Predicting stroke complications in hospital and functional status at discharge by clustering of cardiovascular diseases a multi-centre registry-based study of acute stroke

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ABSTRACT

Objective: Indicators for outcomes following acute stroke are lacking. We have developed novel evidence-based criteria for identifying outcomes of acute stroke using the presence of clusters of coexisting cardiovascular disease (CVD).

Materials and methods: Analysis of prospectively collected data from the Sentinel Stroke National Audit Programme (SSNAP). A total of 1656 men (mean age ±SD=73.1yrs±13.2) and 1653 women (79.3yrs±13.0) were admitted with acute stroke (83.3% ischaemic, 15.7% intracranial haemorrhagic), 1.0% unspecified) in four major UK hyperacute stroke units (HASU) between 2014 and 2016. Four categories from CVD including *C*ongestive heart failure, *A*trial fibrillation, history of prior *S*troke and *H*ypertension (CASH).were constructed: CASH-0 (no coexisting CVD); CASH-1 (any one coexisting CVD); CASH-2 (any two coexisting CVD); CASH-3 (any three or all four coexisting CVD). These were tested against outcomes, adjusted for age and sex.

Results: Compared to CASH-0, individuals with CASH-3 had greatest risks of in-hospital mortality (11.1% *vs* 24.5%, OR=1.8, 95%CI=1.3-2.7) and disability (modified Rankin Scale score ≥4) at discharge (24.2% *vs* 46.2%, OR=1.9, 95%CI=1.4-2.7), urinary tract infection (3.8% *vs* 14.6%, OR= 3.3, 95%CI= 1.9-5.5), and pneumonia (7.1% *vs* 20.6%, OR= 2.6, 95%CI= 1.7-4.0); length of stay on HASU >14 days (29.8% *vs* 39.3%, OR=1.8, 95%CI=1.3-2.6); and joint-care planning (20.9% *vs* 29.8%, OR=1.4, 95%CI=1.0-2.0).

Conclusions: We present a simple tool for estimating the risk of adverse outcomes of acute stroke including death, disability at discharge, nosocomial infections, prolonged length of stay, as well as any joint care planning. CASH-0 indicates a low level and CASH-3 indicates a high level of risk of such complications after stroke.

INTRODUCTION

Patient outcomes after an acute hospital admission are an important indicator of healthcare quality. A number of indices have been developed to measure multimorbidity and used to predict outcomes in general medical patients. The Charlson Comorbidity Index (CCI)[1] and Elixhauser Index[2] are two of the commonly used indices and perform similarly in predicting mortality.[3] The CCI was designed to predict mortality based on 16 conditions (including stroke) and age whilst the Elixhauser index comprises 30 acute and chronic conditions, developed to predict hospital length of stay (LOS) and in-hospital mortality.

Although there exists no model of multimorbidity that applies specifically to acute stroke,[4,5] many studies have used the CCI and Elixhauser Index to predict outcomes in stroke patients.[6,7] However, there are a number of drawbacks with these indices, including the requirement of a large number of conditions, which can be impractical and inconvenient to apply in clinical settings. Moreover, these indices vary widely in their definitions and clustering of conditions[8] making it difficult to compare between populations. In addition, atrial fibrillation (AF), a major risk factor of stroke, is absent; but AF alone associates significantly with post-stroke complications.[9,10] Therefore, new studies have re-examined these indices. In their recent study of outcomes in stroke patients, Hall *et al* found that CCI could be reduced to ten conditions without compromising its predictive power of outcomes. Furthermore, AF was also added to the modified CCI model, but did not show additional improvement.[11] Studies of the impact of multimorbidity on outcomes are few and often yield conflicting findings.[12,13] This lack of agreement suggests that the above indices may not be suitable tools with stroke patients. In this study, we focussed on the most commonly associated

coexisting morbidities including: underlying *C*ongestive heart failure (CHF), *AF*, history of prior *S*troke and *H*ypertension (CASH). Here, we used evidence-based criteria for identifying a variety of outcomes following acute stroke using the presence of clusters of coexisting cardiovascular disease (CVD).

METHODS

Study design, participants and setting

We analysed prospectively collected data from the UK national register of stroke care. These data contain clinical characteristics and care quality determinants of patients admitted to acute care hospitals in England and Wales.[14] Data for this study were gathered from 3309 patients consecutively admitted with an acute stroke to four UK hyperacute stroke units (HASU) in the south of England between January 2014 and February 2016: Ashford & St Peter's (n = 1038), Frimley Park (n = 1010), Royal Surrey County (n = 612) and Epsom General (n = 649) hospitals.[15,16] SSNAP has approval from the Confidentiality Advisory Group of the Health Research Authority to collect patient data under section 251 of the NHS Act 2006 and thus no additional ethical approval was required.

Socio-demographic factors, medical history and stroke diagnosis

Demographic data were collected and documented by stroke consultants and nurse specialists; including age at arrival, gender and comorbidities: CHF, AF, previous stroke, HT, and diabetes mellitus.[14-16] Stroke was diagnosed based on clinical presentation and brain imaging.[14-16]

Selection of independent variables

Selection of independent variables: CHF, AF, history of prior stroke and HT, history of prior stroke and hypertension (HT) was based on their common occurrence and coexistence in patients with CVD,[17-20] and outlined by the Sentinel Stroke National Audit Programme (SSNAP).[14] Four categories were constructed based on four CVD conditions CHF, AF, history of previous stroke or HT. These were: CASH-0 (no coexisting CVD); CASH-1 (any one coexisting CVD); CASH-2 (any two coexisting CVD); CASH-3 (any three or all four coexisting CVD).

Adverse outcomes

Nosocomial infections, including urinary tract infection (UTI) and pneumonia, acquired within 7-days of admission were recorded. The length of stay on HASU as well as in-patient mortality were also documented.

Post-stroke disability was assessed by modified Rankin Scale (mRS) at discharge. The mRS scores indicate the patients' degree of disability or dependence on daily activities: 0 = no symptoms at all; 1 = no significant disability despite symptoms, able to carry out all usual duties and activities; 2 = slight disability, unable to carry out all previous activities but able to look after their own affairs without assistance; 3 = moderate disability; requiring some help, but able to walk without assistance; 4 = moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = severe disability, bedridden, incontinent and requiring constant nursing care and attention.[21,22]

Nutritional status was assessed at discharge using the Malnutrition Universal Screening Tool (MUST) protocol to identify those at risk of malnutrition.[23,24]

Level of care support planned at discharge

The planned level of care-support was recorded, including: help for activities for daily living, the frequency of home visits per week, and joint-care planning between health and social care for post-discharge management. Information was also documented on the decision to introduce palliative care by discharge date, as well as discharge to a new care home, either on a temporarily or permanent basis.[14-16]

Categorisation of variables

Dichotomisation was applied for CHF, AF, previous stroke and HT, as well as in-patient infections according to the presence or absence of any history of the condition, and mortality. Moderately-severe to severe disability at discharge was defined as an mRS score ≥4. Prolonged length of stay (LOS) on HASU was defined as those who stayed >14 days.

Statistical analysis

The associations of individual CVD conditions and outcomes were explored by chi-squared tests. Differences in LOS between CASH categories were assessed by Kruskal-Wallis tests. Multivariable logistic regression was conducted to estimate the risk of in-patient mortality and mRS ≥4 at discharge; UTI and pneumonia within 7-days of admission; LOS on HASU >14 days; and support planned at discharge (dependent variables) from patients with CASH: patients without CASH were used as a reference group (independent variables). The results are presented as two models: model 1, unadjusted; model 2, adjusted for age and sex by entering these two variables as confounding factors to the logistic regression equations. Results were expressed as

odds ratios (OR) and 95% confidence intervals (CI). Analyses were performed using SPSS Statistics for Windows, v.23.0 (IBM Corp., Armonk, NY, USA). The null hypothesis was rejected when $P<0.05$.

RESULTS

Table 1 shows the characteristics of patients. Genders were equally distributed across the cohort. The majority of patients presented with ischaemic stroke, with the remainder mostly as haemorrhagic stroke. **Table 2** shows that the rates of mortality and disability at discharge were significantly higher among stroke patients with CHF, AF, HT (only for disability) and history of prior stroke. The prevalences of other adverse outcomes were generally higher among patients with positive CASH scores than those with zero score. These included UTI and pneumonia within seven days of admission, LOS >14 days and risk of malnutrition. Among the four coexisting conditions, AF was most consistently and closely associated with stroke adverse outcomes. There were also greater but not consistent, requirements for increased levels of support at discharge, including help for activities of daily living, joint-care planning, discharge to a care-home and palliative care. For comparison, diabetes (a non-CASH condition) did not show any relationship with outcomes.

The rates of mortality (**Figure 1A**), disability at discharge (**Figure 1B**), and LOS on HASU >14 days (**Figure 1C**) increased with progressively greater CASH categories, whilst Kruskal-Wallis tests showed a significant codominant relationship in LOS on HASU and different CASH category groups ($\chi^2 = 32.1$, $P < 0.001$) (**Figure 2**). The proportions of other adverse clinical outcomes and some aspects of level of support planned at discharge including palliative care, joint-care planning between health and

social care for post-discharge management and activities of daily living support required by patients were also increased with cluster size of CASH (**Table 3**).

Logistic regression showed progressive increase in the risk of having adverse outcomes with cluster size of CASH (**Table 4A**). After adjustment for age and sex, compared with patients in CASH-0 (reference group), individuals with the largest cluster size (CASH-3) had the greatest adjusted risks (OR; 95%CI) of: mortality in hospital (1.8; 1.3 to 2.7) and disability at discharge (1.9; 1.4 to 2.7); UTI (3.3; 1.9 to 5.5), pneumonia (2.6; 1.7 to 4.0) within seven days of admission, and LOS >14 days (1.8; 1.3 to 2.6). The relationship between cluster size and risk of malnutrition, planning of palliative care and help with activity of daily living became non-significant after adjustment for age and sex. Joint-care planning was the only level of support component to be increased with two larger cluster sizes (1.4; 1.0 to 2.0) (**Table 4B**).

The mean unadjusted and age- and sex-adjusted ORs for each cluster of CASH were calculated from ORs of the six adverse outcomes shown in **Table 4A**. These ORs rose progressive with CASH-1 and CASH-2, and CASH-3 (**Figure 3**).

DISCUSSION

We present a novel and simple tool for predicting outcome following acute stroke. Based on the overall calculations, CASH could be used as a tool for estimating the risk of adverse outcomes: CASH-0 = low level, CASH-1 and CASH-2 = intermediate level, and CASH-3 = high level of risk of complications associated with acute stroke. We demonstrate a progressive increase in the risk of adverse outcomes with the number of coexisting CVD in patients with acute stroke. Compared to patients in

CASH-0 (no coexisting CVD), those with CASH-3 (any 3 or all 4 coexisting CVD) had 2-3 times greater risk of in-hospital mortality and disability at discharge, and a wide range of other clinical outcomes including severe stroke, nosocomial infections, and longer LOS on HASU.

The clustering of stroke with other CVD is well-established, while the coexisting multiple morbidities on post-stroke outcomes is less-well known. Our findings showed a clear relationship between CASH-score and a wide range of outcomes, which have not been examined previously. There exists only a handful of studies of limited outcome measures, such as those by Schnitzler *et al*[12] and Berlowitz *et al*.[13] Both of these studies used CCI to determine functional outcomes in stroke but their findings were inconclusive.

The CCI is not necessarily the right tool for outcomes after stroke since it was originally derived using data from general medical in-patients, did not include AF among its co-morbidities and was developed to predict one-year mortality.[1] Moreover, it was derived from a single medical centre (New York Hospital-Cornell Medical Center) in 1984 and may not be relevant to the present due to considerable improvement in the treatment of many conditions associated with the score. Therefore the conditions included in the original model may not add the same weights to the scores at the present time because new treatments of many conditions have improved drastically. Recognising these changes, Hall *et al*[11] recently developed a modified CCI for ischaemic stroke (ISCCI) based on 6988 patients from 100 hospitals in Canada found only ten comorbidities were required to perform with similar predictive power to 17 included in the CCI for mortality one-year after an acute ischaemic stroke. These authors

observed that the addition of AF to the ISCCI did not improve the prediction of outcome in stroke patients in their study. In the present study, we focussed on CHF, AF, previous stroke and HT because of their common links in pathophysiologies associated with CVD. It is also of importance that we also found diabetes (a non-CASH condition) to have no significant relationship with any of the post-stroke outcomes.

Our study identifies a high-risk group of those patients who presented with an acute stroke and will help clinicians to focus particularly on their management. This includes the optimisation of treatment of CASH to reduce post-stroke adverse outcomes. Further prospective interventional studies are necessary to assess the effectiveness of intensive CASH treatment in the reduction of post-stroke adverse outcomes among patients with multiple morbidities. These findings are also timely as increasingly more people are living with chronic conditions including further strokes, as well as physical and cognitive impairments.[25,26] Longitudinal studies are suggested to assess the association of clusters of CASH with longer-term outcomes such as hospital readmissions, dependency, disability and mortality, as well as the healthcare costs.

Strengths and limitations

The strengths of the present study lie in its relatively large cohort of patients derived from one of the largest NHS regions in the UK and who have similar characteristics to the rest of the stroke population in England and Wales.[14] SSNAP requires the four components of CASH to be routinely recorded for every patient admitted with an acute stroke in England and Wales,[14] therefore CASH is available for assessing stroke adverse outcomes nationwide. CASH contains few, but well-recognised conditions which has advantages over indices with large numbers, such the CCI. Too many

conditions in an index increase the risk of being missed in certain individuals due to inaccurate recall or incomplete documentation by clinicians. Data were collected in accordance with the national SSNAP protocol which used standardised outcome measures including mRS for disability,[21] as well as with other measures commonly used in national stroke surveys such as nosocomial infection.[14] The present study is limited by a lack of external validation therefore caution should be taken when applying the CASH scale to other populations. The outcome measures were short-term – studies of longer-term outcomes using a CASH scale would also be desirable. In addition, the four components of the CASH scale may be incomplete, which may lead to an underestimation of the predictive power of outcomes. Finally, further studies of CASH against other indices such CCI or SICCI and Elixhauser Index would be helpful to assess the performance of the simple CASH scale compared with more complex indices.

In conclusion, CASH is a novel and simple outcome risk scale which can be used to identify patients who are at increased risk of a variety of stroke associated adverse outcomes.

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LEGENDS

Figure 1. In-hospital mortality (**A**), mRS at hospital discharge ≥4 (**B**), and length of stay on HASU (**C**) in different clusters of CASH in patients admitted with an acute stroke.

Figure 2. Length of stay on HASU in different clusters of CASH in patients admitted with acute stroke with box plots representing median and interquartile ranges; whiskers represent the 5th and 95th percentiles.

Figure 3. Mean odds ratios calculated from six outcomes from Table 4A (mortality in hospital, mRS at hospital discharge ≥4, urinary tract infection and pneumonia within 7-days, LOS on HASU >14 days, and risk of malnutrition) for each cluster of CASH in patients admitted with an acute stroke.

Table 1. Distribution of 3309 patients, 1656 men and 1653 women admitted with stroke to hospitals in Surrey between January 2014 and February 2016.

	n	Proportion (%)
On admission		
Men (73.1 ±13.2 yr): Women (79.3 ±13.0 yr)	1656: 1653	50.0: 50.0
Ischaemic stroke: haemorrhagic stroke: unspecified	2758: 518: 33	83.3: 15.7: 1.0
Comorbidities		
Congestive heart failure	194	5.9
Atrial fibrillation	666	20.1
Stroke (previous history)	766	23.1
Hypertension	1729	52.3
Diabetes	531	16.0
Stroke outcomes during hospitalisation		
mRS score on discharge ≥4	989	29.9
In-patient mortality	480	14.5
Urinary tract infection within 7-days	243	7.3
Pneumonia within 7-days	258	10.8
Length of stay on HASU >14 days	892	27.0
Risk of malnutrition	853	25.8
Level of support planned on discharge		
Palliative care planning	253	7.6
Weekly visits	342	10.3
Joint-care planning*	771	23.3
Activities of daily living support	544	16.4
New care home discharge	177	5.3

LOS, length of stay; HASU, hyperacute stroke unit; *Joint-care planning between health and social care for post-discharge management.

Table 2. Adverse outcomes according to presence or absence of coexisting cardiovascular disease.

	Congestive heart failure			Arial fibrillation			History of prior stroke			Hypertension		
Poststroke adverse outcomes	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*
Mortality in hospital	14.4	22.2	0.002	11.8	25.4	<0.001	13.7	17.2	0.009	13.9	15.1	0.169
mRS on discharge ≥4	29.2	40.7	0.001	26.8	42.2	<0.001	27.8	36.8	<0.001	28.3	31.3	0.030
Urinary tract infection within 7-days	7.6	9.0	0.265	6.2	13.2	<0.001	7.1	9.3	0.036	5.7	9.4	<0.001
Pneumonia within 7-days	11.2	12.8	0.283	9.0	20.3	<0.001	10.4	14.1	0.005	9.0	13.3	<0.001
LOS on HASU >14 days	33.0	34.0	0.521	32.2	:41.7	<0.001	32.9	37.7	0.018	30.3	37.3	<0.001
Risk of malnutrition	27.1	28.1	0.415	24.8	36.8	<0.001	26.3	30.2	0.022	26.7	27.7	0.277
Support planned at discharge												
Palliative care	5.4	7.1	0.166	17.9	34.0	<0.001	22.2	27.7	0.030	52.0	51.8	0.498
Weekly visits	5.9	6.5	0.465	20.5	19.0	0.387	22.6	26.6	0.055	51.9	55.3	0.132
Joint care planning[§]	5.8	6.2	0.340	19.5	22.2	0.059	22.6	24.9	0.103	50.6	57.7	<0.001
Help with activity of daily living	5.2	6.1	0.252	17.1	20.2	0.054	21.3	25.9	0.012	50.7	56.8	0.006
New discharge to care home	5.8	6.2	0.467	20.1	20.3	0.503	23.0	25.4	0.256	52.0	56.5	0.139

LOS, length of stay; HASU, hyperacute stroke unit; [§]Joint care planning between health and social care for post-discharge management.

Table 3. Adverse outcomes among acute stroke patients according to CASH score.

	Categories of CASH				Group differences
	CASH-0	CASH-1	CASH-2	CASH-3	
Poststroke adverse outcomes	%	%	%	%	*P*
Mortality in hospital	11.1	13.1	19.8	24.5	<0.001
mRS on discharge ≥4	24.2	28.4	37.6	46.2	<0.001
Urinary tract infection within 7-days	3.8	8.5	9.8	14.6	<0.001
Pneumonia within 7-days	7.1	10.6	16.4	20.6	<0.001
LOS on HASU >14 days	29.8	33.1	38.5	39.3	<0.001
Risk of malnutrition	23.9	26.4	31.9	34.7	<0.001
Support planned on discharge					
Palliative care	7.1	7.4	11.2	14.6	<0.001
Weekly visits	10.1	10.4	12.5	11.1	0.426
Joint-care planning*	20.9	22.4	26.8	29.8	0.004
Activity of daily living support	17.7	19.9	24.6	26.9	0.004
New discharge to care home	4.2	6.0	6.0	4.8	0.082

LOS, length of stay; HASU, hyperacute stroke unit; *Joint-care planning between health and social care for post-discharge management.

Table 4A. Risk of poststroke adverse outcomes in hospital in different categories of CASH among patients admitted with acute stroke.

	CASH-1			CASH-2			CASH-3		
Unadjusted	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Mortality	1.20	0.94-1.54	0.150	1.97	1.50-2.58	<0.001	2.59	1.79-3.75	<0.001
mRS ≥4 at discharge	1.25	1.04-1.50	0.017	1.84	1.49-2.27	<0.001	2.69	1.98-3.66	<0.001
UTI within 7-days	2.32	1.82-3.38	<0.001	2.74	1.82-4.14	<0.001	4.29	2.58-7.12	<0.001
Pneumonia within 7-days	1.56	1.16-2.09	<0.001	2.59	1.88-3.56	<0.001	3.41	2.25-5.19	<0.001
LOS on HASU >14 days	1.17	0.97-1.42	0.111	1.47	1.17-1.86	<0.001	2.30	1.61-3.27	<0.001
Risk of malnutrition	1.14	0.94-1.38	0.172	1.49	1.20-1.86	<0.001	1.70	1.22-2.36	0.002
Adjusted for age and sex									
Mortality	1.02	0.79-1.31	0.911	1.47	1.12-1.95	0.006	1.83	1.25-2.67	0.002
mRS ≥4 at discharge	1.06	0.87-1.28	0.585	1.37	1.10-1.71	0.005	1.89	1.37-2.71	<0.001
UTI within 7-days	2.04	1.40-2.98	<0.001	2.18	1.43-3.33	<0.001	3.26	1.94-5.49	<0.001
Pneumonia within 7-days	1.38	1.02-1.86	0.037	2.08	1.50-2.88	<0.001	2.58	1.68-3.96	<0.001
LOS on HASU >14 days	1.04	0.85-1.26	0.725	1.20	0.94-1.52	0.140	1.80	1.25-2.58	0.002
Risk of malnutrition	1.01	0.83-1.23	0.914	1.21	0.96-1.52	0.102	1.30	0.92-1.82	0.133

Reference group: CASH-0 (no coexisting CVD). UTI, urinary tract infection; LOS, length of stay; HASU, hyperacute stroke unit.

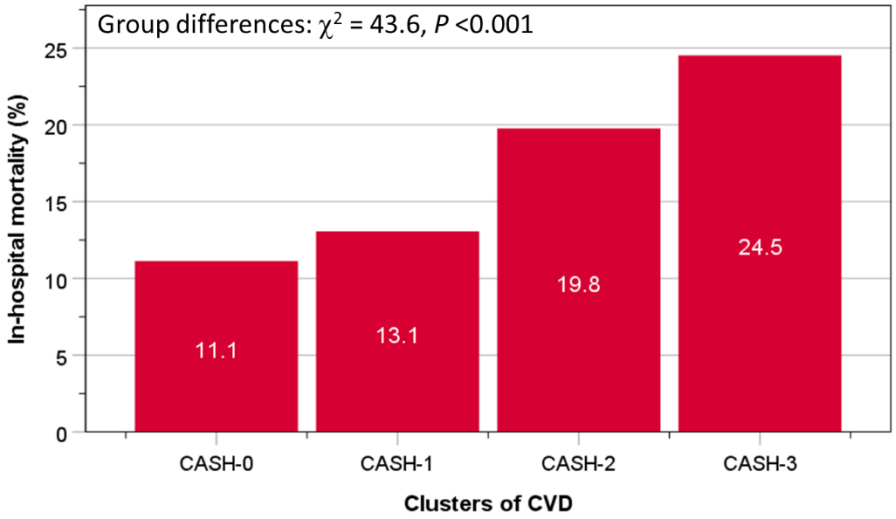
Table 4B. Level of support planned at discharge in different categories of CVD among patients admitted with acute stroke.

	CASH-1			CASH-2			CASH-3		
Unadjusted	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Palliative care planning	1.05	0.76-1.45	0.777	1.65	1.16-2.35	0.006	2.24	1.39-3.64	0.001
Discharge visits	1.04	0.80-1.36	0.769	1.23	0.94-1.75	0.118	1.11	0.68-1.81	0.672
Joint care planning*	1.09	0.90-1.33	0.380	1.39	1.10-1.34	0.005	1.60	1.15-2.23	0.005
ADL support†	1.16	0.92-1.45	0.206	1.52	1.16-1.98	0.002	1.72	1.14-2.57	0.009
New discharge to care home	1.43	0.98-2.07	0.061	1.45	0.94-2.24	0.097	1.14	0.57-2.30	0.716
Adjusted for age and sex									
Palliative care planning	0.86	0.62-1.21	0.390	1.12	0.77-1.62	0.558	1.39	0.84-2.29	0.200
Weekly visits	0.94	0.71-1.24	0.655	1.01	0.73-1.39	0.955	0.82	0.50-1.34	0.425
Joint-care planning*	1.05	0.86-1.28	0.622	1.26	1.00-1.59	0.050	1.43	1.02-2.01	0.037
ADL support†	0.99	0.78-1.26	0.944	1.08	0.82-1.44	0.576	1.12	0.73-1.72	0.601
New discharge to care-home	1.18	0.81-1.73	0.398	0.97	0.62-1.51	0.880	0.68	0.34-1.39	0.295

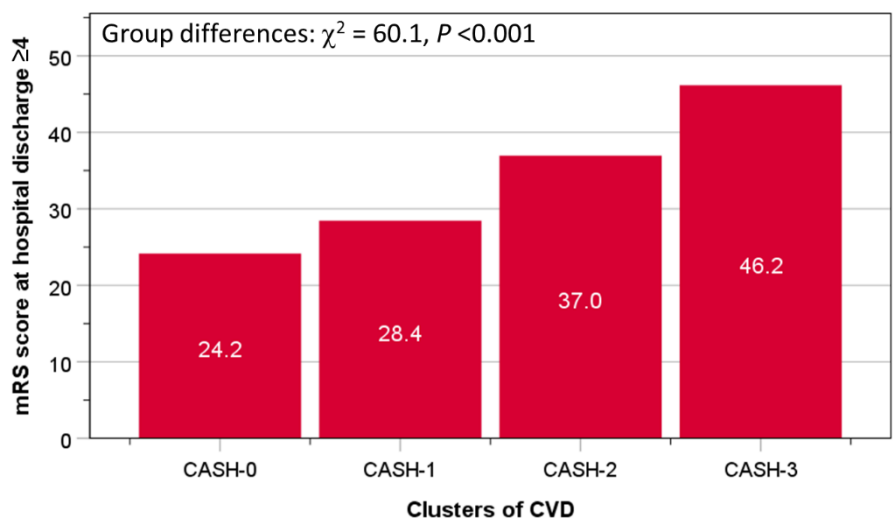
Reference group: CASH-0 (no coexisting CVD); *Joint-care planning between health and social care for post-discharge management; †Activities of daily living support required by patients.

Figure 1.

(**A**)


Group differences: χ^2 = 43.6, *P* <0.001
In-hospital mortality (%)
25
20
15
10
5
0
11.1
13.1
19.8
24.5
CASH-0
CASH-1
CASH-2
CASH-3
Clusters of CVD

(**B**)


Group differences: χ^2 = 60.1, *P* <0.001
mRS score at hospital discharge ≥4
50
40
30
20
10
0
24.2
28.4
37.0
46.2
CASH-0
CASH-1
CASH-2
CASH-3
Clusters of CVD

(**C**)

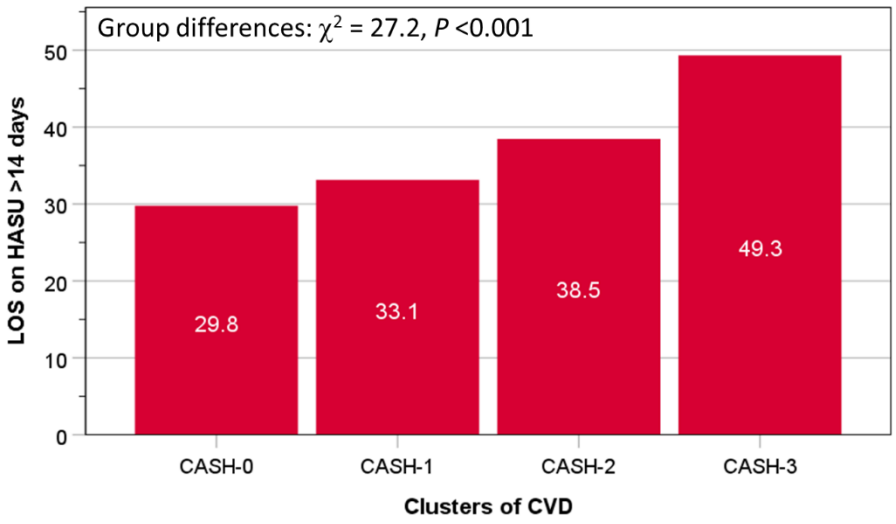

Group differences: χ^2 = 27.2, *P* <0.001
LOS on HASU >14 days
50
40
30
20
10
0
29.8
33.1
38.5
49.3
CASH-0
CASH-1
CASH-2
CASH-3
Clusters of CVD

Figure 2.

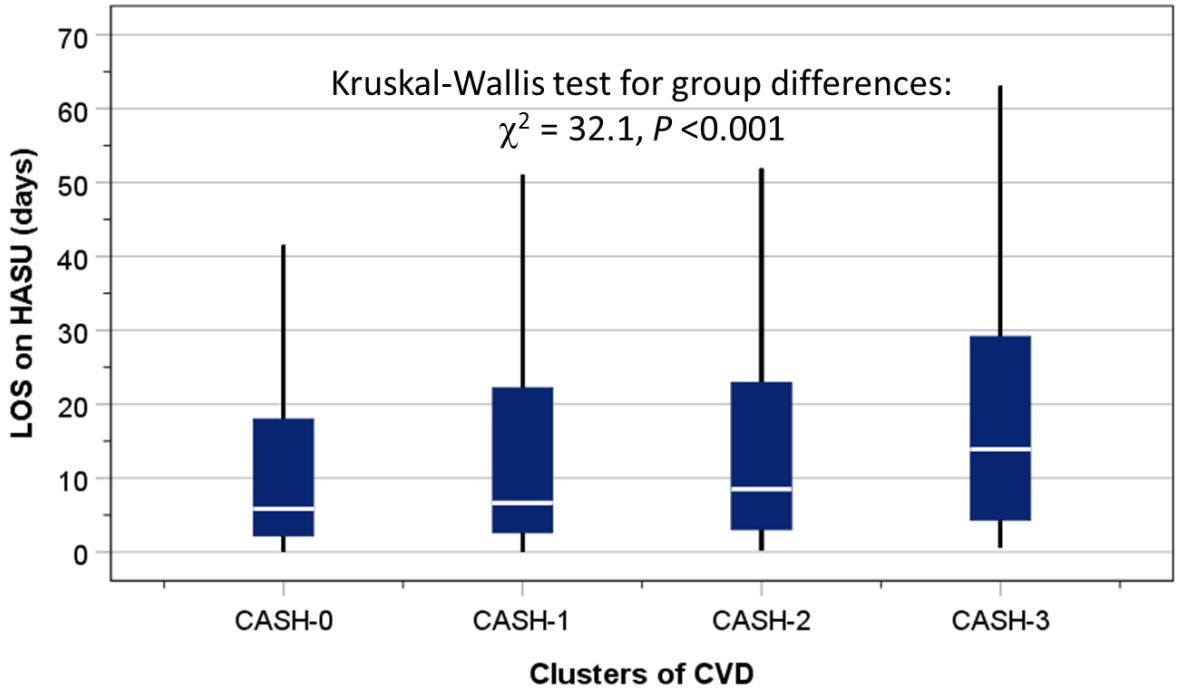
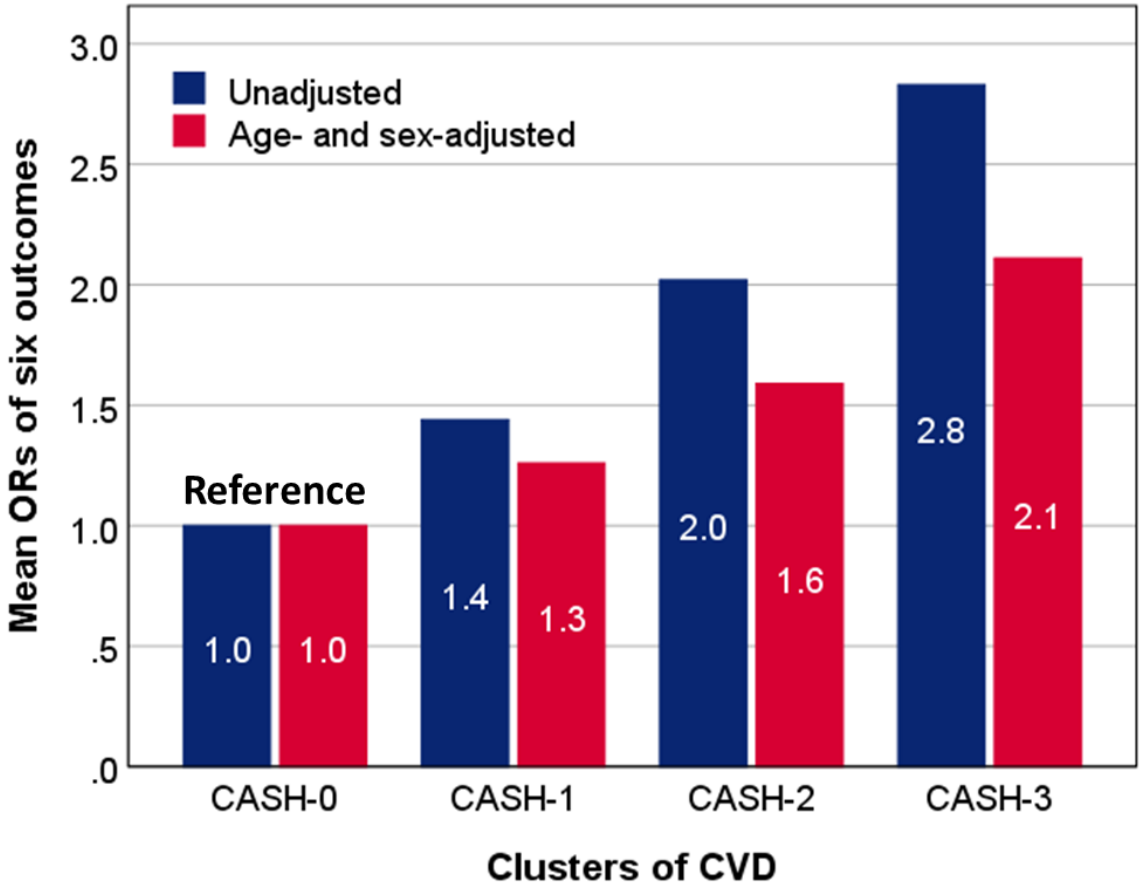

Kruskal-Wallis test for group differences:
χ^2 = 32.1, *P* <0.001
LOS on HASU (days)
70
60
50
40
30
20
10
0
CASH-0
CASH-1
CASH-2
CASH-3
Clusters of CVD

Figure 3.


Unadjusted
Age- and sex-adjusted
Mean ORs of six outcomes
3.0
2.5
2.0
1.5
1.0
.5
.0
Reference
1.0
1.0
1.4
1.3
2.0
1.6
2.8
2.1
CASH-0
CASH-1
CASH-2
CASH-3
Clusters of CVD