

# **Relative Survival – What Can Cardiovascular Disease Learn From Cancer?**

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## **ABSTRACT**

### **Aims**

To illustrate the application of relative survival to observational studies in coronary heart disease and potential advantages compared to all-cause survival methods. Survival after myocardial infarction is generally assessed using all-cause or cause-specific methods. Neither method is able to assess the impact of the disease or condition of interest in comparison to expected survival in a similar population. Relative survival, the ratio of the observed and the expected survival rates, is applied routinely in cancer studies and may improve on current methods for assessment of survival in coronary heart disease.

### **Methods and results**

Using a cohort of subjects after a first recorded acute myocardial infarction, we discuss the application of relative survival in coronary heart disease and illustrate a number of the key issues. We compare the findings from relative survival with those obtained using Cox proportional and non-proportional hazards models in standard all-cause survival. Estimated survival rates are higher using relative survival models compared to all-cause methods.

### **Conclusion**

Estimates obtained from all-cause mortality fail to disentangle mortality associated with the condition of interest from that due to all other causes. Relative survival gives an estimate of survival due to the disease of interest without the need for cause of death information.

**Keywords:** relative survival, survival analysis, population based research

## **INTRODUCTION/METHODS**

### **Why measure mortality in heart disease?**

Coronary heart disease (CHD) is the leading cause of mortality in industrialised societies (1, 2), accounting for over 105,000 deaths in the UK in 2004 (3). Understanding both short and long term patient survival may help to inform improved management after presentation with CHD. Much of what we know about survival for patients with CHD comes from randomised controlled trials (RCT). Such trials usually recruit relatively selected populations followed over relatively short times, and the findings of RCTs may not easily be generalisable to the general population. Thus the assessment of patient survival in unselected clinical populations can be informative to the patient, the clinician, and in terms of future health-service provision. Important prognostic factors related to survival can be evaluated along with comparisons over time and between centres.

### **How would we ideally assess mortality?**

To understand the natural history of a disease or condition of interest, and the influence of risk-factors and co-morbidity properly, it is essential to use appropriate statistical techniques. Ideally, the impact on mortality of a particular disease or condition would be measured by assessment of mortality specifically due to, or associated with, the disease of interest. However in broad population-based studies, cause of death is often difficult to establish with certainty.

### **Cause-specific survival analysis**

Cause-specific (or net) survival considers as events only deaths that can be directly attributed to the disease of interest, with deaths from all other causes being censored. The probability of survival can be evaluated, but avoiding consideration of competing risks. When considering

cause-specific survival, it is usually of interest to fit statistical models to investigate simultaneously the influence of covariates, such as age and sex.

### **What are the limitations of cause-specific analyses?**

The main limitation of cause-specific survival is its dependence upon reliable coding of information on the cause of death. This reliance is not well founded, particularly when the source of information is the death certificate. For example a patient may be recorded as dying of renal failure where this is the result of cardiogenic shock following acute MI. Three trained physician-adjudicators assessed cause of death in 2686 Framingham Heart Study participants (4). Of cases adjudicated as attributable to CHD, only 83.8% were recorded as such on the death certificates. Moreover, of cases recorded as due to CHD on the death certificate, this was confirmed in less than 70% by the physician-adjudicators. In this context, arguments have been presented that are critical of cause-specific survival. Lauer et al. (2) argue that data obtained from death certificates or from medical records are haphazard, biased and often inaccurate. These authors also suggest that all-cause death should be assessed as the primary end point, as it is both objective and unbiased. More recently, Mant et al.(5) argued that cause-specific methods are also flawed when attempting to differentiate among causes of cardiac death. These authors highlighted that this was the result of the inability of clinicians to agree on a cause of death; even where autopsy information was available, disagreement remained for a third of all deaths.

### **All-cause survival analysis**

All-cause (or crude) survival includes all deaths within the cohort under investigation, and does not separate those due to the disease of interest from those due to other causes. All

deaths are considered as events with only those surviving the follow-up period, or those lost to follow-up, being censored.

### **How are all-cause methods also limited?**

Clearly, in a cohort of patients with a given condition, some deaths will occur which are unrelated to the disease of interest. However all-cause analysis cannot disentangle deaths related to the disease of interest from deaths due to competing risks. A further, and important, limitation of all-cause survival methodology is its relative inability to disentangle the effect of strong covariates. For example, age is a strong confounder in most conditions. When we adjust for age at diagnosis in an all-cause model we are adjusting for the combination of the impact of age on mortality associated with the disease of interest, and its impact on mortality from all other causes, the magnitudes of which may differ.

### **Relative survival analysis - What can cancer share with CHD?**

Analysis of survival in population based cancer studies often includes *relative survival*, used alongside, or instead of, crude and cause-specific methods (6, 7). Relative survival estimates the mortality rate for patients with the condition of interest after correcting for estimated mortality from all other causes. This methodology considers survival in patients with a specific malignancy compared to survival in a comparator population. Large scale examples can be found in the EURO CARE studies (8). As some parallels exist between heart disease and cancer; for example, extended survival and follow-up is common to both disease areas, consideration of relative survival methodology may be worthwhile in CHD. An investigation of the practical application in CHD of relative survival methodology would be informative regarding the impact on outcome of CHD compared to what might be expected in the absence

of that condition. In particular, relative survival allows for the use of appropriate statistical models to adjust adequately for confounders.

To date there are limited numbers of published relative survival applications and related methods in cardiovascular disease, most involving heart surgery. Of these, Norman et al. describes a review of the limitations of current methods that use expected survival and how many authors focus on observed survival(9). Others describe various relative survival statistical models applied in patients undergoing cardiac surgery (10-13) 13). Few such reports pertain to patients with non-surgical conditions, such as atrial fibrillation (14), MI (15) and stroke (16, 17). For the most part these analyses fail to model the influence of covariates and none fully utilises relative survival methodology.

### **What is relative survival?**

As noted above, relative survival attempts to separate mortality from the disease of interest from mortality due to all other causes. To do this the ratio of the observed (all-cause) survival in the cohort of interest and the expected survival in a similar group in the general population is calculated (18).

$$\text{Relative survival} = \frac{\text{Observed (all-cause) survival in cohort studied}}{\text{Expected survival based on rates in a comparator population}}$$

The cohort of interest may comprise a sample of individuals with a specific diagnosis, for example acute myocardial infarction (AMI). The comparator group is obtained from routine data, matched to the cohort of interest by age, sex, deprivation and other potentially important

covariates. In a relative survival model, the observed mortality rate within the cohort of interest is made up of the background mortality rate in the general, comparator population (ie deaths due to all causes) plus the excess mortality rate associated with the condition of interest, i.e. all deaths resulting from the AMI.

$$\text{Total observed mortality rate} = \text{Expected mortality rate} + \text{Excess mortality rate}$$

So when modelling relative survival we attempt to estimate *directly* the excess mortality experienced by patients diagnosed with the condition of interest, compared to that of the general population, thereby obtaining an estimate of net survival.

An advantage of relative survival is that information on individual cause of death is not required; this removes the main problem associated with cause-specific mortality. However the method assumes that deaths due to the disease of interest are independent of mortality in the general population (18) , to which we will return later. Relative survival yields excess hazard ratios, as opposed to the standard hazard ratios obtained in Cox and other survival models. Excess hazard ratios can also be used to estimate variability in the excess risk of death due to the disease of interest when, for example, comparing one demographic group to another, or temporal patterns of survival after AMI. As patterns of survival in AMI change, with increasing interest in long-term survival, we can expect the use of relative survival methods to become increasingly important and relevant.

### **What are the assumptions made within relative survival?**

An assumption when using relative survival is that the matched population group used to obtain expected mortality is appropriate for the particular disease under study. The mortality

rates should thus represent the expected mortality if the subject did not have the disease under study. A further issue is that when using national or regional life tables to obtain the expected mortality rates, the disease under study is included in these figures. If the prevalence of disease is low then this will have little impact on the estimates and for even the most common cancers it has been shown that this introduces negligible bias(18). In older age groups AMI has a higher prevalence than most cancers and thus the prevalence issue needs to be considered. In subjects aged 75, there is negligible bias in the estimate of relative survival. However, the bias increases with age as the prevalence of AMI increases and the estimate of relative survival in the most elderly groups, for example those over 90 is potentially biased. Fortunately, there is very little bias in excess hazard ratios when comparing groups as any bias will be in the same direction.

### **Relative survival - An example analysis in cancer**

A recent population-based study (19) investigated changes in colorectal cancer survival, using all-cause and relative survival methods. Using all-cause analysis, the analysis showed that for patients aged  $\geq 75$  years, for all stages of disease, 5-year survival was 41.4% in 1976-87 and 43.3% in 1988-99, suggesting improved survival between these periods. By comparison, the estimates of relative survival were much higher and, moreover, nearly identical for the two periods (68.0% and 67.9%), suggesting no improvement. This observation could be explained by improved survival in the background population, as well as in the cohort of interest and/or a change in the age distribution of patients with colorectal cancer. In other words, the apparent improvement over time in survival in the cancer cohort could represent improved survival in the general population, rather than cause-specific survival improvement in the cohort of interest.

### **Relative survival in CHD: an illustration**

Using information from a large database, we here illustrate the application of relative survival methodology in CHD. The data come from Leicester Royal Infirmary Coronary Care Unit. For all admissions to this CCU, details are recorded regarding details of presentation, comorbidity and other clinical data. Patients are followed prospectively for mortality. Here we use data pertaining to patients admitted between 1993-2006, with a presentation of acute ST elevation myocardial infarction. The total of 4747 individual events includes 3231 men. Men (64.1 years) had a mean age 8 years younger than women (72.2 years), the average age of the population being 66.7 years. Of this cohort, 1759 (37.1%) died within the six year follow-up period used here. Follow-up began at hospitalisation and not after 30 days survival as is sometimes the case (20). The expected mortality was calculated using rates from the United Kingdom Government Actuary's Department with each individual in the study cohort matched using age, year of hospitalisation and sex to the England and Wales population (21).

### **What statistical methods are used?**

In this paper we conduct a simple analysis in order to illustrate the methods. We start with simple lifetables and compare the findings from all-cause and relative survival approaches, stratified by age groups, defined as <60 years, 60-75 years and >75 years old. We then look at the effect of age using a relative survival model with proportional excess hazards and compare this to a standard (all-cause) Cox proportional hazards model. We also investigate non-proportional models for both the relative survival and Cox approach. Finally proportional models investigating the effect of sex, with and without adjustment for age groups, are performed for both relative survival and all-cause approaches. The variables we have analysed in this paper are also used as matching variables. However, it is important to note that other

variables, for example glucose levels at admission, can easily be incorporated into the statistical model.

## **RESULTS**

### **What do relative survival lifetables contain?**

Relative survival estimates can be presented in lifetables similar to those for standard survival analyses but with emphasis on relative survival and evaluating survival probabilities. The lifetables for each age group are shown in Table 1. In this table, in addition to the interval specific standard (observed) survival results, the expected [lightly shaded] and interval-specific relative survival estimates [shaded] are also shown. If the observed number of deaths is equal to the expected number of deaths during an interval then the probability of survival for patients with the condition of interest is the same as that in the general population. Investigation of the <60 years old age group shows the observed number of deaths dropping from 88 in the first month to just 14 in year 2-3 of follow-up. However the expected numbers of deaths by 30 days and during year 2-3 of follow up are 0.5 and 5.8 respectively. Thus, acute ST elevation MI is associated with almost all excess deaths in the 30 day period following the event, and with an excess of less than 10 deaths in year 2-3.

Clearly, AMI is associated with a marked excess in mortality in the immediate, post AMI period. However, how much of the later mortality excess, and indeed of overall mortality in our cohort, can be ascribed to the index AMI? Consideration of the cumulative survival data illustrates the information to be gained from relative survival analysis. By the end of follow-up, an all cause approach shows cumulative survival of 0.258 for the >75 years old group. However taking expected mortality into account, the cumulative relative survival rate is

0.460. In other words, if we ignore expected, background mortality in the population, the survival proportion is over 20% lower in absolute terms, as mortality due to other causes is included in the all-cause analysis.

Using the table we can also see that expected survival decreases with age. By 4-6 years of follow-up, the youngest age group had a cumulative expected survival rate of 0.964 and the oldest age group 0.561. The relative survival rate can be found as the ratio of the observed survival and expected survival shown in the table. Note how cumulative relative survival is greater compared to cumulative observed survival at all times, for all ages. Also worthy of note is that the interval specific relative survival is lowest during the first 30 days after AMI, in spite of this being the shortest time period considered in the analysis. The same is true for absolute survival (not shown).

### **Can we see this graphically?**

Lifetable information is often easier to interpret in graphical form. Figure 1 shows the relative survival curve, along with the expected and observed (all cause) survival probabilities split by age groups, (under 60 years old, 60-75 and >75 years). The figure highlights the difference between a relative survival and an all cause survival approach. The observed values shown on the figure represent all of the deaths in the cohort, i.e. the survival rate if we assumed an all-cause approach. The expected survival is the survival rate we would expect if the cohort was in the general population without experiencing the index AMI, and the relative survival is the ratio of these two lines.

The initial drop in survival is smallest for the youngest age group. Moreover, relative and observed survival are very similar in this age group, as expected survival is close to 1. As

background mortality is very low in this age group, nearly all deaths experienced within this cohort are likely to be attributable to the index AMI. In the other age groups, particularly the eldest, there is also very little difference between the observed and relative survival rates for the first year post MI. However there is a relatively high expected mortality rate in this oldest age group; some of the deaths in this population are not due to the index AMI. Later, the relative survival curve begins to plateau, although never flattening completely. If the relative survival curve flattens out completely then the mortality rate of these surviving individuals is the same as expected in the general population. When this effect occurs it is known as statistical or population cure.

### **How do we use statistical models in relative survival?**

The influence of cofactors or comorbidity on relative survival can be obtained by modelling, and expressed as excess hazard ratios; their interpretation is straightforward. For example, an excess hazard ratio of 2 for males would suggest that the excess mortality rate in men (i.e. deaths associated to the disease of interest) is twice as high as in women.

Table 2 illustrates the impact of age on hazard ratios estimated from a Cox proportional hazards model and on excess hazards ratios from a relative survival model. Using <60years as the comparator group, for both 60-75 and >75 age groups, estimates of the excess hazard ratios are lower with relative survival modelling than with the hazard ratios from the Cox model. Once again this illustrates the increasing influence of competing risks in a population as that population ages.

The effect of age can also be assessed by the excess mortality rate. During the first month the excess mortality rate ranges from 800 [<60 age group] to 5450 [>75 age group] excess deaths

per thousand person years. We can conclude that during the first month there is a huge increased risk of death associated with the index event.

### **How do we look at time-dependent effects?**

In their simplest form the models assume the impact on mortality to be proportional over time, which may not be the case. As with Cox models, it is possible to investigate whether the excess hazard ratio changes over time (Figure 2). For the 6-12 month follow-up interval, and using the all-cause method, we would estimate that patients aged 60-75 are at approximately three-fold greater risk of death, and patients aged >75 are near 8-fold greater risk, compared to a patient aged <60. In comparison, the relative survival method estimates of excess risk are rather lower, at 2-fold for patients aged 60-75, and 4-fold for those aged >75 years. Over time the subjects in the cohort are ageing and the expected mortality rate is also increasing with age. Relative survival methodology takes account of this, giving a more realistic estimate of the excess mortality associated with the previous AMI. This is shown for illustrative purposes even though a likelihood ratio test proved non-significant suggesting that the proportional model is more appropriate.

### **What are the results from further analyses?**

An unadjusted Cox model found that male gender was associated with a hazard ratio of 0.60 (0.55 , 0.66), suggesting a 40% lower risk of death for males in our cohort. Using the relative survival estimate, which allows for the fact that the females (on average older) are more likely to die of other causes, the excess hazard ratio is 0.52 (0.45 , 0.58) for males, a 48% lower risk compared to females. As with Cox models it is possible to adjust for multiple covariates, and for illustration we considered both sex and age in the models. The adjusted Cox estimate for males was 0.90 (0.82 , 1.00), indicating a 10% lower risk of mortality after AMI. However, as

we have seen, this methodology fails to separate death due to the index AMI from deaths due to other causes. Females in this cohort are older (mean 72.2) than males (mean of 64.1) and are thus more likely to die from causes other than the AMI. The adjusted relative survival model gives an estimate of 0.78 (0.69 , 0.88) for males, suggesting a 22% lower excess mortality due to CHD for males compared to females post MI, after adjustment for age. The advantage of this model is that it adjusts for the disease associated mortality associated with age separately from the expected mortality experienced in the general population.

## **DISCUSSION**

### **What can relative survival methodology add to the assessment of CHD?**

Relative survival provides clinically relevant information. Investigation of excess mortality rates has potential implications regarding patients' long term survival. For example while much resource is dedicated to the management of “young” patients with CHD, our initial estimates from the proportional excess hazards model suggest that for patients aged <60 years, the excess risk due to the index MI is around 30 additional deaths per 1000 person years over the first 6 months, but as few as 6 excess deaths estimated per 1000 person years after 3 years.

### **What are the limitations of relative survival?**

Relative survival can be interpreted as a measure of mortality due to the disease of interest only if deaths due to the disease of interest are independent of the mortality in the general population. Even if this is not the case, relative survival still provides a useful comparison with mortality in the comparator population, which is usually the general population(22). It

may be worth considering alternative comparator groups when using relative survival methods in CHD to derive the expected mortality rates. For example, patients with CHD have a high prevalence of co-morbidities and of risk-factors which put them at risk of mortality from causes other than CHD, such as pulmonary disease. We have used expected mortality from the general population, but use of expected mortality from a population with similar co-morbidities could be selected. For example, to assess survival after AMI in patients treated with insulin during the index admission, one could consider matching with expected survival by diabetic status. However, obtaining reliable information from such a population is often difficult.

A potentially important issue in the use of relative survival to the assessment of CHD survival, is that in using population life tables to derive the expected mortality rates, deaths due to the condition of interest are included. If the prevalence of that condition in the background population is low enough, then this will have little impact, a reasonable assumption for individual malignancies (18). However, given the predominant contribution of heart disease to mortality in industrialised society, the appropriateness of this assumption in CHD needs to be assessed, in particular for oldest age groups.

We have presented some of the simpler statistical models for relative survival. However, there are several extensions that would also be applicable to CHD. For example, modelling time-dependent effects on a continuous scale through the use of splines (23-25) and fractional polynomials (26).

Relative survival methodology merits attention in observational and population-based assessments of CHD mortality. Application of relative survival methods is still in early

development in heart disease but its application in cancer is common, and informative. In order to obtain an estimate of net survival in population based studies, relative survival applies sensible assumptions based on the deaths that we would expect to occur in a cohort of patients if they were from the general population. One development relevant in CHD may be calculating expected mortality in groups that are at a potentially higher risk of mortality from CHD, such as ethnic minorities, or social deprivation cohorts.

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## Legends

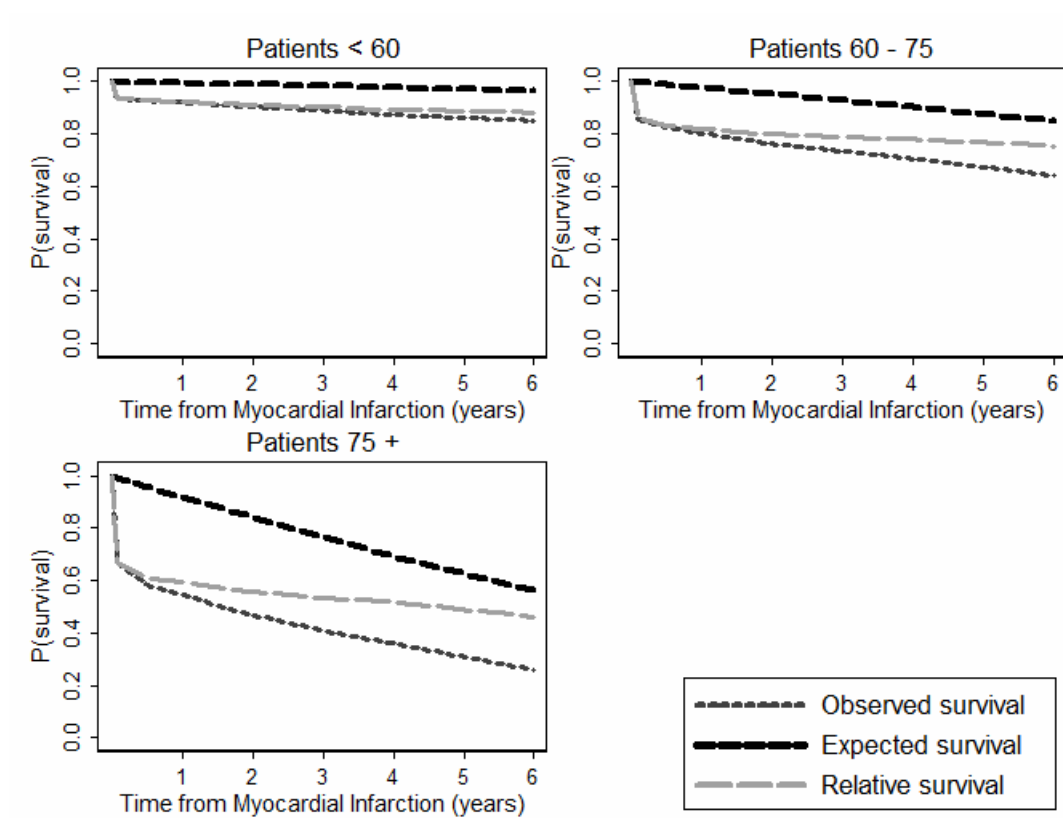


Figure 1 - Observed (all-cause), Expected and Relative survival split by age groups

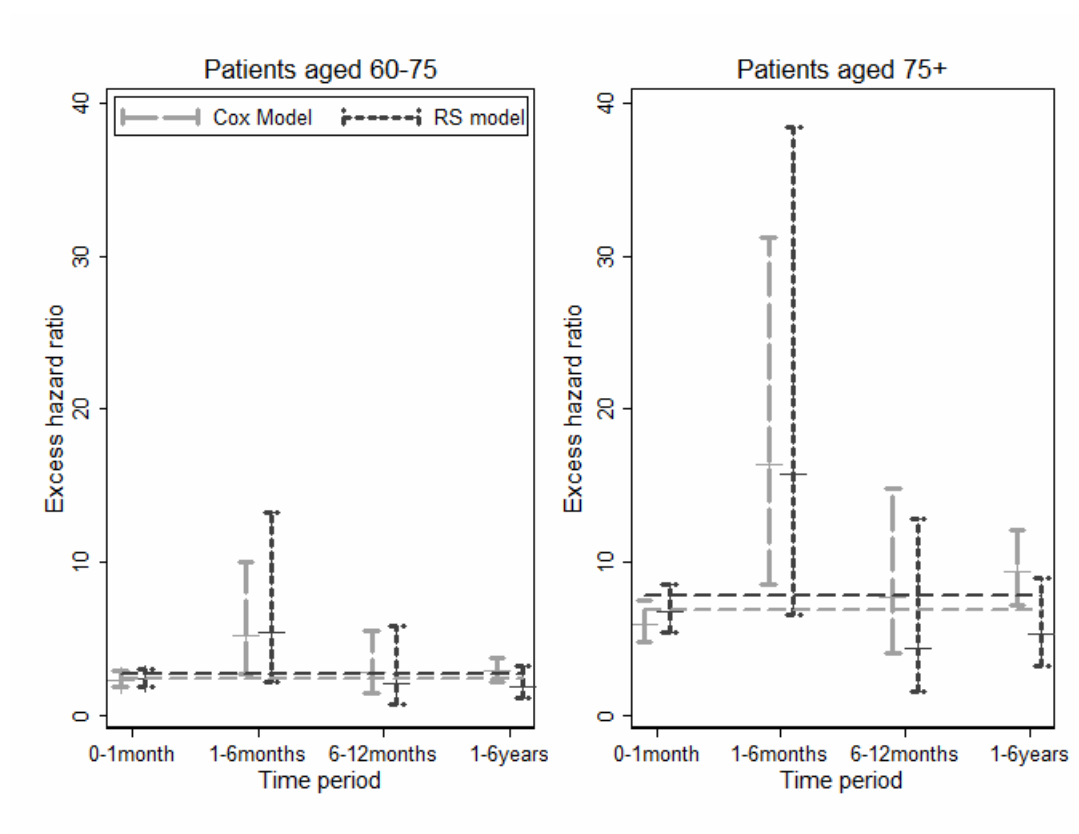


Figure 2 - Time-dependent effects. Excess hazard ratio at intervals after index STEMI. The graphs illustrate excess risk of death for patients aged 60-75 or >75 years, each compared to patients aged <60 years. Vertical lines show the 95% confidence limits and point estimates of the excess hazard ratios from a relative survival model and hazard ratios from a Cox model. Horizontal lines ----- show the point estimate of the excess hazard rate ratio from a relative survival model shown in table 2 and PH mortality rate ratio from a Cox model

# TABLES

Table 1 – Abbreviated lifetables for the youngest and oldest age group.

Age group	Start of interval (years)	End of Interval (years)	No alive at the start of the interval	Deaths in interval	Cumulative observed (all-cause) survival	Expected deaths in interval	Cumulative expected survival	Relative survival for interval	Cumulative relative survival
<60	0	0.0833	1373	88	0.936	0.5	1.000	0.936	0.936
	0.0833	0.5	1280	10	0.928	2.6	0.998	0.994	0.931
	0.5	1	1245	11	0.920	3	0.995	0.993	0.925
	1	2	1182	20	0.904	6	0.990	0.987	0.913
	2	3	1047	14	0.891	5.8	0.984	0.992	0.905
	3	4	938	18	0.873	5.7	0.978	0.986	0.893
	4	6	832	18	0.852	10.1	0.964	0.989	0.883
75+	0	0.0833	1436	481	0.665	7.5	0.993	0.670	0.670
	0.0833	0.5	955	115	0.584	30.7	0.958	0.910	0.610
	0.5	1	822	55	0.545	32.4	0.919	0.972	0.593
	1	2	748	101	0.468	59	0.841	0.938	0.556
	2	3	584	71	0.409	49.6	0.766	0.959	0.533
	3	4	464	52	0.359	40.8	0.692	0.973	0.519
	4	6	346	87	0.258	56	0.561	0.887	0.460

0.0833 years = One month

Table 2 – Comparing results from a Cox model and a relative survival model.

		Hazard ratios (95% CI)	
		Cox Model	Relative Survival model
Age group	<60	1.00	1.00
	60-75	2.71 (2.30 , 3.20)	2.43 (1.97 , 2.99)
	75+	7.84 (6.68 , 9.21)	6.92 (5.67 , 8.44)

Models comparing the hazard ratios and excess hazard ratios from a Cox proportional hazards model and a relative survival model with proportional excess hazards (with 95% confidence intervals).