Factors Associated With Impaired Kidney Function and Its Impact on Long-Term Outcome in Young Ischemic Stroke

Jukka Putaala, MD, PhD*; Elena Haapaniemi, MD, PhD*; Daniel Gordin, MD, PhD; Ron Liebkind, MD, PhD; Per-Henrik Groop, MD, PhD; Markku Kaste, MD, PhD; Turgut Tatlisumak, MD, PhD

Background and Purpose—After ischemic stroke, kidney dysfunction is linked to poor outcomes in the elderly, but regarding young patients, data are lacking.

Methods—We investigated estimated glomerular filtration rate (eGFR) on admission according to the Modification of Diet in Renal Disease equation in 958 consecutive patients aged 15 to 49 years with their first-ever ischemic stroke. Logistic regression adjusted for demographics and stroke risk factors served to identify factors related to low (<60) and high (>120 mL/min/1.73 m²) eGFR. In the long-term follow-up (mean, 8.9±3.8 years) study, Cox proportional hazards analysis described the association between eGFR and the following end points: nonfatal/fatal ischemic stroke; composite vascular event of any stroke, myocardial infarction, revascularization/other arterial occlusive event, or vascular death; and death of any cause.

Results—Estimated GFR was normal in 809 (84.4%), low in 43 (4.5%), and high in 106 (11.1%) patients. Type 1 diabetes (OR, 18.84; 95% CI, 8.65 to 41.03), hypertension (4.29; 1.94 to 9.48), and cardiovascular disease (2.66; 1.19 to 5.96) were independently associated with low eGFR. Type 2 diabetes (3.82; 1.93 to 7.55), lower age (0.95 per year; 0.93 to 0.98), and male gender (1.74; 1.08 to 2.82) were associated with high eGFR. Both low (hazard ratio, 5.73; 95% CI, 3.54 to 9.25) and high eGFR (1.78; 1.01 to 3.14) were associated with long-term mortality when adjusted for age, gender, risk factors, stroke severity, and subtype. No independent association appeared between eGFR and vascular events.

Conclusions—Despite their different associated risk factors in our young patient cohort, both low and high eGFR predicted long-term mortality after ischemic stroke. (Stroke. 2011;42:2459-2464.)

Key Words: glomerular filtration rate ■ ischemic stroke ■ outcome ■ recurrence ■ stroke in the young

Impaired kidney function, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m², is associated with increased risk for both ischemic and hemorrhagic stroke. Hypertension, diabetes, and increasing age are key predictors of low eGFR in the general population, thus sharing the same risk factors with cerebral small-vessel disease.

Patients with stroke with kidney dysfunction, irrespective of the method of defining the condition, are at considerably higher short- and long-term risk of death. Moreover, an association has been suggested between low eGFR and recurrent vascular event. In addition to low eGFR, also glomerular hyperfiltration (eGFR >125 mL/min/1.73 m²)—suggested to be an early sign of kidney disease—has been linked to higher mortality in patients with stroke.

Earlier stroke studies focusing on kidney function included mainly elderly patients; prevalence of kidney dysfunction in the young adult stroke population is unknown. Because young adult patients with stroke have different risk factor and etiologic profiles than do elderly ones, factors associated with impaired kidney function may also differ. Furthermore, cerebral small-vessel disease—the most likely etiologic diagnosis related to poor kidney function in a patient with acute stroke—is relatively rare in the young with a favorable long-term prognosis.

Our aim was to investigate the clinical factors associated with kidney function estimated by eGFR and whether low or high eGFR would indicate higher mortality or risk for subsequent vascular events in young adults after first-ever ischemic stroke.

Patients and Methods

This hospital-based observational cohort study was approved by the appropriate local authorities and the ethics committee and carried out...
at the Department of Neurology, Helsinki University Central Hospital. The Helsinki Young Stroke Registry was set up by searching a prospective computerized hospital discharge database of all consecutive patients aged 15 to 49 years with their first-ever ischemic stroke occurring between January 1994 and May 2007. Of the 1194 consecutive patients found by this computer search, we excluded 186 patients with an incorrect primary diagnosis of ischemic stroke, transient ischemic attack, cerebral venous thrombosis, stroke due to direct head trauma or strangulation, ischemic lesion due to immediate complications of subarachnoidal hemorrhage, and any iatrogenic stroke as a consequence of angiographic imaging or major surgery. Of those 1008 fulfilling the predetermined eligibility criteria for the registry, we included here patients with creatinine measured within 30 days after the index stroke to reflect any close temporal relationship with the event.

Information on traditional vascular risk factors came from the medical records and consistent definitions appearing in that prior publication were applied over the 13-year study period. Risk factors analyzed were gender, age, dyslipidemia (treated or total cholesterol level ≥5.0 mmol/L, low-density lipoprotein level ≥3.0 mmol/L, or high-density lipoprotein level <1.0 mmol/L), current smoking, hypertension (treated or a history of hypertension as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or both), obesity (body mass index ≥30 kg/m² or patient clearly described as heavily obese), cardiovascular disease (prior diagnosis of coronary heart disease, heart failure [ejection fraction <55%], previous myocardial infarction, or peripheral arterial disease), atrial fibrillation, and history of transient ischemic attack. Diabetes was defined as treated or presently diagnosed according to the 1999 World Health Organization criteria (fasting blood glucose of ≥7.0 mmol/L or 2-hour oral glucose tolerance test glucose of ≥11.1 mmol/L). Type 1 diabetes (T1D) was distinguished from Type 2 diabetes (T2D) by the observance of insulin dependence within 1 year of diagnosis. Additionally, heavy drinking (more than clearly moderate drinking, i.e., estimated intake of >200 g of pure alcohol per week consistently as reported by patient or relative) and active malignancy (diagnosed within 1 year or prior malignancy not in remission) were included in the analysis because they predicted long-term mortality in this patient population.

We assessed stroke severity on the National Institutes of Health Stroke Scale.12 Etiology was categorized with the Trial of Org 10172 in Acute Stroke Treatment criteria (large-artery atherosclerosis, cardioembolism, small-vessel disease, other determined etiology, and undetermined etiology).13

Creatinine was measured with Jaffe’s method until January 2002 and thereafter by enzymatic methods at a central laboratory with a high correlation between the methods ($R^2=0.977$). GFR was estimated, taking into account ethnicity, with the original 4-variable Modification of Diet in Renal Disease (MDRD-4) equation14 and thereafter by enzymatic methods at a central laboratory with a high correlation between the methods ($R^2=0.977$). GFR was estimated, taking into account ethnicity, with the original 4-variable Modification of Diet in Renal Disease (MDRD-4) equation14 and thereafter by enzymatic methods at a central laboratory with a high correlation between the methods ($R^2=0.977$). GFR was estimated, taking into account ethnicity, with the original 4-variable Modification of Diet in Renal Disease (MDRD-4) equation14 and thereafter by enzymatic methods at a central laboratory with a high correlation between the methods ($R^2=0.977$). GFR was estimated, taking into account ethnicity, with the original 4-variable Modification of Diet in Renal Disease (MDRD-4) equation14 and thereafter by enzymatic methods at a central laboratory with a high correlation between the methods ($R^2=0.977$). GFR was estimated, taking into account ethnicity, with the original 4-variable Modification of Diet in Renal Disease (MDRD-4) equation14 and thereafter by enzymatic methods at a central laboratory with a high correlation between the methods ($R^2=0.977$). GFR was estimated, taking into account ethnicity, with the original 4-variable Modification of Diet in Renal Disease (MDRD-4) equation14 and thereafter by enzymatic methods at a central laboratory with a high correlation between the methods ($R^2=0.977$). GFR was estimated, taking into account ethnicity, with the original 4-variable Modification of Diet in Renal Disease (MDRD-4) equation14 and thereafter by enzymatic methods at a central laboratory with a high correlation between the methods ($R^2=0.977$).

Follow-up of the surviving patients took place between November 2009 and January 2010 by means of a structured telephone interview of patients, their next of kin, or nursing staff. The information source was a letter in those not contacted by telephone. Mortality data came from Statistics Finland. Outcome events analyzed were nonfatal or fatal recurrent ischemic stroke; composite vascular event of any stroke (ischemic or hemorrhagic), myocardial infarction, revascularization procedure (eg, coronary artery bypass), other arterial occlusive event, or vascular death; and death from any cause. Evaluation of all patient records confirmed outcome events.

Chi-square, Fisher exact, and 1-way analysis of variance tests allowed univariate comparisons between eGFR groups. Binary logistic regression analysis identified baseline risk factors associated with low eGFR and high eGFR. Adjustments in that analysis were based on univariate significance and included age, gender, hypertension, cardiovascular disease, T1D, T2D, and heavy drinking. In the follow-up study, the Kaplan-Meier log rank test served for analysis of the effect of age, gender, risk factors, and stroke features on risk for end point events. Patients dying within 30 days after the index stroke were excluded from mortality analysis, because their death was likely associated with the index event. Those who died from other than the defined fatal end points in later follow-up were considered censored. Cox proportional hazards models were constructed by selecting variables with $P<0.10$ in the univariate Kaplan-Meier analysis to investigate factors independently associated with the end point events. Normal eGFR served as a referent for low and high eGFR. Due to relatively low number of patients in the low and high eGFR groups, we could not stratify analyses by gender.

All statistical analyses used PASW 18.0 for Macintosh. Two-sided values of $P<0.05$ were considered significant.

Results

Of the 1008 patients in the registry, admission serum or plasma creatinine values were available for 999. Of these, creatinine level was measured >30 days after the known stroke date in 41 patients, and these were excluded, leaving 958 patients for analysis. Compared with the eligible patients, those excluded were more often evaluated as outpatients, and they failed to report any exact date for symptom onset. They also more frequently had hypertension (38.4% versus 56.1%), a history of transient ischemic attack (8.2% versus 24.4%), or mostly mild strokes (76.3% versus 97.6%) of undetermined etiology (32.0% versus 51.2%), but their renal function (mean eGFR 95 versus 84 mL/min/1.73 m²; $t$ test $P=0.103$) and frequencies of end point events (12.4% versus 14.6% for ischemic stroke; 21.0% versus 17.1% for composite vascular event; 15.3% versus 7.3% for death) were comparable with figures for those included.

Of the 958 patients (median eGFR 93; interquartile range, 80 to 107 mL/min/1.73 m²) included at baseline, low eGFR (<60 mL/min/1.73 m²) appeared in 43 (4.5%) and high eGFR (>120 mL/min/1.73 m²) in 106 (11.1%). Four patients had undergone kidney transplantation, and 1 was undergoing dialysis before the index stroke.

Patients with low eGFR were more likely to have hypertension, cardiovascular disease, and T1D than were patients with normal eGFR. A majority of the index strokes in the low eGFR group were attributable to small-vessel occlusion and less often to undetermined cause. Antihypertensive and statin medication were more frequently initiated after the index stroke in those with low eGFR. Patients in the high eGFR group were more likely to be male, to be heavy drinkers, to be younger, and to have T2D than were those with normal eGFR (Table 1).

Logistic regression analysis adjusted for baseline imbalances demonstrated that T1D had, statistically, the strongest independent association with low eGFR followed by hypertension and cardiovascular disease. However, factors independently associated with high eGFR were distinct: T2D, lower age, male gender, and heavy drinking (Table 2).

In the follow-up part of the study, 5 refused to participate and 7 were lost to follow-up, leaving 946 patients for the outcome analysis (146 had died, 784 were contacted by telephone, and 16 replied with a letter). Mean follow-up for
survivors was 8.9 (±3.8) years. Altogether 11 (25.6%) ischemic strokes occurred during the follow-up in the low eGFR group, 95 (12.5%) in the normal eGFR group, and 11 (11.2%) in those with high eGFR. The corresponding numbers for the composite vascular end point were a respective 22 (51.2%), 158 (20.2%), and 19 (19.4%). One (2.3%) patient experienced hemorrhagic stroke in the low-eGFR group, 3 (2.9%) in the high-eGFR group, and 15 (1.9%) among those with normal eGFR. Due to the low number of hemorrhagic strokes, these were not analyzed separately.

Within 30 days, 24 deaths occurred: none in the low-eGFR group, 18 (2.3%) in the normal-eGFR group, and 6 (5.8%) in the high-eGFR group. Among the 30-day survivors (n=922), 23 (53.5%) deaths occurred in patients low eGFR, 84 (10.8%) in the normal-eGFR group, and 15 (15.3%) in the high-eGFR group during the long-term follow-up. Causes of death according to eGFR group are in Supplemental Table I (http://stroke.ahajournals.org).

Kaplan-Meier analysis revealed that age >40 years, hypertension, cardiovascular disease, prior transient ischemic at-
tack, both T1D and T2D, large-artery atherosclerosis or small-vessel occlusion as the etiologic subtype, and low eGFR (Figure 1A) were all associated with increased risk for recurrent nonfatal or fatal ischemic stroke (log rank \(P<0.05\)). The same risk factors were associated with the composite vascular event, but additionally, male gender, obesity, and smoking were associated with that end point (all \(P<0.05\)). Moreover, the univariate association between low eGFR and the composite vascular end point was significantly stronger than that regarding ischemic stroke (Figure 1B). No correlation emerged between high eGFR and risk for ischemic stroke or any composite vascular event. In this patient group, age \(>40\) years, cardiovascular disease, T1D, T2D, heavy drinking, malignancy, stroke severity and subtype, and both low and high eGFR (Figure 1C) were associated with long-term mortality.

In the multivariate Cox proportional hazards analysis, both low (hazard ratio, 5.73; 95% CI, 3.54 to 9.25; \(P<0.001\)) and high eGFR (hazard ratio, 1.78; 95% CI, 1.01 to 3.14; \(P=0.045\)) were independently associated with long-term risk of death, but not with the other end points (Figure 2).

**Discussion**

After an ischemic stroke, both low and high eGFR were independent predictors of long-term mortality in young adults. Approximately 5% of our patients had impaired kidney function (eGFR <60 mL/min/1.73 m\(^2\))—most noticeably associated with T1D—followed by hypertension and cardiovascular disease. High eGFR (approximately 11%) was, in turn, associated with younger age, T2D, and heavy drinking.

The prevalence of low eGFR in the present study was higher than that seen among young adults in the general population (<1%) but was similar to that among individuals aged 40 to 59 years with diabetes or hypertension (<5%). In elderly patients with stroke, the prevalence of low eGFR has ranged from 16% to 40% among various cohorts. T1D, hypertension, and cardiovascular disease were associated with low eGFR, reflecting the well-documented predictors of impaired kidney function in the general population. Additionally, increasing age has been predictive of low eGFR in 1 large acute-stroke patient population. Nevertheless, in contrast to findings from studies comprising the general population and elderly patients with stroke, here, higher age was not associated with low eGFR. This emphasizes the role of T1D in particular, present in 44% in the low-eGFR group, in the development of early-onset kidney dysfunction. The predisposing factors for high eGFR that reflect renal hyperfiltration that have been found to precede progressive kidney disease differed from those of low eGFR in our study.

![Figure 1](http://stroke.ahajournals.org/)

**Table 2. Multivariate Logistic Regression Analyses Investigating the Relationship Between Baseline Demographic and Risk Factors and Low Estimated Glomerular Filtration Rate (eGFR, <60 mL/min/1.73 m\(^2\)) and High eGFR (>120 mL/min/1.73 m\(^2\))*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Low eGFR OR (95% CI)</th>
<th>P</th>
<th>High eGFR OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age per y</td>
<td>0.98 (0.93–1.04)</td>
<td>0.440</td>
<td>0.95 (0.93–0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.86 (0.40–1.82)</td>
<td>0.684</td>
<td>1.74 (1.08–2.82)</td>
<td>0.023</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.29 (1.94–9.48)</td>
<td>&lt;0.001</td>
<td>0.77 (0.48–1.25)</td>
<td>0.287</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2.66 (1.19–5.96)</td>
<td>0.017</td>
<td>1.10 (0.57–2.11)</td>
<td>0.774</td>
</tr>
<tr>
<td>Diabetes mellitus, Type 1</td>
<td>18.84 (8.65–41.03)</td>
<td>&lt;0.001</td>
<td>1.49 (0.55–4.05)</td>
<td>0.417</td>
</tr>
<tr>
<td>Diabetes mellitus, Type 2</td>
<td>NA</td>
<td>NA</td>
<td>3.82 (1.93–7.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heavy drinking</td>
<td>NA</td>
<td>NA</td>
<td>2.22 (1.32–3.76)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

NA indicates not applicable; eGFR, estimated glomerular filtration rate; CI, confidence interval.

*All variables shown were included in the models.

Figure 1. Cumulative risks for (A) nonfatal or fatal ischemic stroke (log rank \(P=0.001\) for pooled comparison); (B) composite vascular end point of any stroke, myocardial infarct, revascularization, other arterial event, or vascular death (\(P<0.001\)); and (C) death from any cause (log rank \(P<0.001\) for pooled comparison, \(P=0.029\) for comparison between high and normal estimated glomerular filtration rate [eGFR]). Low eGFR, <60; normal eGFR, 60 to 120; high eGFR, >120 mL/min/1.73 m\(^2\).
In contrast to the association between T1D and low eGFR, T2D was independently associated with high eGFR, whereas T1D was not. Many of our cohort with T1D likely already harbored advanced kidney disease, and patients with T2D may show an earlier stage of diabetic vascular damage in their kidneys. We also found that heavy drinking was independently associated with hyperfiltration. This may reflect early vascular pathological changes in the kidneys, like in a recent population-based study observing an association between moderate to heavy drinking and albuminuria.19

An association between cerebral small-vessel disease and kidney function occurs in the elderly.3,4 In our study, 40% had small-vessel occlusion as the etiologic stroke subtype in the low-eGFR group, a fact in accordance with others’ findings. The differing risk factor profile related to high eGFR likely explains its lack of correlation with cerebral small-vessel disease or other stroke subtypes.

In our patient cohort, those with low eGFR were at strikingly high risk for new vascular events relatively early after the index stroke. Independent associations between low eGFR and composite stroke or cardiovascular events among elderly patients with stroke have been demonstrated.5 We could, however, discover no such association after adjustments in young adult patients. A likely reason is that low eGFR merely reflects the presence of prognostically important risk factors, namely T1D, hypertension, and established cardiovascular disease, which account for the high rates of events.11

Several studies on general stroke populations have found an independent association between poor kidney function and long-term mortality.4,5,7,17 We found in our young patient cohort relationships between both low and high eGFR and long-term mortality. This is in line with findings from a general stroke-patient population,7 from a large T1D-patient cohort,16 and from a study comprising a general population.20 One study including patients with stroke found a U-shaped correlation between eGFR and mortality but could not account for stroke severity in multivariate models, leaving an uncertainty as to associations.7 After accounting in our study for multiple clinically relevant confounders, including baseline stroke severity, the higher mortality in association with hyperfiltration remained significant.

The mechanisms underlying the higher mortality risk associated with either low or high eGFR are less than well known, although cardiovascular disease per se is a well-known complication of chronic kidney disease.21 Nevertheless, our data on the primary causes of death do not support the view that the excess mortality risk in young patients with ischemic stroke with either low or high eGFR is due to cardiovascular causes. In fact, vascular death was more frequent in those with normal eGFR (Supplemental Table I). Because of the relatively low number of events, our study cannot draw firm conclusions on this issue, however.

Limitations of our study include variability in our methods for measuring creatinine within the study period. Data on chronic kidney disease were not systematically collected in all patients. Furthermore, we could not use a separate formula to estimate GFR for patients <20 years. Regarding the inaccuracy of the kidney-function estimation in adolescents with the adults’ MDRD-4 equation and with no adjustment for height or body surface area,22,23 its possible impact on the study results or interpretation is likely to be limited because only 14 patients were aged 15 to 19 years in our cohort. Finally, because our patient population was entirely white, these results may not be directly generalizable to other ethnic stroke-patient cohorts.

Conclusions

Despite their differing associated risk factors discovered, either low or high eGFR on hospital admission for first-ever ischemic stroke in young adults each seems to impact long-term prognosis. Multifactorial preventive strategies in these high-risk patients with either established or early-stage
kidney disease are warranted, including aggressive glycemic and blood pressure control and a reduction in alcohol intake.

Acknowledgments
We are indebted to Carol Norris, PhD, for revising the language.

Sources of Funding
Supported by the Helsinki University Central Hospital (T.T.: TYH2008253, TYH2009236; J.P.: TKK2011003), the Finnish Medical Foundation (J.P.), the Finnish Brain Foundation (J.P.), the Maire Taponen Foundation (J.J.), and the Emil Aaltonen Foundation (E.H.).

Disclosures
None.

References
Factors Associated With Impaired Kidney Function and Its Impact on Long-Term Outcome in Young Ischemic Stroke

Jukka Putaala, Elena Haapaniemi, Daniel Gordin, Ron Liebkind, Per-Henrik Groop, Markku Kaste and Turgut Tatlisumak

Stroke. 2011;42:2459-2464; originally published online July 7, 2011;
doi: 10.1161/STROKEAHA.110.612721

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/42/9/2459

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2011/07/07/STROKEAHA.110.612721.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
### SUPPLEMENTAL MATERIAL

**E-Table.** Primary causes of death during long-term follow-up in patients who survived the first 30 days after index stroke according to subgroup of the estimated glomerular filtration rate (eGFR). Low eGFR, <60; normal eGFR, 60-120; high eGFR, >120 ml/min/1.73 m².

<table>
<thead>
<tr>
<th>Cause</th>
<th>All n=122</th>
<th>Low eGFR (&lt;60) n=23</th>
<th>Normal eGFR (60-120) n=84</th>
<th>High eGFR (&gt;120) n=15</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All vascular causes</td>
<td>62 (50.8)</td>
<td>8 (34.8)</td>
<td>49 (58.3)</td>
<td>5 (33.3)</td>
<td>0.047</td>
</tr>
<tr>
<td>Stroke</td>
<td>20 (16.4)</td>
<td>1 (4.3)</td>
<td>18 (21.4)</td>
<td>1 (6.7)</td>
<td>0.081</td>
</tr>
<tr>
<td>Cardioaortic</td>
<td>38 (31.1)</td>
<td>7 (30.4)</td>
<td>28 (33.3)</td>
<td>3 (20.0)</td>
<td>0.588</td>
</tr>
<tr>
<td>Other vascular</td>
<td>4 (3.3)</td>
<td>0</td>
<td>3 (3.6)</td>
<td>1 (6.7)</td>
<td>0.510</td>
</tr>
<tr>
<td>Malignancy</td>
<td>15 (12.3)</td>
<td>2 (8.7)</td>
<td>9 (10.7)</td>
<td>4 (26.7)</td>
<td>0.188</td>
</tr>
<tr>
<td>Infection</td>
<td>17 (13.9)</td>
<td>4 (17.4)</td>
<td>11 (13.3)</td>
<td>2 (13.3)</td>
<td>0.868</td>
</tr>
<tr>
<td>Renal disease</td>
<td>4 (3.3)</td>
<td>4 (17.4)</td>
<td>0</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Miscellaneous causes</td>
<td>24 (19.7)</td>
<td>5 (21.7)</td>
<td>15 (17.9)</td>
<td>4 (26.7)</td>
<td>0.093</td>
</tr>
</tbody>
</table>
Author Contributions List:

**All authors**: Manuscript drafting or manuscript revision for important intellectual content, and manuscript final version approval.

**Jukka Putaala**: study concept and planning, analysis, literature search, interpretation, and manuscript writing and editing. Jukka Putaala had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Elena Haapaniemi**: study concept and planning, data acquisition, literature search, interpretation, and manuscript writing and editing.

**Daniel Gordin**: study concept and planning, literature search, data acquisition, interpretation, and manuscript writing and editing.

**Ron Liebkind**: study concept and planning, data acquisition, literature search, interpretation, and manuscript writing and editing.

**Per-Henrik Groop**: study concept and planning, interpretation, manuscript editing.

**Markku Kaste**: study concept and planning, interpretation, manuscript editing, and logistic and administrative support.

**Turgut Tatlisumak**: study concept and planning, interpretation, manuscript writing and editing, logistic and administrative support, and funding.