Hyponatremia predicts mortality after stroke

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Abstract

Background: Hyponatremia, the commonest electrolyte imbalance encountered in clinical practice, is associated with adverse outcomes. Despite this, understanding of the association between hyponatremia and stroke mortality outcome is limited.

Aims: To investigate the association between admission serum sodium and mortality at various time-points after stroke.

Methods: Cases of acute stroke admitted to Norfolk and Norwich University Hospital consecutively from January 2003 until June 2013 were included, with mortality outcomes ascertained until the end of December 2013. Odds ratios (OR) or Hazards ratio (HR) for death were constructed for various time points (within 7 days, 8-30 days, within 1 year and over full follow-up).

Results: 8540 participants were included (47.4% male, mean age 77.3 (± 12.0) years). Point prevalence of hypernatremia and hyponatremia were 3.3% and 13.8%, respectively. In fully adjusted models controlling for age, sex, pre-stroke modified Rankin score, stroke type, Oxford community stroke project class and laboratory biochemical and hematological results, the ORs (up to one year)/HRs (for full follow up) for the above time points were 1.00, 1.11, 1.03, 1.05 for mild hyponatremia, 1.97, 0.78, 1.11, 1.2 for moderate hyponatremia, 3.31, 1.57, 2.45, 1.67 for severe hyponatremia and 0.47, 1.23, 1.30, 1.10 for hypernatremia. When stratified by age-groups, outcomes were poorer in younger hyponatremic patients (aged <75 years).

Conclusions: Hyponatremia is prevalent in acute stroke admissions and is independently associated with higher mortality in patients <75 years.

Introduction

Hyponatremia (serum sodium <135 mmol/L), even when mild, is associated with increased mortality [1-3]. It is the commonest electrolyte abnormality encountered in the general population [4] and in patients with stroke [5]. Furthermore, low sodium is a recognised risk factor for stroke even at levels normally regarded as normonatremic [6]. Moreover, in a study of first ever stroke in patients with chronic kidney disease, hyponatremia was an independent predictor of mortality [7].

Despite this, only two published studies have specifically investigated the association between admission hyponatremia and outcomes after stroke. Hyponatremia was reportedly a predictor of 3-year mortality in acute first-ever ischemic stroke independent of other prognostic predictors [8]. More recently, hyponatremia was associated with higher mortality in hospital, at 3-months and 12-months follow acute stroke [9]. However, it is unclear whether prognosis following acute stroke is affected by the severity of hyponatremia and whether poor outcome persists in patients with mild hyponatremia (Na 130-134 mmol/L). Additionally, hypernatremia (Na >145 mmol/L) has been reported to be associated with early neurological worsening following stroke [10].

Aims

This study investigated the association between admission serum sodium and mortality at various time-points after stroke. Since hyponatremia in older patients is especially common and particularly challenging to manage [12], we looked for differences in the impact of dysnatraemias in older versus younger patients, hypothesising that the prognostic value of serum sodium would vary with age.

Methods

We used the Norfolk and Norwich Stroke Register that prospectively recorded consecutive patients with a diagnosis of acute stroke admitted to Norfolk and Norwich University Hospital since 1996. The hospital hosts the only acute stroke unit for a population of approximately 750,000 inhabitants in the city of Norwich and surrounding rural areas. Data collection methods of the register have been previously reported [13]. Briefly, data were obtained from paper-based and electronic records, reviewed and entered onto the register database by the hospital stroke data team. All participants were reviewed and diagnosed by a specialist stroke team. Ethical approval was obtained from the Newcastle and Tyneside National Health Service (NHS) Research Ethics Committee (12/NE/0170) and the study protocol was approved by the Steering Committee of the Norfolk and Norwich Stroke Register.

For the current study, prospectively collected data included basic demographic characteristics, pre-stroke modified Rankin score (mRS) [14], stroke type using the Oxfordshire Community Stroke Project (OCSP) classification [15], co-morbidities and results of hematological and biochemistry investigations (hemoglobin, white cell count, glucose, urea and sodium). For each patient, the modified pre-stroke mRS, was ascertained from nursing and medical records by stroke specialist nurses. Since biochemistry data were electronically available after January 2003, we included patients admitted to the unit between January 2003 and June 2013. We included all cases of acute ischemic or hemorrhagic stroke, but excluded subarachnoid hemorrhage (SAH) and cases of recurrent stroke.

Admission serum sodium was used to classify participants into mild (Na 130-134 mmol/L), moderate (Na 125-129 mmol/L) and severe (Na<125mmol/L) hyponatremia, normonatremia (Na 135-145 mmol//L) and hypernatremia (Na>145 mmol/L). Follow-up was conducted from admission until December 2013 using the hospital administration system and validated using the NHS demographics system.

The statistical analysis was conducted using Stata 11.2/SE (College Station, TX, USA). One-way rank-based ANOVA or chi-squared tests compared baseline characteristics and mortality across sodium groups. A sequence of logistic regression models were then fitted to data to estimate the odds ratio of outcome (7 day mortality, death within 8-30 days, 1 year mortality) for each sodium group relative to the comparator group. The models were adjusted for a) age; b) age, sex, mRS and comorbidities (history of MI, Stroke, TIA, Dementia, Diabetes, PVD, heart failure, COPD and asthma); c) factors in (b) and stroke type and OSCP class; d) factors in (c) and glucose, urea, white cell count and hemoglobin. For mortality outcome at end of follow up, a Cox proportional

hazards model was used along with Kaplan-Meier survival curves, with the same covariates as the model above, with censoring at the date of follow-up for those individuals still alive. A stratified analysis for those aged <75 years and those aged 75 or more was conducted using model (d) and a formal test of interaction was used to test the equality of the association with sodium group and outcome between these two age groups.

Results

There were 9835 admissions during the study period. We excluded 99 individuals with no follow-up data, 156 individuals with SAH, 695 individuals with recurrent stroke and 494 individuals who had no available sodium results within one day of admission. Therefore, 8391 cases were included (47.4% male, mean (±SD) age 77.3 (± 12.0) years).

The baseline point prevalence of hypernatremia was 3.3%. The prevalences of mild, moderate and severe hyponatremia were 10.5%, 2.7% and 0.6%, respectively. A comparison of baseline characteristics and outcomes according to natremic group is shown in Table 1. The mortality for the entire cohort of 8391 patients was 12.9% at one week, 15.0% at 30 days and 39.1% at one year. Patients with sodium disturbances were older, had higher prior disability (depicted by pre-stroke mRS), higher white cell counts and higher prevalence of diabetes. Hyponatremia was more common in females whilst the prevalence of dementia was higher in hypernatremic patients.

Both hypo- and hypernatremia were associated with increased mortality at all selected time-points (Table 2 and Figure 1). However, the increased odds of death in mild hyponatremia (Na 130-134 mmol/L) and hypernatremia (Na >145 mmol/L) did not reach statistical significance and were similar to the normonatremic group after adjustments.

The fully-adjusted sub-group analysis by age categories (Table 3) showed that hyponatremia in younger patients, especially when severe, was independently associated with higher mortality at all time-points. Intriguingly, younger patients with hyponatremia continued to have increased risk of death beyond one year after their stroke, even when hyponatremia was mild. In older patients, difference in odds of death by sodium level did not reach statistical significance at most time-points.

Discussion

Our study is the largest to date to investigate the association between admission sodium levels and mortality after stroke. It confirms findings from smaller studies reporting that hyponatremia is an independent predictor of poor outcome after stroke both in the short [9] and long term [8]. Additionally, our findings show for the first time that this association is driven mostly by increased risk of death with hyponatremia in younger stroke patients. Also, the increased mortality with hypernatremia disappears after adjustment for potential confounders such as urea, a marker of hydration [16].

The 13.8% prevalence of hyponatremia on admission in our sample of stroke patients was similar to that observed in comparable literature by Rodrigues *et al.* (16%) [9] and Huang *et al.* (12%) [8], but lower than that seen in acute geriatric medicine wards (18%) [17], where patients are older. However, mortality in our study was much higher than in the study by Huang, where mortality was just 8.8% at 3 years follow-up [8]. We also observed a higher mortality than the 29% seen at 1 year in the registry study by Rodrigues [9]. These differences are possibly due to our older, unselected sample population. It is unclear why our population is older than other published studies but probably reflects that frail older people in our study registry were not excluded from access to an acute stroke unit, as per best practice guidelines [18]. Also, our inclusion of both hemorrhagic and ischemic stroke, rather than just ischemic stroke, may have contributed to these differences.

Strikingly, younger patients with hyponatremia are at a higher risk of death. We initially hypothesised that older people would be at highest risk due to frailty and increased susceptibility to other adverse effects of hyponatremia, including confusion [12], falls [19] and fractures [20]. There are a number of possible explanations for this unexpected observation. Acute hyponatremia is well known to cause cerebral oedema [21] but older individuals may be more likely to survive because age-related cerebral atrophy will protect against fatal coning due to raised intracranial pressure. Also, the increased susceptibility to dyshomeostasis (and consequent hyponatremia) in older people [22] suggests that they may become hyponatremic due to less severe and/or more easily remediable causes than younger individuals. Such cases of hyponatremia, in older people, are predominantly mild and chronic (*i.e.* developing >48 hours) [11]. In this study we did not account for rate of development of hyponatremia which is a more important prognostic predictor than absolute serum sodium measurements [23]. Therefore, it is plausible that acute hyponatremia may be more common in younger people and that rate of development of hyponatremia may account for the worse prognosis in younger people with

stroke. Since hyponatremia in younger patients continued to predict mortality beyond the short-term, it seems unlikely that cerebral oedema alone could continue to explain the association with increased mortality.

There were important differences at baseline (Table 1) between the various natremic groups, many of which may partly explain the unadjusted association between dysnatremias and death. In particular, older, frailer individuals with diabetes were more prone to dysnatremia, and those with hypernatremia were more likely to have dementia and present with total anterior circulation stroke. Hyponatremia was more common in women, in keeping with other observational studies [24].

Dysnatremia was associated with increased odds of death at all time-points, albeit with attenuation in magnitude of association after adjustment for multiple potential confounders. Surprisingly, the exception was that the odds of death with hypernatremia were significantly lower in the fully adjusted model. This suggests it is dehydration rather than hypernatremia that accounts for the excess mortality in the hypernatremic group. This is important as dehydration should be easily remediable, although stroke and hypernatremia may be terminal events for some individuals, and a palliative approach may have been appropriately instituted. The increased odds of death with mild hyponatremia were modest and did not reach statistical significance, but this may reflect a lack of power and would be unwise to dismiss since hyponatremia may also be very treatable. Previous groups have found that both mild hyponatremia and serum sodium levels within the lower range of normonatremia (serum sodium<137) are associated with increased mortality in hospitalised adult patients [25, 26].

Since hyponatremia is often chronic and notoriously challenging to manage [12], it is possible that many patients in this cohort remained chronically hyponatremic, as observed in non-stroke populations [27]. However, because we only utilised admission serum sodium measurements, this could not be assessed. Chronic hyponatremia in the general population is associated with increased mortality, even when mild [1], potentially explaining the longer term association with increased mortality in younger patients who have longer life expectancy compared to their older counterparts. Due to the limited life expectancy of our older co-morbid participants, it is possible that our analysis lacked power to detect an independent association with mortality at longer-term follow-up in the older patients due to the modest numbers of survivors and because moderate and severe hyponatremic cases were uncommon. There are no studies that carefully examine the causes of hyponatremia after stroke. Unfortunately, we do not have data on aetiology of hyponatremia encountered in this study either, which is a limitation of this report.

Our study has some other limitations that should be considered. We used only baseline sodium measurements to highlight the potential impact of dysnatremia on stroke outcome. Also, in any observational study it is possible that there are unmeasured confounders. However, we robustly adjusted for patient related factors (demographics/co-morbidities/prestroke disability), stroke related factors (type), and acute haematological and biochemical parameters. We did not measure the severity of stroke other than by OCSP class. Despite these limitations, this report makes an important contribution to understanding of dysnatremia and post-stroke mortality. We studied a large and unselected study population and availability of outcome data was complete.

Whilst the association between hyponatraemia and mortality cannot prove causation, the independent association observed in this prospective study raises an important question. Would timely and appropriate management of hyponatraemia improve stroke mortality? This requires further study in a randomised controlled trial as it remains possible hyponatraemia is a marker of severity of underlying dyshomeostasis or disease. Our study does not provide information on the causes of hyponatremia, or what efforts were made to correct it. We therefore do not know how often hyponatremia was resistant to treatment.

In summary, our study provides the strongest and largest evidence to date on the association between admission dysnatraemias and mortality after stroke. This is clinically significant as it raises the possibility that better prevention and management of hypo- and hypernatremia may improve outcomes after stroke. Future studies should investigate the causes of hyponatremia after stroke, and whether therapeutic strategies to achieve normonatremia may lead to improved outcomes.

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Conflicts of interest

The authors declare no conflicts of interest.

Contributions

RLS and PKM conceived the idea and designed the analysis plan with the input from ABC. JHB performed the record linkages. ABC analysed the data. PKM is the PI of the NNUH Stroke & TIA register. RLS and KC drafted the manuscript. All authors contributed to the writing of the paper.

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Tables

Table 1: Sample characteristics categorised by sodium measurement (mmol/L)

Variable	Sodium<125	Sodium 125-129	Sodium 130-134	Sodium 135-144	Sodium≥145	P value
Number (N)	57	230	884	6945	275	
Age	79.3 (9.72)	80.32 (8.92)	79.92 (10.35)	76.8 (12.13)	77.63 (13.31)	<0.001
Male sex	19 (33.3)	77 (33.5)	328 (37.1)	3413 (49.1)	138 (50.2)	<0.001
Pre-stroke mRs*						<0.001
0	23 (46.9)	100 (48.3)	425 (53.3)	4286 (66.3)	119 (49.4)	
1	8 (16.3)	35 (16.9)	108 (13.5)	680 (10.5)	19 (7.9)	
2	5 (10.2)	20 (9.7)	84 (10.5)	501 (7.7)	16 (6.6)	
3	9 (18.4)	28 (13.5)	104 (13)	564 (8.7)	43 (17.8)	
4	2 (4.1)	16 (7.7)	48 (6)	313 (4.8)	23 (9.5)	
5	2 (4.1)	8 (3.9)	29 (3.6)	121 (1.9)	21 (8.7)	
Previous stroke	17 (29.8)	55 (23.9)	183 (20.7)	1319 (19)	69 (25.1)	0.007
Previous TIA	1 (1.8)	12 (5.2)	36 (4.1)	286 (4.1)	8 (2.9)	0.639
Stroke type						0.003
Bleed	8 (14)	44 (19.1)	140 (15.8)	916 (13.2)	24 (8.7)	
Infarct	49 (86)	186 (80.9)	744 (84.2)	6029 (86.8)	251 (91.3)	
Bamford Classification						<0.001
LACS**	15 (26.3)	43 (18.8)	171 (19.5)	1597 (23.1)	48 (17.5)	
PACS***	14 (24.6)	74 (32.3)	278 (31.7)	2253 (32.6)	70 (25.5)	
POCS****	12 (21.1)	43 (18.8)	151 (17.2)	1155 (16.7)	35 (12.8)	
TACS*****	10 (17.5)	42 (18.3)	196 (22.3)	1434 (20.8)	74 (27)	
UNK******	6 (10.5)	27 (11.8)	81 (9.2)	466 (6.7)	47 (17.2)	
Follow-up period/ period till death	725.81 (1016.42)	736 (933.23)	763.15 (957.28)	1029.05 (1100.21)	895.94 (1181.48)	<0.001

Glucose	7.75 (4.59)	7.78 (4.52)	8.18 (4.56)	7.2 (2.86)	7.58 (3.96)	0.001
Urea	7.31 (6.19)	7.29 (5.55)	7.8 (5.01)	7.69 (4.12)	13.95 (11.02)	<0.001
Sodium	120.18 (4.34)	127.55 (1.35)	132.53 (1.37)	139.37 (2.32)	147.69 (4.67)	<0.001
HB	12.8 (2.12)	12.8 (1.81)	12.89 (2)	13.58 (1.9)	13.6 (2.35)	<0.001
WBC	10.67 (5.26)	10.94 (5.38)	10.77 (7.27)	9.98 (8.85)	11.73 (6)	<0.001
Asthma	3(5.3)	21(9.1)	81(9.2)	470(6.8)	23(8.4)	0.056
COPD	8(14)	14(6.1)	60(6.8)	393(5.7)	17(6.2)	0.065
CHF	8(14)	21(9.1)	105(11.9)	706(10.2)	39(14.2)	0.099
Diabetes	11(19.3)	34(14.8)	131(14.8)	762(11)	36(13.1)	0.001
Dementia	1(1.8)	15(6.5)	39(4.4)	249(3.6)	29(10.5)	<0.001
PVD	2(3.5)	3(1.3)	35(4)	242(3.5)	9(3.3)	0.421
MI	4(7)	10(4.3)	55(6.2)	394(5.7)	21(7.6)	0.520
Dead within 7 days	12(21.1)	47(20.4)	133(15)	845(12.2)	62(22.5)	<0.001
Death 8-30 days	7(12.3)	26(11.3)	105(11.9)	618(8.9)	44(16)	<0.001
Death within 1 year*	33(60)	115(50.4)	401(47.2)	2491(37.4)	148(54.8)	<0.001
Death	40(70.2)	156(67.8)	553(62.6)	3736(53.8)	206(74.9)	<0.001

* mRs= modified Rankin score (0=no symptoms, 1=no significant disability, 2=slight disability, 3=moderate disability, 4=moderately-severe disability, 5= severe disability, 6=dead)

LAC = lacunar stroke ***PACS = partial anterior circulation stroke ****POCS = Posterior circulation stroke *** TACS = Total anterior stroke ****** UNK = Unknown

Table 2: Odds Ratios (OR) for death at various time-points and Cox proportional hazards ratio (HR) for death using normonatremia as the reference category

Variable	Sodium<125	Sodium 125-129	Sodium 130-134	Sodium 135-144	Sodium≥145
7 day mortality (OR)					
Model A*	1.83 (0.96-3.49)	1.72 (1.24-2.39)	1.19 (0.97-1.45)	1	2.06 (1.54-2.77)
Model B**	2.19 (1.10-4.36)	1.98 (1.39-2.82)	1.17 (0.93-1.45)	1	1.97 (1.42-2.73)
Model C***	2.84 (1.29-6.22)	2.03 (1.35-3.08)	1.01 (0.79-1.30)	1	1.51 (1.04-2.19)
Model D****	3.31 (1.27-8.62)	1.97 (1.15-3.38)	1.00 (0.72-1.38)	1	0.47 (0.25-0.88)
Death between 8-30 days (OR)					
Model A*	1.41 (0.62-3.22)	1.24 (0.80-1.90)	1.21 (0.97-1.52)	1	2.28 (1.60-3.26)
Model B**	1.43 (0.58-3.55)	0.94 (0.56-1.57)	1.27 (0.99-1.61)	1	1.93 (1.29-2.88)
Model C***	1.66 (0.64-4.34)	1.04 (0.61-1.78)	1.24 (0.96-1.60)	1	1.73 (1.12-2.67)
Model D****	1.57 (0.47-5.32)	0.78 (0.37-1.63)	1.11 (0.79-1.57)	1	1.23 (0.69-2.21)
Death within 1 year (OR)					
Model A*	2.43 (1.38-4.27)	1.48 (1.12-1.95)	1.30 (1.12-1.51)	1	2.08 (1.60-2.71)
Model B**	2.69 (1.44-5.04)	1.36 (1.01-1.83)	1.27 (1.08-1.49)	1	1.80 (1.34-2.41)
Model C***	3.23 (1.66-6.30)	1.37 (1.00-1.89)	1.23 (1.03-1.48)	1	1.61 (1.16-2.23)
Model D****	2.45 (1.08-5.55)	1.11 (0.73-1.68)	1.03 (0.82-1.31)	1	1.30 (0.82-2.08)
Death (HR)					
Model A*	1.39 (1.02-1.91)	1.30 (1.11-1.53)	1.16 (1.06-1.27)	1	1.68 (1.45-1.94)
Model B**	1.46 (1.05-2.04)	1.26 (1.06-1.50)	1.14 (1.03-1.26)	1	1.55 (1.33-1.81)
Model C***	1.43 (1.03-2.00)	1.29 (1.08-1.53)	1.08 (0.98-1.19)	1	1.42 (1.22-1.66)
Model D****	1.67 (1.13-2.47)	1.20 (0.96-1.51)	1.05 (0.92-1.19)	1	1.10 (0.88-1.36)

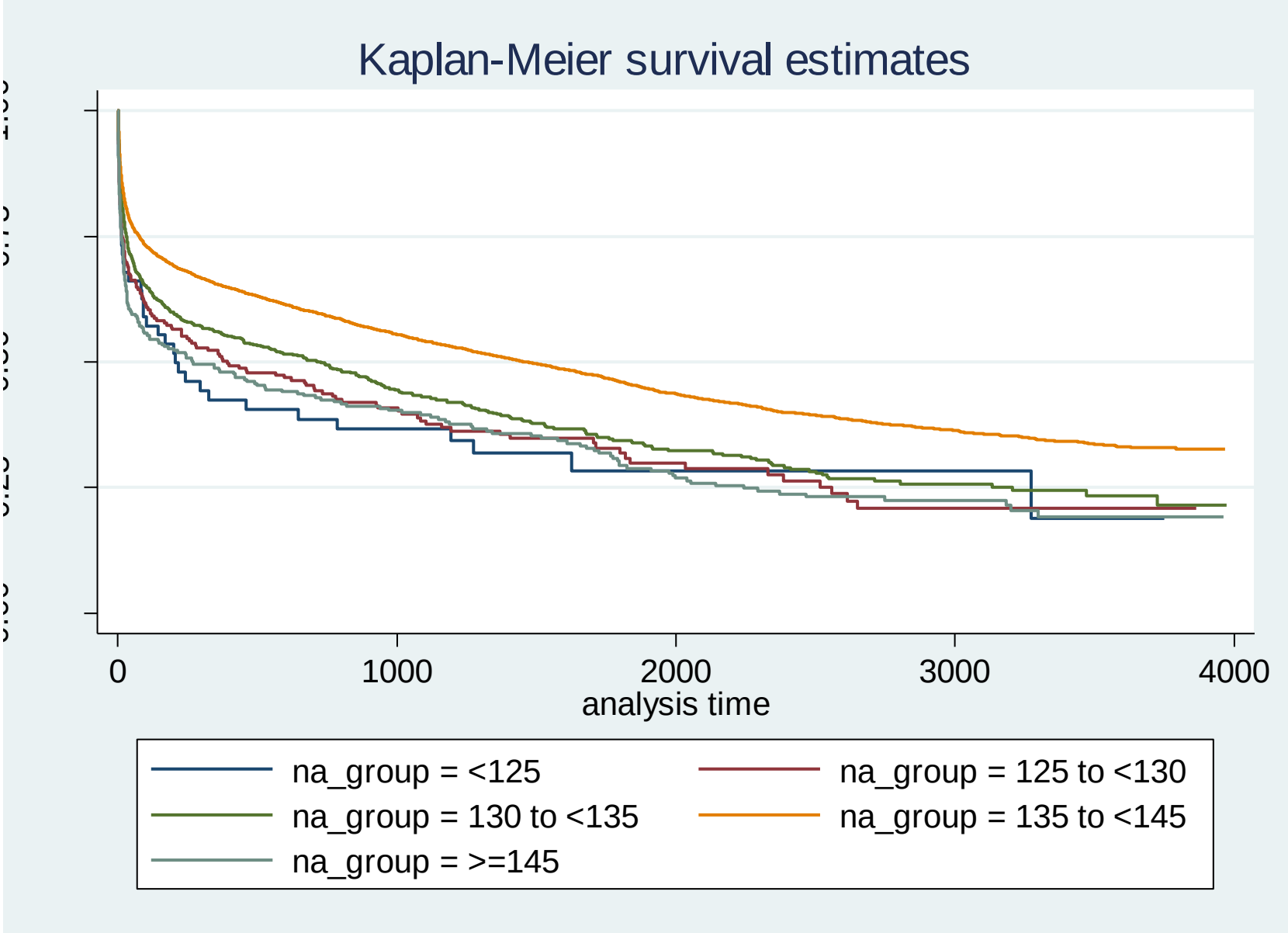
*model a- adjusted for age **model b- adjusted for age, sex, co-morbidities and pre-stroke mRs ***model c- adjustment as for model b plus stroke type and OCSP classification

****model d- adjustment as for model c plus adjustment for haematological and biochemistry data

Table 3: Fully-adjusted sub-group analysis by age categories

Age group	Sodium<125	Sodium 125-129	Sodium 130-134	Sodium 135-144	Sodium ≥145	p-value
7 day mortality						0.3279
<75 years	13.9 (2.41-80.5)	1.89 (0.57-6.30)	1.41 (0.71-2.80)	1	0.53 (0.16-1.81)	
≥75 years	1.72 (0.49-5.96)	2.00 (1.09-3.66)	0.93 (0.64-1.36)	1	0.46 (0.22-0.95)	
						0.1662
Death between 8-30 days						
<75 years	8.92 (0.67-119)	1.22 (0.14-10.8)	2.47 (1.04-5.85)	1	0.40 (0.046-3.54)	
≥75 years	1.09 (0.27-4.43)	0.74 (0.34-1.63)	0.97 (0.67-1.41)	1	1.40 (0.76-2.59)	
						0.0809
Death within 1 year						
<75 years	8.21 (1.40-48.1)	0.90 (0.32-2.59)	1.56 (0.94-2.59)	1	0.92 (0.38-2.22)	
≥75 years	1.44 (0.54-3.80)	1.17 (0.75-1.82)	0.92 (0.71-1.20)	1	1.29 (0.74-2.23)	
						0.0011
Death						
<75 years	4.21 (1.99-8.88)	0.98 (0.55-1.76)	1.45 (1.07-1.95)	1	1.03 (0.66-1.61)	
≥75 years	1.21 (0.76-1.92)	1.22 (0.96-1.56)	0.96 (0.83-1.11)	1	1.05 (0.82-1.34)	

Figure 1: Kaplan Meier Survival Curves


Kaplan-Meier survival estimates
0
1000
2000
3000
4000
analysis time
na_group = <125
na_group = 125 to <130
na_group = 130 to <135
na_group = 135 to <145
na_group = >=145