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Anaemia and incidence of post stroke dementia

Running Head: Anaemia and post-stroke dementia

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Abstract

Background: Whilst lack of concentration is a known symptom of anaemia, its association with post-stroke dementia is unclear.

Methods: We used data from a UK regional stroke register. To be eligible, patient must have survived to discharge and had anaemia by WHO criteria. Dementia status and other prevalent co-morbidities were assessed using ICD-10 codes. Patients were followed till May 2015 (mean follow-up 3.7 years, total person years = 27,769). Hazard Ratio for incident dementia was calculated using Cox-proportional hazards model controlling for potential confounders. Fine and Gray model was additionally constructed using mortality as the competing risk.

Results: A total of 7,454 stroke patients were included with mean age (SD) of 75.9(12.3) years (50.2% men). Those with anaemia were older, has higher disability and co-morbidity burden prior to stroke. We observed a large amount of variation in the dementia incidence rates over time and that the hazard ratio increased every year. The significant association between anaemia and dementia incidence was lost after controlling for pre-stroke Modified Rankin score (HR1.17(0.97,1.40)). With every 20g/dL increase in Hb was associated with a significant reduction in the risk of dementia after adjustment for age, sex, stroke factors and disability but lost significance after adjustment for vascular risk factors. Competing risk analyses showed similar results.

Conclusion: Whilst we found no evidence of anaemia as a risk factor for post-stroke dementia, the findings may be limited by potential under recognition of post stroke dementia.

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Introduction

Anaemia is common in patients with acute stroke. The prevalence figure of up to 30% has been reported in hospital-based studies [1][2]. Our recent work demonstrated that 25% of stroke patients were anaemic at the time of hospital admission [3]. The link between anaemia and cognition has grown considerable interest over the last few decades [4][5][6]. Systematic reviews and meta-analyses published in this area suggest potential link between anaemia and cognitive decline or dementia in older aged cohorts [7][8][9].

An estimated 47 million people had dementia in 2015, and this is expected to triple by 2050 [10]. Dementia after stroke (or post-stroke dementia) poses a significant problem considering up to 30% of patients developing significant cognitive impairment early post-stroke [11]. Furthermore, a significant proportion of these patients may already have mild cognitive impairment [12]. Post-stroke dementia is associated with dependency and it can also predict recurrence of ischaemic stroke up to 12 year follow-up [13]. Indeed, the World Alzheimer Report thus emphasized the benefit of early diagnosis with future savings from delayed institutionalization, and care cost across the disease course [14]. An effective strategy in preventing vascular dementia could have major resource implications, with at least one in five people with dementia having a vascular dementia and dementia costing the UK economy alone £23 billion per year [15].

It is estimated that about 10% of stroke patients have dementia [16]; recent work by Pendlebury and Rothwell demonstrated pre-event dementia prevalence ranged from 4·9% (95% CI 3·4–6·9) in patients with a transient ischaemic attack to 20·6% (15·8–26·5) in those with severe stroke [17]. In addition, the aetiology of dementia after a stroke or transient ischaemic attack (TIA) has been highlighted in research [18]. Vascular Dementia (VaD),

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Alzheimer's Dementia (AD) and Mixed Dementia (mixture of VaD & AD) are the three most common forms of dementia [19]. VaD includes multi-infarct dementia, stroke with dementia and sub-cortical VaD. Both VaD and mixed types are related to cerebrovascular disease and impose a significant problem in those who suffer from these conditions. With an ageing population, the cerebrovascular disease burden is set to rise in the UK; with significant concerns regarding rising incidence of VaD for which there is no established treatment. Most importantly, "how best to improve cognition after stroke" was reported to be the highest priority research topic in a survey of patients with stroke [20].

There is now a pressing need for greater understanding of risk factors for dementia in this patient group. One potential risk factor may be anaemia as suggested in general populations [8][9]. The proposed pathophysiology mechanisms include direct effect of chronic cerebral hypoxia., as a marker of diseases and processes such as ischemic and lower erythropoietin levels increasing the risk of neuronal degeneration. Others include iron dysregulation associated with increased brain oxidative stress, and chronic cerebral hypoperfusion in the prefrontal cortex or inflammatory neurodegenerative processes. It was also suggested that anaemia may cause the progression of white matter disease and through its negative effect physical function [8]. Despite different pathological mechanisms, post stroke dementia occurs as the result of vascular dementia or mixed (Alzheimer's and vascular dementia) and thus regarded as a single clinical entity.

However, few studies have examined this link in stroke patients. Given that stroke has high mortality in the first year and the fact that anaemia contribute this mortality risk [3], it is unclear whether stroke survivors who were anaemic would have either increased or decreased risk of post-stroke dementia.

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Methods

The study population consisted of 7,454 stroke patients consecutively admitted between January 2003 – May 2015 to Norfolk and Norwich University Hospital, a regional tertiary centre in East Anglia, UK, with a catchment population of approximately 750,000. 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 Register. Of 11,727 entries, 991 repeated entries (with second or third stroke recorded in the register were excluded. After further exclusion of 2,404 who died as in-patient, there were a total of 8,332 who were discharged from hospital for the first recorded stroke in the register, 379 had previous history of dementia prior to stroke and therefore excluded. 499 participants did not have haemoglobin values and had missing data for other co-variates and thus further excluded.

The data collection methods for this prospective hospital-based register have been previously reported [21]. Briefly, the data were obtained from paper and electronic records, reviewed and then entered onto the register database by the hospital stroke data team and vetted by clinical team members for accuracy. For each patient admitted, the pre-stroke modified Rankin score (mRS), as modified by UK-TIA investigators [22], was ascertained from nursing and medical records by stroke specialist nurses. At discharge, the dead or alive status was recorded to capture in-hospital mortality. Follow-up for mortality was obtained by electronic record linkage with Office of National Statistics data through hospital episodes in May 2015.

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To be eligible in the current study, patients could not have history of dementia (any type) prior to stroke and they must have survived to hospital discharge. Haemoglobin level obtained closed to discharge was used to determine the Hb or anaemia status. Only confirmed cases of stroke were included. Stroke was diagnosed using evidence from clinical features and neuroimaging (typically CT and in some cases MRI). Anaemia was defined according to the WHO criteria of Hb <12.0 g/dL in females and <13.0 g/dL in males and elevated haemoglobin was defined as >15.5g/dL in females and >17.0g/dL in males [23].

The variables included were age, sex, stroke sub-type (ischaemic/haemorrhagic), pre-stroke disability depicted by modified Rankin score (mRS), Oxfordshire Community Stroke Project (OCSP) classification (Total Anterior Circulation Stroke, Partial Anterior Circulation Stroke, Posterior Circulation Stroke, Lacunar Stroke), haemoglobin levels at discharge, co-morbidities (coronary heart disease including myocardial infarction, congestive heart failure (CHF), atrial fibrillation, hypertension, hyperlipidaemia, previous Stroke, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), and malignancy).

Dementia incidence was captured through UK NHS record linkage system via the patient administrative system (PAS) which records both secondary care and primary care based diagnosis of dementia in the NHS setting. International Classification of Disease (ICD) 10 codes F00, F01, F02 and F051 were used to capture both prevalent and incident dementia.

Statistical analysis

Characteristics of the individuals with and without anaemia were summarized using descriptive statistics and compared using a chi-squared test for categorical variables and a t-test for continuous variables. Annual incidence rates of stroke were calculated for each

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calendar year of follow-up stratified by year of study entry, excluding individuals who died in the year from the denominator.

The association between anaemia and dementia incidence was described using Kaplan-Meier plots and estimated using a cox proportional hazards model. This was done for six separate models A-F using hierarchical adjustments. The association was adjusted for age and sex in model A; model B adjusted additionally for stroke characteristics, model C additionally adjusted for pre-stroke modified Rankin score, model D additionally adjusted for key risk factors for dementia namely atrial fibrillation, coronary heart disease, previous stroke or TIA, peripheral vascular disease and history of hypertension. Model E additionally adjusted for other major co-morbidities which included COPD, CKD, CHF, hyperlipidaemia, diabetes, and malignancy. Model F additionally adjusted for year of stroke to account for the possibility that dementia diagnoses changed of the course of the follow-up period. The association between haemoglobin (Hb) and stroke incidence was assessed in a similar fashion using the same models. No major departures from the model assumptions were observed. As anaemia is also associated with death a competing risk model (Fine and Gray) was fitted using the same modelling strategies as above.

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Results

A total of 7,454 stroke patients were included in the current report; their mean age (SD) was 75.9 (12.3) years and there were 3,742 (50.2%) men. (mean follow up = 3.7 years, median follow up = 2.9 years, total person years = 27,769 years). Table 1 shows the sample characteristic comparison between those with and without anaemia at the time of discharge by sex specific analysis. It demonstrates that most factors considered are significantly different between individuals with anaemia and those without; those with anaemia tended to be older and significantly more likely to be more disabled prior to stroke with higher burden of co-morbidities.

Figure 1 shows the Kaplan Meier Curve showing linear trends in development of dementia in patients without (top line) and with (bottom line) anaemia. **Supplementary Table 1** shows that there is a large amount of variation in the incidence rates over time. Kaplan-Meier plot with each year being a separate line demonstrate clearly demonstrating the hazard ratio has generally increased every year (apart from 2015 which does not have full year of follow-up) (see **Figure 2**).

Table 2 shows the estimated hazards ratios and corresponding 95% confidence intervals. This shows a significant association between anaemia and dementia incidence, but this loses significance on adjusted for pre-stroke mRS. A similar pattern is observed when Hb was entered into model as a linear variable (with every 20g/dL increase) with a significant reduction in the risk of dementia until adjustment for key risk factors of dementia. Once competing risks are accounted for, this association loses significant in all but model A. This is suggestive that the association observed before adjustment is due to the imbalance in the

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206 characteristics at baseline between the two groups and that once the competing risk of death
207 is taken into account the association is not significant.
208
209
210 **Discussion**
211
212 To the best of our knowledge, we are the first group to report the association between
213 presence or absence of anaemia or haemoglobin levels and incidence of dementia over long-
214 term follow-up in a large cohort of unselected stroke survivors. Our study results highlight
215 the importance of death as the competing risk in development of post-stroke dementia, which
216 carries substantial mortality risk after hospital discharge. Whilst we did not demonstrate the
217 clear dose–response relationship between anaemia and dementia risk, Kaplan-Meier curves
218 demonstrate the potential effect of whether diagnosis of dementia was made after stroke.
219 Given that dementia diagnosis is based on progressive nature of clinical assessment criteria,
220 this complex nature should be taken into account in risk prediction studies of post-stroke
221 dementia.
222
223 The key strengths of the study include relatively large sample of unselected consecutive
224 stroke admissions. We were also able to control for acute stroke factors and comprehensive
225 list of co-morbidities as well as functional disability. We were able to follow up for long-
226 term with minimal loss to follow-up due to record linkage nature of the study in UK NHS
227 setting. In UK, almost everyone has NHS number and Office of National Statistics data are
228 linked to local NHS databases regularly and vital status ascertained, which included
229 mortality. Local NHS record linkage allows us to determine the date of dementia diagnosis

appearing in health records hence able to estimate hazards ratios rather than odds ratio. We were able to robustly considered death as competing risk by Fine & Gray methods [24].

Indeed, numerous risk factors for cognitive decline and dementia have been previously reported in stroke survivors. These included age, history of cardio-metabolic disease, atrial fibrillation, lower educational attainment, stroke severity, aphasia, recurrent stroke, pre-stroke cognitive impairment, and neuroimaging makers such as medial temporal lobe atrophy and hippocampal changes [25]. Currently developed are complex [26][27][28] and it is unlikely to be of clinical utility. For prediction tools to be of clinical utility, criteria should include readily available parameters that can be reliably measured with minimal resources. Discharge haemoglobin offers potential role given that there are several plausible pathophysiological mechanisms. Anaemia could lead to chronic reduction of cerebral oxygenation secondary to decreased oxygen-carrying capacity of the blood. Alternatively, it serves as a marker of diseases and processes such as ischemic and lower erythropoietin levels, thereby increasing the risk of neuronal degeneration, iron dysregulation and associated with increased brain oxidative stress [29]. Anaemia could also be associated with the progression of white matter disease [30]. Another potential causal pathway could operate through the negative effect of anaemia on reduced physical function. It was proposed that cardiorespiratory fitness is linked to executive functions through an increase in brain derived neurotrophin factor or a parasympathetic related increase in efficiency of prefrontal neural function [31]. Therefore, presence of functional impairment as the results of stroke damage may increase the risk of dementia in anaemic older people.

We observe that the significant relationship between anaemia and dementia risk was attenuated after controlling for pre-stroke disability assessed using modified Rankin scale and

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other risk factors. This is in agreement with results from an early systematic review on this topic [32]. We observe the higher risk of dementia associated with the latter years of the study suggesting there may be bias towards under diagnosis of dementia in earlier years of this study. Of note, dementia diagnosis has changed over the study period; changing trends in diagnosis of dementia in the UK has been reported between 2005 and 2015. The proportion of people diagnosed with dementia in the UK doubled from 0·42% (19,635 of 4,640,290 participants) in 2005 to 0·82% (25,925 of 3,159,754 participants) in 2015 (χ^2 test for trend, p<0·0001) [33].

There are some limitations. As a registry based observational study we were not able to fully adjust for treatment effects (e.g. blood transfusion, use of iron supplements and erythropoietin stimulating agents) after hospital discharge which might have attenuated the actual effect size of the relationship between anaemia of low Hb levels and subsequent risk of dementia. We were unable to take into account the duration of anaemia or assess the impact of abnormal haemoglobin levels after hospital discharge. We did not stratify analysis by anaemia subtype as this will reduce the number of outcomes (dementia) further unlikely to produce any meaningful results due to loss of power. We also did not control for some haematological parameters and biological parameters such as B12, folate levels and kidney function which may have confounded the association. As an observational study there may be residual confounding as well as effect of known or unknown confounders which were not taken into account. As a record linkage study, we were not able to confidently differentiate between different types of common dementias, although majority of cases are most likely to be either vascular dementia or dementia of mixed pathology. We also relied on dementia diagnosis made by clinicians in various setting evident by variation in annual diagnosis rates but perhaps this reflects the real world nature of the study. This variation may vary with time

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due to increasing awareness and better diagnosis. Due to relatively small sample size coupled with potential under-estimation of dementia diagnosis we were not able to examine the specific cause of anaemia and risk of dementia.

In summary, while we did not find strong association between anaemia and incident dementia in stroke survivors, the study should be replicated in the future with follow-up data specifically collected to diagnose dementia in stroke survivors. Future studies should also examine the link between specific type of anaemia and dementia risk in patients with stroke. With improvement in awareness of dementia after stroke and improvement in diagnosis of dementia, it presents an opportunity to revisit the actual risk estimates of previously identified risk factors as well as potential new risk factors with the view of developing simple prediction rule that is pragmatic and applicable in low resource setting thus useful for daily clinical practice.

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298

299 **Contributors**

300 PKM and TOS conceived the idea. JHBS performed record linkage. ABC analysed the data.
301 Draft manuscript was prepared by PKM and TOS and all authors made contribution to data
302 interpretation and writing of the paper. PKM is the guarantor.

303

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308

309 **Conflict of Interest**

310 All authors declare no conflict of interest.

311

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434 **Figure Legends**

435 **Figure 1:** Kaplan Meier Curves showing the incidence of dementia in patients without
436 anaemia (top line) and with anaemia (bottom line)

437 **Figure 2:** Kaplan-Meier Curve for dementia incidence for individual year

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441 **Table 1:** Sex-specific sample characteristics comparison between stroke patients who were
442 anaemic at discharge and those without anaemia

	No Anaemia	Anaemia	p-value
Men	2863	879	
Age (mean/SD)	71.5 (12.2)	78.9 (10.5)	<0.001
Stroke Type			
Haemorrhagic	340 (11.9%)	66 (7.6%)	<0.001
Ischaemic	2506 (88.1%)	807 (92.4%)	
OCSP			
LACS	726 (27.4%)	212 (25.9%)	0.004
PACS	937 (35.4%)	331 (40.4%)	
POCS	556 (21.0%)	136 (16.6%)	
TACS	325 (12.3%)	94 (11.5%)	
Undefined	105 (4.0%)	46 (5.6%)	
Pre-stroke mRS			
0	2201 (79.8%)	493 (60.4%)	<0.001
1	275 (10.0%)	124 (15.2%)	
2	126 (4.6%)	78 (9.6%)	
3	97 (3.5%)	85 (10.4%)	
4	46 (1.7%)	26 (3.2%)	
5	13 (0.5%)	10 (1.2%)	
Comorbidities			
Previous stroke/TIA	587 (20.9%)	237 (27.9%)	
CHD including MI	401 (14.0%)	231 (26.3%)	<0.001
PVD	40 (1.4%)	45 (5.1%)	<0.001
COPD (incl. Emphysema/bronchitis)	102 (3.6%)	65 (7.4%)	<0.001
CKD	39 (1.4%)	72 (8.2%)	<0.001
Congestive Cardiac Failure	125 (4.4%)	100 (11.4%)	<0.001
Atrial Fibrillation	263 (9.2%)	144 (16.4%)	<0.001
Hypertension	615 (21.5%)	345 (39.2%)	<0.001
Hyperlipidemia	104 (3.6%)	69 (7.9%)	<0.001
Diabetes Mellitus	209 (7.3%)	166 (18.9%)	<0.001
Cancers	259 (9.0%)	191 (21.7%)	<0.001
Women	2156	1556	
Age (mean/SD)	77.3 (12.1)	80.5 (10.8)	<0.001
Stroke Type			
Haemorrhagic	262 (12.2%)	127 (8.2%)	<0.001
Ischaemic	1887 (87.8%)	1424 (91.8%)	
OCSP			
LACS	581 (28.8%)	379 (26.0%)	0.026
PACS	762 (37.7%)	581 (39.9%)	
POCS	346 (17.1%)	216 (14.8%)	
TACS	267 (13.2%)	218 (15.0%)	
Undefined	64 (3.2%)	63 (4.3%)	

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Pre-stroke mRS			
0	1469 (70.8%)	795 (54.6%)	<0.001
1	219 (10.6%)	231 (15.9%)	
2	158 (7.6%)	149 (10.2%)	
3	153 (7.4%)	184 (12.6%)	
4	61 (2.9%)	77 (5.3%)	
5	14 (0.7%)	19 (1.3%)	
Comorbidities			
Previous stroke/TIA	465 (21.9%)	408 (26.9%)	<0.001
CHD including MI	236 (10.9%)	267 (17.2%)	<0.001
PVD	28 (1.3%)	30 (1.9%)	0.13
COPD (incl. Emphysema/bronchitis)	60 (2.8%)	61 (3.9%)	0.054
CKD	34 (1.6%)	58 (3.7%)	<0.001
Congestive Cardiac Failure	113 (5.2%)	143 (9.2%)	<0.001
Atrial Fibrillation	243 (11.3%)	212 (13.6%)	0.031
Hypertension	603 (28.0%)	538 (34.6%)	<0.001
Hyperlipidemia	71 (3.3%)	72 (4.6%)	0.037
Diabetes Mellitus	106 (4.9%)	173 (11.1%)	<0.001
Cancers	174 (8.1%)	172 (11.1%)	0.002

443 SD – standard deviation

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Table 2: Hazard Ratios (95% CI) for dementia incidence post stroke after hospital discharge –anaemia

Model	HR (95% CI) for anaemia	HR (95% CI) for 20 g/dL unit increase in HB	HR (95% CI) for anaemia*	HR (95% CI) for 20 g/dL unit increase in HB*
	N=578 failures / 7454	N=578 failures / 7454	N=578 failures / 7454	N=578 failures / 7454
A	1.21 (1.01,1.43)	0.70 (0.64,0.77)	1.34 (1.13,1.58)	1.00 (0.91,1.10)
B	1.21 (1.01,1.44)	0.88 (0.80,0.97)	1.03 (0.86,1.22)	1.01 (0.92,1.11)
C	1.17 (0.97,1.40)	0.89 (0.80,0.98)	1.02 (0.85,1.26)	1.02 (0.93,1.13)
D	1.13 (0.94,1.36)	0.91 (0.82,1.01)	1.00 (0.89,1.22)	1.04 (0.94,1.15)
E	1.10 (0.91,1.33)	0.93 (0.83,1.03)	0.97 (0.80,1.17)	1.05 (0.95,1.16)
F	1.10 (0.92,1.33)	0.95 (0.85,1.06)	0.97 (0.80,1.17)	1.05(0.95,1.16)

*Competing risk model with death as competing risk
A: age, sex adjusted
B: age, sex, stroke characteristics adjusted (subtype, OCSP)
C: age, sex, stroke type, OCSP and pre-stroke mRS adjusted
D: C + additional adjustments for key risk factors for vascular dementia AF, CHD, previous stroke/TIA, PVD, hypertension
E: D+ other co-morbidities
F: E + year of admission

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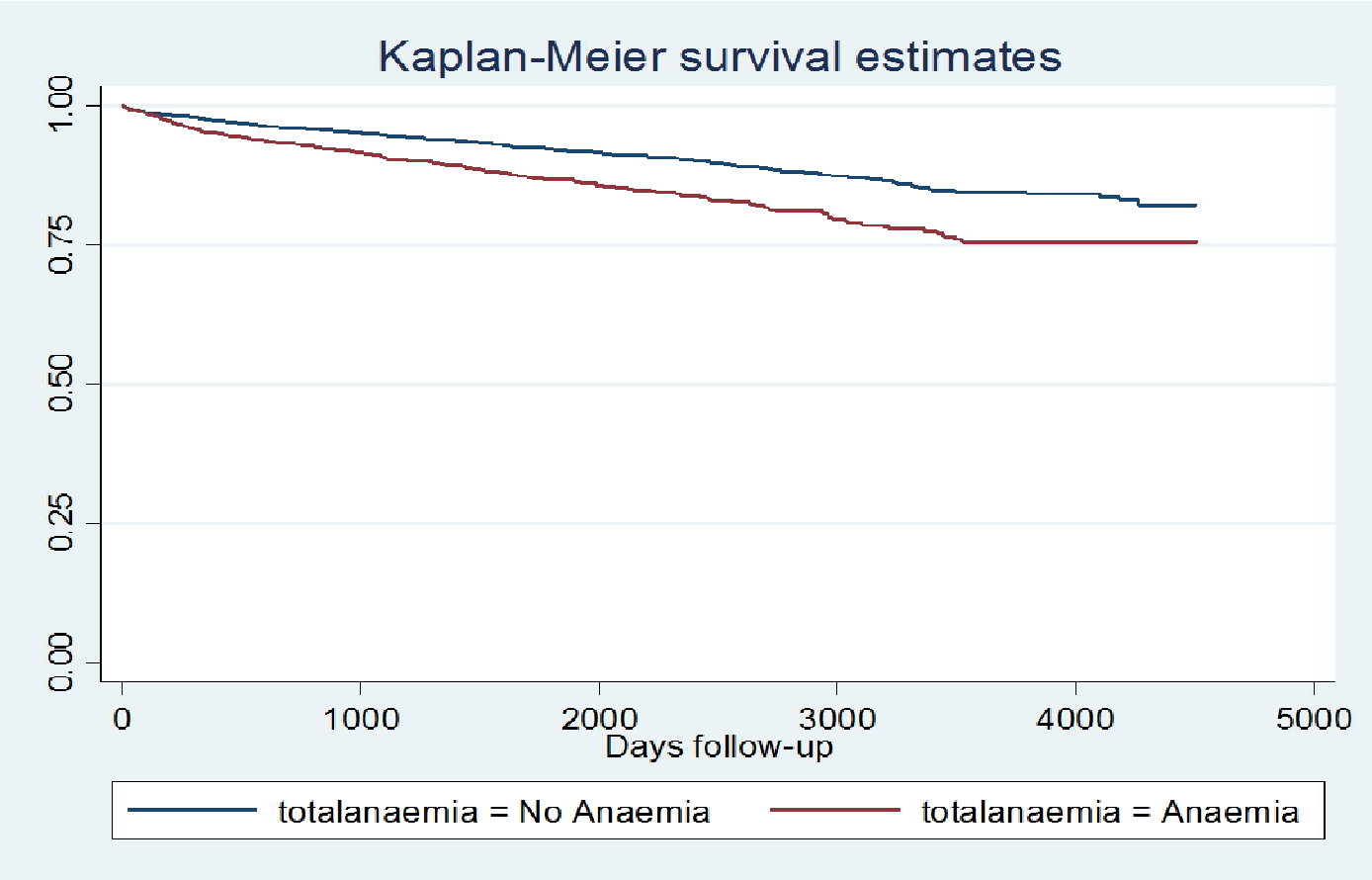
Figure 1: Kaplan Meier Curves showing the incidence of dementia in patients without anaemia (top line) and with anaemia (bottom line)



	N at risk					
No anaemia	5019	2848	1413	755	216	0
Anaemia	2435	1035	457	240	68	0

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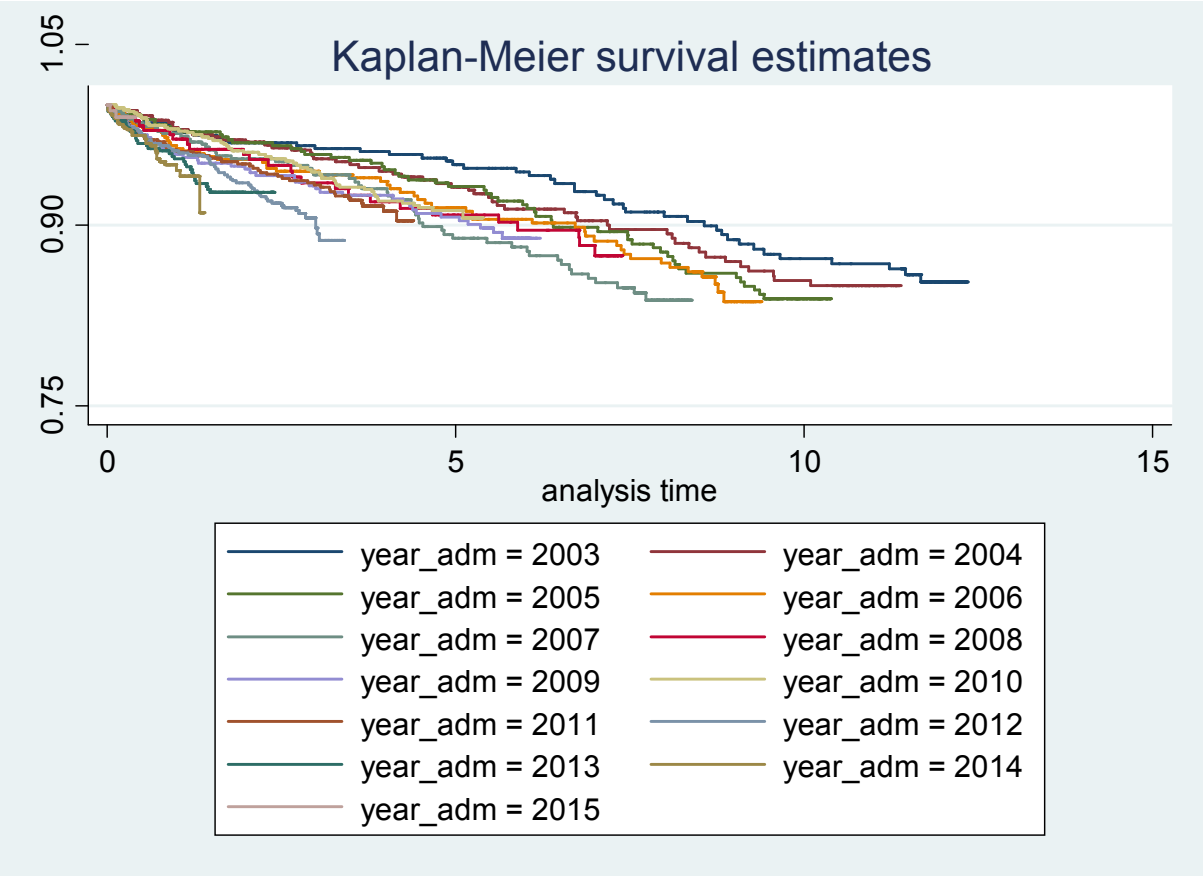
Figure 2: Kaplan-Meier Curve for dementia incidence for individual year



Year (vs. 2003)	Hazard Ratios (95% CI)
2004	1.16 (0.78,1.71)
2005	1.27 (0.86,1.86)
2006	1.46 (0.99,2.17)
2007	1.75 (1.18,2.59)
2008	1.56 (0.96,2.54)
2009	1.76 (1.15,2.69)
2010	1.56 (1.04,2.34)
2011	1.99 (1.32,2.99)
2012	2.82 (1.89,4.22)
2013	2.99 (1.88,4.76)
2014	3.24 (2.01,5.2)

Note 2015 data is not shown as it doesn't have full annul follow up.

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Supplementary Table 1: Annual incidence of dementia overtime in patients who survived to hospital discharge over 10 years follow up

		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
2003	N at risk	469	418	391	353	316	291	263	242	220	207	206	201
	Incidence/1,000	14.93	4.78	5.12	5.67	12.66	10.31	30.42	12.4	22.73	9.66	19.42	0
2004	N at risk	538	469	424	385	350	307	281	252	232	218	214	211
	Incidence/1,000	9.29	19.19	9.43	20.78	2.86	19.54	24.91	7.94	21.55	22.94	9.35	0
2005	N at risk		528	452	408	377	343	311	288	263	250	245	237
	Incidence/1,000		9.47	15.49	12.25	13.26	17.49	12.86	27.78	15.21	28	28.57	0
2006	N at risk			493	427	361	328	304	275	254	239	240	232
	Incidence/1,000			16.23	30.44	8.31	9.15	23.03	10.91	23.62	4.18	33.33	12.93
2007	N at risk				490	414	362	326	297	254	232	228	221
	Incidence/1,000				14.29	31.4	2.76	15.34	40.4	19.69	21.55	30.7	4.52
2008	N at risk					265	227	194	174	160	146	145	142
	Incidence/1,000					18.87	22.03	25.77	22.99	6.25	6.85	20.69	14.08
2009	N at risk						460	398	361	324	309	308	301
	Incidence/1,000						17.39	30.15	16.62	18.52	9.71	22.73	3.32
2010	N at risk							692	611	543	508	497	482
	Incidence/1,000							11.56	18.00	18.42	21.65	20.12	6.22
2011	N at risk								651	575	540	531	521
	Incidence/1,000								24.58	20.87	18.52	16.95	11.52
2012	N at risk									671	587	565	547
	Incidence/1,000									23.85	34.07	28.32	16.45
2013	N at risk										487	426	395
	Incidence/1,000										26.69	44.6	5.06
2014	N at risk											671	612
	Incidence/1,000											37.26	13.07
2015	N at risk												191
	Incidence/1,000												10.47

N at risk = total number of patients – Number of deaths occurring within the year