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Estimated glomerular filtration rate and risk of poor outcomes after stroke

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Abstract

Background: Relationship of estimated glomerular filtration rate (eGFR) with complications after stroke has not been fully characterized for entire clinical spectrum of eGFR and for the fluctuation in eGFR during hospital stay.

Methods: Data from the Norfolk and Norwich Stroke Registry recorded between January 2003 and April 2015 was analysed. eGFR was categorized into six clinically relevant categories as per Kidney Disease Improving Global Outcomes guidelines. Change in eGFR during acute admission was categorized into: within 5% change (ref.), 5-20% decline, >20% decline, 5-20% increase and >20% increase. All-cause mortality, recurrent stroke, incident myocardial infarction, prolonged hospital stay and stroke disability at discharge were outcomes of interest.

Results: 10,329 stroke patients (mean age 77.8 years) were followed for a mean of 2.9 years (30,126 person years). Multivariable adjusted hazard ratios (HRs) (95%CI) for all-cause mortality were 0.91 (0.80-1.04), 0.96 (0.83-1.11), 1.23 (1.06-1.43), 1.54 (1.31-1.82) and 2.38 (1.91-2.97) for eGFR levels 60-89, 45-59, 30-44, 15-29 and <15 respectively, compared to eGFR ≥90 mL/min/1.73m^2. The HR (95%CI) for eGFR change were 1.56 (1.36-1.79), 1.17 (1.05-1.30), 1.47 (1.32-1.62) and 1.71 (1.55-1.88) for >20% decline, 5-20% decline, 5-20% increase and >20 % increase, respectively, compared to change within 5%. Results were similar for other outcomes except recurrent stroke.

Conclusions: Stroke patients with eGFR <45 mL/min/1.73m^2 at hospital admission and > 5% decline or increase in eGFR during hospital stay were at substantially high risk of poor outcomes, particularly all-cause mortality, myocardial infarction, prolonged hospital stay and disability at discharge.

Introduction

Low estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73m^2) is highly prevalent in stroke. Indeed, more than a third of stroke patients has been found to have low eGFR at hospital admission [1-3]. Previous studies suggested that stroke patients with low eGFR are at increased risk of poor clinical outcomes including death, prolonged hospital stay and disability after hospital discharge [4-10]. However, there are few studies assessing the association between eGFR divided into all clinically relevant categories and stroke outcomes. Understanding the size and shape of the association across all clinically relevant categories of eGFR is not only essential for clinical decision making but is also vital in helping patients and their families understand the course of the disease. In addition, in previous studies eGFR was only assessed at single time point on admission, thus whether change in eGFR during hospital stay could be a prognostic factor in stroke patients is virtually unknown. Previously, short term change in eGFR has been shown to be associated with poor clinical outcomes in a general population [11].

This study aimed to examine the association of eGFR categorised as per recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines [12] with complications including all-cause mortality, stroke recurrence, incident myocardial infarction, prolonged hospital stay and disability at hospital discharge in stroke patients. In addition, we examined the association between change in eGFR during hospital stay and aforementioned outcomes using a second assessment of eGFR at hospital discharge.

Materials and Methods

Sample population

Data of unselected consecutive patients from the Norfolk and Norwich Stroke Registry at the Norfolk and Norwich University Hospital which serves a population of~750,000 were used. Methods of data collection have been described elsewhere [13]. In summary, data were obtained from paper-based, reviewed and entered onto the register database by the hospital stroke data team and data linkage with electronic records [14]. Newcastle and Tyneside National Health Service (NHS) Research Ethics Committee delivered ethical approval (12/NE/0170) and the Steering Committee of the Norfolk and Norwich Stroke Register approved the study protocol.

Between January 2003 and April 30, 2015, 10,683 stroke patients (age ≥18 years) with either ischemic or hemorrhagic stroke were admitted to the hospital. Because biochemistry data were electronically available only after January 2003, patients were included from the beginning of 2003. Patients with missing information of serum creatinine were excluded (n=354). Complete information was available on comorbidities including diabetes, hypertension, heart failure, hypercholesterolemia, coronary heart disease, atrial fibrillation, and pneumonia. After exclusion, final analytic sample included 10,329 stroke patients.

Estimated glomerular filtration rate

Two serum creatinine measurements, on hospital admission and near to hospital discharge (alive or dead) using the Jaffe method and standardized to isotype dilution mass spectrometry values. The Chronic Kidney Disease-Epidemiology collaboration equation was used to estimate kidney function [15]. Although data for race were not available, misclassification of eGFR was expected to be minimal because less than 2% of the Norwich population is of non-

white ethnic origin [16]. As per KDIGO guidelines [12], admission eGFR was categorized into following stages: <15, 15-29, 30-44, 45-59, 60-89 and ≥90 mL/min/1.73m^2.

Covariates

Data on age, sex, history of stroke, type of stroke (ischemic or hemorrhagic), pre-stroke modified Rankin Score (mRS) (modified by the UK transient ischemic attack investigators) [17] (0-5), and Oxfordshire Community Stroke Project (OCSP) Classification were collected by specialist stroke nurses or doctors. For each patient, when admitted data on the pre-stroke mRS were collected from nursing and medical records. Co-morbidities including diabetes, hypertension, dyslipidaemia, heart failure, atrial fibrillation, coronary heart disease and pneumonia were obtained through record linkage.

Outcome(s)

All-cause mortality, recurrent stroke, incident myocardial infarction, prolonged hospital stay, and stroke disability were selected as outcomes for the study purpose. Mortality status was recorded at discharge to record in-hospital mortality. Linkage with the Office of National Statistics was established in UK National Health Service order to obtain follow-up mortality data. Information on recurrent stroke and post stroke incidence of myocardial infarction was obtained through electronic record linkage. Recurrent stroke cases were additionally identified by assessing repeated admission(s) of a patient for stroke recorded in the registry. Prolonged hospital stay was defined as hospital stay longer than median days of hospital stay. Disability at discharge was assessed using mRS scores at hospital discharge and was classified into three groups: mild (0-1), moderate (2-3) and severe (4-6). For all-cause mortality, recurrent stroke and myocardial infarction, patients were followed until May 30, 2015 so as to have minimal follow up of one month. For clinical relevance, the risk of <30, 30-365 and >365 day mortality was examined separately in addition to overall mortality over the whole follow up.

Statistical analysis

Cox proportional hazards regression analysis was performed to estimate hazard ratios (HRs) for the association between eGFR categories (with eGFR ≥90 mL/min/1.73 m^2 as the reference group) and all-cause mortality. Competing risk regression analysis (using Fine and Gray's method) [18] was performed to calculate sub-distribution HRs for recurrent stroke and incident myocardial infarction, considering all-cause mortality as a competing risk. Bi-nominal logistic regression analyses was performed for prolonged hospital stay and Ordinal logistic regression for stroke disability at discharge. Since death may skew analyses for prolonged hospital stay, this analyses was performed for patients that were alive at discharge. Multivariable models were constructed to adjust for potential confounders. Model 1 was adjusted for demographic factors (age and sex). Model 2 was additionally adjusted for previous stroke, pre-stroke mRS, stroke type, stroke severity (using OCSP classification), and the comorbid conditions listed above. Test of models assumptions indicated that our models fit the data well.

The proportional hazards assumption was tested with log-log survival curves. Parallel lines for eGFR categories implied that the proportional-hazards assumption was not violated (eFigure 1). For competing risk regression analysis, proportional hazard assumption was tested by examining the interaction between individual covariates and follow-up time. Model did not violate proportional hazard assumption (p for interaction for each covariate was >0.05). Hosmer and Lemeshow's goodness-of-fit test [19] for binary logistic regression and Log-likelihood ratio as goodness-of-fit test for ordinal logistic regression indicated that our model fitted the data well (p=0.12 and 0.34, respectively).

In addition, we explored the association between eGFR distribution and outcomes by dividing eGFR into groups spanning 10 mL/min/1.73 m^2: <20, 20-29, 30-39, 40–49, 50–59, 60–69, 70–79, 80–89, 90-99 (reference), 100-109 and ≥110 mL/min/1.73 m^2. There were

fewer incident myocardial infarction and recurrent stroke due to multiple groups. Thus, a combined end point of myocardial infarction, recurrent stroke and all-cause mortality was used in this analysis.

To assess the association between change in eGFR during hospital stay and outcomes after hospital discharge, percentage change in eGFR during hospital stay (($eGFR_{discharge}$-$eGFR_{admission}$)/$eGFR_{admission}$)×100 was categorized into the following categories: change within 5% (reference), 5-20% decline, >20% decline, 5-20% increase and >20% [20]. Association was examined for patients who were alive at discharge (N=8,021). This association was additionally adjusted for length of hospital stay. For recurrent stroke and incident myocardial infarction, analysis was performed for patients who did not develop these outcomes during hospital stay (N=7,928 and N=7,937, respectively).

Multiple imputation was performed by chained equations with 10 iterations to impute missing data (previous stroke (n=253), stroke severity (n=631) and pre-stroke modified Rankin score (n=674)) [21]. The following variables were incorporated into the model for imputations: age, sex, history of stroke, stroke type, serum creatinine, diabetes, hypertension, hypercholesterolemia, heart failure, atrial fibrillation, and coronary heart disease.

A two tailed p-value of <0.05 was considered significant. All analyses were performed using Stata/SE version 14.0.

Additional analyses

First, previous studies reported differences in the association between eGFR and adverse outcomes by high risk groups [5,20]. Thus, we tested for interaction and presented the results by stratifying according to two major high risk groups including diabetes and hypertension status (no/yes). Second, to investigate study period effect, we evaluated the interaction between eGFR and study period (i.e. 2003-2006, 2007-2010 and 2011-2015) for the risk of

adverse clinical outcomes. Third, we examined association between eGFR change and outcomes when adjusting for baseline eGFR. Finally, for change in eGFR during hospital stay, we examined association when using different cut-off of change in eGFR (i.e. 5% (reference), 5-25% decline, >25% decline, 5-25% increase and >25% increase).

Results

Baseline characteristics

Characteristics of the sample population are presented according to eGFR levels in Table 1. Median duration of hospital stay was 8 days (inter-quartile interval 4-18 days). The mean eGFR was 63.7±22.1 mL/min/1.73 m^2. Low levels of eGFR were more prevalent in patients aged ≥65 years compared to patients aged <65 years. A similar pattern was observed for females and those with ischemic stroke.

Clinical Outcomes by eGFR Levels

Incidences of clinical outcomes assessed across eGFR categories are shown in Table 2. In general, incidence of adverse outcomes was higher in patients with eGFR <90 mL/min/1.73m^2. However, in the case of recurrent stroke, the incidence tended to have an inverse 'U' shaped distribution across eGFR categories.

Association between eGFR and adverse outcomes

In the age and sex adjusted model, compared to eGFR level of ≥90 mL/min/1.73 m^2, lower levels of eGFR (<15, 15-29 and 30-44 mL/min/1.73 m^2) were associated with increased risks of all clinical outcomes, including all-cause mortality, incident myocardial infarction, prolonged hospital stay and post stroke disability but not with recurrent stroke. In the multivariable adjusted models, these associations remained statistically significant. Similar to overall risk of mortality, generally lower levels of eGFR (<15, 15-29 and 30-44 mL/min/1.73m^2) were associated with increased risk of <30, 30-365 or over 365-day mortality (Table 3).

The association between clinical outcomes and eGFR categories stratified by 10 mL/min/1.73 m^2 showed that, compared to eGFR category of 90-99 mL/min/1.73m^2, risk of all-cause mortality was high in eGFR categories of <20, 20-29 and 30-39 mL/min/1.73m^2 and

risk also appeared to be high in eGFR category of ≥109 mL/min/1.73m^2. A similar trend in associations was observed for the composite end point, prolonged hospital stay and stroke disability at discharge (Figure 1).

Regarding change in eGFR during hospital stay, greater than 5% decline or increase in eGFR during hospital stay, was associated with an increased risk of all-cause mortality, and stroke disability at discharge. For myocardial infarction, >20% change in eGFR tended to be associated with increased risk. No statistically significant association was observed for recurrent stroke (Table 4).

Additional analyses

No statistical interaction was observed for diabetes and hypertension status (no/yes) for any of the outcomes (eTable 1-eTable 4). Similarly, no statically significant interaction was observed between eGFR and study period for the risk of adverse clinical outcomes (p=0.21, 0.18, 0.58 and 0.25 for all-cause mortality, composite outcome, prolonged hospital stay and post stroke disability at discharge, respectively) . Association with outcomes was essentially similar to our main results when adjusting for eGFR at admission for this predictor (eTable 5) and using different cut-off of eGFR change (eTable 6).

Discussion

In this large unselected prospective cohort of stroke patients, low eGFR levels of <15, 15-29 and 30-44 mL/min/1.73m^2 which clinically correspond to very severely (or kidney failure), severely or moderate to severely impaired kidney function, respectively, were associated with increased risk of poor clinical outcomes. This association was particularly strong for the risk of all-cause mortality, incident myocardial infarction, prolonged hospital stay and disability at discharge. In addition, ≥5% change in eGFR during hospital stay was associated with increased risk of adverse clinical outcomes except recurrent stroke.

Whilst a number of previous studies have examined the association between eGFR and risk of adverse clinical outcomes in stroke patients [4-10, 21], our study expands current knowledge in a number of ways. Firstly, our study provides risk (both absolute and relative) of poor outcomes across all clinically relevant categories of eGFR which is critically important for clinical decision making. Secondly, this study confirms the association between eGFR and poor clinical outcomes in a relatively large Western population of stroke patients where average age of stroke onset is higher than in Asian populations where a number of previous studies were conducted. Thirdly, to best of our knowledge, this is the first study to examine the association between change in eGFR during hospital stay and relevant and important clinical outcomes, and demonstrates that both significant increase and decline in eGFR during hospital stay may indicate poor prognosis in stroke patients.

While our findings show higher risk of poor outcomes for moderately to severely reduced eGFR but lower risk for mildly and mild to moderately decreased eGFR. This is likely due to severity of illness of patients in eGFR category of ≥90 mL/min/1.73m^2. Due to loss of muscle mass in chronically ill patients, serum creatinine based eGFR may over-estimate their kidney function. Thus, patients in creatinine based eGFR category of ≥90

mL/min/1.73m^2 may actually be at increased risk of poor clinical outcomes. This was apparent when association was examined between eGFR divided into groups spanning 10 mL/min/1.73 m^2 and outcomes, indicating that along with the increased risk of poor outcomes in low eGFR levels, this risk also tended to be higher in eGFR category of 100-109 and ≥110 compared to eGFR category of 90-99 mL/min/1.73m^2 (Figure 1). Moreover, tendency for reduced risk of short term mortality and increased risk of long term mortality in eGFR category of 60-89 and 45-59 mL/min/1.73m^2 (Table 3) also indicate likelihood of overestimation of kidney function in these patients.

Another finding of our study was that change (≥5%) in eGFR during hospital stay also predicted prognosis in stroke patients. Importantly, this association was independent of eGFR at admission. Decline in kidney function during hospital stay likely signifies deteriorating kidney function and consequently poor prognosis in these patients. Causes of increased risk for poor prognosis with increase in eGFR during hospital stay is unclear to us. However, it may be because of withdrawal of antihypertensive agents (especially ACEi/ARB) as is commonly done in the patients presenting with acute stroke Furthermore it is also possible that an increase in eGFR during hospital stay may not indicate true improvement in kidney function but may indicate deterioration of their physical condition which may have resulted in overestimation of their kidney function at second measurement closer to discharge. We further explored the relationship and found that during hospital stay there was greater increase in mRS in patients with increase in eGFR (>5%) compared to patients with stable eGFR (<5%) (mean mRS score increase 3.1 vs 2.1, respectively).

In this study we did not find a statistically significant association between low eGFR with recurrent stroke. This could be due to fewer number of recurrent stroke events in low eGFR categories. Moreover, higher short-term mortality may be obscuring the true relationship. Indeed, previous studies that observed this association either examined fatal and

non-fatal re-occupant stroke together [8,12,14] or found association with stroke reoccurrence only in a composite outcome analysis [22]. Similar to our study, one study that examined non-fatal stroke recurrence found no association between low eGFR and stroke recurrence [23]. Although we accounted for mortality occurring before stroke recurrence in our analysis, we cannot entirely rule out possibility of this phenomenon.

This study has a number of clinical and research implications. Our findings suggest that in stroke management, eGFR may be used as an additional early biomarker to identify high risk patients for complications. Our findings of independent association between change in eGFR during hospital stay and clinical outcomes provide an additional tool in prediction of prognosis in stroke patients. Since this association was also independent of eGFR at baseline, a second assessment of kidney function at/around discharge may be valuable in predicting longer term prognosis. Our findings also suggest that there should be caution in interpreting high eGFR values at hospital admission (when estimated using serum creatinine) in stroke patients in routing clinical practice since they may not always mean better kidney function and thus a better prognosis, particularly in chronically ill patients.

The present study has some limitations. First, eGFR was estimated using serum creatinine which is influenced by muscle mass [24], and thus may not provide the most reliable assessment of kidney function, particularly in chronically ill patients. Other biomarkers of kidney function that are less dependent on muscle mass (e.g. Cystatin C) may be used for more accurate assessment of kidney function [25]. However, in routine clinical practice serum creatinine still remains the main biomarker for assessment of kidney function and thus highlights the usefulness of our findings in routine patient care. Second, data was not available on smoking and alcohol intake, and body mass index. However, we adjusted for major determinants of eGFR and poor outcomes including diabetes, hypertension and CVDs which are also linked to lifestyle factors listed above and thus likely have reduced

confounding related to the unmeasured lifestyle factors. It should also be noted that the aim of this study was not to establish causation but to investigate the association between eGFR and poor outcomes which is potentially useful in providing additional prognostic marker for early identification of stroke patients that are at increased risk of complications.

This study also has a number of strengths. Our large sample population allowed us to conduct a rigorous analysis, so as to examine the size and shape of the association between eGFR and poor clinical outcomes across all clinically relevant categories of eGFR. In addition, we were also able to examine the consistency of these association across various sub groups. The availability of information on a number of clinical outcomes allowed us to comprehensively assess the association of admission eGFR with stroke prognosis. Furthermore, as a study using data from a hospital-based disease register, the patient population under evaluation represents real world clinical events. Finally, the current study included a second measurement of serum creatinine, which allowed analysis of the importance of change in eGFR during hospital stay in stroke prognosis.

In summary, stroke patients with low levels of eGFR at hospital admission (particularly in categories of <15, 15-29 and 30-44 mL/min/1.73m^2) and greater than 5% change in eGFR during hospital stay (decline or increase) were associated with increased risk of poor clinical outcomes of all-cause mortality, myocardial infarction, prolonged hospital stay and stroke disability at discharge. These findings emphasize the importance of assessing eGFR in stroke patients so as to aid in management and prediction of prognosis in routine care.

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Disclosure

None.

Conflicts of interests

None.

Contributors

Study conception, literature search, data analysis, and drafting the manuscript: PV; Data acquisition and data management: JHBS; Supervisor or mentorship: PKM, AKM, KMB and JFP; All authors contributed in interpretation of results. Each author contributed important intellectual content during manuscript drafting or revision.

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Figure 1: HRs (95% CIs) for: A) all-cause mortality; B) combined end point, and ORs (95% CIs) for; C) prolonged hospital stay and; D) stroke disability at discharge, according to the level of eGFR categorized by 10 mL/min/1.73 m^2 difference, with eGFR of 90-99 mL/min/1.73 m^2 serving as the reference group

A) All-cause mortality

B) Combined end point

C) Prolonged hospital stay

D) Stroke disability at hospital

Table 1: Characteristics of sample population by level of estimated glomerular filtration rate

(N=10,329)	Overall	Level of estimated glomerular filtration rate (mL/min/1.73m²) ≥90 (n=1,106)	60-89 (4,866)	45-59 (2,177)	30-44 (1,427)	15-29 (n=596)	<15 (n=157)	p
Age (years)	77.8 ± 11.9	59.7 ± 12.8	77.1 ± 10.4	81.8 ± 8.9	84.2 ± 7.9	83.8 ± 8.5	78.5 ± 12.1	<0.001
Sex (male)	47.5 (4,902)	62.8 (731)	48.9 (2,425)	42.6 (938)	38.5 (556)	40.8 (247)	50.3 (79)	<0.001
History of stroke*, %(n)	24.6 (2,474)	16.3 (173)	23.2 (1,100)	26.8 (572)	28.2 (394)	33.4 (196)	26.5 (39)	<0.001
Stroke type (Ischemic), %(n)	86.6 (8,942)	80.4 (889)	84.9 (4,135)	88.3 (1,923)	90.7 (1,294)	93.3 (556)	92.4 (145)	<0.001
OSCP classification*								<0.001
-TACS	20.9 (2,028)	14.5 (149)	19.7 (895)	22.8 (470)	23.8 (322)	27.5 (157)	23.8 (35)	
-PACS	33.2 (3,215)	29.1 (299)	33.1 (1,503)	34.9 (720)	35.3 (478)	31.2 (178)	25.2 (37)	
-LACS	22.6 (2,188)	24.7 (253)	23.6 (1,072)	21.9 (452)	20.9 (284)	18.3 (104)	15.7 (23)	
-POCS	16.8 (1,629)	24.3 (249)	17.6 (799)	14.3 (294)	13.4 (181)	14.4 (82)	16.3 (24)	
-Other	6.6 (638)	7.3 (76)	5.9 (269)	6.1 (127)	6.5 (89)	8.5 (49)	19.1 (28)	
Pre-stroke mRS*								
-0	63.3 (6,113)	76.7 (779)	67.8 (3,121)	60.7 (1,236)	51.9 (677)	42.1 (230)	39.7 (50)	<0.001
-1	12.1 (1,167)	9.9 (103)	12.3 (566)	11.2 (228)	12.8 (167)	15.4 (84)	15.1 (19)	
-2	8.2 (794)	5.7 (59)	7.4 (341)	8.9 (182)	10.1 (131)	12.1 (66)	11.9 (15)	
-3	9.5 (918)	4.4 (46)	7.4 (339)	11.4 (232)	14.0 (183)	17.8 (97)	16.7 (23)	
-4	4.8 (466)	2.1 (22)	3.7 (171)	4.9 (100)	8.3 (108)	10.3 (56)	7.1 (9)	
-5	2.0 (197)	1.3 (13)	1.4 (63)	2.9 (58)	2.9 (38)	2.4 (13)	9.5 (12)	
Diabetes, %(n)	14.6 (1,505)	11.6 (128)	11.6 (564)	13.4 (291)	15.3 (218)	21.1 (126)	28.0 (44)	<0.001
Hypertension, %(n)	51.8 (5,354)	32.0 (354)	46.2 (2,249)	48.9 (1,064)	52.6 (750)	59.4 (354)	59.9 (94)	<0.001
Dyslipidemia, %(n)	10.3 (1,062)	11.5 (127)	9.8 (478)	8.5 (186)	7.6 (109)	8.1 (48)	9.6 (15)	0.059
Coronary heart disease, %(n)	23.4 (2,417)	9.5 (105)	18.7 (912)	23.3 (507)	29.4 (419)	35.2 (210)	37.6 (59)	<0.001
Heart failure, %(n)	11.8 (1,219)	3.4 (38)	7.5 (365)	12.4 (271)	17.8 (254)	28.0 (167)	27.4 (43)	<0.001
Atrial fibrillation, %(n)	26.9 (2,786)	8.1 (89)	22.6 (1,098)	29.2 (635)	32.4 (463)	36.1 (215)	27.4 (43)	<0.001
Length of hospital stay (days)	8 (4 – 18)	6 (2 – 12)	7 (3 – 16)	10 (4 – 20)	11 (4 – 21)	11 (5 – 23)	8 (3 – 18)	<0.001

Abbreviations: OSCP=Oxfordshire Community Stroke Project; TACS: total anterior circulation stroke; PACS: partial anterior circulation stroke; LACS: lacunar stroke; POCS: posterior circulation stroke; mRS=modified Rankin score

Continuous variables with normal distribution are presented as mean ± standard deviation and non-normal distribution are presented as median (interquartile interval); categorical variables are presented as percentages (n)

*253 participants missing information on previous stroke, 631 on OSCP classification and 674 on mRS

Table 2: Clinical outcomes in patients with stroke during follow-up according to eGFR level

	Level of eGFR (mL/min/1.73m²)					
(N=10,329)	≥90 (n=1,106)	60-89 (4,866)	45-59 (2,177)	30-44 (1,427)	15-29 (n=596)	<15 (n=157)
All-cause mortality						
- % (n)	27.0 (299)	45.8 (2229)	57.5 (1251)	69.7 (995)	80.5 (480)	86.6 (136)
- incidence rate (1000-person years)	71 (63 – 80)	143 (138 – 149)	196 (186 – 207)	335 (315 – 357)	563 (514 – 615)	760 (642 – 899)
Recurrent stroke						
- % (n)	7.1 (79)	8.7 (423)	8.8 (192)	8.7 (124)	5.9 (35)	4.5 (7)
- incidence rate (1000-person years)	20 (16 – 24)	28 (26 – 31)	32 (28 – 37)	45 (38 – 53)	43 (31 – 60)	41 (19 – 85)
Myocardial infarction						
- % (n)	1.1 (12)	1.9 (95)	2.5 (55)	2.4 (34)	3.0 (18)	3.2 (5)
- incidence rate (1000-person years)	3.3 (1.9 – 5.6)	7.4 (6.1 – 8.9)	9.9 (7.7 – 12.6)	13 (9 – 18)	24 (15– 37)	28 (12 – 68)
Prolonged hospital stay, % (n)						
- above median (>8 days)	35.0 (387)	45.8 (2,227)	54.4 (1,182)	57.9 (827)	57.9 (345)	49.0 (77)
Stroke disability*†, %(n)						
- Mild (0-1)	46.9 (379)	32.4 (1,074)	22.7 (304)	18.6 (172)	12.0 (48)	14.2 (18)
- Moderate (2-3)	21.6 (175)	23.8 (790)	22.1 (296)	17.8 (165)	14.8 (59)	14.9 (19)
- Severe (4-6)	31.5 (255)	43.8 (1,454)	55.3 (742)	63.6 (589)	73.2 (292)	70.9 (90)

Abbreviation: eGFR=estimated glomerular filtration rate

*assessed using modified Rankin score; †N=6,921 as 3,408 patients were missing information on stroke disability at discharge

Table 3: Association of eGFR at admission with clinical outcomes during follow-up in patients with stroke

Abbreviation: eGFR=estimated glomerular filtration rate. Missing information was handled with multiple imputation.

	Level of eGFR (mL/min/1.73m^2)					
(N=10,329)	≥90 (n=1,106)	60-89 (4,866)	45-59 (2,177)	30-44 (1,427)	15-29 (n=596)	<15 (n=157)
			Hazard ratio (95% Confidence interval)†			
All-cause mortality						
-Model 1	Ref.	0.81 (0.71 – 0.93)	0.87 (0.75 – 1.00)	1.18 (1.02 – 1.37)	1.56 (1.33 – 1.84)	2.64 (2.14 – 3.26)
-Model 2	Ref.	0.91 (0.80 – 1.04)	0.96 (0.83 – 1.11)	1.23 (1.06 – 1.43)	1.54 (1.31 – 1.82)	2.38 (1.91 – 2.97)
<30 day						
-Model 1	Ref.	0.66 (0.55 – 0.80)	0.69 (0.56 – 0.84)	0.84 (0.67 – 1.04)	1.19 (0.95 – 1.51)	2.15 (1.61 – 2.87)
-Model 2	Ref.	0.77 (0.64 – 0.94)	0.80 (0.64 – 0.98)	1.00 (0.81 – 1.25)	1.26 (0.99 – 1.60)	2.19 (1.62 – 2.96)
30-365 day						
-Model 1	Ref.	0.74 (0.57 – 0.96)	0.82 (0.62 – 1.08)	1.08 (0.81 – 1.43)	1.53 (1.13 – 2.08)	2.65 (1.75 – 4.00)
-Model 2	Ref.	0.81 (0.63 – 1.05)	0.87 (0.66 – 1.15)	1.13 (0.85 – 1.51)	1.43 (1.05 – 1.96)	2.47 (1.63 – 3.75)
Over 365 day						
-Model 1	Ref.	1.19 (0.92 – 1.54)	1.29 (0.98 – 1.69)	1.71 (1.28 – 2.27)	2.42 (1.76 – 3.34)	3.45 (2.16 – 5.52)
-Model 2	Ref.	1.21 (0.94 – 1.57)	1.27 (0.97 – 1.68)	1.67 (1.25 – 2.23)	2.10 (1.51 – 2.91)	2.64 (1.63 – 4.28)
Recurrent stroke						
-Model 1	Ref.	1.11 (0.85 – 1.44)	1.13 (0.83 – 1.53)	1.43 (1.03 – 2.00)	1.25 (0.82 – 1.92)	1.23 (0.55 – 2.74)
-Model 2	Ref.	1.05 (0.81 – 1.38)	1.06 (0.77 – 1.43)	1.33 (0.95 – 1.87)	1.14 (0.74 – 1.77)	1.21 (0.54 – 2.69)
Myocardial infarction						
-Model 1	Ref.	1.46 (0.81 – 2.63)	1.74 (0.91 – 3.32)	2.10 (1.05 – 4.21)	3.60 (1.70 – 7.63)	4.74 (1.65 – 13.65)
-Model 2	Ref.	1.33 (0.74 – 2.40)	1.56 (0.82 – 2.97)	1.82 (0.91 – 3.63)	2.96 (1.37 – 6.39)	4.06 (1.40 – 11.75)
			Odds ratio (95% Confidence interval)			
Prolonged hospital stay*						
- Model 1	Ref.	0.88 (0.75 – 1.04)	1.14 (0.94 – 1.37)	1.35 (1.09 – 1.67)	1.63 (1.23 – 2.15)	2.12 (1.28 – 3.51)
- Model 2	Ref.	0.95 (0.81 – 1.13)	1.19 (0.97 – 1.49)	1.44 (1.15 – 1.80)	1.60 (1.20 – 2.13)	1.99 (1.19 – 3.35)
Stroke disability						
- Model 1	Ref.	0.84 (0.74 – 0.97)	1.03 (0.88 – 1.21)	1.24 (1.03 – 1.48)	1.94 (1.56 – 2.41)	3.73 (2.57 – 5.40)
- Model 2	Ref.	0.98 (0.85 – 1.13)	1.14 (0.94 – 1.38)	1.34 (1.09 – 1.66)	1.93 (1.54 – 2.44)	3.47 (2.32 – 5.21)

†For recurrent stroke and myocardial infarction it is sub-distribution hazard ratio from competing risk regression analysis

*N=8,054, as patients who were dead at discharge were excluded (n=2,275)

Model 1: Age and sex

Model 2: Model 1 + history of stroke, stroke type, pre-stroke modified Rankin score, stroke severity, diabetes, hypertension, dyslipidemia, atrial fibrillation, heart failure, coronary heart disease, pneumonia

Table 4: Association of change in eGFR during hospital stay with clinical outcomes in patients with stroke

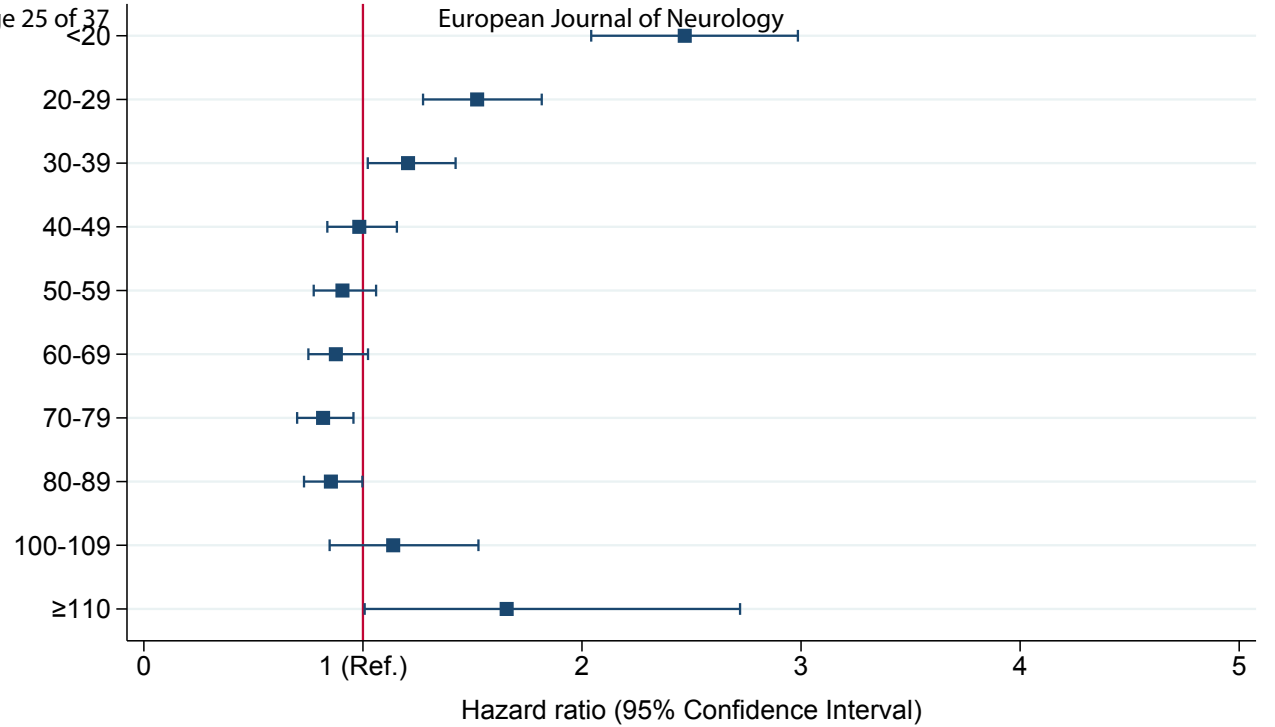
	Change in eGFR during hospital stay				
	Decline >20%	**Decline 5-20%**	**Within 5% of eGFR at admission**	**Increase 5-20%**	**Increase >20%**
			Hazard ratio (95% Confidence interval)*		
All-cause mortality (N= 8,021)†	484	1,296	3,721	1,263	1,257
-Events, %(n)	52.7 (255)	38.0 (493)	27.9 (1,041)	46.5 (587)	56.2 (706)
-Model 1	1.52 (1.32 – 1.74)	1.17 (1.05 – 1.30)	Ref.	1.40 (1.27 – 1.56)	1.58 (1.43 – 1.76)
-Model 2	1.56 (1.36 – 1.79)	1.17 (1.05 – 1.30)	Ref.	1.47 (1.32 – 1.62)	1.71 (1.55 – 1.88)
Recurrent stroke (N=7,928)	483	1,292	3,637	1,260	1,256
-Events, %(n)	13.2 (64)	10.5 (135)	11.3 (412)	10.9 (138)	7.4 (93)
-Model 1	1.11 (0.85 – 1.45)	0.85 (0.70 – 1.03)	Ref.	0.98 (0.80 – 1.19)	0.69 (0.55 – 0.87)
-Model 2	1.08 (0.82 – 1.41)	0.83 (0.69 – 1.02)	Ref.	0.97 (0.80 – 1.18)	0.68 (0.54 – 0.86)
Myocardial infarction (N=7,937)	483	1,293	3,643	1,261	1,257
-Events, %(n)	4.6 (22)	2.8 (36)	2.9 (107)	2.6 (33)	3.1 (39)
-Model 1	1.68 (1.10 – 2.57)	0.91 (0.63 – 1.32)	Ref.	0.93 (0.63 – 1.36)	1.22 (0.85 – 1.74)
-Model 2	1.66 (1.08 – 2.54)	0.92 (0.64 – 1.34)	Ref.	0.98 (0.67 – 1.45)	1.34 (0.93 – 1.93)
			Odds ratio (95% Confidence interval)		
Stroke disability (N=6,921)	529	796	3,511	963	1,122
-Events (severe), %(n)	68.1 (360)	37.6 (299)	40.7 (1,430)	53.4 (514)	72.9 (819)
-Model 1	2.06 (1.62 – 2.61)	1.47 (1.26 – 1.71)	Ref.	2.79 (2.39 – 3.26)	4.89 (4.13 – 5.78)
-Model 2	1.93 (1.52 – 2.46)	1.38 (1.18 – 1.61)	Ref.	2.54 (2.18 – 2.97)	4.14 (3.39 – 4.91)

Abbreviation: eGFR=estimated glomerular filtration rate. Missing information was handled with multiple imputation

*sub-distribution hazard ratios for recurrent stroke and myocardial infarction from competing risk regression analysis, †excluded patients who were dead at discharge

Model 1: Age, sex and length of hospital stay

Model 2: Model 1 + history of stroke, stroke type, pre-stroke modified Rankin score, stroke severity, diabetes, hypertension, dyslipidemia, atrial fibrillation, heart failure, coronary heart disease, pneumonia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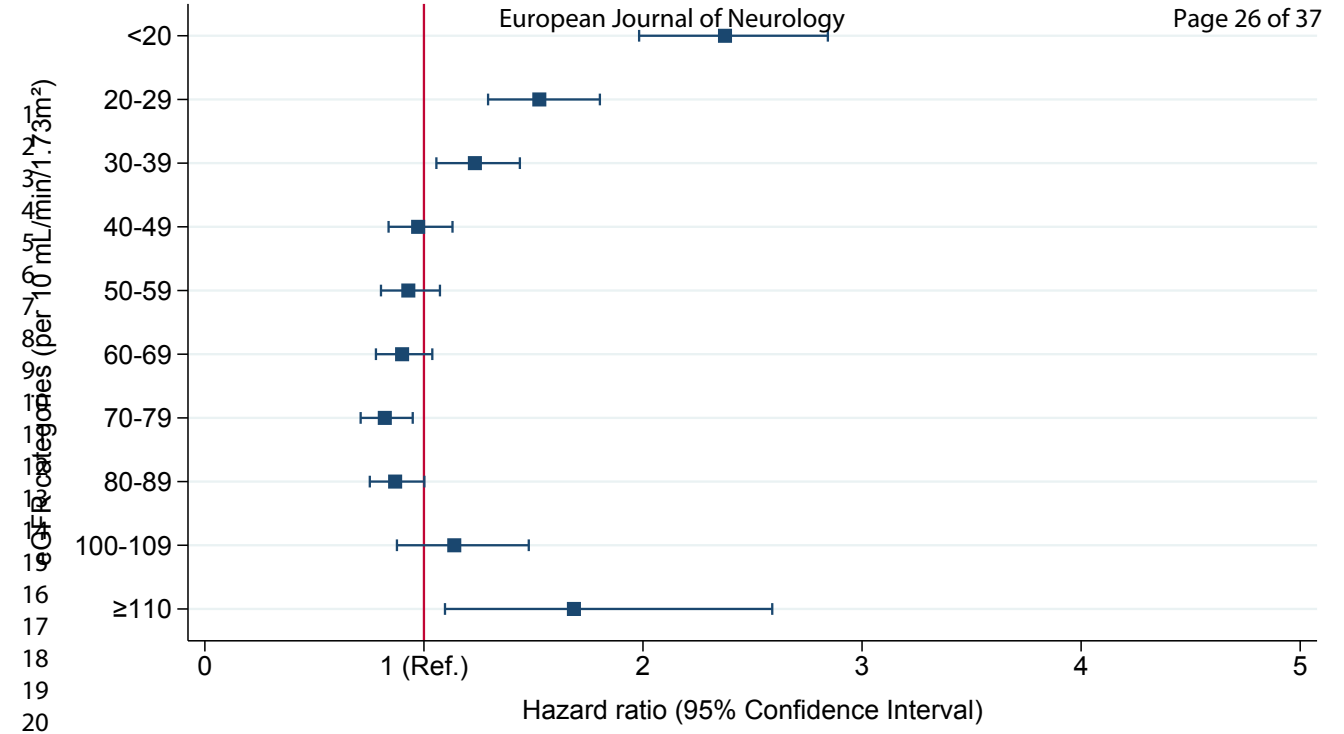
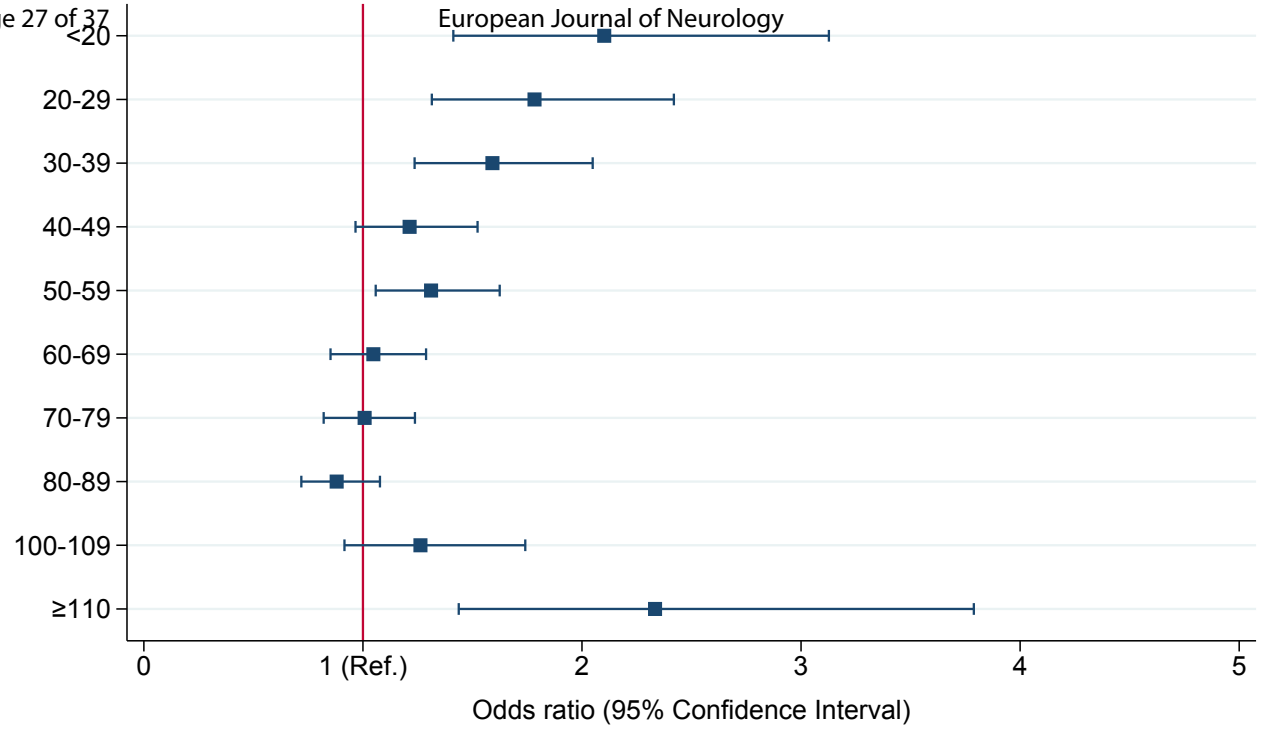
30-39
40-49
50-59
60-69
70-79
80-89
100-109
≥110
0
1 (Ref.)
2
3
4
5
Hazard ratio (95% Confidence Interval)


<20
20-29
30-39
40-49
50-59
60-69
70-79
80-89
100-109
≥110
eGFR categories (per 10 mL/min/1.73m²)
0
1 (Ref.)
2
3
4
5
Hazard ratio (95% Confidence Interval)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50-59
60-69
70-79
80-89
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≥110
eGFR categories (per 10 mL/min/1.73m²)
0
1 (Ref.)
2
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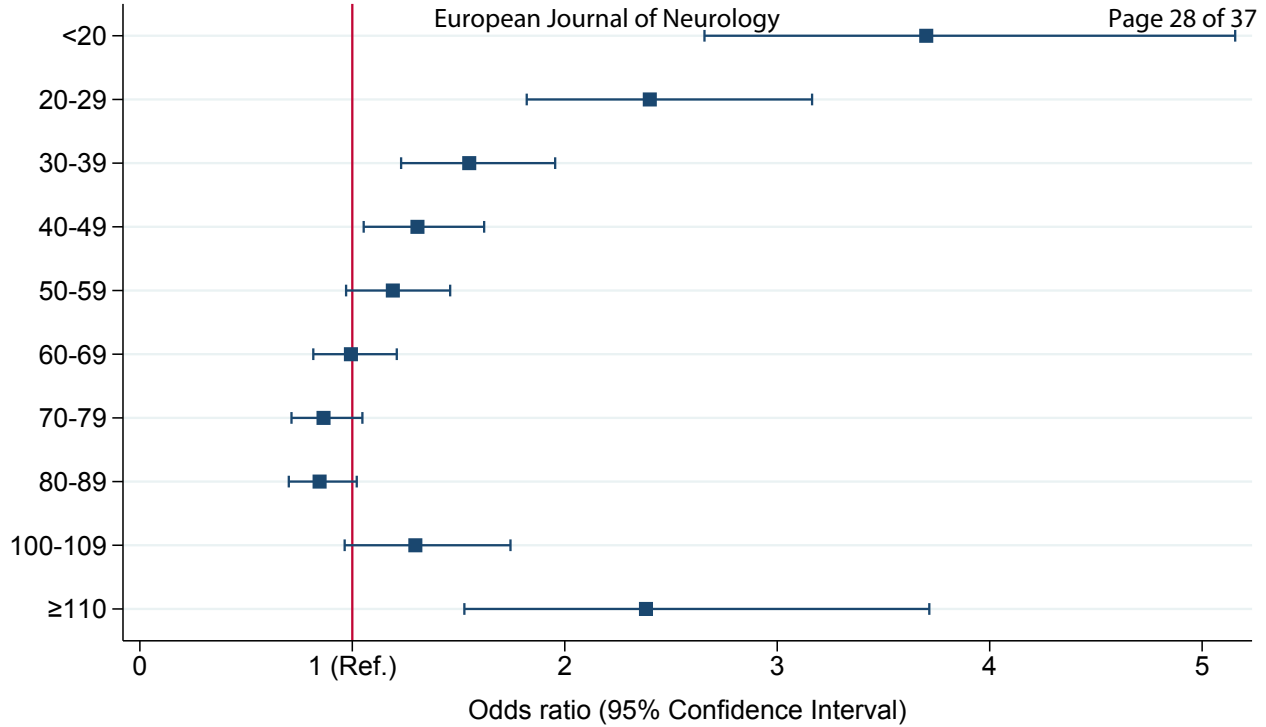
4
5
Odds ratio (95% Confidence Interval)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20-29
30-39
40-49
50-59
60-69
70-79
80-89
100-109
≥110
eGFR categories (per 10 mL/min/1.73m²)
0
1 (Ref.)
2
3
4
5
Odds ratio (95% Confidence Interval)

Supplemental material

Estimated glomerular filtration rate and risk of poor outcomes after stroke

Contents

Table S1: Association between estimated glomerular filtration rate and <u>all-cause mortality</u> in stroke patients stratified by high risk groups

	Level of estimated glomerular filtration rate (mL/min/1.73m^2)						
(N=10,329)	≥90 (n=1,106)	60-89 (4,866)	45-59 (2,177)	30-44 (1,427)	15-29 (n=596)	<15 (n=157)	*p* for interaction
	Hazard ratio (95% Confidence interval)*						
Diabetes							
- No	Ref.	0.85 (0.74 – 0.98)	0.90 (0.77 – 1.05)	1.14 (0.97 – 1.34)	1.47 (1.23 – 1.76)	2.34 (1.83 – 2.99)	0.64
- Yes	Ref.	1.17 (0.82 – 1.68)	1.13 (0.77 – 1.64)	1.50 (1.02 – 2.21)	1.76 (1.17 – 2.65)	2.55 (1.59 – 4.09)	
Hypertension							
- No	Ref.	0.81 (0.68 – 0.95)	0.80 (0.67 – 0.97)	1.00 (0.82 – 1.21)	1.42 (1.13 – 1.78)	1.85 (1.34 – 2.57)	0.17
- Yes	Ref.	1.07 (0.85 – 1.35)	1.17 (0.92 – 1.48)	1.50 (1.18 – 1.92)	1.75 (1.35 – 2.26)	3.07 (2.25 – 4.21)	

*results are from fully adjusted model (adjusted for Age, sex, history of stroke, pre-stroke modified Rankin score, stroke severity, diabetes, hypertension, dyslipidemia, heart failure, arterial fibrillation, coronary heart disease, pneumonia)

Table S2: Association between estimated glomerular filtration rate and composite outcome (all-cause mortality, recurrent stroke and myocardial infarction) in stroke patients stratified by high risk groups

	Level of estimated glomerular filtration rate (mL/min/1.73m²)						
(N=10,329)	≥90 (n=1,106)	60-89 (4,866)	45-59 (2,177)	30-44 (1,427)	15-29 (n=596)	<15 (n=157)	p for interaction
	Hazard ratio (95% Confidence interval)*						
Diabetes							
- No	Ref.	0.85 (0.74 – 0.96)	0.89 (0.77 – 1.03)	1.11 (0.96 – 1.29)	1.42 (1.20 – 1.68)	2.19 (1.72 – 2.79)	0.66
- Yes	Ref.	1.17 (0.84 – 1.63)	1.17 (0.82 – 1.65)	1.54 (1.08 – 2.20)	1.83 (1.25 – 2.68)	2.37 (1.51 – 3.71)	
Hypertension							
- No	Ref.	0.84 (0.72 – 0.98)	0.85 (0.72 – 1.01)	1.07 (0.89 – 1.29)	1.49 (1.19 – 1.85)	1.89 (1.37 – 2.61)	0.19
- Yes	Ref.	0.96 (0.79 – 1.17)	1.03 (0.83 – 1.26)	1.29 (1.04 – 1.60)	1.52 (1.21 – 1.91)	2.50 (1.87 – 3.33)	

*results are from fully adjusted model (adjusted for Age, sex, history of stroke, pre-stroke modified Rankin score, stroke severity, diabetes, hypertension, dyslipidemia, heart failure, arterial fibrillation, coronary heart disease, pneumonia)

Table S3: Association between estimated glomerular filtration rate and prolonged hospital stay in stroke patients stratified by high risk groups

	Level of estimated glomerular filtration rate (mL/min/1.73m^2)						
(N=10,329)	≥90 (n=1,106)	60-89 (4,866)	45-59 (2,177)	30-44 (1,427)	15-29 (n=596)	<15 (n=157)	p for interaction
	Hazard ratio (95% Confidence interval)*						
Diabetes							
- No	Ref.	0.94 (0.78 – 1.13)	1.22 (0.99 – 1.51)	1.43 (1.12 – 1.82)	1.67 (1.21 – 2.31)	2.59 (1.35 – 4.99)	0.75
- Yes	Ref.	1.10 (0.69 – 1.75)	1.28 (0.77 – 2.14)	1.61 (0.92 – 2.79)	1.47 (0.77 – 2.82)	1.55 (0.62 – 3.87)	
Hypertension							
- No	Ref.	1.07 (0.86 – 1.34)	1.37 (1.04 – 1.79)	1.80 (1.30 – 2.49)	1.42 (0.89 – 2.26)	2.91 (1.11 – 7.58)	0.47
- Yes	Ref.	0.81 (0.62 – 1.06)	1.05 (0.79 – 1.41)	1.15 (0.84 – 1.58)	1.53 (1.05 – 2.24)	1.64 (0.87 – 3.09)	

*results are from fully adjusted model (adjusted for Age, sex, history of stroke, pre-stroke modified Rankin score, stroke severity, diabetes, hypertension, dyslipidemia, heart failure, arterial fibrillation, coronary heart disease, pneumonia)

Table S4: Association between estimated glomerular filtration rate and disability at discharge in stroke patients stratified by high risk groups

	Level of estimated glomerular filtration rate (mL/min/1.73m^2)						
(N=10,329)	≥90 (n=1,106)	60-89 (4,866)	45-59 (2,177)	30-44 (1,427)	15-29 (n=596)	<15 (n=157)	p for interaction
	Odds ratio (95% Confidence interval)*						
Diabetes							
- No	Ref.	0.89 (0.75 – 1.07)	1.13 (0.92 – 1.40)	1.41 (1.12 – 1.78)	2.41 (1.77 – 3.28)	2.83 (1.71 – 4.69)	0.49
- Yes	Ref.	1.10 (0.69 – 1.75)	1.28 (0.77 – 2.14)	1.61 (0.92 – 2.79)	1.47 (0.77 – 2.82)	1.55 (0.62 – 3.87)	
Hypertension							
- No	Ref.	1.07 (0.86 – 1.34)	1.37 (1.04 – 1.79)	1.80 (1.30 – 2.49)	1.42 (0.89 – 2.26)	2.91 (1.11 – 7.58)	0.65
- Yes	Ref.	0.80 (0.64 – 0.99)	1.10 (0.83 – 1.45)	1.51 (1.09 – 2.08)	2.49 (1.57 – 3.96)	3.75 (1.77 – 7.92)	

*P<0.05 for interaction for all subgroups in fully adjusted model (adjusted for Age, sex, history of stroke, pre-stroke modified Rankin score, stroke severity, diabetes, hypertension, dyslipidemia, heart failure, arterial fibrillation, coronary heart disease, pneumonia)

Table S5: Results after adjusting for estimated glomerular filtration rate at admission for the association between change in estimated glomerular filtration rate during hospital stay and clinical outcomes in patients with stroke

	Change in eGFR during hospital stay				
	Decline >20%	**Decline 5-20%**	**Within 5% of eGFR at admission**	**Increase 5-20%**	**Increase >20%**
			Hazard ratio (95% Confidence interval)*		
All-cause mortality (N= 8,021)†	484	1,296	3,721	1,263	1,257
- Events, % (n)	52.7 (255)	38.0 (493)	27.9 (1,041)	46.5 (587)	56.2 (706)
- Model 1	1.58 (1.37 – 1.81)	1.23 (1.10 – 1.37)	Ref.	1.52 (1.37 - 1.68)	1.72 (1.55 – 1.91)
- Model 2	1.50 (1.31 – 1.73)	1.19 (1.06 – 1.32)	Ref.	1.42 (1.28 – 1.58)	1.52 (1.37 – 1.69)
Recurrent stroke (N=7,928)	483	1,292	3,637	1,260	1,256
- Events, % (n)	13.2 (64)	10.5 (135)	11.3 (412)	10.9 (138)	7.4 (93)
- Model 1	1.09 (0.83 – 1.42)	0.85 (0.70 – 1.03)	Ref.	0.96 (0.79 – 1.16)	0.63 (0.50 – 0.80)
- Model 2	1.09 (0.78 – 1.53)	0.87 (0.73 – 1.04)	Ref.	0.92 (0.76 – 1.11)	0.72 (0.55 – 0.93)
Myocardial infarction (N=7,937)	483	1,293	3,643	1,261	1,257
- Events, % (n)	4.6 (22)	2.8 (36)	2.9 (107)	2.6 (33)	3.1 (39)
- Model 1	1.62 (1.06 – 2.48)	0.91 (0.63 – 1.32)	Ref.	0.88 (0.60 – 1.29)	0.97 (0.67 – 1.41)
- Model 2	1.60 (1.04 – 2.46)	0.93 (0.64 – 1.34)	Ref.	0.95 (0.65 – 1.40)	1.13 (0.77 – 1.66)
			Odd ratio (95% Confidence interval)		
Prolonged hospital stay (N=8,021)†	491	1,293	3,656	1,264	1,264
- Events, % (n)	68.2 (335)	57.9 (749)	29.5 (1,080)	67.9 (859)	82.8 (1,046)
- Model 1	4.58 (3.72 – 5.63)	3.25 (2.84 – 3.72)	Ref.	4.96 (4.31 – 5.71)	11.08 (9.30 – 13.20)
- Model 2	4.49 (3.63 – 5.56)	3.27 (2.85 – 3.75)	Ref.	4.53 (3.92 – 5.25)	9.17 (7.67 – 10.97)
Stroke disability (N=6,921)	529	796	3,511	963	1,122
- Events (severe), % (n)	68.1 (360)	37.6 (299)	40.7 (1,430)	53.4 (514)	72.9 (819)
- Model 1	2.17 (1.70 – 2.79)	1.50 (1.27 – 1.77)	Ref.	2.97 (2.52 – 3.49)	6.16 (5.09 – 7.46)
- Model 2	2.12 (1.64 – 2.75)	1.48 (1.24 – 1.75)	Ref.	2.62 (2.21 – 3.11)	5.03 (4.11 – 6.15)

*sub-distribution hazard ratios for recurrent stroke and myocardial infarction from competing risk regression analysis, †excluded patients who were dead at discharge

Model 1: Age, sex and length of hospital stay

Model 2: Model 1 + history of stroke, stroke type, pre-stroke modified Rankin score, stroke severity, diabetes, hypertension, dyslipidemia, atrial fibrillation, heart failure, coronary heart disease, pneumonia

Table S6: Results after using a different cut-off of change in estimated glomerular filtration rate during hospital stay for its association with clinical outcomes in patients with stroke

	Change in eGFR during hospital stay				
	Decline >25%	**Decline 5-25%**	**Within 5% of eGFR at admission**	**Increase 5-25%**	**Increase >25%**
	Hazard ratio (95% Confidence interval)*				
All-cause mortality (N= 8,021)†	296	1,484	3,721	1,506	1,014
- Events, % (n)	53.4 (158)	39.7 (590)	27.9 (1,041)	47.1 (710)	57.5 (583)
- Model 1	1.63 (1.38 – 1.93)	1.27 (1.15 – 1.41)	Ref.	1.55 (1.41 - 1.71)	2.01 (1.82 – 2.23)
- Model 2	1.53 (1.29 – 1.81)	1.22 (1.11 – 1.36)	Ref.	1.43 (1.30 – 1.58)	1.75 (1.58 – 1.95)
Recurrent stroke (N=7,928)†	295	1,480	3,637	1,503	1,013
- Events, % (n)	12.9 (38)	10.9 (161)	11.3 (412)	10.4 (156)	7.4 (75)
- Model 1	1.14 (0.81 – 1.60)	0.88 (0.74 – 1.06)	Ref.	0.92 (0.77 – 1.11)	0.73 (0.57 – 0.94)
- Model 2	1.06 (0.96 – 1.17)	0.83 (0.69 – 1.02)	Ref.	0.97 (0.80 – 1.18)	0.68 (0.58 – 0.95)
Myocardial infarction (N=7,937)†	295	1,481	3,643	1,504	1,014
- Events, % (n)	3.4 (10)	3.2 (48)	2.9 (107)	2.7 (40)	3.2 (32)
- Model 1	1.58 (1.03 – 2.48)	1.00 (0.71 – 1.41)	Ref.	0.89 (0.62 – 1.28)	1.21 (0.81 – 1.81)
- Model 2	1.53 (1.00 – 2.45)	0.93 (0.64 – 1.34)	Ref.	0.95 (0.65 – 1.40)	1.13 (0.77 – 1.66)
	Odd ratio (95% Confidence interval)				
Stroke disability (N=6,921)†	401	924	3,511	1,138	947
- Events (severe), % (n)	72.6 (291)	39.8 (368)	40.7 (1,430)	56.3 (641)	73.1 (692)
- Model 1	4.06 (3.22 – 5.12)	1.14 (0.99 – 1.30)	Ref.	2.07 (1.81 – 2.36)	3.92 (3.34 – 4.60)
- Model 2	4.01 (3.12 – 5.17)	1.22 (1.05 – 1.42)	Ref.	1.87 (1.62 – 2.17)	3.54 (2.96 – 4.22)

*sub-distribution hazard ratios for recurrent stroke and myocardial infarction from competing risk regression analysis, †excluded patients who were dead at discharge

Model 1: Age, sex and length of stay

Model 2: Model 1 + history of stroke, stroke type, pre-stroke modified Rankin score, stroke severity, diabetes, hypertension, dyslipidemia, atrial fibrillation, heart failure, coronary heart disease, pneumonia

Figure S1: Proportional hazard assumption test for all-cause mortality