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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

More than a third of stroke patients have low estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73m^2) at hospital admission [1,2]. 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 [3-5]. 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.

This study aimed to examine the association of eGFR categorised as per recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines [6] 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. Details of data collection has been described previously [7]. Briefly, data was originally obtained in paper-form which was reviewed and entered onto the register database by the hospital stroke data team and was linked with electronic records [8]. 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. Because Norfolk and Norwich Stroke registry was a research database of all consecutive patients, individual patients were not required to provide written informed consent.

Between January 2003 and April 30, 2015, 10,683 cases of ischemic or hemorrhagic stroke patients (age ≥18 years) 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 on variable needed to obtain eGFR i.e. 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, 10,329 stroke patients were available for analysis.

Estimated glomerular filtration rate

Two serum creatinine measurements were obtained, once on hospital admission and another near to hospital discharge (alive or dead) using the Jaffe method and standardized to isotype dilution mass spectrometry values. eGFR was obtained using serum creatinine based Chronic

Kidney Disease-Epidemiology collaboration equation [9]. Chronic Kidney Disease-Epidemiology collaboration equation employ separate equation for subjects of non-white origin. We lacked data on race/ethnicity. However, non-white ethnicity makes less than 2% of Norwich population. Thus, eGFR misclassification due to lack of information on race/ethnicity is likely to be minimal [10]. As per KDIGO guidelines [6], admission eGFR was categorized into following stages: <15, 15-29, 30-44, 45-59, 60-89 and ≥90 mL/min/1.73m^2.

Covariates

Specialist stroke nurses or doctors collected information on demographic factors including age and sex, and information on medical history including history of stroke, type of stroke (ischemic or hemorrhagic), pre-stroke modified Rankin Score (mRS) (modified by the UK transient ischemic attack investigators) [11] (0-5), and Oxfordshire Community Stroke Project (OCSP) Classification. Co-morbidities including diabetes, hypertension, dyslipidaemia, heart failure, atrial fibrillation, coronary heart disease and pneumonia were obtained through linking registry data to electronic health record.

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 [12] was performed to calculate sub-distribution HRs for recurrent stroke and incident myocardial infarction, considering all-cause mortality as a competing risk. 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 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.

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% [13]. 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)) [14].

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

Additional analyses

First, we tested for interaction and presented results by stratifying according to two major high risk groups including diabetes and hypertension status (no/yes). Second, we examined association between eGFR change and outcomes when adjusting for baseline eGFR. Third, 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). Finally, because ischemic stroke and hemorrhagic stroke can have different prognosis, we also examined results when analyzing data by stroke type.

Results

Baseline characteristics

Table 1 shows characteristics of sample population presented according to eGFR levels. 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% decline or increase 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). 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). There were a total of 8,942 cases of ischemic stroke and 1,387 cases of hemorrhagic stroke. When analyzing data by stroke type, results were essentially similar to overall results except that there were not sufficient number of events for myocardial infarction in hemorrhagic stroke (eTables 7-10).

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 [3-5], 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, to 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. Similar findings has been observed previously in general population cohorts [15,16]. These findings are 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.

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. It could also be because of withdrawal of antihypertensive agents (especially ACEi/ARB) which lowers kidney function.

Withdrawal of antihypertensive agents is commonly done in the patients presenting with acute stroke [17]. Causes of increased risk for poor prognosis with increase in eGFR during hospital stay is unclear to us. It is 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 [15,16].

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 [3] or found association with stroke reoccurrence only in a composite outcome analysis [4]. Similar to our study, one study that examined non-fatal stroke recurrence found no association between low eGFR and stroke recurrence [18]. Lack of association between eGFR and stroke has also been observed in other high risk populations such as those with chronic kidney disease [19].

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 creatinine based high eGFR values since high eGFR 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 [20], and thus may not provide the most reliable assessment of kidney function, particularly in chronically ill patients where Cystatin C may be used for more accurate assessment of kidney function [21]. 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.

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. Furthermore, 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

		Level of estimated glomerular filtration rate (mL/min/1.73m^2)						
	Overall	≥90	60-89	45-59	30-44	15-29	<15	p
(N=10,329)		(n=1,106)	(4,866)	(2,177)	(1,427)	(n=596)	(n=157)	
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/1.73m^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)
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

	Level of eGFR (mL/min/1.73m^2)					
	≥90	60-89	45-59	30-44	15-29	<15
(N=10,329)	(n=1,106)	(4,866)	(2,177)	(1,427)	(n=596)	(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)

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