

# Serum Creatinine May Indicate Risk of Symptomatic Intracranial Hemorrhage After Intravenous Tissue Plasminogen Activator (IV tPA)

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**Abstract:** Symptomatic intracranial hemorrhage (sICH) is a known complication following administration of intravenous tissue plasminogen activator (IV tPA) for acute ischemic stroke. sICH results in high rates of death or long-term disability. Our ability to predict its occurrence is important in clinical decision making and when counseling families. The initial National Institute of Neurological Disorders and Stroke (NINDS) investigators developed a list of relative contraindications to IV tPA meant to decrease the risk of subsequent sICH. To date, the impact of renal impairment has not been well studied. In the current study we evaluate the potential association between renal impairment and post-tPA intracranial hemorrhage (ICH).

Admission serum creatinine and estimated glomerular filtration rate (eGFR) were recorded in 224 patients presenting within 4.5 hours from symptom onset and treated with IV tPA based on NINDS criteria. Neuroimaging was obtained 1 day post-tPA and for any change in neurologic status to evaluate for ICH. Images were retrospectively evaluated for hemorrhage by a board-certified neuroradiologist and 2 reviewers blinded to the patient's neurologic status. Medical records were reviewed retrospectively for evidence of neurologic decline indicating a "symptomatic" hemorrhage. sICH was defined as subjective clinical deterioration (documented by the primary neurology team) and hemorrhage on neuroimaging that was felt to be the most likely cause. Renal impairment was evaluated using both serum creatinine and eGFR in a number of ways: 1) continuous creatinine; 2) any renal impairment by creatinine (serum creatinine >1.0 mg/dL); 3) continuous eGFR; and 4) any renal impairment by eGFR (eGFR <60 mL/min per 1.73 m<sup>2</sup>). Student paired t tests, Fisher exact tests, and multivariable logistic regression (adjusted for demographics and vascular risk factors) were used to evaluate the relationship between renal impairment and ICH.

Fifty-seven (25%) of the 224 patients had some evidence of hemorrhage on neuroimaging. The majority of patients were asymptomatic. Renal impairment (defined by serum creatinine >1.0 mg/dL) was not associated with combined symptomatic and asymptomatic intracranial bleeding ( $p = 0.359$ ); however, there was an adjusted 5.5-fold increased odds of sICH when creatinine was >1.0 mg/dL (95% confidence interval, 1.08–28.39), and the frequency of sICH for patients with elevated serum creatinine was 10.6% (12/113), versus 1.8% (2/111) in those with normal renal function ( $p = 0.010$ ).

Our study suggests that renal impairment is associated with higher risk of sICH after administration of IV tPA. As IV tPA is an important and effective treatment for acute ischemic stroke, a multicenter study

is needed to determine whether the observation that renal dysfunction is associated with sICH from this retrospective study holds true in a larger prospective trial.

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**Abbreviations:** CI = confidence interval, CT = computerized tomography, ECASS = European Cooperative Acute Stroke Study, eGFR = estimated glomerular filtration rate, H1I = hemorrhagic infarct type 1, H2I = hemorrhagic infarct type 2, ICH = intracranial hemorrhage, INR = international normalized ratio, IV = intravenous, LDL = low-density lipoprotein, MDRD = Modification of Diet in Renal Disease, MRI = magnetic resonance imaging, NIHSS = NIH stroke scale, NINDS = National Institute of Neurological Disorders and Stroke, OR = odds ratio, PH1 = parenchymal hematoma type 1, PH2 = parenchymal hematoma type 2, sICH = symptomatic intracranial hemorrhage, tPA = tissue plasminogen activator.

## INTRODUCTION

Intravenous tissue plasminogen activator (IV tPA) improves long-term outcomes in patients with acute ischemic stroke.<sup>19</sup> However, given its thrombolytic properties, IV tPA is associated with a 6% risk of symptomatic intracranial hemorrhage (sICH).<sup>19</sup> Patients who hemorrhage have a mortality rate of up to 50%.<sup>20</sup> Studies have evaluated factors such as: blood pressure control, infarct volume, blood glucose, and the use of antiplatelet agents or anticoagulants that may increase risk of sICH following administration of IV tPA,<sup>7–9,16,23</sup> however, only a few small case series have examined the effect of renal impairment.<sup>2,13,18</sup>

There is increasing evidence to suggest that renal impairment results in a higher risk of intracranial hemorrhage in general.<sup>4,21</sup> "Uremic platelets" have been hypothesized to be the cause of increased systemic (epistaxis, gastrointestinal, urologic) bleeding in patients with end-stage renal disease.<sup>5</sup> Less is known about the effect of milder renal impairment on hemorrhage risk. We recently evaluated patients presenting with ischemic stroke and an indication for anticoagulation, and found that those with even mild renal impairment (GFR 30–59 mL/min) were 1.5 times more likely to have hemorrhagic conversion of their infarct compared to those with normal renal function.<sup>14</sup>

In this retrospective analysis, we evaluate the association between renal impairment and ICH in patients after administration of IV tPA. Identification of renal impairment as 1 of the predictors of ICH after tPA may help to stratify patients into "high" and "low risk" categories to better inform clinical decision making.

## METHODS

### Study Population

Our study used a retrospective cohort design. We reviewed the charts and neuroimaging of all patients presenting to our

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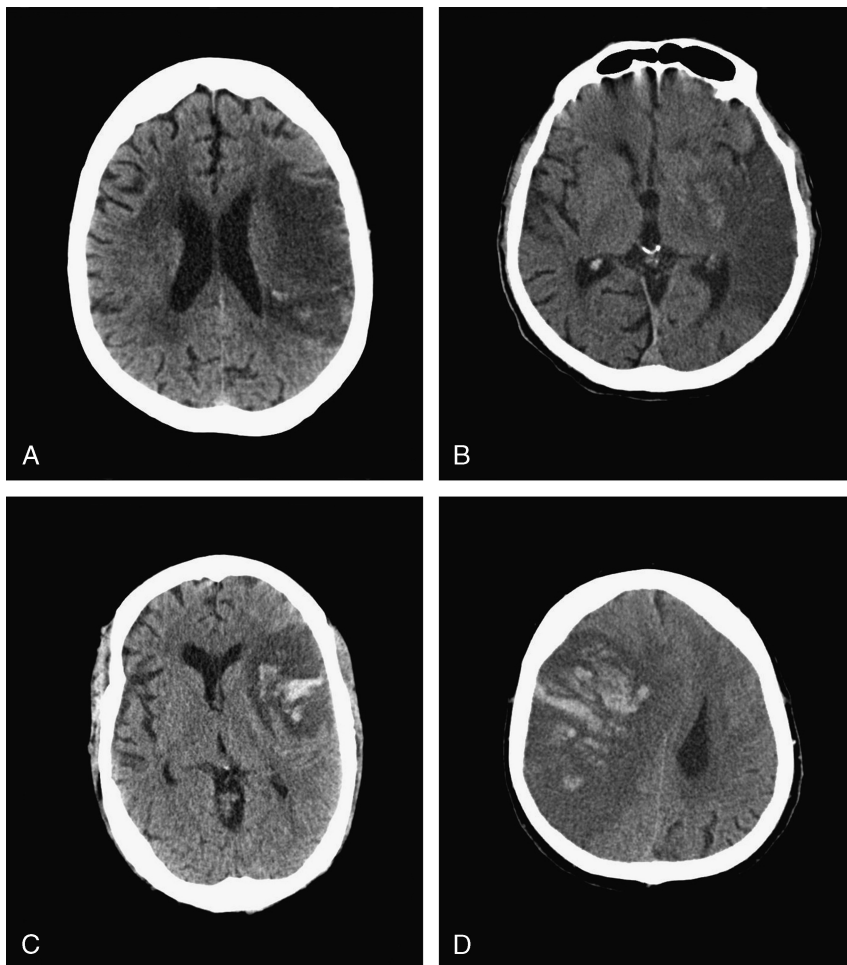
institution within 3 hours of symptom onset who were treated with tPA based on National Institute of Neurological Disorders and Stroke (NINDS) criteria<sup>19</sup> between January 2004 and October 2011. After the results of the European Cooperative Acute Stroke Study (ECASS) III were released,<sup>10</sup> patients presenting up to 4.5 hours were also included. Patients who received endovascular intervention were excluded. This study was approved by the Johns Hopkins Institutional Review Board.

Information regarding each patient's age, race, sex, National Institutes of Health Stroke Scale (NIHSS) prior to administration of tPA, comorbidities (reported history of hypertension, hyperlipidemia, diabetes, atrial fibrillation), and distribution of their stroke (anterior versus posterior fossa) was obtained from the electronic medical record. If, following tPA, no stroke was seen on imaging, the most likely location of ischemia was determined given the patient's presenting constellation of symptoms. A baseline blood glucose and creatinine were drawn in the Emergency Department prior to tPA administration, and a low-density lipoprotein (LDL) was obtained during admission. Estimated glomerular filtration rate (eGFR) was calculated for each patient using the Modification of Diet in Renal Disease (MDRD) equation<sup>12</sup> based on age, race, sex, and serum creatinine. All data were de-identified to ensure adequate blinding during analysis.

## Classifying Hemorrhage

### Imaging

The majority of patients had a repeat noncontrast head computerized tomography (CT) scan the day after administration of tPA to evaluate for ICH, as part of standard clinical care. Eleven had magnetic resonance imaging (MRI) of the brain with gradient echo sequencing instead. Patients underwent additional neuroimaging for any subsequent change in neurologic status. Imaging was reviewed clinically by a board-certified neuroradiology attending. If the report was positive for ICH, imaging was further reviewed by 1 of the investigators (EBM), and degree of hemorrhage was scored based on ECASS criteria<sup>11</sup> (Figure 1). A subset of images (symptomatic hemorrhages,  $n = 14$ ) was reviewed by a second investigator (RHL), and a kappa statistic was calculated to assess inter-rater agreement of hemorrhage grading. Images were reviewed independent of the clinical record to ensure that reviewers remained blinded to the neurologic condition of the patient. Hemorrhagic transformation type 1 (HI1) was defined as petechiae along the margins of the infarct. HI2 was defined as confluent petechiae within the infarcted area, without mass effect. Parenchymal hematoma type 1 (PH1) was defined as hematoma with some



**FIGURE 1.** Sample CT scans of intracranial hemorrhages. A, hemorrhagic transformation type 1 (HI1): petechiae around the area of infarction. B, hemorrhagic transformation type 2 (HI2): petechiae confluent within the area of infarction. C, parenchymal hematoma type 1 (PH1): space-occupying hematoma <30% of the infarcted area. D, parenchymal hematoma type 2 (PH2): space-occupying hematoma >30% of the infarcted area with significant mass effect.

degree of space-occupying effect and involving  $\leq 30\%$  of the infarcted area. PH2 was defined as hematoma with significant mass effect encompassing  $>30\%$  of the infarction. For asymptomatic hemorrhages, questionable images were discussed between raters and consensus was obtained ( $n = 3$ ). Hemorrhages occurring at any point during a patient's hospitalization (after receiving tPA) were recorded in the data set. Two patients underwent hemicraniectomy. Their head CTs were analyzed for hemorrhage only prior to surgery to avoid including bleeding related to the procedure.

### Symptomatic versus Asymptomatic Hemorrhage

In concordance with NINDS criteria, a patient was determined to have a symptomatic hemorrhage if he or she had subjective clinical deterioration (documented by the primary neurology team) and hemorrhage on neuroimaging that was felt to be the most likely cause.<sup>19</sup> Several patients developed significant edema as a result of large infarcts and had associated petechial hemorrhage. These were classified as asymptomatic, as symptoms were felt to be secondary to the cerebral edema rather than the hemorrhage itself.

### Statistical Analysis

Data were analyzed using STATA version 11.1 for Macintosh (College Station, TX). The primary outcome of interest was hemorrhage. We performed separate analyses evaluating ICH overall (either symptomatic or asymptomatic), and sICH alone. We also evaluated hemorrhage type, combining HI1 and HI2 as hemorrhagic transformation versus parenchymal hematoma (PH1 and PH2). The primary predictor of interest was renal impairment, which we evaluated using serum creatinine and eGFR in a number of ways: 1) continuous creatinine; 2) any renal impairment by creatinine (serum creatinine  $>1.0$  mg/dL); 3) continuous eGFR; and 4) any renal impairment by eGFR (eGFR  $<60$  mL/min per  $1.73$  m<sup>2</sup>). A creatinine cutoff of  $1.0$  mg/dL was felt to be most clinically relevant after preliminary results showed that roughly half of the population presented with values of  $>1.0$  mg/dL.

We used Fisher exact tests to explore univariate associations between categorical variables and hemorrhage, and Student paired *t* tests to evaluate the relationship between continuous variables and hemorrhage. A *p* value of  $<0.05$  was considered statistically significant. Multivariable logistic regression was then used to evaluate the relationship between renal impairment (defined above) and ICH. Three separate models were included for each exposure variable: Model 1, a basic demographic-adjusted model including age, race, and sex; Model 2, a risk factor-adjusted model (including demographics and hypertension, hyperlipidemia, diabetes, and atrial fibrillation); and Model 3, a model also including other factors felt to be important in predicting hemorrhage (Model 2 plus LDL, NIHSS, and admission blood glucose). Data regarding NIHSS were missing in some patients so the sample size included in Model 3 was lower ( $n = 197$ ). We kept variables in the models that we felt were clinically significant and potentially associated with risk of post-tPA hemorrhage, even if they were not statistically significant individually. We also explored interactions between renal impairment and NIHSS, age, diabetes, and blood glucose in predicting hemorrhage. Finally, we performed secondary analyses looking at in-hospital mortality among individuals who were administered tPA and had renal impairment.

## RESULTS

Between January 2004 and October 2011, 227 patients received IV tPA. Three went on to intraarterial therapy. The 224

remaining patients were included in analysis. Their average age was 66.8 years (range, 23–95 yr); 51% were female; and 32% were African American. The median NIHSS was 11 (SD  $\pm 6$ ) and the majority of the strokes ( $n = 208$ , 93%) were in the anterior fossa. Further demographic information is summarized in Table 1.

### Hemorrhage Risk

Fifty-seven (25.4%) of the patients had evidence of intracranial hemorrhage on neuroimaging. Sample post-tPA head CTs are shown in Figure 1. Inter-rater reliability for classification of hemorrhages was high ( $\kappa = 0.76$ ). The median time from administration of tPA to diagnosis of hemorrhage on imaging was 1 day (range, 0–13 d). Only 7 of the hemorrhages occurred after the first 3 days (1 symptomatic). A total of 14/57 hemorrhages (25%) were symptomatic (6.3% of the entire population). The characteristics of these patients including ECASS classification, renal function, baseline blood sugar, LDL, and location of the stroke compared to the rest of the population, are summarized in Table 1. The groups were similar; however, patients with sICH were more likely to be older, African American, and male, with atrial fibrillation. These factors were not significant when entered into our regression model. Not surprisingly, the patients with sICH also had longer inpatient admissions and higher mortality rates, and were more likely to be classified as having parenchymal hematomas by ECASS criteria.

### Symptomatic Hemorrhages

#### Effect of Renal Impairment Using Serum Creatinine

Approximately half (113 patients) of the patients in our population had a creatinine level of  $>1.0$  mg/dL, with a median value of  $1.1$  mg/dL (range,  $0.1$ – $14.1$  mg/dL). Only 1 patient was dialysis dependent (he did not develop ICH). There was no association between renal impairment and the presence versus absence of any (combined symptomatic and asymptomatic) ICH ( $p = 0.359$ ). However, within the group that bled, 12 (86%) of the patients with symptomatic hemorrhages had renal impairment (creatinine  $>1.0$  mg/dL), and for the entire population there was an unadjusted 6.5-fold increased risk of sICH when creatinine was  $>1.0$  mg/dL (95% confidence interval [CI],  $1.41$ – $29.64$  mg/dL). When serum creatinine was  $>1.0$  mg/dL, the frequency of sICH for patients was 10.6% (12/113), compared to 1.8% (2/111) in those without ( $p = 0.010$ ) (Table 2, Figure 2). This association remained statistically significant when controlling for age, race, sex, and comorbidities (odds ratio [OR], 5.5; 95% CI,  $1.08$ – $28.39$ ), but dropped below statistical significance when NIHSS, LDL, and blood sugar were added into the model (OR, 10.4; 95% CI,  $0.95$ – $112.88$ ) (Table 3).

We subsequently looked at possible interactions between these variables and renal impairment. There was no interaction between renal function and NIHSS, age, or diabetes in the prediction of sICH. It is noteworthy, however, that none of the patients with a low admission blood glucose (below the median value of  $122$  mg/dL) and normal creatinine had sICH. When either blood glucose or creatinine was elevated there was intermediate bleeding risk. The frequency increased dramatically to 14.5% when both glucose and creatinine were elevated.

#### Effect of Renal Impairment Using eGFR

Like increased creatinine, reduced eGFR also appeared to predict sICH, although results were not statistically significant. Patients with an eGFR  $<60$  mL/min per  $1.73$  m<sup>2</sup> were 2.5 times more likely to hemorrhage (95% CI,  $0.82$ – $7.33$ ), and those with an eGFR  $<30$  mL/min per  $1.73$  m<sup>2</sup> were 2.8 times more likely (95% CI,  $0.55$ – $13.71$ ) compared to those with normal eGFR.

**TABLE 1.** Characteristics of Patients With Symptomatic Hemorrhages Compared to the Rest of the Population

| Characteristic                       | Symptomatic Hemorrhages (n=14) | Rest of Population* (n = 210) | P      |
|--------------------------------------|--------------------------------|-------------------------------|--------|
| Age, yr, mean (range)                | 69.3 (47–86)                   | 66.6 (23–95)                  | 0.56   |
| Race, African American, n (%)        | 7 (50%)                        | 65 (31%)                      | 0.15   |
| Sex, female, n (%)                   | 5 (36%)                        | 109 (52%)                     | 0.28   |
| <b>Characteristics of Severity</b>   |                                |                               |        |
| Length of stay, d, mean (range)      | 12 (1–31)                      | 8 (1–29)                      | 0.21   |
| NIHSS, median (SD)                   | 12.5 (4)                       | 11 (6)                        | 0.19   |
| Distribution, anterior fossa, n (%)  | 13 (93%)                       | 195 (93%)                     | 1.00   |
| Time to ICH, d, median (SD)          | 1 (3)                          | 1 (3)                         | 1.00   |
| Hemorrhage classification, PH, n (%) | 14 (100%)                      | 7 (16%)                       | <0.001 |
| Mortality, n (%)                     | 9 (64%)                        | 17 (8%)                       | <0.001 |
| <b>Laboratory Values</b>             |                                |                               |        |
| Creatinine (mg/dL), mean (SD)        | 1.4 (0.7)                      | 1.2 (1.0)                     | 0.41   |
| n >1.0 (%)                           | 12 (86%)                       | 101 (48%)                     | 0.01   |
| eGFR (mL/min), mean (SD)             | 61 (26)                        | 71 (27)                       | 0.15   |
| <30 n (%)                            | 2 (14%)                        | 12 (6%)                       | }0.14  |
| 30–59 n (%)                          | 6 (43%)                        | 62 (29%)                      |        |
| ≥60 n (%)                            | 6 (43%)                        | 136 (65%)                     |        |
| LDL (mg/dL), mean (SD)               | 99 (39)                        | 98 (37)                       | 0.98   |
| Glucose (mg/dL), mean (SD)           | 159 (63)                       | 137 (57)                      | 0.18   |
| <125 n (%)                           | 3 (21%)                        | 117 (56%)                     | }0.02  |
| 126–199 n (%)                        | 10 (72%)                       | 74 (35%)                      |        |
| ≥200 n (%)                           | 1 (7%)                         | 19 (9%)                       |        |
| <b>Comorbidities</b>                 |                                |                               |        |
| Hypertension, n (%)                  | 12 (86%)                       | 161 (77%)                     | 0.74   |
| Hyperlipidemia, n (%)                | 6 (43%)                        | 104 (50%)                     | 0.78   |
| Diabetes, n (%)                      | 4 (29%)                        | 54 (26%)                      | 0.76   |
| Atrial fibrillation, n (%)           | 6 (43%)                        | 71 (34%)                      | 0.56   |

\*Includes patients with asymptomatic hemorrhages.

When both eGFR and creatinine were evaluated as continuous linear variables, patients with sICH were more likely to have higher degrees of renal impairment. The mean creatinine was 1.4 mg/dL in patients with symptomatic hemorrhage versus 1.2 mg/dL in those without ( $p = 0.41$ ). The mean eGFR was 61 mL/min per 1.73 m<sup>2</sup> in patients with symptomatic hemorrhage versus 71 mL/min per 1.73 m<sup>2</sup> in those without ( $p = 0.15$ ).

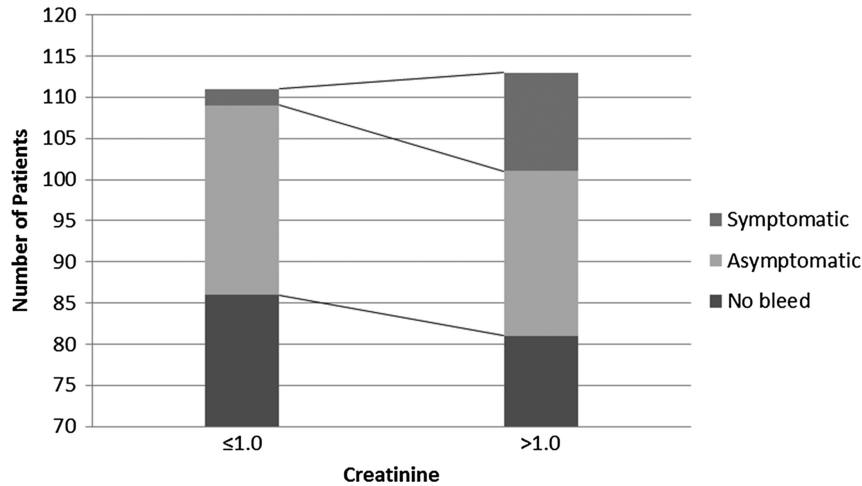
### Hemorrhage Severity (ECASS Classification)

Renal impairment (defined by creatinine >1.0 mg/dL) also predicted the severity of ICH. Seventeen of the 21 (81%)

patients with parenchymal hemorrhages (PH1 and PH2) had renal impairment. Additionally, over half (53%) of patients with elevated serum creatinine who bled had parenchymal hemorrhages, versus only 16% of those with normal renal function ( $p = 0.006$ ). When we re-defined sICH by severity (combining PH1 and PH2 into 1 category—parenchymal hematomas), results were similar to our primary analysis. For individuals with creatinine >1.0 mg/dL, the odds of symptomatic hemorrhage following administration of IV tPA were 4.7 times greater (95% CI, 1.54–14.57) than for individuals with creatinine ≤1.0 mg/dL. Results remained statistically significant in models adjusted for age, race, sex, and comorbidities (OR, 4.9;

**TABLE 2.** Rates of Intracranial Hemorrhage Based on Creatinine: Patients With Renal Impairment Had Higher Rates of Symptomatic Intracranial Hemorrhage and Higher Mortality Than Patients With Normal Renal Function

| Hemorrhage          | Creatinine >1.0 mg/dL<br>(n = 113) | Creatinine ≤1.0 mg/dL<br>(n = 111) | Total (n = 224) | P             |
|---------------------|------------------------------------|------------------------------------|-----------------|---------------|
| Symptomatic, n (%)  | 12 (10.6%)                         | 2 (1.8%)                           | 14 (6.3%)       | <b>0.010*</b> |
| Died, n (%)         | 7 (6.2%)                           | 2 (1.8%)                           | 9 (4.0%)        |               |
| Asymptomatic, n (%) | 20 (17.7%)                         | 23 (20.7%)                         | 43 (19.2%)      | 0.613         |
| Died, n (%)         | 4 (3.5%)                           | 1 (0.9%)                           | 5 (2.2%)        |               |
| All Bleeds, n (%)   | 32 (28.3%)                         | 25 (22.5%)                         | 57 (25.4%)      | 0.359         |
| Died, n (%)         | 11 (9.7%)                          | 3 (2.7%)                           | 14 (6.3%)       |               |



**FIGURE 2.** Frequency of intracranial hemorrhage based on creatinine. Patients with a creatinine level <1.0 mg/dL had a 10.6% risk of symptomatic intracranial hemorrhage after IV tPA compared with a 1.8% risk seen in those with normal renal function.

95% CI, 1.44–16.53); and also when NIHSS, LDL, and blood glucose were added (OR, 5.5; 95% CI, 1.28–23.43).

**Mortality**

Renal impairment (defined by elevated serum creatinine) initially appeared to be a predictor of mortality (adjusted OR, 6.4; 95% CI, 1.32–30.96) (see Table 2). This effect disappeared after controlling for symptomatic hemorrhage. Those with symptomatic hemorrhage were over 20 times more likely to die (adjusted OR, 26.9; 95% CI, 6.40–112.89) than were patients without symptomatic hemorrhage.

**DISCUSSION**

The current study suggests that patients with even mild degrees of renal impairment may have an increased risk of developing sICH following administration of IV tPA compared to patients with normal renal function (10.6% vs. 1.8%). The increased risk of symptomatic hemorrhage appears to be independent of age, race, sex, or comorbidities (including diabetes). Results were somewhat attenuated when NIHSS (which can serve as a rough surrogate marker for size/severity<sup>15</sup>), baseline blood glucose, and LDL were added to the model. This is noteworthy, as all 3 have been proposed to increase the likelihood of ICH.<sup>6,7,23,25</sup> The lack of statistical significance is at least partially a result of our smaller sample size (n = 197 vs. 224 secondary to missing NIHSS data in our data set). It may also indicate that some of the potential effect of renal impairment on symptomatic hemorrhage is due to larger strokes occurring more frequently in individuals with renal impairment. When analyzed separately, only elevated blood glucose (>122 mg/dL) was associated with increased risk of symptomatic hemorrhage beyond renal impairment. Hyperglycemia may serve as a marker for diabetes, or a prediabetic state, which has been shown to be associated with a higher risk of symptomatic hemorrhage and poor outcome.<sup>7,22</sup> History of diabetes did not appear to play a significant role, however this may be in part because we defined diabetes by history alone rather than hemoglobin A1c value, which is a better marker of true impaired glucose tolerance.

In our study, renal impairment was not associated with an increased risk of asymptomatic hemorrhage. The majority of the asymptomatic hemorrhages were petechial and occurred in patients with large strokes who went on to develop

significant edema and uncal herniation. In contrast, patients with renal impairment were more likely to develop spontaneous, space-occupying hematomas after tPA, leading to a change in clinical status. At 6.3%, our overall frequency of symptomatic hemorrhage (combining patients with normal and impaired renal function) was consistent with previously published data.<sup>19,20</sup>

Along with creatinine, we evaluated eGFR as a marker of renal impairment. As the serum creatinine level increases, glomerular filtration rate typically falls. However, eGFR is also dependent on factors such as age, sex, and race. In our study, as expected, the likelihood of symptomatic hemorrhage doubled when eGFR was <60 mL/min per 1.73 m<sup>2</sup>, and was even higher when eGFR was <30 mL/min per 1.73 m<sup>2</sup>. Results did not reach statistical significance, but are similar to several small, previously published reports. For example, Lyrer et al<sup>13</sup> found that patients with an eGFR <90 mL/min per 1.73 m<sup>2</sup> had an 8% risk of sICH compared to 2% in those with an eGFR ≥90 mL/min per 1.73 m<sup>2</sup> (p = 0.096). The lack of statistical significance in both cases may be due to the relatively small sample size (only 14 and 12 sICH), rather than other confounding factors. We evaluated this further by controlling for age, race, and sex. Creatinine remained a significant predictor of sICH.

The current study is one of the few that addresses the role of renal impairment in predicting sICH after thrombolytic therapy. Agrawal et al<sup>2</sup> retrospectively evaluated patients with chronic kidney disease who were administered IV thrombolysis

**TABLE 3.** Statistical Models of Creatinine as a Predictor of Symptomatic Intracranial Hemorrhage: Odds Ratios for the Impact of Any Renal Impairment (Creatinine >1.0 mg/dL) on Symptomatic Hemorrhage

| Statistical Model                                                                                           | Odds Ratio | 95% Confidence Interval |
|-------------------------------------------------------------------------------------------------------------|------------|-------------------------|
| Univariate (n = 224)                                                                                        | 6.5        | 1.41–29.64              |
| Model 1: age, race, sex (n = 224)                                                                           | 5.4        | 1.08–27.06              |
| Model 2: Model 1 plus comorbidities (diabetes, hyperlipidemia, atrial fibrillation, hypertension) (n = 224) | 5.5        | 1.08–28.39              |
| Model 3: Model 2 plus LDL, blood sugar, NIHSS score (n = 197)                                               | 10.4       | 0.95–112.88             |

within 3 hours of symptom onset; however, only 20 had an eGFR of  $<60$  mL/min per  $1.73$  m<sup>2</sup>. Twenty percent of patients with eGFR  $<60$  mL/min per  $1.73$  m<sup>2</sup> had ICH (either symptomatic or asymptomatic), compared with 11% of those with eGFR  $\geq 60$  mL/min per  $1.73$  m<sup>2</sup>. Results were not statistically significant ( $p = 0.321$ ).<sup>2</sup> Similarly, Nagganuma and colleagues<sup>18</sup> evaluated administration of IV tPA to patients on hemodialysis and found that 25% of patients had subsequent ICH. However, this totaled only 4 patients, and they were treated with only a partial dose (0.6 mg/kg) of IV tPA. Still other studies have shown that the presence of moderate to severe chronic kidney disease among patients with ICH is associated with larger hematomas and poor outcome.<sup>17</sup> Although in line with these previous reports, the current study is one of the first to evaluate a wide range of renal impairment on full-dose (0.9 mg/kg) IV tPA therapy, and includes patients up to 4.5 hours, which is the current standard of care. Unfortunately, we were unable to evaluate length from symptom onset to treatment as a confounding factor for symptomatic hemorrhage.

The current study is not without limitations. It is a retrospective analysis of a relatively small number of patients. While in the majority of cases clinical deterioration was well documented, relying on daily progress notes has the potential to result in the misclassification of a symptomatic hemorrhage as asymptomatic. Following the NINDS trial, other groups defined symptomatic hemorrhage by an objective increase in NIHSS of 4 points or more.<sup>11</sup> Unfortunately, we did not have access to repeat NIHSS testing within our study population.

There are undoubtedly multiple additional factors that influence hemorrhagic transformation that are not accounted for in the current study. We were limited by the data available within the tPA database and do not have information regarding the site of arterial occlusion, recanalization rates, or stroke subtypes. Information regarding the use of antiplatelet agents, anticoagulants, or statins was also not available. To be a candidate for administration of IV tPA, all patients had international normalized ratio (INR) values of  $<1.7$ . In concordance with the current guidelines from the American Stroke Association,<sup>1</sup> systolic blood pressure goal for all patients following administration of IV tPA was  $<185$  mm Hg; however, we do not have documentation of how consistently patients were maintained within that range. We did not have lesion volume measurements; however, this was approximated using the NIHSS as a surrogate marker of severity. Our sample is also potentially biased by the preconceived notion that renal impairment increases hemorrhage risk; although, excluding patients with end-stage renal disease from tPA administration, if anything, should dilute the apparent effect.

A final concern is that serum creatinine was recorded only on the day of admission, and may not have reflected overall baseline renal function or how it changed through the course of a patient's hospitalization. It is well known that a single measurement of serum creatinine is not an ideal measure of renal function.<sup>24</sup> Not only can creatinine be transiently elevated, but other markers, such as cystatin C, have been shown to be better predictors of renal impairment.<sup>3</sup> Since eGFR did not predict sICH, this raises the possibility that creatinine elevation is actually an epiphenomenon, and that other, unidentified risk factors, are responsible for the increased hemorrhage risk rather than impaired renal function. We feel this is less likely, given that there was a definite trend toward eGFR being associated with higher risk of sICH, and that this trend was present for all definitions of renal impairment in our study (either by creatinine or eGFR). Regardless, we would argue that admission creatinine appears to be an important predictor of sICH, and is

still the most practical assessment of renal function, allowing for timely assessment of risk when "time is brain."

A symptomatic hemorrhage risk of 10.6% in patients with renal impairment is relatively low and should not deter treatment with IV tPA. However, the results of the current study raise several important issues. Larger, prospective studies are needed to confirm that renal impairment is an important risk factor for sICH as we suggest. Further studies will also help to determine if there is an inflection point (creatinine or eGFR cutoff) at which the risk of sICH may outweigh the potential benefit of treatment with IV tPA. Evaluating the association of renal impairment and sICH in a larger population may identify groups of patients who are at particularly high risk for hemorrhage and would benefit from going directly to intra-arterial therapy. Conversely, our findings may be clinically valuable in identifying a group at particularly low risk of sICH after IV tPA (that is, those with normal renal function whose sICH risk was only 1.8%). Without a larger trial, we do not recommend changing current clinical practice.

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