1 **Impact of delay in early swallow screening on pneumonia, length of stay in**

2 **hospital, disability and mortality in acute stroke patients**

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15

16 **Running title:** Delayed swallow screening in acute stroke.

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ABSTRACT

BACKGROUND/OBJECTIVES: Early swallow screening, within 4hrs of admission, is required for all acute stroke patients to commence nutritional support, as recommended. We evaluated the impact of delay in early swallow screening on outcomes in patients admitted with acute stroke.

SUBJECTS/METHODS: Prospective cohort study of 1656 men (mean±SD age=73.1y±13.2) and 1653 women (79.3y±13.0) admitted with stroke to hyperacute stroke units (HASUs) in Surrey. Logistic regression was used to assess the risk (adjusted for age, stroke severity and co-morbidities) of delay in swallow screening on pneumonia, length of stay (LOS) >3weeks in HASU or hospital, moderately-severe to severe disability on discharge (modified Rankin scale score=4-5) and mortality during admission.

RESULTS: Compared with those who received swallow screening within 4hrs of admission, a delay between 4-72hrs was associated with greater risks of pneumonia: OR=1.4 (95%CI:1.1-1.9, P=0.022), moderately-severe to severe disability on discharge: OR=1.4 (1.1-1.7, P=0.007) and a delay beyond 72hrs was associated with even greater risks of pneumonia: OR=2.3 (1.4-3.6, P<0.001), prolonged LOS in HASU: OR=1.7 (1.0-3.0, P=0.047, median LOS=6.2days *v.s.* 14.7days) and hospital: OR=2.1-fold (1.3-3.4, P=0.007, median LOS=6.8days *v.s.* 14.9days), moderately-severe to severe disability on discharge: OR=2.5 (1.7-3.7, P<0.001) and mortality: OR=3.8 (2.5-5.6, P<0.001). These risks persisted after excluding 103 patients who died within 72hrs.

CONCLUSIONS: Delay in early screening for swallow capacity in acute stroke patients is detrimental to outcomes, possibly due to delaying nutritional provision or through inappropriate feeding leading to aspiration. Routine early screening needs greater attention in HASUs.

INTRODUCTION

Oropharyngeal dysphagia, a common feature of severe stroke and an indicator of poor prognosis, is identified in about half of patients with acute stroke by swallow screening[1-4] and up to three quarters by videofluoroscopy.[4] Dysphagia not only prevents patients from oral intake but is also a high risk-factor for a number of complications, particularly aspiration pneumonia[4,5] which occurs in 22 to 49% among these patients[6] and death.[5] Stroke patients with dysphagia have been shown to be more likely to stay longer in hospital and less likely to be discharged back to their own home than non-dysphagic stroke patients.[5,7]

Early nutrition support is vital for the survival and clinical outcomes in patients with dysphagia, including stroke patients.[8] Evidence from small studies has shown that early swallow screening reduces the incidence of aspiration pneumonia,[6] length of stay (LOS) in hospital, disability and mortality.[2,7] The decision to commence nutrition support depends on the outcome from the assessment of the patient's ability to swallow. There are several methods of assessment including videofluoroscopy which is time consuming, more invasive and requires high level of expertise while swallow screening, which is less sensitive than videofluoroscopy,[4] is a rapid bedside test which can be performed by the majority of healthcare providers. Swallow screening is therefore recommended to be carried out routinely within 4 hours of admission for all patients with acute stroke.[9] A recent report by the Royal College of Physicians[10] however has shown that about a one in four of acute stroke patients in the UK did not have swallow screening by 4 hours and one in eight by 72 hours of admission.

76 The present study evaluated the impact of delay in early swallow screening on

77 pneumonia developed within seven days of admission, LOS in hyperacute stroke

78 unit (HASU) or in hospital, disability on discharge, and mortality during admission in

79 patients admitted with acute stroke.

80

81 **SUBJECTS/METHODS**

82 **Study design, patients and setting**

83 We carried out this registry-based, prospective cohort study using Sentinel Stroke

84 National Audit Programme (SSNAP) data, which were collected from the time of

85 admission up to six months following stroke. The data were validated by Stroke

86 teams and entered into the secure SSNAP database. These data composed of

87 clinical characteristics and care quality of patients admitted with acute stroke to all

88 acute care hospitals in England and Wales.[11] An anonymised extract of a total of

89 3309 patients admitted between January 2014 and February 2016 to four hospitals

90 in the County of Surrey were used: Ashford and St Peter's (n = 1038), Royal Surrey

91 County (n = 612), Epsom (n = 649) and Frimley Park (n = 1010). There were 22

92 patients admitted twice and 2 patients admitted thrice and their data from the first

93 admission were used.

94

95 SSNAP was approved by the Confidentiality Advisory Group of the Health Research

96 Authority to gather patient data under section 251 of the National Health Service Act

97 2006.

98

99 **Data recording**

100 All four study centres participated in SSNAP using identical protocols (available on

101 request). Data were collected for gender, age at arrival and comorbidities including

102 atrial fibrillation, diabetes, congestive cardiac failure and hypertension. Treatment

103 from the point of admission to discharge were documented by the consultants and

104 stroke nurse specialists.

105

106 **Swallow screening**

107 Swallow screening was carried out by the same validated screening tool in all four

108 study centres as soon as possible after arrival at hospital and before patients had

109 been given any oral fluid, food or medication. The following sequences of screening

110 were conducted by a trained healthcare professional for patients who had to be able

111 to independently remain awake and alert for at least 15 minutes and sit upright. The

112 procedure started initially with 3 spoons of water, and if there was no risk of

113 aspiration, followed by a challenge with 1 cup of water, and then further continued

114 with a trial of soft diet meal. The procedure was discontinued if there was a risk of

115 aspiration at any stage of screening.

116

117 **Diagnosis of stroke and pneumonia**

118 Stroke was diagnosed on the basis of clinical presentation and brain computerised

119 tomography[12] and the severity of stroke symptoms was determined by the National

120 Institutes of Health for Stroke and Scale (NIHSS) ranging from no symptoms to

121 severe stroke symptoms (NIHSS score = 0 to 42). Pneumonia was diagnosed by

122 clinical examination which was supported and confirmed by biochemical,

123 microbiological and radiological evidence.

124

Disability and mortality

The degree of disability or dependence in the daily activities was determined by modified Rankin Scale (mRS) ranging from no symptoms to severe symptoms of disability (mRS score = 0 to 5) and also includes mortality (mRS score = 6).

Categorisation of variables

Swallow screening status was categorised into three groups: 1) screening performed within 4 hours, 2) between 4 and 72 hours and 3) beyond 72 hours of admission. Severity and disability of stroke were categorised into two groups of "no symptoms to moderate symptoms" (NIHSS score <16 and mRS score <4) and "moderately-severe to severe symptoms" (NIHSS score ≥16 and mRS score = 4-5). Age was categorised into two groups at median value (79 years). Prolonged stay in HASU or in hospital was categorised into those who stayed three weeks or longer (upper fourth quartile).

Data handling and statistical analysis

Normality of the data were examined initially by histogram and confirmed statistically by Shapiro-Wilk test. Log_{10} transformation was applied to variables that displayed right skewness (LOS in HASU and in hospital) before proceeding to analysis of variance (ANOVA) to examine differences between groups of swallow screening status.

Chi-squared test was carried out to determine the proportions of patients with severe disability on discharge or mortality within each category of swallow screening status, logistic regression to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the risk of delay in early swallow screening (independent variable) in stroke

patients for having pneumonia within 7 days of admission, moderately-severe to severe disability on discharge, mortality and prolonged stay in HASU or hospital (≥3 weeks) (dependent variables). Results were presented as unadjusted data or adjusted for age, severity of stroke on arrival and stroke subtype (ischaemic or haemorrhagic).

Since early mortality may influence the decision to perform swallow screening, we further conducted data analysis with the exclusion of 103 patients who died within 72 hours of admission, *i.e.* 377 patients who died beyond 72 hours remained for analysis. For analyses of LOS in HASU and in hospital, all 480 patients who died were excluded.

RESULTS

Men and women were equally distributed with women being older (mean age 79.3 years ±SD 13.0) than men (73.1 years ±13.2) by 6.1 years (95% CI: 5.2-7.0, P <0.001). On arrival, 83.3% patients presented with infarct and 15.7% with haemorrhagic stroke and 1% unspecified, 255 patients (7.7%) with moderately severe (NIHSS score 16-20) and 227 (6.9%) with severe stroke (NIHSS score 21-42). Among the 3309 cases reviewed, swallow screening was conducted within 4hrs for 80% (reference category). For the remaining 20%, 15.7% were screened between 4 and 72 hours and 4.3% had over 72hrs delay between admission and screening. There were 358 (10.8%) with pneumonia within 7 days of admission, 657 (23.2%) stayed in HASU and 674 (23.8%) in hospital longer than 3 weeks. On discharge, 355 (11.1%) had moderately-severe (mRS score = 4) and 154 (4.9%) with severe disability (mRS score = 5). There were 480 (15.1%) deaths during admission

175 with 103 died within 72 hours (**Table 1**). The median number of days for those who

176 died after admission was 10.7 (IQR = 3.7-24.1).

177

178 The median LOS in HASU was 6.2 days (IQR=2.6-20.0 days) for patients who were

179 screened within 4 hours of admission and rose to 8.5 days (IQR=3.0-22.8 days) for

180 those who received screening between 4 and 72 hours and 14.7 days (IQR=3.8-28.4

181 days) for those who received screening beyond 72 hours of admission (ANOVA for

182 group differences: F = 5.3; P = 0.005). Similarly, the median LOS in hospital was 6.8

183 days (IQR=2.9-20.4 days) for patients who were screened within 4 hours of

184 admission and rose to 9.3 days (IQR=3.9-20.6 days) for those who received

185 screening between 4 and 72 hours and 14.9 days (IQR=6.5-34.6 days) for those who

186 received screening beyond 72 hours of admission (ANOVA for group differences: F =

187 14.8; P <0.001) (**Figure**).

188

189 Compared to patients who received swallow screening within 4 hours of admission,

190 the proportions of patients who received swallow screening between 4 and 72 hours

191 or beyond 72 hours were higher for pneumonia developed within 7 days of

192 admission (10.1% v.s. 13.6% v.s. 23.8%, P <0.001), moderately-severe to severe

193 disability on discharge (27.6% v.s. 34.8% v.s. 54.9%, P <0.001), mortality (13.1%

194 v.s. 14.2% v.s. 40.8%, P <0.001) and prolonged stay in HASU (24.2% v.s. 27.2%

195 v.s. 37.7%, P = 0.029) or hospital over 3 weeks (23.9% v.s. 28.1% v.s. 41.7%, P

196 <0.001). Similar patterns were observed when 103 men who died within 72 hours of

197 admission were excluded from analyses (**Table 2**).

198

199 Compared with those who received swallow screening within 4 hours of admission, a

200 delay between 4-72 hours was associated with greater risks of pneumonia by 1.4-

201 fold (95%CI: 1.1-1.9, P = 0.022), moderately-severe to severe disability on discharge

202 1.4-fold (1.1-1.7, P = 0.007) and a delay beyond 72 hours was associated with even

203 greater risks of pneumonia by 2.3-fold (1.4-3.6, P <0.001), prolonged stay in stroke

204 unit 1.7-fold (1.0-3.0, P = 0.047) and in hospital 2.1-fold (1.3-3.4, P = 0.007),

205 moderately-severe to severe disability on discharge 2.5-fold (1.7-3.7, P <0.001), and

206 mortality 3.8-fold (2.5-5.6, P <0.001) (**Table 3a**). These risks continued to persist and

207 significant when patients who died within 72 hours of admission were excluded from

208 analyses (**Table 3b**).

209

210 **DISCUSSION**

211 We show that delay in early swallow screening of patients admitted with acute stroke

212 associated with increased risk of pneumonia, prolonged hospital stay, severe

213 disability on discharge and mortality during admission. The longer the delay (from 4

214 hours to 72 hours and beyond), the worse were the outcomes. These risks were

215 independent of age of patients, severity of stroke on admission, type of stroke and

216 early mortality as well as a number of chronic co-existing health conditions, thus

217 justifying the need for early swallow screening for every patient admitted to hospital

218 with acute stroke.

219

220 The strengths of this study include its large number which is representative of UK

221 population, and robustness in adjusting potential factors that may bias the results:

222 age, stroke severity, haemorrhagic stroke, and major co-morbidities including

223 hypertension, diabetes, congestive cardiac failure and atrial fibrillation as well as an

224 exclusion of early mortality cases. We recognise that although bedside screening is

225 a valuable first step in identifying dysphagic patients, but due to its relatively low

226 sensitivity,[13] patients may need further instrumental diagnostic assessment such as

227 fiberoptic evaluation of swallowing.[14] The study is restricted to short term follow-up of

228 stroke outcomes during acute hospital admissions, and a potential limitation of this

229 type of study is that it is not possible to ascribe causality with certainty. Swallow

230 screening is more likely to be delayed if the overall clinical condition is very poor, or if

231 the patient has other coexisting health problems on admission, such that feeding is

232 not considered appropriate. Swallow screening might then be delayed until there is

233 major clinical improvement. However, a strength of this study is that the data were

234 adjusted for stroke severity, to remove this potential confounder. It is very possible

235 that some poorer stroke outcomes associated with delay in swallow screening are

236 due to inappropriate feeding and aspiration. Delayed screening may also entail a

237 delay in providing early nutritional support, leading to a number of complications that

238 weaken the body and delay in recuperation process associated with under-

239 nourishment.[15,16] Undernutrition has been found in 16% of acute stroke patient on

240 arrival[17] and in about a quarter of stroke patients in the first few weeks after stroke

241 which continues to increase with increasing time spent in hospital.[18,19] The risk of

242 malnourishment is greater in dysphagic stroke patients than non-dysphagic stroke

243 patients.[20] Based on this evidence, any delay in swallow screening would be

244 detrimental to this group of patients who are highly susceptible to malnutrition.

245 Studies have shown that early nutrition support for patients with acute stroke

246 reduces LOS in hospital.[21] Although it is unclear whether early nutritional support has

247 an impact of the improvement of stroke outcomes due to paucity of randomised

248 controlled trials,[22] it is clear that patients with who are malnourished on admission[23]

249 or after admission for acute stroke[18,19,24,25] had worse clinical and functional

250 outcomes and increased risk of mortality.

251

252 Early swallow screening to allow early nutritional support is supported by a number

253 of randomised controlled trials of non-stroke patients - acutely unwell patients who

254 received early feeding within 24 to 36 hours of admission to the intensive care unit

255 were associated with greater reduction in infection, LOS in hospital and mortality

256 than those who were randomised to start feeding later based on standard care.[26-28]

257 These benefits of early feeding are almost certainly applicable to acute stroke

258 patients.

259

260 Recommendations for early swallow screening after stroke have been advocated by

261 a number of authorities in order to implement suitable early nutrition support.[10,12]

262 Although swallow screening has improved, this remains variable across UK stroke

263 centres: approximately 15% of patients do not have swallow screening within 72

264 hours of admission.[10]

265

266 If earlier swallow screening avoids some cases of aspiration pneumonia, and permits

267 earlier nutrition support leading to improved outcomes, there are major benefits for

268 patients and also for healthcare budgets. Prolonged stay in hospital imposes heavy

269 healthcare costs. Most patients (92.2%) are managed in acute HASUs where each

270 bed day costs £350 (€395, US $460),[29] the remainder in non-specialist hospital beds

271 at £222 (€250, US $290) but costs increase with serious complications such as

272 pneumonia.[30]

273

274   In conclusion, routine early screening for stroke patients, within 4-hours according to

275   guidelines, is not being provided or all and needs greater attention. Although

276   causality cannot be determined from this survey, data were adjusted for stroke

277   severity and there are plausible reasons why delay in early screening for swallow

278   capacity in acute stroke patients might account for the observed poorer clinical

279   outcomes, by delaying nutritional provision or through inappropriate feeding leading

280   to aspiration.

287 **Conflict of Interest**

288 None declared.

289

290 **Authors' Contributions**

291 TSH and PS designed research (project conception, development of overall research

292 plan and study oversight). BA, GG, TP, CB, PK and AB conducted data collection.

293 TSH analysed data and wrote the first draft of the paper and MEJL and PS edited

294 subsequent versions of the paper. TSH had primary responsibility for final content.

295 All authors reviewed and approved the final version of the paper.

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382   **LEGENDS**

383   **Figure.** Box plots showing swallow screening status in relation to LOS in HASU (**a**)

384   and in hospital (**b**). ANOVA showed significant group differences (P <0.005)

385   therefore *post hoc* least significant difference tests were performed to compare LOS

386   between those who received swallow screening within 4 hours of admission and

387   other two groups of different swallow screening status (between 4-72 hours and

388   beyond 72 hours). Box plots represent median and interquartile ranges and whiskers

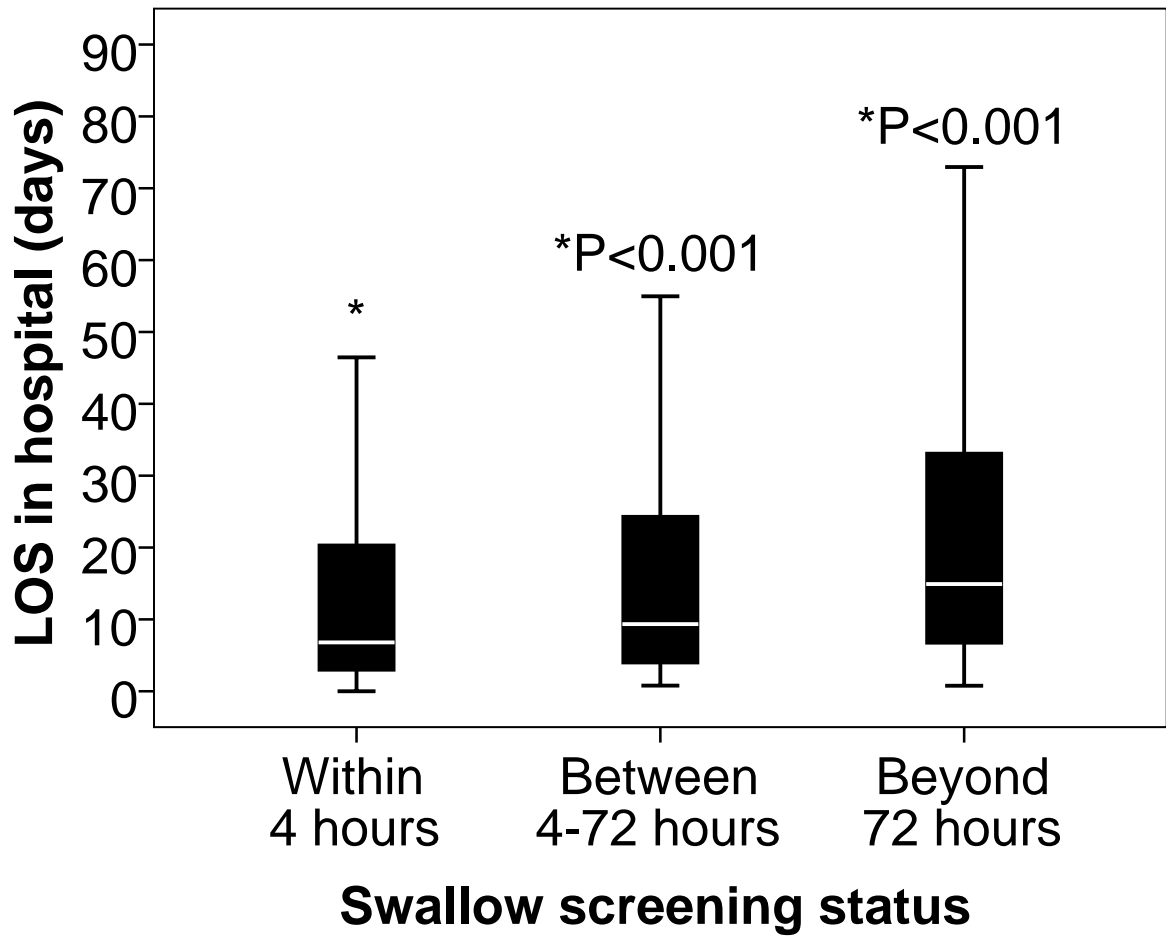389   represent the 5th and 95th percentiles.
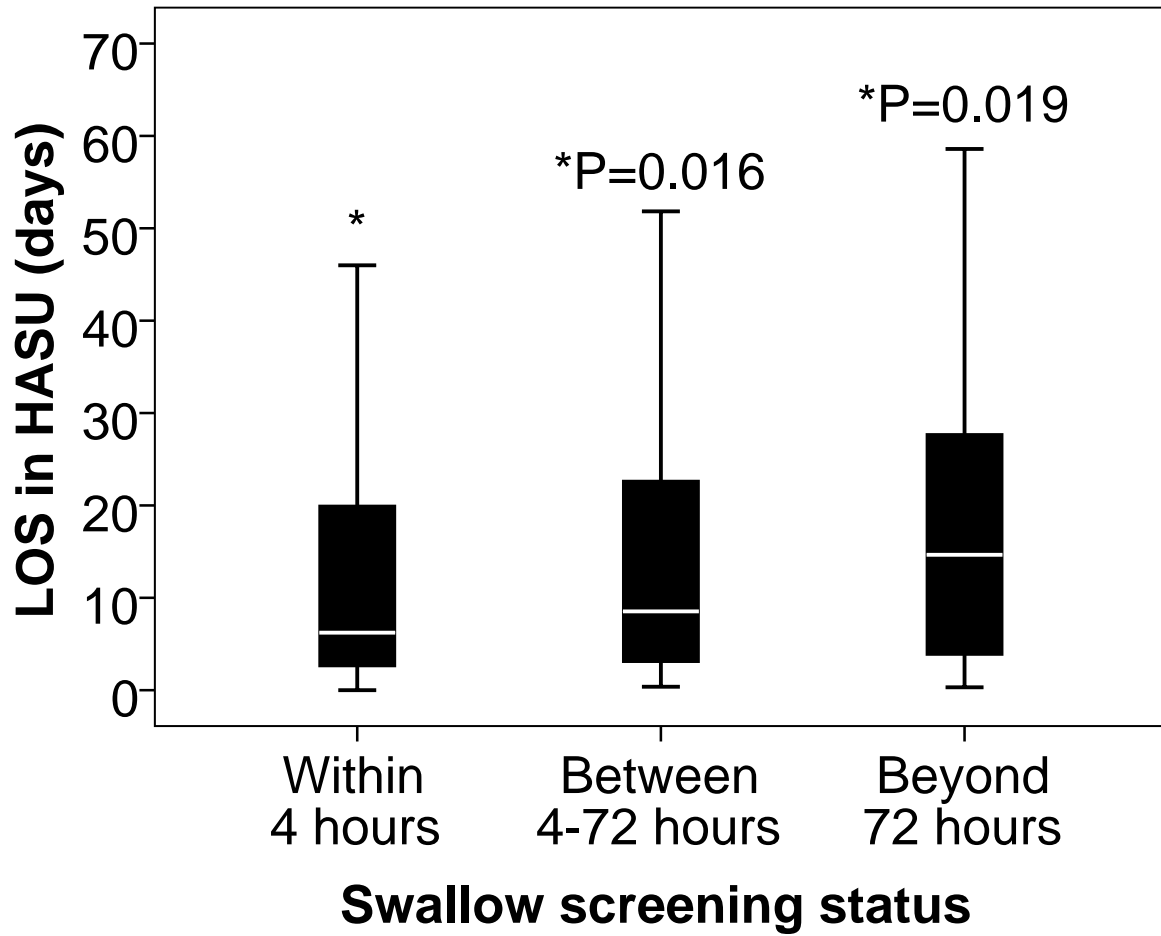
Table 1. Distribution of 3309 patients admitted with acute stroke to hospitals in Surrey between January 2014 and February 2016. All data were complete except information not available for pneumonia in 129 patients (3.9%), stroke subtype in 33 (1.0%) patients, LOS in HASU in 201 (7.1%) and hospital in 135 (4.8%) patients.

	n	Proportion (%)
Gender distribution		
Men: women	1656: 1653	50.0: 50.0
Stroke subtype		
Infarct stroke: haemorrhagic stroke	2758: 518	83.3: 15.7
Swallow screening status		
Swallow screened within 4 hours of admission	2647	80.0
Swallow screened between 4 and 72 hrs of admission[†]	520	15.7
Swallow screened beyond 72 hrs of admission	142	4.3
Stroke severity on arrival		
No stroke symptoms (NIHSS score = 0)	444	13.4
Minor stroke (NIHSS score = 1-4)	1263	38.2
Moderate stroke (NIHSS score = 5-15)	1120	33.8
Moderate to severe stroke (NIHSS score = 16-20)	255	7.7
Severe stroke (NIHSS score = 21-42)	227	6.9
Pneumonia within 7 days of admission	358	11.3
Prolonged stay		
Acute stroke unit stay longer than 3 weeks	657	23.2[‡]
Hospital stay longer than 3 weeks	674	23.8[‡]
Modified Rankin Scale on discharge (n = 3174)		
No symptoms (mRS score = 0)	760	23.9
No significant disability (mRS = 1)	553	17.4
Slight disability (mRS score = 2)	448	14.1
Moderate disability (mRS score = 3)	424	13.4
Moderately severe disability (mRS score = 4)	355	11.2
Severe disability (mRS score = 5)	154	4.9
Dead (mRS score = 6)	480	15.1
Dead within 72 hours of admission	103	3.1

[†]This group are those who were screened between 4 and 72 hours of admission. 80 patients who died were excluded.

Table 2. Proportions of patients according to swallow screening status for acute stroke in relation to pneumonia developed within 7 days of admission, moderately-severe to severe disability on discharge, mortality during admission and prolonged stay in acute HASU or hospital.

	Pneumonia within 7 days of admission		Stay in acute HASU >3 weeks[†]		Stay in hospital >3 weeks[†]		Moderately-severe to severe disability on discharge		Mortality during admission	
All patients (n = 3309)	%	χ^2 (P-value)	%	χ^2 (P-value)	%	χ^2 (P-value)	%	χ^2 (P-value)	%	χ^2 (P-value)
Swallow screened within 4 hrs	10.1	26.7	--		--		27.6	55.2	13.1	83.4
Swallow screened between 4 and 72 hrs	13.6	(<0.001)	--	--	--	--	34.8	(<0.001)	14.2	(<0.001)
Swallow screened beyond 72 hrs	23.8		--		--		54.9		40.8	
Excluding 103 patients who died within 72 hrs of admission (n = 3206)										
Swallow screened within 4 hrs	9.4	25.5	24.2		23.9	14.4	25.8	29.8	11.0	29.7
Swallow screened between 4 and 72 hrs	12.8	(<0.001)	27.2	7.1	28.1	(0.001)	33.3	(<0.001)	12.2	(<0.001)
Swallow screened beyond 72 hrs	23.8		37.7	(0.029)	41.7		44.8		27.6	

[†] All 480 patients who died during admission or exclusion of all 480 patients who died during admission.

Table 3a. Logistic regression assessing the risk of delay in swallow screening on pneumonia developed within 7 days of admission, prolonged stay in HASU and in hospital, moderately-severe to severe disability on discharge and mortality during admission, unadjusted and adjusted for age, stroke severity and type of stroke in all patients.

	Unadjusted			Adjusted for age, stroke severity and type of stroke			Adjusted for age, stroke severity, type of stroke and co-morbidities[‡]		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Pneumonia within 7 days of admission									
Swallow screened within 4 hrs (Referent)	1	--	--	1	--	--	1	--	--
Swallow screened between 4 and 72 hrs	1.40	1.05-1.86	0.021	1.45	1.08-1.95	0.014	1.42	1.05-1.92	0.022
Swallow screened beyond 72 hrs	2.77	1.82-4.24	<0.001	2.32	1.47-3.66	<0.001	2.29	1.44-3.63	<0.001
Stayed in HASU >3 weeks[†]									
Swallow screened within 4 hrs (Referent)	1	--	--	1	--	--	1	--	--
Swallow screened between 4 and 72 hrs	1.17	0.92-1.48	0.193	1.10	0.86-1.41	0.444	1.10	0.86-1.41	0.452
Swallow screened beyond 72 hrs	1.90	1.12-3.21	0.017	1.72	0.99-2.97	0.053	1.74	1.01-3.01	0.047
Stayed in hospital >3 weeks[†]									
Swallow screened within 4 hrs (Referent)	1	--	--	1	--	--	1	--	--
Swallow screened between 4 and 72 hrs	1.25	0.99-1.57	0.064	1.18	0.93-1.51	0.175	1.18	0.92-1.50	0.188
Swallow screened beyond 72 hrs	2.28	1.41-3.68	0.001	2.04	1.24-3.35	0.005	2.09	1.27-3.43	0.004
Moderately-severe to severe disability on discharge									
Swallow screened within 4 hrs (Referent)	1	--	--	1	--	--	1	--	--
Swallow screened between 4 and 72 hrs	1.40	1.15-1.71	0.001	1.39	1.12-1.73	0.003	1.35	1.09-1.68	0.007
Swallow screened beyond 72 hrs	3.20	2.28-4.50	<0.001	2.56	1.76-3.73	<0.001	2.52	1.73-3.68	<0.001
Mortality during admission									
Swallow screened within 4 hrs (Referent)	1	--	--	1	--	--	1	--	--
Swallow screened between 4 and 72 hrs	1.10	0.84-1.44	0.506	1.10	0.82-1.47	0.536	1.04	0.77-1.49	0.815
Swallow screened beyond 72 hrs	4.56	3.21-6.49	<0.001	3.79	2.55-5.63	<0.001	3.75	2.51-5.58	<0.001

[†]480 patients who died during admission were excluded for LOS analysis. [‡]Co-morbidities = atrial fibrillation, hypertension, congestive cardiac failure and diabetes.

Table 3b. Logistic regression assessing the risk of delay in swallow screening on pneumonia developed within 7 days of admission, moderately-severe to severe disability on discharge and mortality during admission, unadjusted and adjusted for age, stroke severity and type of stroke in patients who survived beyond 72 hours (i.e. 103 patients who died within 72 hours of admission were excluded).

	Unadjusted			Adjusted for age, stroke severity and type of stroke			Adjusted for age, stroke severity, type of stroke and co-morbidities[‡]		
	OR	95% CI	P	OR	95% CI	P			
Pneumonia within 7 days of admission									
Swallow screened within 4 hrs (Referent)	1	--	--	1	--	--	1	--	--
Swallow screened between 4 and 72 hrs	1.40	1.04-1.89	0.025	1.41	1.04-1.92	0.030	1.38	1.01-188	0.046
Swallow screened beyond 72 hrs	3.00	1.88-4.79	<0.001	2.44	1.47-4.04	0.001	2.54	1.53-4.23	<0.001
Moderately-severe to severe disability on discharge									
Swallow screened within 4 hrs (Referent)	1	--	--	1	--	--	1	--	--
Swallow screened between 4 and 72 hrs	1.44	1.17-1.76	0.001	1.40	1.13-1.75	0.003	1.37	1.09-1.71	0.006
Swallow screened beyond 72 hrs	2.34	1.61-3.41	<0.001	1.84	1.21-2.79	0.004	1.83	1.20-2.77	0.005
Mortality during admission									
Swallow screened within 4 hrs (Referent)	1	--	--	1	--	--	1	--	--
Swallow screened between 4 and 72 hrs	1.13	0.84-1.51	0.416	1.11	0.81-1.52	0.529	1.04	0.76-1.43	0.813
Swallow screened beyond 72 hrs	3.10	2.02-4.74	<0.001	2.42	1.50-3.91	<0.001	2.43	1.50-3.93	<0.001

[‡]Co-morbidities = atrial fibrillation, hypertension, congestive cardiac failure and diabetes.