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Estimated glomerular filtration rate and risk of poor outcomes after stroke

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Manuscripts

1   **Estimated glomerular filtration rate and risk of poor outcomes after stroke**

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19   **Running title:** eGFR and prognosis after stroke

20   **Abstract word count:** 245

21   **Manuscript word count:** 3,500 (title page, abstract, main text, acknowledgement)

22   **Key words:** eGFR; stroke; prognosis; mortality; disability

23   **Abstract**

24   **Background:** Relationship of estimated glomerular filtration rate (eGFR) with complications

25   after stroke has not been fully characterized for entire clinical spectrum of eGFR and for the

26   fluctuation in eGFR during hospital stay.

27   **Methods:** Data from the Norfolk and Norwich Stroke Registry recorded between January

28   2003 and April 2015 was analysed. eGFR was categorized into six clinically relevant

29   categories as per Kidney Disease Improving Global Outcomes guidelines. Change in eGFR

30   during acute admission was categorized into: within 5% change (ref.), 5-20% decline, >20%

31   decline, 5-20% increase and >20% increase. All-cause mortality, recurrent stroke, incident

32   myocardial infarction, prolonged hospital stay and stroke disability at discharge were

33   outcomes of interest.

34   **Results:** 10,329 stroke patients (mean age 77.8 years) were followed for a mean of 2.9 years

35   (30,126 person years). Multivariable adjusted hazard ratios (HRs) (95%CI) for all-cause

36   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

37   (1.91-2.97) for eGFR levels 60-89, 45-59, 30-44, 15-29 and <15 respectively, compared to

38   eGFR $\geq$90 mL/min/1.73m^2. The HR (95%CI) for eGFR change were 1.56 (1.36-1.79), 1.17

39   (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%

40   increase and >20 % increase, respectively, compared to change within 5%. Results were

41   similar for other outcomes except recurrent stroke.

42   **Conclusions:** Stroke patients with eGFR <45 mL/min/1.73m^2 at hospital admission and > 5%

43   decline or increase in eGFR during hospital stay were at substantially high risk of poor

44   outcomes, particularly all-cause mortality, myocardial infarction, prolonged hospital stay and

45   disability at discharge.

46 **Introduction**

47 Low estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73m^2) is highly prevalent in

48 stroke. Indeed, more than a third of stroke patients has been found to have low eGFR at

49 hospital admission [1-3]. Previous studies suggested that stroke patients with low eGFR are at

50 increased risk of poor clinical outcomes including death, prolonged hospital stay and

51 disability after hospital discharge [4-10]. However, there are few studies assessing the

52 association between eGFR divided into all clinically relevant categories and stroke outcomes.

53 Understanding the size and shape of the association across all clinically relevant categories of

54 eGFR is not only essential for clinical decision making but is also vital in helping patients

55 and their families understand the course of the disease. In addition, in previous studies eGFR

56 was only assessed at single time point on admission, thus whether change in eGFR during

57 hospital stay could be a prognostic factor in stroke patients is virtually unknown. Previously,

58 short term change in eGFR has been shown to be associated with poor clinical outcomes in a

59 general population [11].

60 This study aimed to examine the association of eGFR categorised as per recent

61 Kidney Disease Improving Global Outcomes (KDIGO) guidelines [12] with complications

62 including all-cause mortality, stroke recurrence, incident myocardial infarction, prolonged

63 hospital stay and disability at hospital discharge in stroke patients. In addition, we examined

64 the association between change in eGFR during hospital stay and aforementioned outcomes

65 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-

90   white ethnic origin [16]. As per KDIGO guidelines [12], admission eGFR was categorized

91   into following stages: <15, 15-29, 30-44, 45-59, 60-89 and ≥90 mL/min/1.73m^2.

92   *Covariates*

93   Data on age, sex, history of stroke, type of stroke (ischemic or hemorrhagic), pre-stroke

94   modified Rankin Score (mRS) (modified by the UK transient ischemic attack investigators)

95   [17] (0-5), and Oxfordshire Community Stroke Project (OCSP) Classification were collected

96   by specialist stroke nurses or doctors. For each patient, when admitted data on the pre-stroke

97   mRS were collected from nursing and medical records. Co-morbidities including diabetes,

98   hypertension, dyslipidaemia, heart failure, atrial fibrillation, coronary heart disease and

99   pneumonia were obtained through record linkage.

100   *Outcome(s)*

101   All-cause mortality, recurrent stroke, incident myocardial infarction, prolonged hospital stay,

102   and stroke disability were selected as outcomes for the study purpose. Mortality status was

103   recorded at discharge to record in-hospital mortality. Linkage with the Office of National

104   Statistics was established in UK National Health Service order to obtain follow-up mortality

105   data. Information on recurrent stroke and post stroke incidence of myocardial infarction was

106   obtained through electronic record linkage. Recurrent stroke cases were additionally

107   identified by assessing repeated admission(s) of a patient for stroke recorded in the registry.

108   Prolonged hospital stay was defined as hospital stay longer than median days of hospital stay.

109   Disability at discharge was assessed using mRS scores at hospital discharge and was

110   classified into three groups: mild (0-1), moderate (2-3) and severe (4-6). For all-cause

111   mortality, recurrent stroke and myocardial infarction, patients were followed until May 30,

112   2015 so as to have minimal follow up of one month. For clinical relevance, the risk of <30,

113   30-365 and >365 day mortality was examined separately in addition to overall mortality over

114   the whole follow up.

115   *Statistical analysis*

116   Cox proportional hazards regression analysis was performed to estimate hazard ratios (HRs)

117   for the association between eGFR categories (with eGFR ≥90 mL/min/1.73 m^2 as the

118   reference group) and all-cause mortality. Competing risk regression analysis (using Fine and

119   Gray's method) [18] was performed to calculate sub-distribution HRs for recurrent stroke and

120   incident myocardial infarction, considering all-cause mortality as a competing risk. Bi-

121   nominal logistic regression analyses was performed for prolonged hospital stay and Ordinal

122   logistic regression for stroke disability at discharge. Since death may skew analyses for

123   prolonged hospital stay, this analyses was performed for patients that were alive at discharge.

124   Multivariable models were constructed to adjust for potential confounders. Model 1 was

125   adjusted for demographic factors (age and sex). Model 2 was additionally adjusted for

126   previous stroke, pre-stroke mRS, stroke type, stroke severity (using OCSP classification), and

127   the comorbid conditions listed above. Test of models assumptions indicated that our models

128   fit the data well.

129   The proportional hazards assumption was tested with log-log survival curves. Parallel

130   lines for eGFR categories implied that the proportional-hazards assumption was not violated

131   (eFigure 1). For competing risk regression analysis, proportional hazard assumption was

132   tested by examining the interaction between individual covariates and follow-up time. Model

133   did not violate proportional hazard assumption (p for interaction for each covariate was

134   >0.05). Hosmer and Lemeshow's goodness-of-fit test [19] for binary logistic regression and

135   Log-likelihood ratio as goodness-of-fit test for ordinal logistic regression indicated that our

136   model fitted the data well (p=0.12 and 0.34, respectively).

137   In addition, we explored the association between eGFR distribution and outcomes by

138   dividing eGFR into groups spanning 10 mL/min/1.73 m^2: <20, 20-29, 30-39, 40–49, 50–59,

139   60–69, 70–79, 80–89, 90-99 (reference), 100-109 and ≥110 mL/min/1.73 m^2. There were

140 fewer incident myocardial infarction and recurrent stroke due to multiple groups. Thus, a

141 combined end point of myocardial infarction, recurrent stroke and all-cause mortality was

142 used in this analysis.

143   To assess the association between change in eGFR during hospital stay and outcomes

144 after hospital discharge, percentage change in eGFR during hospital stay (($eGFR_{discharge}$-

145 $eGFR_{admission}$)/$eGFR_{admission}$)×100 was categorized into the following categories: change

146 within 5% (reference), 5-20% decline, >20% decline, 5-20% increase and >20% [20].

147 Association was examined for patients who were alive at discharge (N=8,021). This

148 association was additionally adjusted for length of hospital stay. For recurrent stroke and

149 incident myocardial infarction, analysis was performed for patients who did not develop these

150 outcomes during hospital stay (N=7,928 and N=7,937, respectively).

151   Multiple imputation was performed by chained equations with 10 iterations to impute

152 missing data (previous stroke (n=253), stroke severity (n=631) and pre-stroke modified

153 Rankin score (n=674)) [21]. The following variables were incorporated into the model for

154 imputations: age, sex, history of stroke, stroke type, serum creatinine, diabetes, hypertension,

155 hypercholesterolemia, heart failure, atrial fibrillation, and coronary heart disease.

156   A two tailed p-value of <0.05 was considered significant. All analyses were

157 performed using Stata/SE version 14.0.

158 *Additional analyses*

159 First, previous studies reported differences in the association between eGFR and adverse

160 outcomes by high risk groups [5,20]. Thus, we tested for interaction and presented the results

161 by stratifying according to two major high risk groups including diabetes and hypertension

162 status (no/yes). Second, to investigate study period effect, we evaluated the interaction

163 between eGFR and study period (i.e. 2003-2006, 2007-2010 and 2011-2015) for the risk of

164 adverse clinical outcomes. Third, we examined association between eGFR change and

165 outcomes when adjusting for baseline eGFR. Finally, for change in eGFR during hospital

166 stay, we examined association when using different cut-off of change in eGFR (i.e. 5%

167 (reference), 5-25% decline, >25% decline, 5-25% increase and >25% increase).

168 **Results**

169 *Baseline characteristics*

170 Characteristics of the sample population are presented according to eGFR levels in Table 1.

171 Median duration of hospital stay was 8 days (inter-quartile interval 4-18 days). The mean

172 eGFR was 63.7±22.1 mL/min/1.73 m^2. Low levels of eGFR were more prevalent in patients

173 aged ≥65 years compared to patients aged <65 years. A similar pattern was observed for

174 females and those with ischemic stroke.

175 *Clinical Outcomes by eGFR Levels*

176 Incidences of clinical outcomes assessed across eGFR categories are shown in Table 2. In

177 general, incidence of adverse outcomes was higher in patients with eGFR <90

178 mL/min/1.73m^2. However, in the case of recurrent stroke, the incidence tended to have an

179 inverse 'U' shaped distribution across eGFR categories.

180 *Association between eGFR and adverse outcomes*

181 In the age and sex adjusted model, compared to eGFR level of ≥90 mL/min/1.73 m^2, lower

182 levels of eGFR (<15, 15-29 and 30-44 mL/min/1.73 m^2) were associated with increased risks

183 of all clinical outcomes, including all-cause mortality, incident myocardial infarction,

184 prolonged hospital stay and post stroke disability but not with recurrent stroke. In the

185 multivariable adjusted models, these associations remained statistically significant. Similar to

186 overall risk of mortality, generally lower levels of eGFR (<15, 15-29 and 30-44

187 mL/min/1.73m^2) were associated with increased risk of <30, 30-365 or over 365-day

188 mortality (Table 3).

189   The association between clinical outcomes and eGFR categories stratified by 10

190 mL/min/1.73 m^2 showed that, compared to eGFR category of 90-99 mL/min/1.73m^2, risk of

191 all-cause mortality was high in eGFR categories of <20, 20-29 and 30-39 mL/min/1.73m^2 and

192   risk also appeared to be high in eGFR category of ≥109 mL/min/1.73m^2. A similar trend in

193   associations was observed for the composite end point, prolonged hospital stay and stroke

194   disability at discharge (Figure 1).

195   Regarding change in eGFR during hospital stay, greater than 5% decline or increase

196   in eGFR during hospital stay, was associated with an increased risk of all-cause mortality,

197   and stroke disability at discharge. For myocardial infarction, >20% change in eGFR tended to

198   be associated with increased risk. No statistically significant association was observed for

199   recurrent stroke (Table 4).

200   *Additional analyses*

201   No statistical interaction was observed for diabetes and hypertension status (no/yes) for any

202   of the outcomes (eTable 1-eTable 4). Similarly, no statically significant interaction was

203   observed between eGFR and study period for the risk of adverse clinical outcomes (p=0.21,

204   0.18, 0.58 and 0.25 for all-cause mortality, composite outcome, prolonged hospital stay and

205   post stroke disability at discharge, respectively) . Association with outcomes was essentially

206   similar to our main results when adjusting for eGFR at admission for this predictor (eTable 5)

207   and using different cut-off of eGFR change (eTable 6).

Discussion

208

209 In this large unselected prospective cohort of stroke patients, low eGFR levels of <15, 15-29

210 and 30-44 mL/min/1.73m^2 which clinically correspond to very severely (or kidney failure),

211 severely or moderate to severely impaired kidney function, respectively, were associated with

212 increased risk of poor clinical outcomes. This association was particularly strong for the risk

213 of all-cause mortality, incident myocardial infarction, prolonged hospital stay and disability

214 at discharge. In addition, ≥5% change in eGFR during hospital stay was associated with

215 increased risk of adverse clinical outcomes except recurrent stroke.

216 Whilst a number of previous studies have examined the association between eGFR

217 and risk of adverse clinical outcomes in stroke patients [4-10, 21], our study expands current

218 knowledge in a number of ways. Firstly, our study provides risk (both absolute and relative)

219 of poor outcomes across all clinically relevant categories of eGFR which is critically

220 important for clinical decision making. Secondly, this study confirms the association between

221 eGFR and poor clinical outcomes in a relatively large Western population of stroke patients

222 where average age of stroke onset is higher than in Asian populations where a number of

223 previous studies were conducted. Thirdly, to best of our knowledge, this is the first study to

224 examine the association between change in eGFR during hospital stay and relevant and

225 important clinical outcomes, and demonstrates that both significant increase and decline in

226 eGFR during hospital stay may indicate poor prognosis in stroke patients.

227 While our findings show higher risk of poor outcomes for moderately to severely

228 reduced eGFR but lower risk for mildly and mild to moderately decreased eGFR. This is

229 likely due to severity of illness of patients in eGFR category of ≥90 mL/min/1.73m^2. Due to

230 loss of muscle mass in chronically ill patients, serum creatinine based eGFR may over-

231 estimate their kidney function. Thus, patients in creatinine based eGFR category of ≥90

232   mL/min/1.73m^2 may actually be at increased risk of poor clinical outcomes. This was

233   apparent when association was examined between eGFR divided into groups spanning 10

234   mL/min/1.73 m^2 and outcomes, indicating that along with the increased risk of poor

235   outcomes in low eGFR levels, this risk also tended to be higher in eGFR category of 100-109

236   and ≥110 compared to eGFR category of 90-99 mL/min/1.73m^2 (Figure 1). Moreover,

237   tendency for reduced risk of short term mortality and increased risk of long term mortality in

238   eGFR category of 60-89 and 45-59 mL/min/1.73m^2 (Table 3) also indicate likelihood of

239   overestimation of kidney function in these patients.

240   Another finding of our study was that change (≥5%) in eGFR during hospital stay also

241   predicted prognosis in stroke patients. Importantly, this association was independent of eGFR

242   at admission. Decline in kidney function during hospital stay likely signifies deteriorating

243   kidney function and consequently poor prognosis in these patients. Causes of increased risk

244   for poor prognosis with increase in eGFR during hospital stay is unclear to us. However, it

245   may be because of withdrawal of antihypertensive agents (especially ACEi/ARB) as is

246   commonly done in the patients presenting with acute stroke Furthermore it is also possible

247   that an increase in eGFR during hospital stay may not indicate true improvement in kidney

248   function but may indicate deterioration of their physical condition which may have resulted

249   in overestimation of their kidney function at second measurement closer to discharge. We

250   further explored the relationship and found that during hospital stay there was greater

251   increase in mRS in patients with increase in eGFR (>5%) compared to patients with stable

252   eGFR (<5%) (mean mRS score increase 3.1 vs 2.1, respectively).

253   In this study we did not find a statistically significant association between low eGFR

254   with recurrent stroke. This could be due to fewer number of recurrent stroke events in low

255   eGFR categories. Moreover, higher short-term mortality may be obscuring the true

256   relationship. Indeed, previous studies that observed this association either examined fatal and

257   non-fatal re-occupant stroke together [8,12,14] or found association with stroke reoccurrence

258   only in a composite outcome analysis [22]. Similar to our study, one study that examined

259   non-fatal stroke recurrence found no association between low eGFR and stroke recurrence

260   [23]. Although we accounted for mortality occurring before stroke recurrence in our analysis,

261   we cannot entirely rule out possibility of this phenomenon.

262   This study has a number of clinical and research implications. Our findings suggest

263   that in stroke management, eGFR may be used as an additional early biomarker to identify

264   high risk patients for complications. Our findings of independent association between change

265   in eGFR during hospital stay and clinical outcomes provide an additional tool in prediction of

266   prognosis in stroke patients. Since this association was also independent of eGFR at baseline,

267   a second assessment of kidney function at/around discharge may be valuable in predicting

268   longer term prognosis. Our findings also suggest that there should be caution in interpreting

269   high eGFR values at hospital admission (when estimated using serum creatinine) in stroke

270   patients in routing clinical practice since they may not always mean better kidney function

271   and thus a better prognosis, particularly in chronically ill patients.

272   The present study has some limitations. First, eGFR was estimated using serum

273   creatinine which is influenced by muscle mass [24], and thus may not provide the most

274   reliable assessment of kidney function, particularly in chronically ill patients. Other

275   biomarkers of kidney function that are less dependent on muscle mass (e.g. Cystatin C) may

276   be used for more accurate assessment of kidney function [25]. However, in routine clinical

277   practice serum creatinine still remains the main biomarker for assessment of kidney function

278   and thus highlights the usefulness of our findings in routine patient care. Second, data was

279   not available on smoking and alcohol intake, and body mass index. However, we adjusted for

280   major determinants of eGFR and poor outcomes including diabetes, hypertension and CVDs

281   which are also linked to lifestyle factors listed above and thus likely have reduced

282 confounding related to the unmeasured lifestyle factors. It should also be noted that the aim

283 of this study was not to establish causation but to investigate the association between eGFR

284 and poor outcomes which is potentially useful in providing additional prognostic marker for

285 early identification of stroke patients that are at increased risk of complications.

286   This study also has a number of strengths. Our large sample population allowed us to

287 conduct a rigorous analysis, so as to examine the size and shape of the association between

288 eGFR and poor clinical outcomes across all clinically relevant categories of eGFR. In

289 addition, we were also able to examine the consistency of these association across various

290 sub groups. The availability of information on a number of clinical outcomes allowed us to

291 comprehensively assess the association of admission eGFR with stroke prognosis.

292 Furthermore, as a study using data from a hospital-based disease register, the patient

293 population under evaluation represents real world clinical events. Finally, the current study

294 included a second measurement of serum creatinine, which allowed analysis of the

295 importance of change in eGFR during hospital stay in stroke prognosis.

296   In summary, stroke patients with low levels of eGFR at hospital admission

297 (particularly in categories of <15, 15-29 and 30-44 mL/min/1.73m^2) and greater than 5%

298 change in eGFR during hospital stay (decline or increase) were associated with increased risk

299 of poor clinical outcomes of all-cause mortality, myocardial infarction, prolonged hospital

300 stay and stroke disability at discharge. These findings emphasize the importance of assessing

301 eGFR in stroke patients so as to aid in management and prediction of prognosis in routine

302 care.

Disclosure

308 None.

Conflicts of interests

310 None.

Contributors

312 Study conception, literature search, data analysis, and drafting the manuscript: PV; Data

313 acquisition and data management: JHBS; Supervisor or mentorship: PKM, AKM, KMB and

314 JFP; All authors contributed in interpretation of results. Each author contributed important

315 intellectual content during manuscript drafting or revision.

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381 **Figure 1: HRs (95% CIs) for: A) all-cause mortality; B) combined end point, and ORs (95% CIs) for; C) prolonged hospital stay and;**

382 **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**

383 **mL/min/1.73 m^2 serving as the reference group**

384 **A) All-cause mortality**   **B) Combined end point**

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392 **C) Prolonged hospital stay**   **D) Stroke disability at hospital**

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

| | Overall | Level of estimated glomerular filtration rate (mL/min/1.73m²) | | | | | | p |
	(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)	
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

394 Abbreviations: OSCP=Oxfordshire Community Stroke Project; TACS: total anterior circulation stroke; PACS: partial anterior circulation stroke; LACS: lacunar stroke; POCS: posterior
395 circulation stroke; mRS=modified Rankin score
396 Continuous variables with normal distribution are presented as mean ± standard deviation and non-normal distribution are presented as median (interquartile interval); categorical variables are
397 presented as percentages (n)
398 *253 participants missing information on previous stroke, 631 on OSCP classification and 674 on mRS
399

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

(N=10,329)	Level of eGFR (mL/min/1.73m^2)					
	≥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)

401   Abbreviation: eGFR=estimated glomerular filtration rate

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

22

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

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

	Level of eGFR (mL/min/1.73m²)					
	≥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)

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

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

407 Model 1: Age and sex

408 Model 2: Model 1 + history of stroke, stroke type, pre-stroke modified Rankin score, stroke severity, diabetes, hypertension, dyslipidemia, atrial fibrillation, heart failure,
409 coronary heart disease, pneumonia
410

411   **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)

412   Abbreviation: eGFR=estimated glomerular filtration rate. Missing information was handled with multiple imputation
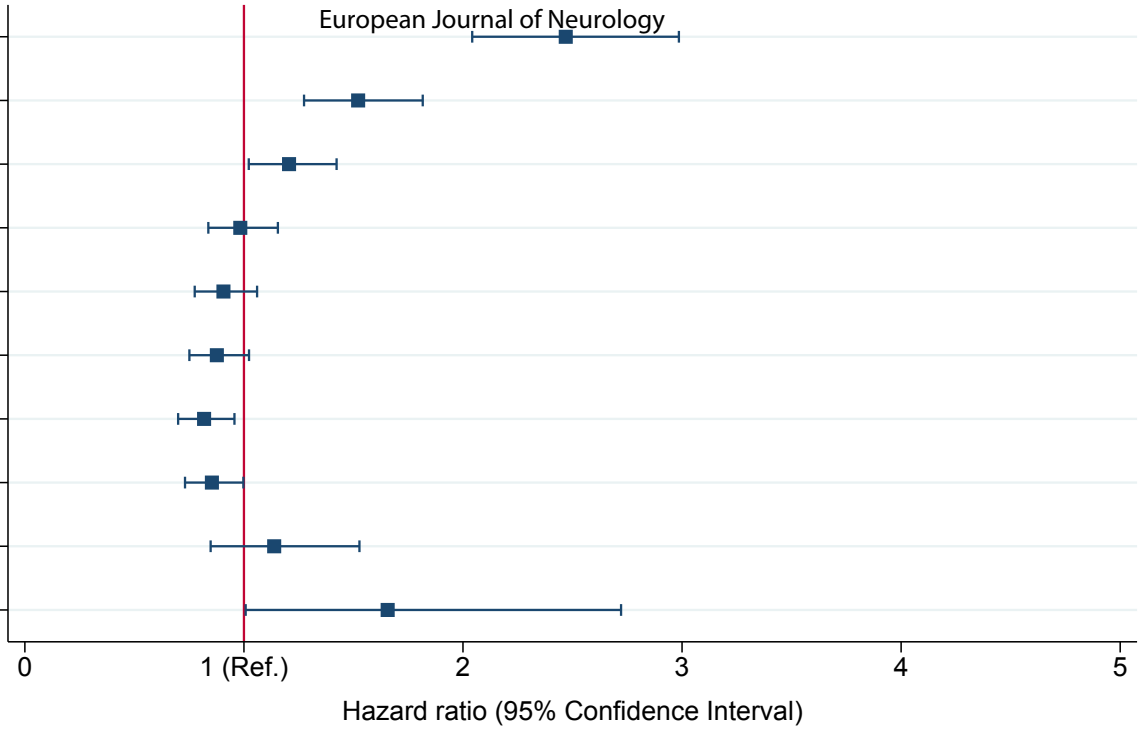413   *sub-distribution hazard ratios for recurrent stroke and myocardial infarction from competing risk regression analysis, †excluded patients who were dead at discharge
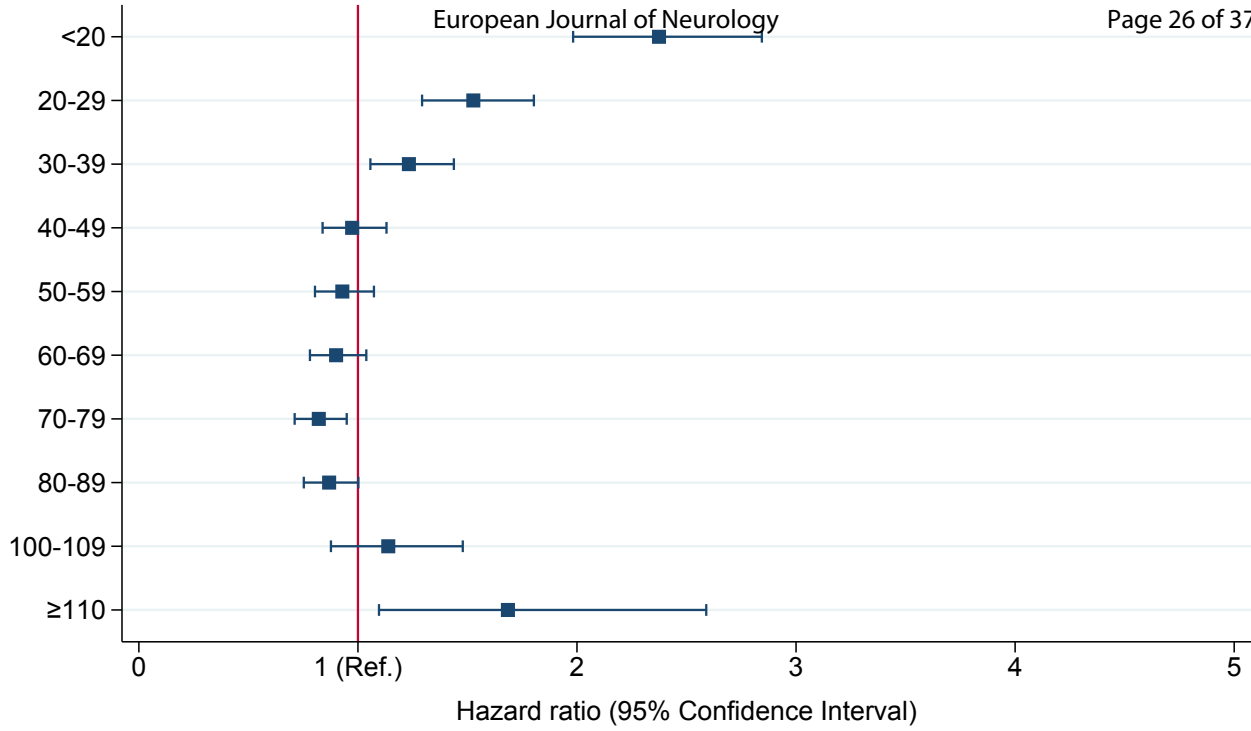414   Model 1: Age, sex and length of hospital stay
415   Model 2: Model 1 + history of stroke, stroke type, pre-stroke modified Rankin score, stroke severity, diabetes, hypertension, dyslipidemia, atrial fibrillation, heart failure,
416   coronary heart disease, pneumonia

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Hazard ratio (95% Confidence Interval)

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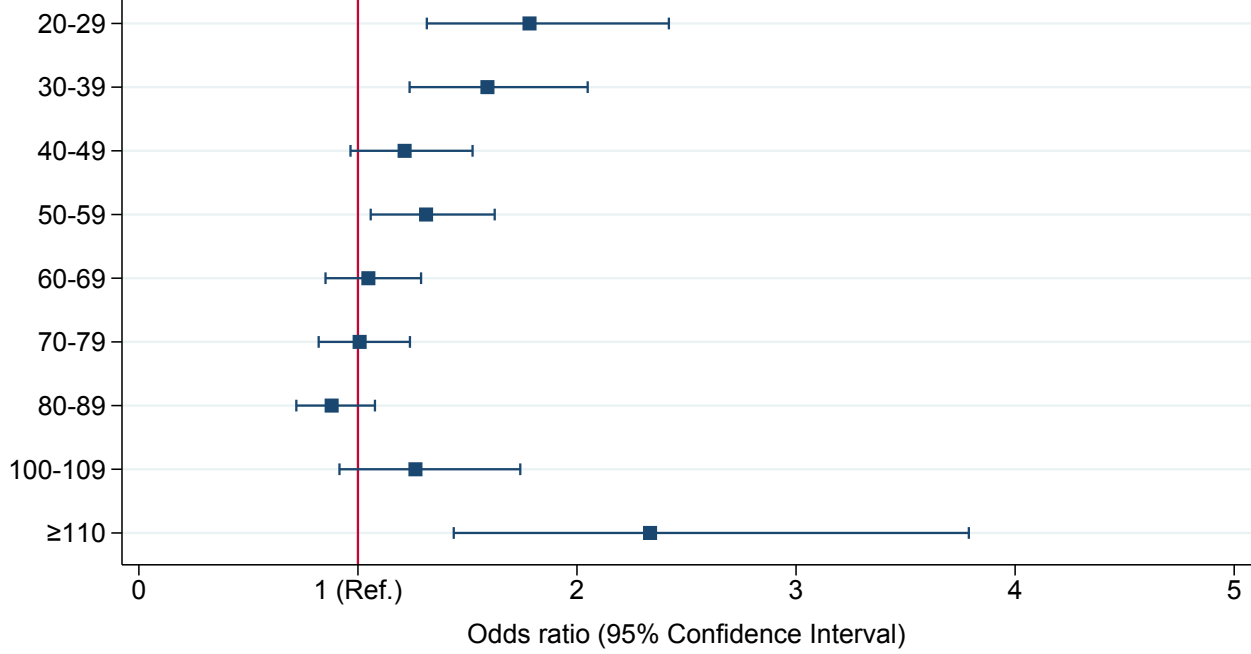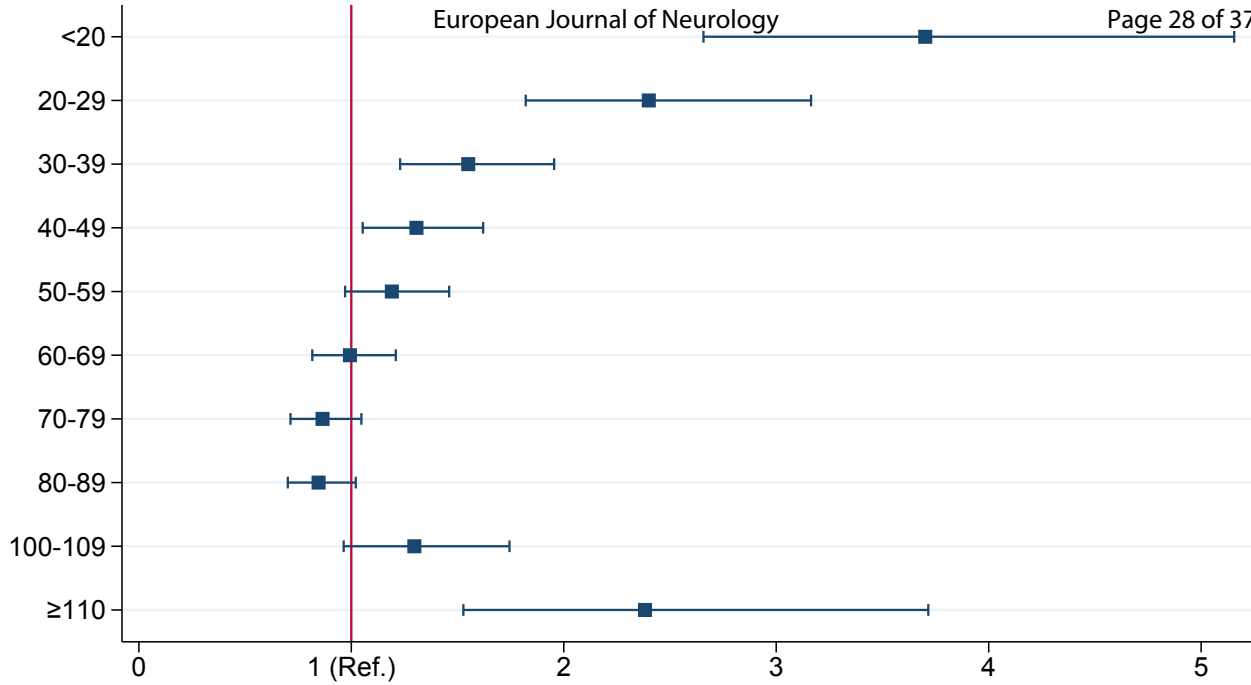
Supplemental material

Estimated glomerular filtration rate and risk of poor outcomes after stroke

Contents

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

(N=10,329)	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* 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)

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

(N=10,329)	Level of estimated glomerular filtration rate (mL/min/1.73m^2)						p for interaction
	≥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)*						
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)

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

(N=10,329)	Level of estimated glomerular filtration rate (mL/min/1.73m^2)						
	≥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)

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

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

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Table S5: Results after <u>adjusting for estimated glomerular filtration rate at admission</u> 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
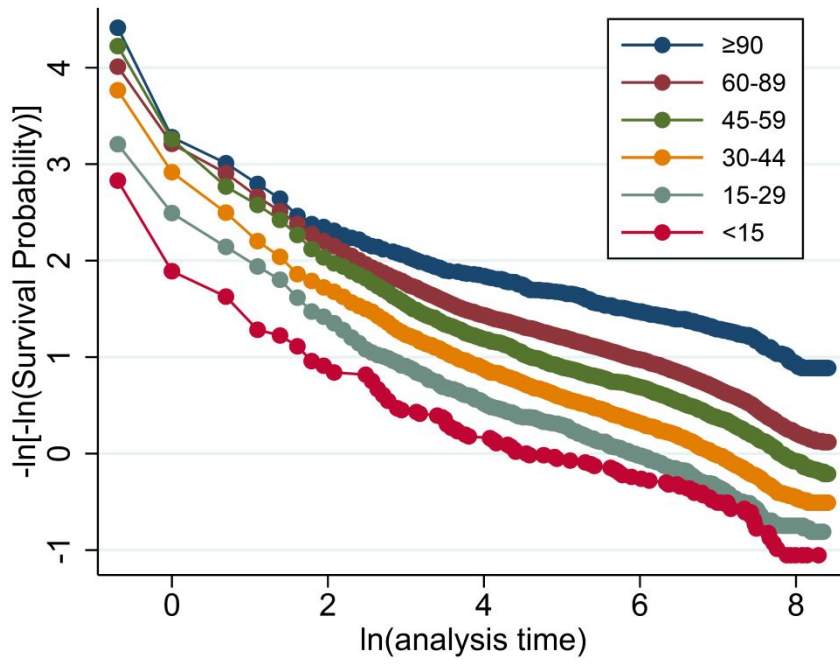
Table S6: Results after <u>using a different cut-off</u> of change in estimated glomerular filtration rate during hospital stay for its association with clinical outcomes in patients with stroke

	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

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