatment</u> | | | | | | |
| Any reversal treatment* | N/A | N/A | N/A | 151 (96.2%) | 148 (94.3%) | 0.43 |
| Admission – reversal† (min) | | | | 95 (52-146) | 95 (60-169) | 0.45 |
| PCC* | | | | 138 (87.9%) | 135 (86.0%) | 0.62 |
| FFP* | | | | 11 (7.0%) | 11 (7.0%) | 1.00 |
| Konakion* | | | | 122 (77.7%) | 125 (79.6%) | 0.68 |
| <u>Coagulation parameters</u> | | | | | | |

| | | | | | | |
|--|------------------|------------------|--------|------------------|------------------|------|
| INR on admission [‡] | 1.01 (0.97-1.09) | 1.03 (0.97-1.07) | 0.74 | 2.53 (2.10-3.19) | 2.50 (2.01-3.32) | 0.96 |
| 1 st INR after reversal [‡] ^d | N/A | N/A | N/A | 1.28 (1.17-1.42) | 1.30 (1.16-1.50) | 0.44 |
| <u>Length of stay (d)</u> [‡] | 14 (8-20) | 9 (7-14) | <0.001 | 11 (6-17) | 10 (7-16) | 0.88 |

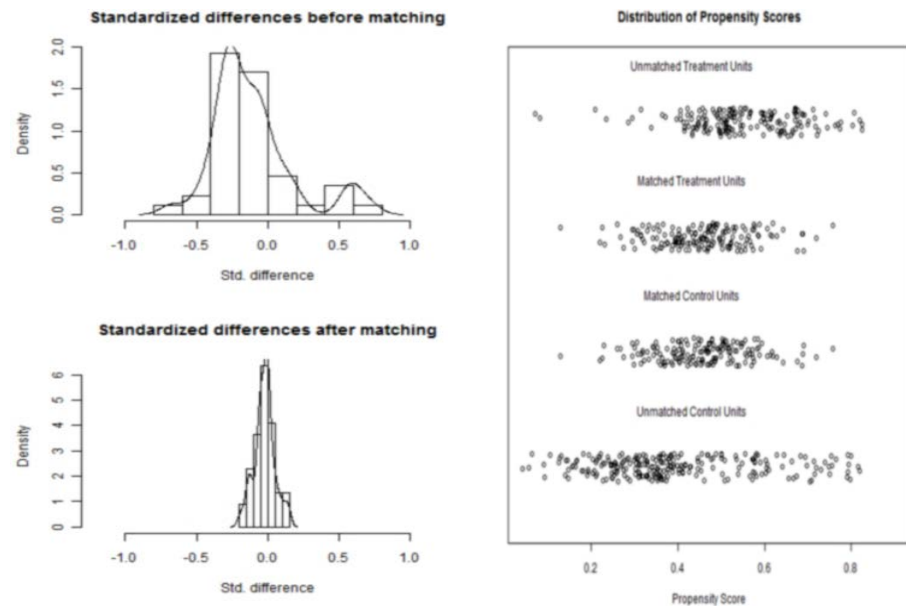
* n (%); † median (Interquartile range, 25th-75th percentile)

Abbreviations: FFP, Fresh frozen plasma; h, hours; ICH, intracerebral hemorrhage; INR, international normalized ratio; m, minutes; N/A, not applicable; NOAC, Non-vitamin K antagonist oral anticoagulants; OAC, Oral anticoagulant; PCC, prothrombin complex concentrate; TIA, transient ischemic attack; yrs, years.

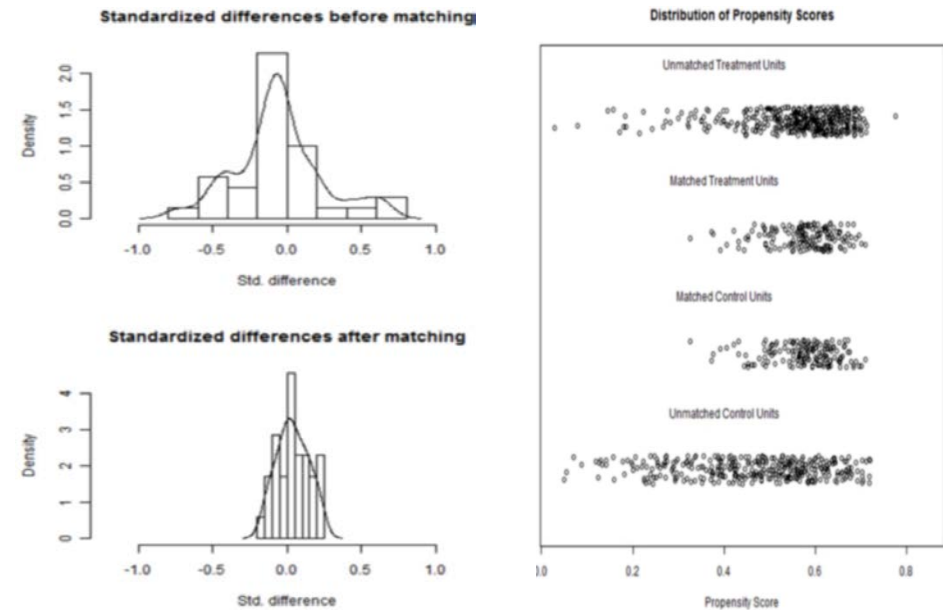
^a modified Rankin Scale, range 0-6, from no disability to death; ^b Glasgow coma scale, range 3-15, from coma to alertness. ^c ICH score, range 0-6, from low to high short-term mortality risk. ^d First value of in-hospital monitoring after reversal treatment, if appropriate. ^e Not significant after performance of Holm's sequential Bonferroni correction.

e-Figure 1. Standardized mean differences and propensity scores before and after matching procedure

Non-OAC-ICH



OAC-ICH



Standardized mean differences of parameters used for calculating of propensity scores as well as distribution of propensity scores before and after the matching procedure. Abbreviations: ICH, intracerebral hemorrhage; OAC, Oral anticoagulant.

eTable 4. Sensitivity analyses of patients excluded and included into propensity-matched analyses

| Characteristics | Comparison of deep ICH patients | | | Comparison of lobar ICH patients | | |
|---------------------------------------|---------------------------------|------------------|--------------------|----------------------------------|------------------|-------------------|
| | Excluded (n=814) | Included (n=292) | p-value | Excluded (n=556) | Included (n=292) | p-value |
| Age† (yrs) | 74 (67-80) | 73 (66-80) | 0.38 | 76 (70-81) | 76 (68-81) | 0.31 |
| Sex* (♀) | 299 (36.7%) | 122 (41.8%) | 0.13 | 242 (43.5%) | 130 (44.5%) | 0.780 |
| Pre-mRS† ^a | 0 (0-1) | 0 (0-1) | 0.65 | 0 (0-2) | 0 (0-2) | 0.58 |
| <u>Prior medical history</u> | | | | | | |
| Hypertension* | 721 (88.6%) | 263 (90.1%) | 0.48 | 477 (85.8%) | 243 (83.2%) | 0.32 |
| Diabetes Mellitus* | 241 (29.6%) | 100 (34.2%) | 0.14 | 162 (29.1%) | 84 (28.8%) | 0.92 |
| Prior ischemic stroke or TIA* | 206 (25.3%) | 86 (29.5%) | 0.17 | 116 (20.9%) | 76 (26.0%) | 0.09 |
| Prior ICH or major bleeding* | 53 (6.5%) | 29 (9.9%) | 0.06 | 75 (13.5%) | 27 (9.2%) | 0.07 |
| Congestive heart failure* | 150 (18.4%) | 36 (12.3%) | 0.02 ^e | 99 (17.8%) | 38 (13.0%) | 0.07 |
| Renal insufficiency* | 183 (22.5%) | 58 (19.9%) | 0.35 | 122 (21.9%) | 50 (17.1%) | 0.10 |
| Antiplatelet use* | 118 (14.5%) | 61 (20.9%) | 0.01 ^e | 112 (20.1%) | 62 (21.2%) | 0.71 |
| Vitamin K Antagonist use* | 539 (66.2%) | 142 (48.6%) | <0.001 | 364 (65.5%) | 141 (48.3%) | <0.001 |
| NOAC use* | 54 (6.6%) | 15 (5.1%) | 0.37 | 22 (4.0%) | 16 (5.5%) | 0.31 |
| <u>On admission status</u> | | | | | | |
| Glasgow coma scale† ^b | 13 (10-15) | 14 (11-15) | 0.007 ^e | 14 (12-15) | 14 (12-15) | 0.44 |
| ICH Score† ^c | 1 (0-2) | 1 (0-2) | 0.76 | 1 (0-2) | 1 (0-2) | <0.001 |
| Systolic blood pressure† (mmHg) | 170 (150-192) | 170 (146-190) | 0.26 | 160 (142-180) | 169 (150-186) | 0.001 |
| <u>Imaging</u> | | | | | | |
| Symptom onset – first imaging† (min) | 140 (81-342) | 189 (93-395) | 0.007 ^e | 445 (177-1365) | 204 (106-359) | <0.001 |
| Symptom onset – second imaging† (h) | 22 (12-35) | 26 (17-38) | 0.002 ^e | 34 (20-64) | 26 (15-39) | <0.001 |
| ICH volume† (mL) | 8.9 (3.9-17.1) | 11.4 (4.2-23.1) | 0.006 ^e | 24.0 (10.2-46.2) | 11.3 (4.4-24.4) | <0.001 |
| Intraventricular hemorrhage* | 394 (48.4%) | 146 (50.0%) | 0.64 | 180 (32.4%) | 60 (20.5%) | <0.001 |
| <u>Reversal treatment^f</u> | | | | | | |
| Any reversal treatment* | 574/593 (96.8%) | 151/157 (96.2%) | 0.70 | 365/386 (94.6%) | 148/157 (94.3%) | 0.890 |
| Admission – reversal† (min) | 95 (60-170) | 95 (52-146) | 0.37 | 116 (68-217) | 95 (60-169) | 0.04 ^e |
| PCC* | 518/593 (87.4%) | 138/157 (87.9%) | 0.86 | 310/386 (80.3%) | 135/157 (86.0%) | 0.12 |
| FFP* | 21/593 (3.5%) | 11/157 (7.0%) | 0.06 | 30/386 (7.8%) | 11/157 (7.0%) | 0.76 |
| Konakion* | 479/539 (88.9%) | 122/142 (85.9%) | 0.33 | 304/364 (83.5%) | 125/141 (88.7%) | 0.15 |

| Coagulation parameters ^f | | | | | | |
|---|------------------|------------------|------|------------------|------------------|------|
| INR on admission [‡] | 2.50 (2.05-3.06) | 2.53 (2.10-3.19) | 0.49 | 2.66 (2.10-3.44) | 2.50 (2.01-3.32) | 0.25 |
| 1 st INR after reversal ^{‡ d} | 1.25 (1.14-1.43) | 1.28 (1.17-1.42) | 0.40 | 1.30 (1.18-1.57) | 1.30 (1.16-1.50) | 0.39 |
| Length of stay (d) [‡] | 13 (8-19) | 12 (7-19) | 0.22 | 11 (7-16) | 10 (7-14) | 0.40 |

* n (%); † median (Interquartile range, 25th-75th percentile)

Abbreviations: BP, blood pressure; d, days; FFP, Fresh frozen plasma; h, hours; ICH, intracerebral hemorrhage; INR, international normalized ratio; m, minutes; N/A, not applicable; PCC, prothrombin complex concentrate; TIA, transient ischemic attack; yrs, years.

^a modified Rankin Scale, range 0-6, from no disability to death; ^b Glasgow coma scale, range 3-15, from coma to alertness. ^c ICH score, range 0-6, from low to high short-term mortality risk. ^d First value of in-hospital monitoring after reversal treatment, if appropriate. ^e Not significant after performance of Holm's sequential Bonferroni correction. ^f Reversal treatment and coagulation parameters are shown for patients using oral anticoagulation only.

eTable 5. Interaction of excluded patients with hematoma enlargement according to ICH location

| Hematoma enlargement | Non-adjusted | | p-value | Adjusted Adjusted odds ratio (95% CI) | p-value |
|---|--------------|-------------|---------|--|---------|
| | Present | Absent | | | |
| Deep ICH patients | | | | | |
| Excluded | 237 (29.1%) | 577 (70.9%) | 0.15 | 0.804 (0.568-1.138) | 0.22 |
| Included | 72 (24.7%) | 220 (75.3%) | | | |
| Lobar ICH patients | | | | | |
| Excluded | 153 (27.5%) | 403 (72.5%) | 0.81 | 1.111 (0.711-1.736) | 0.64 |
| Included | 78 (26.7%) | 214 (73.3%) | | | |
| Interaction of deep*excluded-patients on hematoma enlargement | | | | 0.831 (0.608-1.137) | 0.25 |

Analyses of occurrence of hematoma enlargement (primary outcome) regarding the interaction of ICH location with inclusion of patients into propensity-matched analyses. Displayed are unadjusted frequency distributions, adjusted odds ratios, and p-values for the interaction of ICH location with excluded patients (deep*excluded). Multivariate models were adjusted for ICH volume, time from symptom onset until first and until second imaging, age, Glasgow Coma Scale, and prior anticoagulation status to calculate adjusted odds ratios.

e-Table 6. Location-specific association of time from initial to control imaging with hematoma enlargement

| Multivariate - parameters | Adjusted OR (95% CI) – Hematoma enlargement | p-value |
|--|---|---------|
| Deep ICH | | |
| Time 1 st – 2 nd imaging [hours] | 0.999 (0.995-1.002) | 0.46 |
| Lobar ICH | | |
| Time 1 st – 2 nd imaging [hours] | 0.998 (0.993-1.003) | 0.37 |

Multivariable modeling was adjusted for relevant baseline characteristics, i.e. age, oral anticoagulants, antiplatelets, Glasgow com scale, ICH volume and intraventricular hemorrhage.

Abbreviations: CI, Confidence interval; ICH, Intracerebral hematoma; OR, Odds Ratio.

e-Table 7. Association of hematoma enlargement with mortality in relation to initial intracerebral hematoma volume

| Hematoma enlargement in deep ICH according to quartiles of ICH volume | Adjusted OR (95% CI) – Mortality | p-value |
|--|----------------------------------|---------|
| Overall | 4.62 (3.07-6.95) | <0.001 |
| 1 st quarter (≤ 4.9 mL) | 9.15 (3.61-23.19) | <0.001 |
| 2 nd quarter (>4.9 mL, ≤ 12.1 mL) | 3.42 (1.56-7.51) | <0.01 |
| 3 rd quarter (>12.1 mL, ≤ 34.9 mL) | 3.63 (1.76-7.49) | <0.001 |
| 4 th quarter (>34.9 mL) | 7.76 (1.91-31.58) | <0.01 |
| Hematoma enlargement in lobar ICH according to quartiles of ICH volume | | |
| Overall | 2.41 (1.45-4.00) | <0.001 |
| 1 st quarter (≤ 7.0 mL) | 4.32 (0.87-21.57) | 0.07 |
| 2 nd quarter (>7.0 mL, ≤ 19.5 mL) | 1.99 (0.61-6.52) | 0.25 |
| 3 rd quarter (>19.5 mL, ≤ 38.7 mL) | 1.88 (0.73-4.83) | 0.19 |
| 4 th quarter (>38.7 mL) | 2.83 (1.16-6.88) | 0.02 |

Influence of hematoma enlargement (defined as hematoma volume increase of 33% or 6mL) on functional mortality with respect to initial ICH volume split according to quartiles. Adjusted OR were calculated by multivariable modeling adjusted for relevant outcome predictors, i.e. age, Glasgow Coma Scale, oral anticoagulation, initial ICH volume, and intraventricular hemorrhage.

Abbreviations: CI, Confidence interval; ICH, Intracerebral hematoma; OR, Odds Ratio.