Actuarial Applications of Survival Analysis in Healthcare

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Submitted for the degree of Doctor of Philosophy

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April 2020

ABSTRACT

Healthcare actuaries are increasingly responsible for advising their employers and clients in areas of managed care. Managed care links traditional health actuarial financial work to areas of medical practice, to address the fundamental question: what works? These relatively new responsibilities have required an expansion of actuarial techniques into non-traditional areas, and, in particular, epidemiology and biostatistics.

This study is about a specific area of statistics, survival analysis, a topic of great potential application in non-traditional managed care actuarial practice. Survival analysis is used frequently in biostatistics to evaluate the efficacy of treatments and to identify factors that contribute to patient survival. In this study, we illustrate three applications of survival models to solve real-world problems in areas of health actuarial practice: the estimation of survival of permanently disabled workers receiving lifetime benefits for occupational illness and injury, the rate at which seriously ill hospice patients, at risk of polypharmacy, are weaned from non-life sustaining drugs, and the ability to predict, using a model incorporating drug dosage information and specifically changes in dosage, changes in expected future lifetimes of hospice patients.

All three case studies are examples of practical models that can be applied within a business context. The study will serve a more important purpose, if it shows health actuaries the potential value of the application of a non-traditional technique within their evolving practice.

DEDICATION

To my wife, Janet Duncan, FCAS FSA MAAA for her support while suffering patiently during this research.

I also wish to express my thanks to my supervisors, Angus Macdonald PhD FFA FRSE and George Streftaris PhD for introducing me to the possibilities of survival modelling and guiding this research, and to Nhan Huynh MS for programming assistance.

Thanks are also due to Andrew Horowitz, CEO and Greer Myers, EVP and the team at Enclara Pharmacia Inc. for their support and encouragement throughout this study, and particularly for the use of the hospice dataset in Chapters 5-8.

DECLARATION STATEMENT

HERIOT WATT UNIVERSITY

Research Thesis Submission

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School:	Mathematics & Computer Science		
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This thesis contains one or more multi-author published works. In accordance with Regulation 6 (9.1.2) I hereby declare that the contributions of each author to these publications is as follows:

Citation details	Duncan I Maxwell T Dove H and Ahmed T. "Medicare Cost at End of Life." *Am. J Hospice and Palliative Med.* 36(8) August 2019. Doi: 10.1177/1049909119836204.
Author 1	Ian Duncan: conception; data acquisition; analysis design; paper drafting.
Author 2	Terri Maxwell: hospice and palliative care technical details
Author 3	Henry Dove: literature review
Author 4	Tamim Ahmed: programming and analysis of the Medicare LDS file.
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Date:	16th April 2020

Citation details	Duncan I. Huynh N. Molinari R. and Duncan J. "Using Survival Analysis to Predict Workers' Compensation Termination." In Press. *Variance.* https://www.variancejournal.org/articlespress/
Author 1	Ian Duncan: Hypothesis, study design, data acquisition, summarization of results and paper authorship.
Author 2	Janet Duncan: Workers compensation technical input.
Author 3	Roberto Molinari: Review of statistical methods; MICE routine for estimation of missing data.
Author 4	Nhan Huynh: programming and modelling in R.
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Date:	16th April 2020

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CHAPTER 1 - INTRODUCTION

Actuaries and Statisticians have studied and modelled survival for centuries. Early actuaries studied graveyards and parish records to derive the data from which to build mortality tables. Actuaries, such as Benjamin Gompertz (1779-1865) and William Makeham (1826-91), developed parametric models to predict human mortality. While there is a significant amount of literature in both mortality modelling and the application of survival analysis in medical research, survival models are not as well represented in health actuarial practice. Actuaries traditionally applied complicated exposed-to-risk techniques to estimate mortality rates; it was not until the ground-breaking work of the Scandinavian actuary Jan Hoem [1] (1984) that statistical approaches to mortality modelling began to enter the actuarial syllabus.

David Collett [2] defines survival analysis as "the analysis of data in the form of times from a well-defined *time origin* until the occurrence of a particular event or *end-point."* Macdonald, Richards, and Currie [3] note that "survival modelling is a well-established field of statistics and offers much for actuarial work." It is ironic that these authors have to make this claim in the 21st Century, but the claim is indicative of the lack of interest that exists in much of the actuarial profession. Like much actuarial work, however, Macdonald and colleagues' book is devoted to the study of mortality. Actuarial students are introduced to survival models early in their course of study, in the context of mortality projections. However, most actuaries will not encounter survival models again in practice.

Health actuaries (a small profession outside the United States, but a large one inside North America) have traditionally been responsible for pricing, reserving and risk management of health insurance coverages. Traditionally, financial risk was the province of insurers and health actuaries, while clinical risk was the responsibility of doctors and hospitals. With the widespread penetration of managed care in health insurance in the United States since the 1980s, financial risk has increasingly been shifted to providers (hospitals, physicians, pharmaceutical companies, and other providers of health-related services) and away from payers (employers, insurers, and the government). With the increasing prevalence of managed care, health actuaries have had to become more involved in the provision and assessment of medical care and clinical services. The health actuary is increasingly called on to advise employers and clients on "what works," not clinically, but from a financial perspective, as evidenced by readings from Duncan [4] in the Society of

Actuaries' health fellowship track examinations. This new responsibility has required training in topics and areas unfamiliar to actuaries, such as epidemiology and biostatistics. Professionals trained in these subjects use survival models routinely, and as actuaries become more responsible for evaluating the underlying delivery of care, survival models will become more important to health actuaries. While survival analysis has a part to play in the new and expanded field of managed care actuarial work, health actuaries will need to increase their awareness of the value that survival models can bring to their work. This thesis is intended to provide examples of actuarial applications of survival modelling in healthcare. This study covers three applications in health care:

1. Terminations (largely, but not solely, due to death) of permanently disabled claimants eligible for lifetime medical coverage under U.S. workers compensation law (occupationally disabled claimants). Reserves for workers compensation claims have traditionally been set by claims adjusters examining each claimant's individual circumstances, with the addition of a bulk adjustment for a block of claimant reserves using a Chain-ladder or similar method. To the extent that survival of a claimant is taken into account, it is through the professional judgement of the claims adjuster. Our first example applies survival modelling techniques to the estimation of life expectancy of these claimants. We find that studying the actual experience of a population, using survival methods, allows us both to construct a model that more accurately represents the experience of the population, but also incorporates covariates and other information that is potentially useful to the insurer for claim management purposes.
2. Our second and third examples both apply to patients admitted to hospice at the end of life. In the United States, patients are admitted to hospice and the Medicare program pays for their care, if two physicians certify that the patient has a life expectancy of six months or less. One requirement of hospice is that therapeutic (curative) care be discontinued and palliative care provided instead. As a result, therapeutic medications, except those required to maintain life, are gradually discontinued (deprescribed) and only palliative medications prescribed. The severe nature of illnesses for these patients often results in a multitude of prescriptions (polypharmacy) with many attendant problems. There are relatively few studies about deprescribing for patients at end of life. What studies there are conclude that therapeutic medications are withdrawn slowly. We study the rate at which different medications are deprescribed for patients

with different conditions. To our knowledge, our study is the first to apply survival modelling techniques within a substantial database of hospice patients and their medications to model the length of time and proportion of a hospice stay that a patient has prescriptions for potentially inappropriate medications.

3. Our third example, also from hospice, uses survival models to predict life expectancy of patients in hospice. The literature on this topic indicates that estimates (made by physicians) are not particularly accurate. Empirically, prescriptions and, particularly, dosage of opioids increase during the patient's stay in hospice. Our hypothesis is that by incorporating information about changes in a patient's drug regimen during the stay, it is possible both to estimate dynamically future life expectancy and to do so more accurately than professional judgement alone. A more accurate estimate of life expectancy allows hospice management to tailor services to patient needs, more effectively schedule on-call staff, and reduce the supplies of drugs to avoid wastage at end of life.

The remainder of this study proceeds as follows: In Chapter 2, a review of the theoretical and statistical background to survival analysis and the models used in this study is presented. Chapter 3 consists of a study of survival of permanently disabled claimants under a workers' compensation program. This study was published as "Using Survival Analysis to Predict Workers' Compensation Termination" in *Variance.*[1] Chapter 4 consists of a paper entitled "Medicare Cost at End of Life" and covers the cost of death and dying in the United States, particularly the frequency and cost of end of life services. These patients' costs are covered by the Medicare system in the United States; although the number of Medicare patients dying annually is less than 5%, their cost amounts to between 20% and 25% of total spending by Medicare. This paper was published in the *American Journal of Hospice and Palliative Medicine.* We focus specifically on variables that affect patient life expectancy: age, sex, diagnosis, facility, and most importantly, the drugs that patients are prescribed during stays in hospice. The remainder of Chapter 4 explores the hospice movement and contains a summary of the hospice prescription database on which the hospice study is based. Our database contains very detailed prescription records, including covariates that change over time, such as specific drugs and their dosage, leading,

[1] Journal of the U.S. Casualty Actuarial Society.

in turn, to time-dependent survival models. Because of the multiplicity of different drugs, strengths, and forms (liquid, pills, etc.), Chapter 5 contains an in-depth discussion of the hospice drug database and the process of mapping the data in a manner that allows us to compare the dosage of analgesic drugs prescribed to patients, and the way that this dosage changes during a hospice stay. Chapter 6 is a study of the rate of deprescribing, or termination of therapeutic (curative) drugs administered to patients in hospice. Chapter 7 is a literature review, looking at prior publications on estimation of life expectancy of patients admitted to hospice and reveals that, generally, these estimates are not particularly accurate. We also review prior literature exploring the relationship between analgesic prescriptions and mortality. The literature is inconclusive regarding whether these drugs hasten or slow the passing of a terminal patient. Finally, in Chapter 8 we apply several survival models, including standard Kaplan-Meier and Cox proportional hazards models, as well as time-dependent Cox proportional hazards, log-normal, accelerated failure time (AFT), and time-dependent log-normal AFT models, to the data to estimate both survival curves and life expectancy of terminal patients. Finally, the findings from the different examples are discussed and areas for future study are suggested, particularly the application of stochastic process models.

CHAPTER 2 - STATISTICAL MODELLING OF SURVIVAL

2.1 Introduction

Survival analysis describes the process of statistical modelling of a specific form of data, data that have a beginning and an end-point in time. We are frequently interested in the duration from beginning to end, as, for example, with life-span. Shorter durational studies, such as medical research, could involve time from treatment to either failure or survival of a patient. Actuaries have typically studied survival over lifetimes (or conversely, mortality, or the time to death).

Survival data are inherently different to other types of data, requiring their own set of analytical techniques. Specifically, the data are frequently left-truncated (the subject is not observed at time 0) and right-censored (the end-point of interest is not observed). Survival times, as figure 2.1 shows, are also highly skewed, with more observations at the beginning of the distribution and survival times showing a long tail. As an example, figure 2.1, which is a representation of the probability density of duration (time-to-death) of patients admitted to hospice, illustrates the extreme right-skewed tail of the distribution.

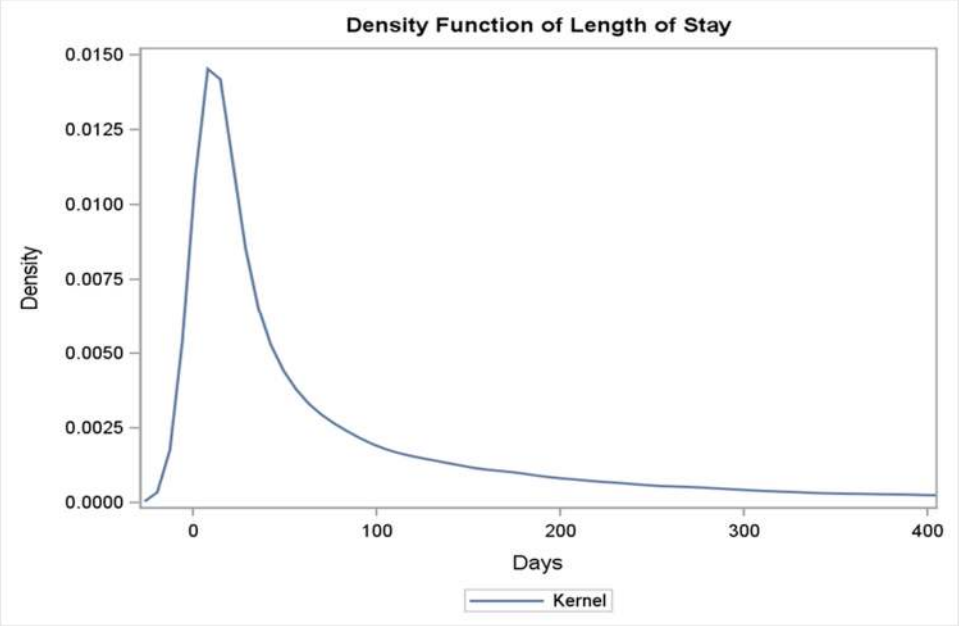


Figure 2. 1 Density of Length-of-Stay

A second issue with survival data is that censoring and truncation occur frequently. “Survival time for that individual is said to be censored when the end-point of interest has

not been observed for that individual" ([2], p.2). Censoring occurs when an individual is still alive at the time of the last observation. In some cases, an individual's final status could be unknown, as when the individual is "lost to follow-up." In this case, the individual is censored at the last observation.

The response variable *T*, in a survival study, is the time from the origin (either the start of the study or the beginning of the observation period of the patient) to a defined end point. A patient enters the study at time t_0 and dies (or otherwise terminates) at time $t_0 + T$, or is still alive at the end of the study. The individual who is still alive is "right-censored," because he is still alive at the observation date. Other types of censoring occur, for example, left-censoring occurs when individuals enter a study *after* the triggering event of interest, and interval censoring occurs when the precise date of the triggering event is unknown, but is believed to be between two observations. In this study we will be concerned with right-censoring, but not the other two types, because our subject populations consist either of permanently disabled employees (Chapter 3) or patients admitted to hospice care (chapters 4-8), both with a precisely recorded beginning point. Our interest is in modelling *T* as a function of explanatory variables.

2.2 Survival Functions

In describing survival data there are two functions of interest: the survival function and the hazard function or, as denoted by actuaries, the force of mortality. The variable representing survival time *T* is a non-negative random variable. *T* can take different values and, thus, represents observations from an underlying probability distribution. The probability density function for this distribution is represented by *f(t)* and the cumulative distribution by *F(t)*. The distribution function of *T* is given by $F(t) = \Pr(T \le t) = \int_0^t f(u)\,du$ and represents the probability that survival time is less than or equal to *t*. The corresponding survival function, *S(t)*, gives the probability that the survival time is greater than, or equal to, *t*; hence, $S(t) = \Pr(T \ge t) = 1 - F(t)$, or the probability that the individual survives to a point beyond *t*.

In actuarial applications, particularly mortality studies, a subscript x is added to indicate that the applicable function is measured from age x forward. In this study, x is a covariate, but we are primarily interested in survival time *T* and, therefore, will omit x, unless it is specifically required. Similarly, we will use the more general terminology for

the instantaneous rate of change of the survival function, the hazard rate, rather than the actuarial terminology, force of mortality that is specific to mortality. We will use the symbol for hazard rate $h(t)$, defined as: $h(t) = \lim_{\delta t \to \infty} \left\{ \frac{\Pr(t \le T < t + \delta t \mid T \ge t}{\delta t} \right\}$, which is the probability that an individual dies in the interval $(t, t + \delta t)$, given that the individual has survived to time t. The cumulative hazard function, $H(t)$, is defined as: $H(t) = \int_0^t h(u)du$.

A number of relationships may be derived from the definition of survival and hazard functions, as is done, for example, in [5] and [3]. Applying Bayes's theorem

$$\Pr\ (t \le T < t + \delta t \mid T \ge t) = \frac{\Pr(t \le T < t + \delta t)}{\Pr(T \ge t)} = \frac{F(t + \delta t) - F(t)}{S(t)} \tag{2.1}$$

Re-writing the earlier result, $h(t) = \lim_{\delta t \to \infty} \left\{ \frac{F(t + \delta t) - F(t)}{\delta t\ S(t)} \right\}$, and because

$\lim_{\delta t \to \infty} \left\{ \frac{F(t + \delta t) - F(t)}{\delta t} \right\}$ is the derivative of $F(t)$, $f(t)$ we have the result $h(t) = \frac{f(t)}{S(t)}$,

implying that $h(t) = -\frac{\mathrm{d}}{\mathrm{d}t}(\ln S(t))$ and $S(t) = \exp\left(-\int_0^t h(u)du) \right)$. Finally, from the survival function $S(t)$, we can calculate a life expectancy at age x for an individual (which we shall need later) as $\dot{e}_x = \int_0^\infty t\, f_x(t)\ \mathrm{dt}$ or $\dot{e}_x = \int_0^\infty S_x(t)\ \mathrm{dt}$. (2.2)

2.3 Estimating the Survival Function

We can estimate the survival function $S(t)$ empirically by

$$\hat{S}(t) = \frac{\text{No. individuals with survival time } \ge t}{\text{Total no. individuals}} = 1 - \hat{F}(t)$$

$$\text{where } \hat{F}(t) = \frac{\text{No. individuals dead at time } t}{\text{Total no. individuals}} \tag{2.3}$$

There are a number of different ways to estimate the survival function; in what follows, we will discuss the life table (actuarial) approach, Kaplan-Meier estimation, Cox proportional hazards, and other semi-parametric and parametric approaches.

2.3.1 Life table (actuarial) estimation

The life table is a summary of survival data grouped into convenient intervals. In actuarial (life table) estimation data are collected in grouped form. In order to estimate the survival

function, using the life table or actuarial approach, we first divide our observation period into a series of time intervals. In mortality studies, these tend to be years, quinquennial, or decennial intervals. In our hospice dataset, analysed later, we are fortunate in having a large population whose drug use is observed (essentially) daily. Generally, however, we define j periods, $j = 1,2,...m$. The $j-th$ period extends from $t_j^{'}$ to $t_{j+1}^{'}$. d_j and c_j denote the number of deaths and censored individuals in period j. n_j denotes the number of individuals alive and at risk of death at the beginning of period j. Typically, actuaries have assumed that censoring occurs uniformly throughout the $j-th$ period. On average, the number of individuals at risk of death during the interval is $n_j^{'} = n_j - c_j/2$. The length of the interval is defined as τ_j , implying that the average time survived in this interval is $(n_j^{'} - d_j/2)\ \tau_j$.

In this interval, the probability of death can be estimated as $d_j / n_j^{'}$ and corresponding survival probability as $(n_j^{'} - d_j)/n_j^{'}$. This value is an estimate of the probability of surviving during the $j-th$ period; cumulatively, the estimated probability of surviving *t* years is $S^*(t) = \prod_{j=1}^{k}\left(\frac{n_j^{'} - d_j}{n_j^{'}}\right)$ for $t_k^{'} \le t < t_{k+1}^{'}, k = 1,2,...m$. The corresponding hazard function, $h^*(t)$, is estimated as $h^*(t) = \frac{d_j}{(n_j^{'} - d_j/2)\tau_j}$. The asymptotic standard error of this estimate has been shown by Gehan [6] to be s.e. $\{h^*(t)\} = \frac{h^*(t)\sqrt{\{1-(h^*(t)\tau_j/2)^2\}}}{d_j}$

and the standard error of the survival function is

s.e. $\{S^*(t)\} \approx S^*(t)\left\{\sum_{j=1}^{k}\frac{d_j}{n_j^{'}(n_j^{'} - d_j)}\right\}^{1/2}$, $t > 0$.

2.3.2 Kaplan-Meier estimation of the survival function

In the case of data that are collected individually and not grouped (as in the case of the data in this study), it is possible to obtain more accurate survival estimates. The most basic survival function is that of Kaplan and Meier [7]. To obtain the Kaplan-Meier estimate, a series of time intervals is constructed (as with the life table estimate), but designed to

include at least one death per interval. Death is assumed to occur at the start of the interval. Following the example of Collett [2], let there be three time points t_1, t_2, t_3 t_1, t_2, t_3, such that $t_1 < t_2 < t_3$. One or more deaths (D) occur at each of these points; in addition, some subjects are censored (C). Collett's [2] figure 2.2 shows the incidence of deaths and censored lives.

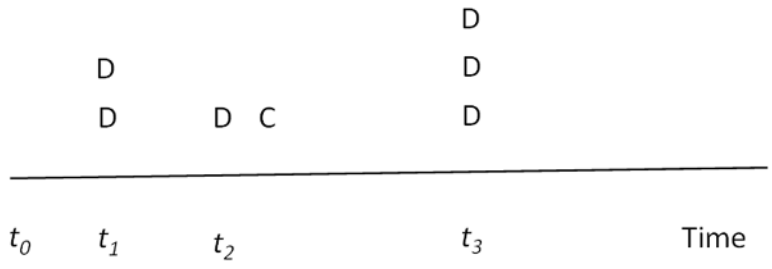


Figure 2. 2 Construction of Intervals used in Kaplan Meier Estimation

In this example, two individuals die at time one, one at time two, and three at time three; one individual is censored between observation points. In general, there are n individuals with survival times $t_1, t_2 ..... t_n$. As in the figure, more than one individual may have the same survival time. We observe r deaths among the individuals, and arranging the death times in ascending order, the $j-th$ death occurs at time $t_j, j = 1, 2..., .s$. d_j denotes the number of individuals dying at time $j,$ and n_j is the number of individuals alive immediately before time t_j. The estimated probability of dying at time t_j is d_j / n_j and the estimated probability of surviving through interval t_j to t_{j+1} is $(n_j - d_j)/n_j$. The Kaplan-Meier estimate of the survival function is then $\hat{S}(t) = \prod_{j=1}^{k} \left(\frac{n_j - d_j}{n_j} \right),\ t > 0$, for $t_{(k)} \le t < t_{(k+1)},\ k = 1, 2, ...r$ and $t_{(1)}, t_{(2)} .... t_{(r)}$ are r ordered death times.

As with the life table estimate, the Kaplan-Meier estimate is the product of a series of estimated probabilities. The Kaplan-Meier estimate is the limiting value of the life table estimate above, as the number of intervals tends to increase and the width of the interval trends to zero. The variance of the Kaplan-Meier estimate may be found in different ways.

Defining $\hat{\lambda}_j = \frac{d_j}{n_j}$, $Var(\hat{\lambda}_j) \approx \frac{\hat{\lambda}_j(1-\hat{\lambda}_j)}{n_j}$. (2.4)

Variance estimate

Method 1 Delta method: $Var(\ln(1-\hat{\lambda}_j)) = \frac{d_j}{n_j(n_j-d_j)}$ (2.5)

Method 2 Greenwood's formula:

The standard error of the Kaplan-Meier function is

s.e. $\{\hat{S}(t)\} \approx \hat{S}(t)\left\{\sum_{j=1}^{k} \frac{d_j}{n_j(n_j-d_j)}\right\}^{1/2}$ (Greenwood's formula). (2.6)

Confidence Intervals for the Survival Function

Original scale: $CI = \hat{S}(t) \pm Z_{1-\alpha/2} se(\hat{S}(t))$. Because the CI may lie outside [0,1] we may use a log transformed confidence interval.

If: $U = \frac{z_{\alpha/2} se(\hat{S}(t))}{(\hat{S}(t))\ln((\hat{S}(t))} = \frac{z_{\alpha/2}}{\ln((\hat{S}(t))}\sqrt{\sum_{t_j \le t} \frac{d_j}{n_j(n_j-d_j)}}$ then the log-transformed CI is:

$\left[\hat{S}(t)^{\exp(-U)}, \hat{S}(t)^{\exp(U)}\right]$

Sometimes we need Confidence Bands, $[L(t), U(t)]$ such that

$\Pr(L(t) \le S(t) \le U(t)$ for all $t_L \le t \le t_U) = 1-\alpha$.

$t_L \ge$ the smallest observed event time, and $t_U \le$ largest event time.

Equal Probability bands for Survival Function

(Log scale): $L(t) = \hat{S}(t)^{1/\theta}, U(t) = \hat{S}(t)^{\theta}$ where $\theta = \exp(c_\alpha(a_L, a_U)\hat{S}(t)/\ln(\hat{S}(t))$

$a_L = \frac{n\sigma_S^2(a_L)}{1+n\sigma_S^2(a_L)}, a_U = \frac{n\sigma_S^2(a_U)}{1+n\sigma_S^2(a_U)}$, $\sigma_S^2(t) = \frac{\widehat{Var}(\hat{S}(t))}{(\hat{S}(t))}$

Hall-Wellner Bands for Survival Functions

(Log scale): $L(t) = \hat{S}(t)^{1/\theta}, U(t) = \hat{S}(t)^{\theta}$

Where $\theta = \exp\left(\frac{k_\alpha(a_L, a_U)(1 + n\sigma_S^2(t))}{n^{1/2} \ln(\hat{S}(t))} \right)$

2.4 Semi-Parametric (Cox Proportional Hazards) Models

The methods discussed above (life table and Kaplan-Meier) are non-parametric. Although explanatory variables may exist in the data, they do not form part of the modelling. Instead, the data (and modelling) would need to be stratified according to the variable of interest, a cumbersome and ultimately unhelpful method. A modelling approach that includes explanatory variables allows us to determine how the experience of subjects depends on the values of explanatory variables.

Modelling survival data allows us to determine the effect of the explanatory variables (or combinations thereof) on the hazard function and to obtain an estimate of the hazard function. From the hazard function, an estimate of the survival function can be obtained. The survival function, in turn, allows the estimation of statistics, such as median survival time and life expectancy (complete expectation of life, in actuarial terms).

The most common model in survival analysis is the Cox proportional hazards model [8-10]. The model is semi-parametric because there is no underlying functional form (such as Poisson, negative binomial, Weibull, etc.) but it, nevertheless, incorporates covariates, allowing an assessment of the relative effect of different explanatory variables.

2.4.1 Proportional hazards model

The general form of the proportional hazards model posits explanatory variables $X_{1,}X_{2,}....X_p$. The *p* explanatory variables take values $x_{1,}x_{2,}.....x_p$ at the commencement of the study (or at entry into the study, if an individual is recruited later). We will later introduce time-dependent variables. The values $x_{1,}x_{2,}.....x_p$ are represented by the vector $\boldsymbol{X}$. Let $h_0(t),\ t > 0$ be the hazard function for an individual when $\boldsymbol{X} = 0$, i.e. when the explanatory variable values are all zeroes. $h_0(t)$ is the baseline hazard function, and the hazard function for the $i-th$ individual is $h_i(t) = \varphi(\boldsymbol{x_i})h_0(t)$, where $\varphi(\boldsymbol{x_i})$ is a function of the values of the explanatory variables at time *t* for individual *i*. The function

$\varphi(\boldsymbol{x}_i)$ is the hazard at time *t* for individual *i*, relative to the hazard for an individual with $\boldsymbol{X}=\boldsymbol{0}$. If we define $\varphi(\boldsymbol{x}_i)$ as $\exp(\eta_i)$, where $\eta_i = \beta_1 x_{1i} + \beta_2 x_{2i} ... + \beta_p x_{pi}$ then the general proportional hazards model is $h_i(t) = \exp(\beta_1 x_{1i} + \beta_2 x_{2i} ... + \beta_p x_{pi}) h_0(t)$, which implies, in turn, that $\ln\left\{\frac{h_i(t)}{h_0(t)}\right\} = \beta_1 x_{1i} + \beta_2 x_{2i} ... + \beta_p x_{pi}$.

(2.7)

The variables $X_1, X_2, ...X_p$ may be *variables* or *factors.* Variables are continuous (for example, age), while factors are categorical. Depending on the software used, we may need to define factors as a series of indicator variables with values (0,1) to accommodate the factor level [2]. For example, in our study of survival of hospice patients, care setting is treated as a categorical variable with four levels: homecare, long-term care, hospital inpatient unit, and assisted living. If homecare is the baseline level, we have three different indicator functions as follows:

$$I_{\{care_i = long-term\}} = \begin{cases} 1, & \text{if } i-th \text{ patient is in long-term care} \\ 0, & \text{otherwise} \end{cases} \quad (2.8a)$$

$$I_{\{care_i = inpatient\}} = \begin{cases} 1, & \text{if } i-th \text{ patient is in an inpatient facility} \\ 0, & \text{otherwise} \end{cases} \quad (2.8b)$$

$$I_{\{care_i = assisted\ living\}} = \begin{cases} 1, & \text{if } i-th \text{ patient is in an assisted-living facility} \\ 0, & \text{otherwise} \end{cases} \quad (2.8c)$$

If all three indicator functions are 0, we have a patient in the homecare setting.

2.5 Estimation of the Proportional Hazards Model

The proportional hazards model requires estimates of both the coefficients of the explanatory variables and the baseline hazard function, in the case of a fully-parametric function (e.g. Weibull). The former may be estimated first, and the latter function estimated when estimates of the coefficients have been found. In the case of the Cox regression model, a semi-parametric function, the β coefficients are found by the method of maximum likelihood. Given that data are available for n individuals, of whom r have died and $n - r$ are right censored, and, for simplicity, that there are no ties in the data (more than one individual dying at the same time) we order the r death times as $t_{(1)} < t_{(2)} ..... < t_{(r)}$ and $t_{(j)}$ is the $j-th$ ordered death time. The set of individuals alive, at

risk, and uncensored at time j is $R(t_{(j)})$. The partial likelihood function for the proportional hazards model is

$\boldsymbol{L}(\boldsymbol{\beta}) = \prod_{j=1}^{r} \frac{\exp(\boldsymbol{\beta}' \boldsymbol{x}_j)}{\sum_{t \in \boldsymbol{R}(t_{(j)})} \exp(\boldsymbol{\beta}' \boldsymbol{x}_t)}$, where $\boldsymbol{x}_j$ is the vector of covariates for the individual who dies at the $j-th$ ordered time t_j. $\sum_{t \in \boldsymbol{R}(t_{(j)})} \exp(\boldsymbol{\beta}' \boldsymbol{x}_t)$ is a summation over all individuals who are at risk at time t_j. Individuals who are censored do not contribute to the numerator of the likelihood function but they do contribute to the denominator up to the time of censoring.

To incorporate the censored observations into the data we assume n survival times $t_1, t_2, ...t_n$. We also introduce an event indicator, δ_t which takes a value of 1 when the individual dies at time *t* and 0 if the individual's observation is (right-) censored. When the subject is censored at T_i: $L_i(\beta) = \Pr(\text{subject } i \text{ survives beyond } T_i) = S(T_i) = \exp\left(-\int_0^{T_i} h_i(s) ds \right)$.

When the subject is not censored at T_i, T_i is the failure time $(\delta_i = 1)$ then:

$L_i(\beta) = S(T_i) h_i(T_i) = h_i(T_i) \exp\left(-\int_0^{T_i} h_i(s) ds \right)$. Full likelihood is then:

$L(\beta) = \prod_{i=1}^{n} h_i(T_i)^{\delta_i} \exp\left(-\int_0^{T_i} h_i(s) ds \right)$. Re-writing:

$L(\beta) = \prod_{i=1}^{n} \left(\frac{h_i(T_i)}{\sum_{j \in R(T_i)} h_j(T_i)} \right)^{\delta_i} \left(\sum_{j \in R(T_i)} h_j(T_i) \right)^{\delta_i} \exp\left(-\int_0^{T_i} h_i(s) ds \right)$. If we focus on the first term, then under the proportional hazards assumption, $L(\beta) = \prod_{i=1}^{n} \left(\frac{h_i(T_i)}{\sum_{j \in R(T_i)} h_i(T_i)} \right)^{\delta_i}$

and defining Z_i as a vector of co-variates,

$$\prod_{i=1}^{n}\left(\frac{h_i(T_i)}{\sum_{j\in R(T_i)} h_j(T_j)}\right)^{\delta_i} = \prod_{i=1}^{n}\left(\frac{h_0(T_i)\exp(\beta Z_i)}{\sum_{j\in R(T_i)} h_0(T_i)\exp(\beta Z_j)}\right)^{\delta_i} \prod_{i=1}^{n}\left(\frac{\exp(\beta Z_i)}{\sum_{j\in R(T_i)} \exp(\beta Z_j)}\right)^{\delta_i}, \quad (2.9)$$

which is the partial likelihood function $L(\boldsymbol{\beta}) = \prod_{j=1}^{r} \frac{\exp(\boldsymbol{\beta}' x_j)}{\sum_{t\in R(t_j)} \exp(\boldsymbol{\beta}' x_t)}$ (2.10)

The full likelihood function has been factored into two parts: the first term which involves $h_0(t)$ and β and the second term the partial likelihood, which involves β only. The first term contains information about contains information about $h_0(t)$ while the second term contains information about β. By discarding the first term and using only the partial likelihood, some information about β is discarded. The resulting estimate is not fully efficient; standard errors are larger than they would be if full likelihood were used. In most cases, Efron [11] showed that the loss of efficiency was small.

In order to accommodate tied observations, this likelihood function needs to be modified. The simplest approximation to the likelihood function when ties are present is that of Breslow [12] $L(\boldsymbol{\beta}) = \prod_{j=1}^{r} \frac{\exp(\boldsymbol{\beta}' s_j)}{\{\sum_{t\in R(t_j)} \exp(\boldsymbol{\beta}' x_t)\}^{d_j}}$ (2.11)

Where d_j are deaths at time j and s_j is the sum of the p covariates for the individuals who die at time j. There are other approximations, due to Efron [11], and Cox [8].

2.5.1 Estimation of the baseline hazard function

If the shape of the baseline hazard follows a recognizable form, we could consider a parametric version of the survival model. For example, if the empirical baseline hazard is a horizontal line, the underlying failure time follows an exponential distribution. If the baseline hazard is concave and increasing, it is possible that the failure time follows a gamma distribution or Weibull distribution. The R function (*basehaz*) allows us visually to discern the shape of the cumulative baseline function. We will explore these possible functions later when we fit models.

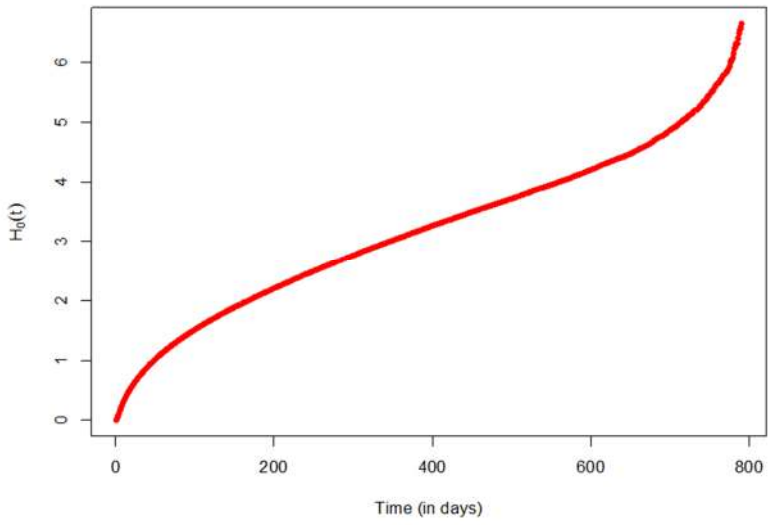


Figure 2. 3 Estimated Baseline Cumulative Hazard Function

2.5.2 Stratified Cox Models

When the proportional hazards assumption is violated hazards will not be proportional on an overall basis but will be proportional in subgroups. In our study of workers' compensation terminations, the proportional hazards assumption is shown to be violated for the covariate "entity group" (essentially the employer or department for which the disabled employee worked). For situations such as this, we assume that subjects have different baseline hazard functions for each of the strata to which the covariate levels map. Now, instead of the Cox proportional hazards model above ($h_i(t) = \varphi(\boldsymbol{x}_i)h_0(t)$) we have instead a stratified model $h_{ij}(t) = \boldsymbol{\varphi}(\boldsymbol{x}_{ij})h_{0j}(t) = \exp(\boldsymbol{\beta}'\boldsymbol{x}_{ij})h_{0j}(t)$ where $\boldsymbol{x}_{ij}$ is the vector of explanatory variables $X_{1,}...X_p$, excluding X_k that violates the PH assumption and $j \in \{1,2,...g\}$ which indicates the categorical level in X_k .

2.6 Parametric Models

A parametric model is one in which survival time is assumed to follow a known distribution. The Cox proportional hazards model has the advantage of being semi-parametric, which makes it flexible. While the regression parameters are known, the baseline survival is not specified in the Cox model, so the distribution of the outcome

remains unknown. The definition of a specific functional form for the parametric model has the advantage of more precise inferences and smaller standard errors.

2.6.1 Accelerated failure time models

Although we are concerned with the estimation of survival in the population, because the outcome is mortality, we are also interested in estimating life expectancy for individuals based on their specific circumstances (co-variates). Ultimately, we need a method to develop life expectancy for the population. Time-dependent models (which we will discuss shortly), such as the time-dependent Cox model are not ideal for this purpose because the future pathway of the time-dependent variable is not determined at any point in time; in fact, the pathway unfolds in a stochastic fashion. One way to estimate life expectancy would be to impute a future pathway to the patient. Other alternatives are to fit parametric models or to apply accelerated failure time (AFT) models. Unlike the semi-parametric Cox model, the AFT model has a completely specified form for the hazard function $h(t)$ and the survival function $S(t)$. The AFT model is a statistical approach to the study of survival, rather than through the hazard function.

In the previous section, the key assumption for the survival model was the proportional hazard (PH) assumption. Many parametric models are accelerated failure time (AFT) models rather than PH models. Interpretation of coefficients also differs between AFT and PH models. The coefficients (βs) in PH models affect the hazard rates, while the coefficients in AFT models affect the survival time. AFT models are consistent with theoretical survival models, while at the same time robust (in the sense that the model does not need to satisfy a proportional hazards assumption) with respect to departure from the proportional hazards assumptions. We can use the complete specified form of the survival function to predict the future survival curve for any patient using the time-quantile function.

2.6.2 Assumptions in the AFT model

AFT models assume that the effect of the predictors is to accelerate or decelerate the survival function by a constant. The example in Kleinbaum and Klein [10], although somewhat trivial, illustrates the point. Kleinbaum and Klein [8] posit two survival functions: $S_D(t)$ for dogs and $S_H(t)$ for humans. They observe that dogs are often believed to age at seven times the rate of humans. The probability of a dog living past 10 years old is (in this model) equal to the probability of a human living beyond age 70. We can therefore write $S_D(t) = S_H(7t)$. In this model, dogs are viewed as "accelerating" through

their lifetimes at seven times the rate of humans; conversely, human survival is decelerated by a factor of seven, compared with that of dogs [8].

More generally, $S_A(t) = S_B(\gamma t)$, where γ is the acceleration factor and the rate of aging for population B is γ times that of population A. In terms of survival time, random variables $\gamma T_A = T_B$. The following summarizes the role of γ:

$\gamma > 1 \Rightarrow$ the effect of the predictor variables increases survival

$\gamma < 1 \Rightarrow$ the effect of the predictor variables decreases survival.

In Figure 2.4, the acceleration factor is $\gamma = \frac{D2}{D1} =$ constant.

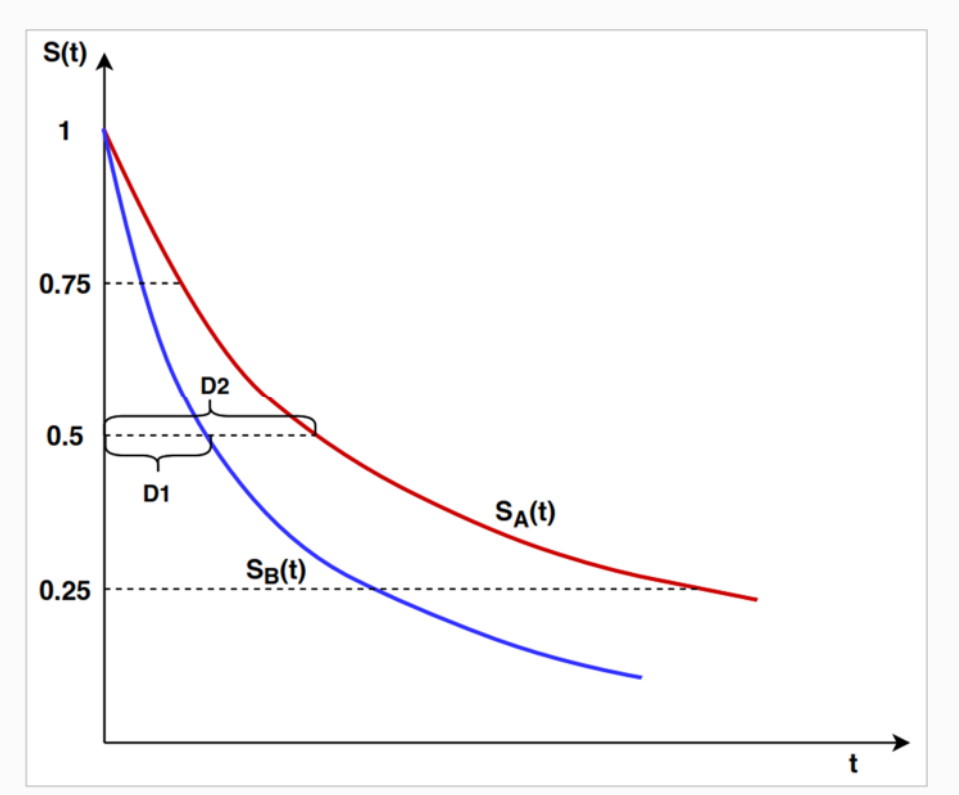


Figure 2. 4 Example of Acceleration

2.6.3 Examples of parametric distributions

A number of different distributions can be used. In this section, we will discuss the exponential, Weibull, lognormal, and log-logistic distributions.

2.6.3.1 Exponential distribution

The simplest model for the hazard function is the exponential distribution (see figure 2.5). In this model, the hazard is constant over time, implying that the risk of death is the same irrespective of the elapsed time since entry to the study. Under this model, $h(t) = \lambda$ for $0 \leq t < \infty$ (λ is replaced by μ in actuarial studies of mortality). The survival function is $S(t) = \exp\left\{-\int_0^t \lambda du\right\} = e^{-\lambda t}$, $t > 0$. The exponential distribution is not particularly realistic and is not much used in practice.

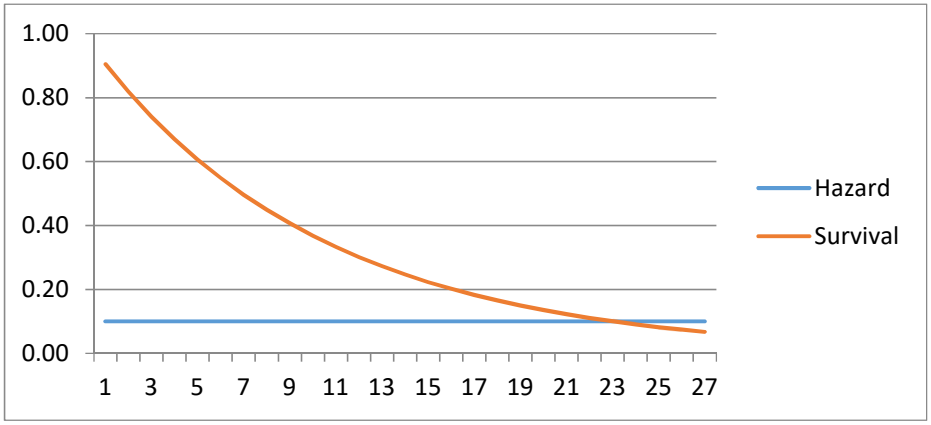


Figure 2. 5 Exponential Distribution (Constant Mortality Hazard)

2.6.3.2 Gompertz distribution

The Gompertz distribution (see figure 2.6) is an early example of an exponential distribution and has particular application in early actuarial mortality modelling, being introduced by Benjamin Gompertz in 1825. The hazard function of the Gompertz distribution is $h(t) = \alpha e^{\beta t}$. When $\beta = 0$, the model defaults to the exponential distribution. The corresponding survival function is $S(t) = \exp\left\{\frac{\alpha}{\beta}(1 - e^{\beta t})\right\}$, $t > 0$. When multiple explanatory variables are introduced $X_1 \ldots X_p$ with values $x_{1i} \ldots x_{pi}$ for the $i-th$ individual $i = 1, 2 \ldots n$, the Gompertz proportional hazards model becomes $h_i(t) = \exp(\gamma_1 x_{1i} + \ldots + \gamma_p x_{pi})\ \alpha e^{\beta t}$. The coefficients γ_1 are log-hazard ratios.

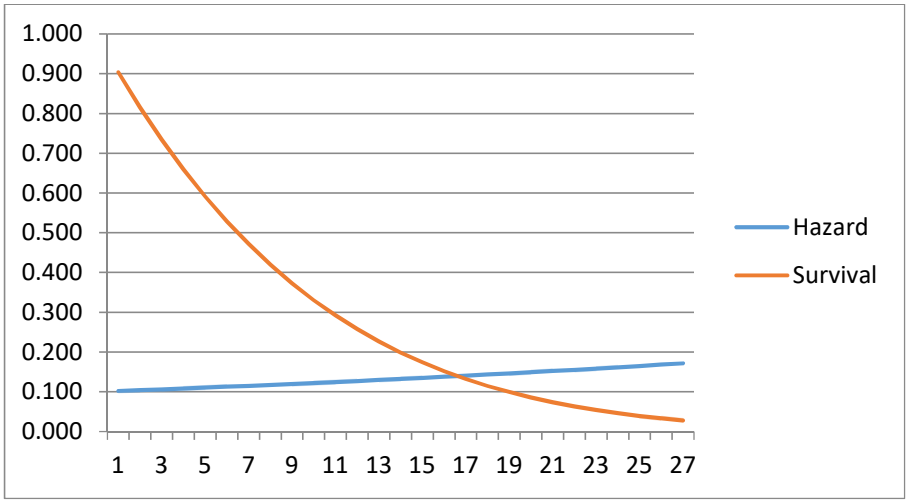


Figure 2. 6 Gompertz Distribution

2.6.3.3 Makeham distribution

The Makeham distribution, sometimes called the Gompertz-Makeham distribution, adds a constant to the Gompertz function (see figure 2.7). It is of the form $h(t) = \theta + \alpha e^{\beta t}$.

The Makeham survival function is:

$$S(t) = \exp\left[-\int_0^t h(s).ds\right] = \exp\left[-\int_0^t \theta + \alpha \exp(\beta s).ds\right], \text{ t>0}$$

$$= \exp-\left[\theta s + \frac{\alpha}{\beta}\exp\beta s\,|_0^t\right] = \exp\left[-\theta t + \frac{\alpha}{\beta}\left(1-e^{\beta t}\right)\right] \qquad (2.12)$$

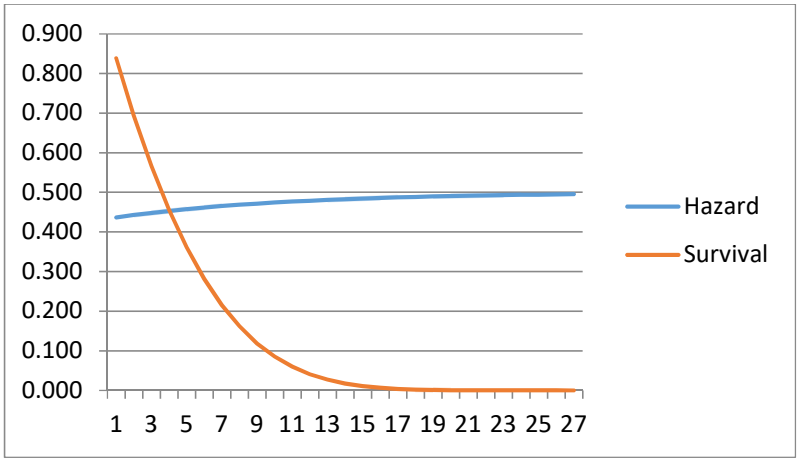


Figure 2. 7 (Gompertz) Makeham Distribution

2.6.3.4 Weibull distribution

A more general form of the hazard function than the Gompertz model is $h(t) = \lambda\gamma t^{\gamma-1}$, $t > 0$. When $\gamma = 1$ the model defaults to the exponential distribution. The hazard function increases or decreases monotonically depending on values of γ. Figure 2.8 illustrates a Weibull distribution with increasing hazard function, a distribution that may be suited to our population that faces increased mortality hazard as duration in hospice increases. The Weibull survival function is $S(t) = \exp\left\{-\int_0^t \lambda\gamma u^{\gamma-1} du\right\} = e^{-\lambda t^{\gamma}}$, $t > 0$ and $f(t) = \lambda\gamma t^{\gamma-1} e^{-\lambda t^{\gamma}}$.

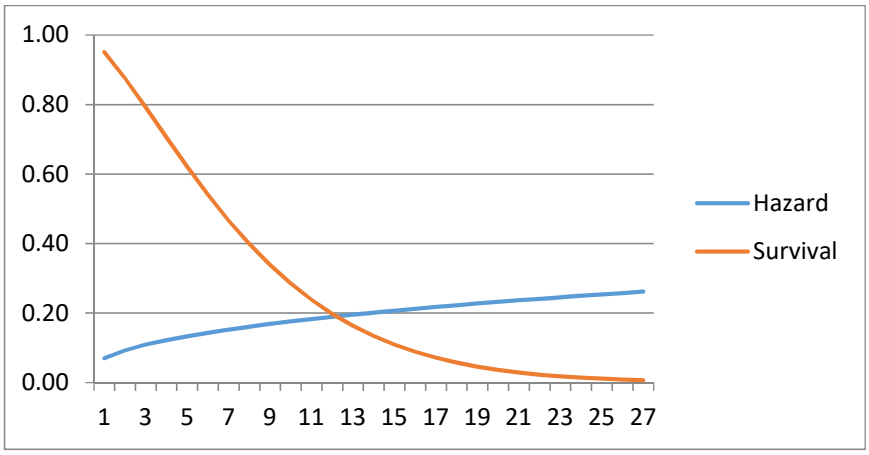


Figure 2. 8 Weibull Distribution with Increasing Mortality Hazard

2.6.3.5 Lognormal distribution

Under the lognormal distribution the form of the hazard function is:

$$h(t) = \frac{\phi\left(\frac{\ln(t)-\mu}{\sigma}\right)}{\sigma t\left[1-\Phi\left(\frac{\ln(t)-\mu}{\sigma}\right)\right]}$$ and the Survival function:

$$S(t) = 1-\Phi\left(\frac{\ln(t)-\mu}{\sigma}\right),\ t > 0, \sigma > 0,$$

Where Φ is the cumulative unit normal distribution and ϕ the unit normal density. The survival and hazard functions are illustrated in figure 2.9.

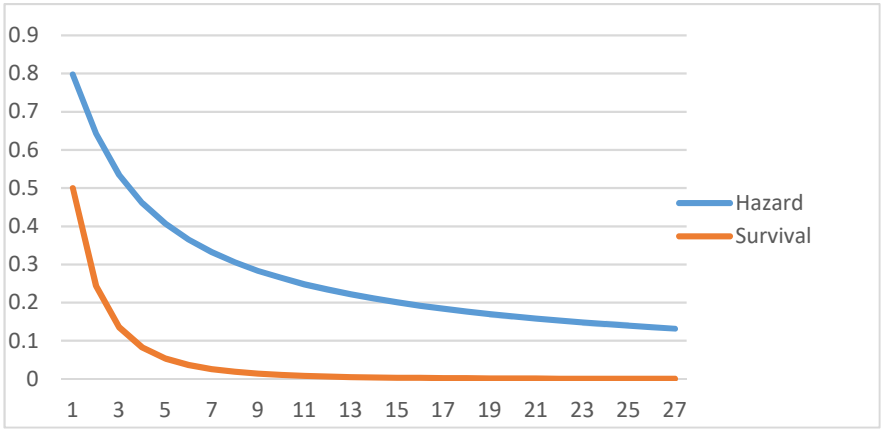


Figure 2. 9 Lognormal [N(0,1)] Distribution

2.6.3.6 Log-logistic distribution

The final parametric function to be considered is the log-logistic. A limitation of the Weibull function is that it is a monotonic function of time. While we would *a priori* expect this to be an appropriate model for the survival of patients in hospice, it is possible that their mortality hazard both decreases and increases (or vice-versa) over time. It is possible, for example, that the addition or change in the strength of a drug could have this effect on survival. The unimodal form of the function in which hazard first increases and then decreases over time is particularly worth considering (see figure 2.10). The hazard function is $h(t) = \dfrac{e^{\theta}\ pt^{p-1}}{1 + e^{\theta}t^{p}},\ t > 0,\ p > 0.$ If $p \leq 1$ the hazard decreases with time. If $p > 1$ the hazard first increases and then decreases (unimodal). The corresponding survival function is $S(t) = \dfrac{1}{1+e^{\theta}t^{p}},\ p > 0..$

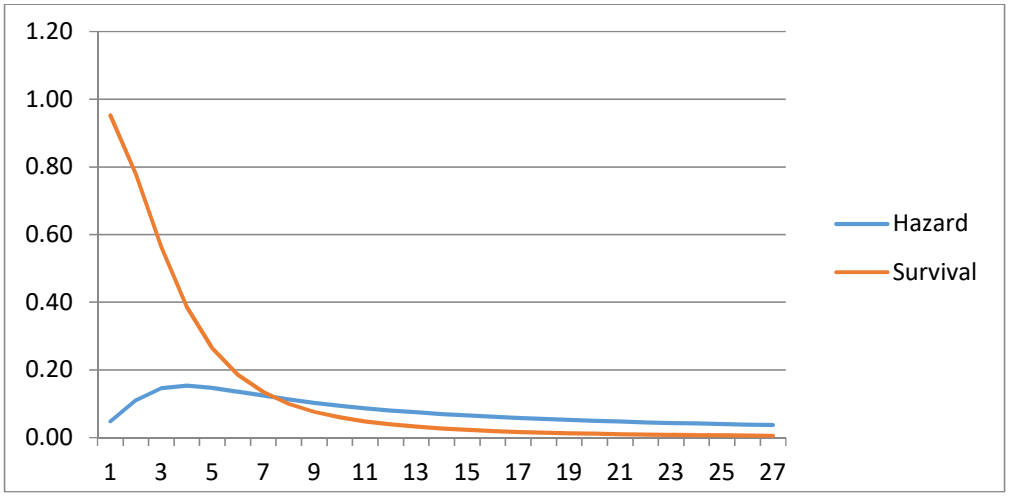


Figure 2. 10 Log-logistic Distribution with Unimodal Mortality Hazard

2.6.4 Prediction using AFT models

Some of the models discussed above (e.g. Weibull, log-normal) are appropriate for modelling AFT survival curves. Below, predicting the survival curve for future observations are discussed.

2.6.4.1 Weibull

Assume $T \sim$ Weibull (λ, p) and hazard function $h(t) = \lambda p t^{p-1}$. For the AFT model we re-parameterize λ as a linear combination of the predictors, such that $\lambda = \exp(\beta_0 + \sum \beta_i X_i)$.

The corresponding survival function is

$$S(t) = e^{-\lambda t^p} \Leftrightarrow -\ln(S(t)) = \lambda t^p \Leftrightarrow t = (-\ln(S(t)))^{1/p} \frac{1}{\lambda^{1/p}},\ t > 0, p > 0. \tag{2.13}$$

$$\frac{1}{\lambda^{1/p}} = e^{\beta_0 + \sum \beta_i X_i} \text{ then } t = \frac{(-\ln(S(t)))^{1/p}}{\left(e^{\beta_0 + \sum \beta_i X_i}\right)^{1/p}}. \tag{2.14}$$

2.6.4.2 Log-normal

Assume $T \sim$ LN (μ, σ); μ is a linear combination of predictors, $\mu = \beta_0 + \sum \beta_i X_i$.

The hazard function is:

$$h(t) = \frac{\phi\left(\frac{\ln(t) - \mu}{\sigma}\right)}{\sigma t\left[1 - \Phi\left(\frac{\ln(t) - \mu}{\sigma}\right)\right]}. \tag{2.15}$$

and the Survival function:

$$S(t) = 1 - \Phi\left(\frac{\ln(t) - \mu}{\sigma}\right) \Rightarrow \ln(t) = \mu + \sigma\ \Phi^{-1}(1 - S(t)),\ t > 0, \sigma > 0 \tag{2.16}$$

We will use expression 2.16 later in predictions.

Solving for *t* in terms of predictors:

$$\ln(t) = (\beta_0 + \sum \beta_i X_i) + \sigma\ \Phi^{-1}(1 - S(t)) \tag{2.17}$$

We will return to these distributions when we perform modelling in Chapter 8.

2.7 Survival Functions with Time-dependent covariates

In studies where individuals are monitored continuously or periodically, values of observed data are generated at different time points. Incorporation of changing values of explanatory variables can result in a more accurate model. Time-dependent variables are those variables whose values change with time. There are two types: internal (endogenous) and external (exogenous). Internal variables relate to an individual in a study and result from repeated observations made on the individual over time. They are often measures of clinical function. External variables are measures of factors that are not dependent on the patient, such as temperature. In Chapter 8, we apply time-dependent models to survival of patients in hospice. For these patients, fixed covariates include age and sex at admission, as well as admitting diagnosis and co-morbidities. Additionally, we have considerable volumes of drug dispensing data that are time-dependent, including drug name, strength, form, and dosage. These co-variates are patient-specific and time-dependent, and indicate changes in medication triggered by changes in patients' conditions.

A distinction needs to be drawn between time-dependent coefficients and time-dependent covariates. In the Cox proportional hazards model, the hazard of death at time *t* for individual $i,\ i \in \{1,..n\}$ is of the form $h_i(t) = \exp\left\{\sum_{j=1}^{p} \beta_j x_{ji}\right\} h_0(t)$, where $X_j,\ j = 1,2...p$ are explanatory variables and $h_0(t)$ is the baseline hazard function. The Cox regression model with time-dependent variables is $h_i(t) = \exp\left\{\sum_{j=1}^{p} \beta_j x_{ji}(t)\right\} h_0(t)$.

In this model, the term $h_0(t)$ is interpreted as the baseline hazard function for an individual whose variables have a value of zero at inception of the study and remain at zero throughout. Values of variables $x_{j\,i}(t)$ depend on time *t*, meaning that $h_i(t) / h_0(t)$ is time

dependent, that is, dependent on the value of variables at time t. Conversely in a model with time-dependent coefficients, $h_i(t) = \exp\left\{\sum_{j=1}^{p} \beta_j(t) x_{ji}\right\} h_0(t)$ the value of the coefficients changes with time. For the remainder of this thesis we will be concerned with time-dependent covariates.

With time-dependent covariates, the hazard of death at time *t* is no longer proportional to the baseline hazard and the model is no longer a proportional hazard model.

Looking at the ratio of two individuals, *r* and *s,*

$h_r(t) / h_s(t) = \exp([\beta_1(x_{r1}(t) - x_{s1}(t)) ... + \beta_p(x_{rp}(t) - x_{sp}(t))]$ the coefficient β_j can be interpreted as the log-hazard ratio for two individuals whose value of variable j differs by one unit at time *t*, holding all other variables constant.

2.7.1 Estimation

The log-likelihood function for the Cox regression model is

$\sum_{t=1}^{n} \delta_i \left\{ \sum_{t=1}^{p} \beta_j x_{ji}(t_i) - \ln \sum_{l \in R(t_i)} \exp\left(\sum_{j=1}^{p} \beta_j x_{ji}(t_l) \right) \right\}$, where $R(t_i)$ is the risk set at time t_i and $\delta_i = 1$ (when the individual has died) and = 0 when the individual is censored. To maximize this expression to obtain values of β_j we require values of time-dependent variables, $X_{ij}(t)$ at the death of the $i-th$ individual. Certain variables are measured, however, at intervals that do not coincide with death. In these cases, a problem can arise because the exact value is not recorded at death, and there are established procedures to deal with this issue (for example, using the last value, interpolating between two values, or developing a model to predict the value at a point in time). In our case, this will not be an issue because key variables, such as drug dispensing data, are recorded at intervals, but represent continuous therapy, adjusted on a periodic basis.

According to the nature of the time-dependent Cox model, it is not correct to incorporate endogenous variables into the model. In order to obtain an unbiased estimate of the effect of a covariate on an outcome variable using standard survival analysis methods, it is necessary that the covariate be measured at all times and without error [13]. Specifically, the value of a time-dependent covariate in the Cox model is changed at the follow-up time point, but must remain constant until the next follow up. This assumption is valid in the case of an exogenous variable, but it is not necessarily true in the case of an

endogenous variable. Said differently, time-dependent covariates are the result of a "stochastic process generated by the subject" [14]. Theoretically, drug strength values could change continuously between two measurement points. That they do not is a function of drug prescribing; patients either receive 28-day supplies of their prescription drugs, using them until the drugs are exhausted or a new (possibly stronger) prescription is filled. Arguably, the nature of prescription drugs suggest that the endogenous variable (drug strength) meets the requirements necessary to obtain an unbiased measurement of the effect of this covariate, and, for this reason, we considered developing an extended Cox regression model. However, there is still endogeneity between the patient and the prescription strength, with the result that this method tends to underestimate both the effect and the standard errors of the examined endogenous variable (drug strength). In this case, one solution is to perform joint modelling of the path of the endogenous variable (repeated measures) and the survival model can be an alternative method for consideration.

The functional form of the joint model is as follows:

$h_i\left(t|\mathrm{M}_i\left(t\right), X_i\right) = h_0\left(t\right)e^{\beta^T \mathrm{X}_i + \alpha m_i(t)}$, $t > 0$, where $\mathrm{M}_i\left(t\right)$ denotes the history of the true unobserved longitudinal process up to time point *t* and $m_i\left(t\right)$ denotes the true and unobserved value of the longitudinal outcome at time *t*. Keep in mind that $m_i\left(t\right)$ is not the same as $\gamma_i\left(t\right)$, as it is measured with error. In addition, we apply an appropriate mixed-effects model to estimate $m_i\left(t\right)$ and reconstruct the complete history $\mathrm{M}_i\left(t\right)$. However, ultimately, it was decided to fit a parametric function and to estimate survival this way.

2.8 Assessing Model Validity

2.8.1 Two types of test

To assess the validity of a particular Cox regression model we need to perform tests of overall fit as well as the proportional hazards assumption.

2.8.2 Overall fit for the Cox regression model

There are several different tests of fit of the Cox regression model:

Method	Primary Use
1. Cox-Snell residuals	Overall Fit
2. Martingale residuals	Form of covariates (should covariates be transformed?)
3. Deviance residuals	Outliers
4. Schoenfeld residuals	Proportional Hazards assumption
5. Score residuals	Influential points

1. Cox-Snell residuals [15] are defined as $r_i = \hat{H}_0(T_i)\, e^{\hat{\beta} x_i}$, which can be used to assess the overall fit of a Cox proportional hazards model. If the model is correct, the estimated cumulative hazard for each observation at the time of death or censoring should be like a censored sample from a unit exponential distribution. Thus a plot of the Cox-Snell residuals versus the estimated cumulative hazard rates $\hat{H}_0(T_i)$ should follow a straight line through the origin, given that the Cox model provides a good fit of the data. In figure 2.11, we see the estimated cumulative hazard is close to the diagonal line for all but large values of Cox-Snell residuals.
2. The Martingale residual for the $i-th$ subject is $M_i = \delta_i - r_i$ where r_i is the Cox-Snell residual and M_i is the difference between the observed number of deaths, ($\delta_i = 0,1$) and the expected number of deaths for subject i between time 0 and T_i. A plot of Martingale residuals vs. covariates indicates whether a transformation of the covariate is appropriate.

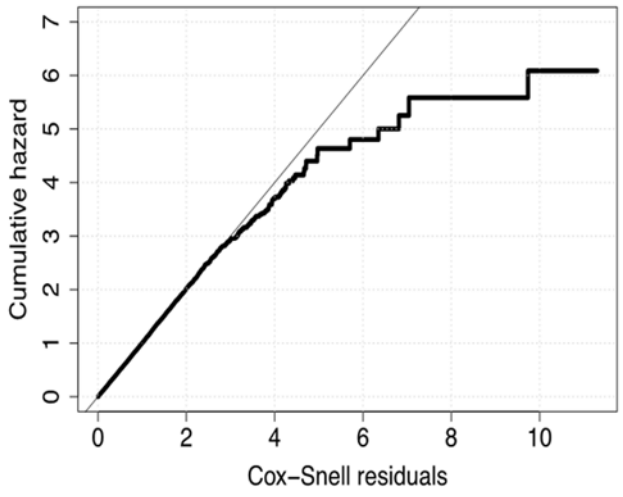


Figure 2. 11 Cox-Snell Residuals

3. Deviance residuals are defined as $\text{sign}(M_j)\left[-2\left\{M_j+\delta_j \ln(\delta_j - M_j)\right\}\right]^{1/2}$ which is less skewed and more symmetrical compared to the distribution of Martingale residuals. A large value of the deviance residual implies a possible outlier.
4. Schoenfeld residuals. Schoenfeld residuals were proposed by Schoenfeld (1982, [16]). Unlike residuals discussed above, there is not a single residual value for each individual but a set of values, one for each explanatory value in the fitted Cox model. The $i-th$ residual for X_j the $j-th$ explanatory variable is $r_{ji}=\delta_j\{x_{ji}-\bar{x}_{ji}\}$, where x_{ji} is the value of the $j-th$ explanatory variable, and r_{ji} represents the difference between the observed covariate and its average over the risk set at time T_i.
5. Score residuals. Score residuals are a modification of Schoenfeld residuals. The score residual is not a single value for each observation but a set of values, one for each covariate in the fitted Cox model. A large value of the score residual implies large influence of the $i-th$ subject on the estimate of β_j.

2.8.3. Appropriateness of the proportional hazard assumption

The departure from proportionality could lead to an incorrect model. The PH assumption may be tested in two ways: 1) by plotting the Schoenfeld residuals [16] and 2) performing a formal hypothesis test for correlation between Schoenfeld residuals and time.

If the PH assumption is true, the trend of β versus time is expected to be a horizontal line for each covariate. A more formal test of the PH assumption was proposed by Grambsch and Therneau [17]. Each parameter in the model is allowed to depend on time $\beta_j(t)=\beta_i(t)+\gamma_j g_j(t)$. If the correlation parameter $\gamma_j=0$, we would reject the hypothesis that parameters are time-dependent.

2.8.4 Model Selection with fully-parametric models

Comparisons between a number of different models (varying, for example by inclusion of more covariates or interaction terms) can be made on the basis of the AIC

statistic. Akaike's information criterion (AIC) is applied to compare the goodness-of-fit between fully-parametric AFT models. By definition,

$AIC = -2Log(likelihood) + 2(p + k)$, where p is the number of parameters, and $k = 1$ for the exponential model and $k = 2$ for the Weibull, log-logistic, and log-normal models. The Log-likelihood is a measure of goodness-of-fit, where the higher the number the better the model fits the data, but penalizes the model for inclusion of additional variables. The AIC statistic is, however, only useable to compare parametric models: "This classic question (comparison of non-parametric and parametric models) cannot be answered by AIC or BIC since a non-parametric model has no likelihood." [18]. To compare semi-parametric models (e.g. Cox regression) and parametric models we need other techniques, which are not well developed.

2.8.5 Overall fit for the log-normal accelerated failure time model

The final log-normal AFT model is assessed using AIC and goodness-of-fit tests. We further assess the overall goodness-of-fit using the Cox-Snell residuals for the log-normal AFT model. For the AFT model, the Cox-Snell residual for the $i-$th observation is defined as $\hat{r}_i = -\ln\left(1-\Phi\left(\frac{\ln(t_i)-\hat{\mu}}{\hat{\sigma}}\right)\right)$,

(2.14)

where Φ is the cumulative distribution function of the standard normal distribution. If the model is correctly specified, the set $(\hat{r}_i, \delta_i), i = 1, 2, \ldots n$ behaves similarly to a censored sample of unit exponentially distributed variables. A drawback of Cox-Snell residuals is that they do not provide insights into the reasons for a model's failure to fit the data.

2.9 Model Validation

The use of the concordance statistic for Cox models was popularized by Harrell et al [19] and is now the most used measure of goodness-of-fit of survival models (Therneau and Atkinson, [17, 20]. If y_i and x_i are observed and predicted data values, Concordance is defined as $\Pr(x_i > x_j \mid y_i > y_j)$, the probability that the prediction x is in the same direction as the actual data y. A pair of observations x, y is considered concordant if the prediction

and data go in the same direction; the concordance statistic is the fraction of concordant pairs.

We validate the model by applying the derived model estimates to a hold-out dataset. The metrics for validation are Somers' D_{xy} correlation index [21] and Harrell's concordance index [19], both of which are used to assess the predictive value of a right-censored survival model. Somers' D_{xy} is a measure of ordinal association between two possibly dependent random variables *X* and *Y*. Somers' D_{xy} takes values between when all pairs of the variables disagree and when all pairs of the variables agree. $D_{xy} = \frac{n_c - n_d}{n(n-1)/2}$, where n_c is the number of pairs that are concordant (i.e. rank orders of predicted and actual pairs are the same, or $y_i < y_j$ and $\hat{y}_i < \hat{y}_j$).

n_d is the number of pairs that are disconcordant (i.e. rank orders of predicted and actual pairs are the different, or $y_i < y_j$ but $\hat{y}_i > \hat{y}_j$). $n(n-1)/2$ is the number of of all possible pairs of observations in the data. A number close to 1 implies a model that generates high concordance, and Harrell's concordance or c-index is defined as $c = \frac{D_{xy} + 1}{2}$. A value of c > 0.5 implies that predictions are better than random.

CHAPTER 3 - USING SURVIVAL ANALYSIS TO PREDICT WORKERS' COMPENSATION TERMINATION

This chapter consists of a study of termination rates of permanently disabled workers eligible for lifetime workers' compensation medical benefits in the State of California.

3.1 Workers Compensation: Background

Workers Compensation (WC) is a compulsory, no-fault insurance system in the United States. The fragmentation of the provision of medical and income benefits between multiple private payers and providers, in the absence of a national system (such as in the United Kingdom), requires oversight and regulation of private providers. The workers compensation system addresses *occupational* illness and injury and operates in parallel with the medical and *non-occupational* disability income systems. Workers compensation regulation requires employers to purchase insurance to compensate employees for lost wages and medical expenses in the event of occupational injuries and illness. Under this system, the employer is deemed to be absolutely liable for occupational injuries and illness, regardless of responsibility. Coverage is compulsory for all U.S. employers, with some exceptions, e.g., employers with fewer than five employees, farm labour, domestic servants, and longshoremen. Employers can purchase private insurance, self-insure and purchase excess (WC) insurance, or use state workers compensation funds – some of which are monopolistic and some of which compete with private insurers.

The United States constitution reserves to the states responsibilities that are not explicitly assigned to the Federal Government. Workers compensation is one such activity whose regulation is the responsibility of the states and benefits are defined by each individual state. Typical benefits are as follows:

- Unlimited medical benefits
- Disability benefits for lost wages. Disability benefits are typically limited to two thirds of a state's average weekly wage (subject to minimums and maximums), so there is an incentive for workers to return to work. WC return-to-work programs are important in controlling costs. Disability income benefits under the workers compensation system are usually classified as:
    - Temporary Total (TT) – Injury is deemed short-term; however, the employee is unable to work while in an injured condition, for example, with broken bones in traction.

- Permanent Total (PT) – Injury is deemed permanent and the employee cannot return to employment, for example, with paralysis or a coma. PT injuries typically result in lifetime disability benefits.
- Temporary Partial (TP) – Injury is deemed short-term and the employee can do some work while injured, for example, having one broken arm.
- Permanent Partial (PP) – Injury is deemed permanent; however, the employee can still work (sometimes with re-training for a different job), for example, the loss of one limb or the loss of sight in one eye.

- Death benefits – for burial.
- Rehabilitation benefits – vocational evaluation and re-training.

PT injuries are the least frequent, but most severe, causing medical benefits for PT injuries to be the most difficult to estimate. Due to the infrequent nature of the claims and their duration (to end of life), as well as medical trend (inflation), a traditional chain ladder (triangle) approach to reserving does not usually work very well for estimating the liability for future medical costs. Tail data is often thin, volatile, and out-dated. The medical condition and treatment of PT workers can and does change over time. Changes in medical technology and medication can cause significant changes in medical cost. End of life costs (e.g., nursing homes) can also cause spikes in benefits. The best way to estimate medical reserves (unpaid claims) for these lifetime cases is often to estimate case reserves[2] and to rely less on bulk IBNR[3] estimates from triangle methods. In order to estimate reliable case reserves, it is important to reflect accurate information about each case. One important factor in these estimates is the duration of claim benefits to the injured employee (claimant), which is the future lifetime of the employee.

The duration of PT benefits, at the case level, is often dependent on mortality tables. However, it is important to use the correct mortality table for the injury. The severity of PT injuries often means that the expected mortality of the claimant is compromised. Hence, a standard mortality may not be appropriate. However, states may regulate the estimation of case reserves by formula, including the use of a standard mortality table. When an

[2] Case Reserves are estimated at the individual level by claims adjusters.

[3] IBNR estimates are bulk estimates for Incurred but Not Reported claims, including development on known claims, claims not yet reported (small in workers' compensation) and re-opened claims.

inappropriate mortality table is used, this can result in inaccurate case reserves and increased reliance on less-reliable bulk IBNR methods.

Although, historically, wage replacement (called "indemnity" in workers compensation contracts) was the larger of the two liabilities, the continual inflation in medical costs has resulted in a shift so that medical benefits now represent over 55% of the total employer liability.

3.2 Mortality of Disabled Lives

Although general insurance companies use mortality tables for workers' compensation case reserving, there are no published tables of disabled life mortality and few comparisons of standard and non-standard mortality. The few studies comparing standard and non-standard mortality suggest that mortality of younger disabled workers is higher than that of a standard population, while older disabled worker mortality does not differ significantly from that of the standard population. The Casualty Actuarial Society has, in the past, published studies of disabled worker mortality. Venter et al. [22], p.117, in a study of mortality of disabled lives, found that: "injured worker mortality after some years comes close to standard mortality, and after some age may actually be lower. Because of this, not much credit can be taken on pension case reserves, even though for younger workers initial mortality is much higher than standard." Gillam [23] tested the hypothesis that the mortality of pensioned (disabled) workers differs significantly from that of the general population. It does appear that, at least for ages below 60, the reported injured worker mortality rate is higher than standard U.S. Life. Between age 60 and 74 the injured worker mortality rate does not differ appreciably from U.S. Life. The differences in mortality, even if accepted, do not imply significant redundancy or inadequacy of tabular reserves.

The data for our study comes from one such excess insurance pool, operated by an entity called California State Association of Counties Excess Insurance Authority (CSAC-EIA). CSAC-EIA is the excess insurer (similar to a reinsurer) for many self-insured California government agencies and bodies, such as municipalities, police forces, fire departments, school boards, etc. The conclusion of our study is that the mortality of disabled lives in the study population is higher than that of the U.S. Life table (the standard table required by the California regulator). The difference between our conclusion and the CAS studies referenced may be due to population differences (including more recent data)

or because we focus only on permanently disabled workers, rather than all disabled workers.

3.3 Workers Compensation Reserves

In California, the state regulator requires that case reserves for medical losses be calculated as the product of an estimate of future life expectancy of the claimant (based on a standard population mortality table) and the average of past costs. Our hypothesis for the published study was that the use of a standard population mortality table (as required by the California regulator) over-estimates the life expectancy of disabled workers, and, thus, the case reserves for future medical payments.

3.4 Author contributions to this paper

Ian Duncan: Hypothesis, study design, data acquisition, summarization of results and paper authorship.

Janet Duncan: Workers compensation technical input.

Roberto Molinari: Review of statistical methods; MICE routine for estimation of missing data.

Nhan Huynh: programming and modelling in R.

Using Survival Analysis to Predict Workers' Compensation Termination

by Ian Duncan, Nhan Huynh, Janet Duncan, and Roberto Molinari

ABSTRACT

The standard method for calculating reserves for permanently injured worker benefits (indemnity and medical) is a combination of adjuster-estimated case reserves and reserves for incurred but not reported claims (IBNR) using a triangle method. There has been some interest in other reserving methodologies based on a calculation of future payments for the expected lifetime of the injured worker using a table of mortality rates. This method (State of California 2011) is required by the State of California for estimating future medical reserves on permanently disabled workers under self-insured plans, using the most recent U.S. Life Tables as the basis. We examined the experience of an excess insurance pool using different methods to determine the appropriateness of the standard table as an estimator of claim termination. The estimated pool termination rates were significantly higher than the standard table for most ages. We also calculated termination hazard rates using both Kaplan-Meier and Cox proportional hazards models and found that the modeled termination hazard was significantly higher than the standard table mortality rates. Finally, because life expectancy is only one component of the State of California reserve formula we cannot conclude that the formula results in over-reserving for future medical claims. If this approach is to continue to be used, a more appropriate method for calculating termination rates should be considered.

KEYWORDS

Workers compensation, reserving, permanently disabled, Kaplan-Meier, Cox proportional hazards

1. Background

Workers' compensation insurance covers all work-related injuries and illnesses with medical care, wage replacement, and death benefits. In California private and public employers are required to have workers' compensation insurance for their employees. Most public entities self-insure their exposures below a Self-Insured Retention (SIR) and insure their exposure above the SIR through an excess workers' compensation insurance policy. The SIR is the amount specified in the insurance policy that must be paid by the insured *before* the excess insurance policy will respond to a loss. Public employers may purchase excess insurance through entities such as the California State Association of Counties-Excess Insurance Authority (CSAC-EIA).

There has been some interest in alternative reserving methodologies for the calculation of future payments for the expected lifetime of the injured worker using a table of mortality rates. The State of California requires self-insured plans to estimate future medical reserves on permanently disabled workers as a product of the average of the last three years' medical costs and life expectancy of the injured worker, based on the U.S. Population table.

To legally self-insure, employers must comply with the reserving policy of the California Office of Self-Insured Plans (OSIP). Reserves are established to cover the future medical costs that are expected for each claimant, including costs associated with expected surgeries, prescription drugs, rehabilitation, physical therapy, etc. The statutorily established reserving methodology for Permanent Disability (PD) claims (State of California 2011) requires that Future Medical (FM) reserves for claimant i at time t be calculated as:

$$\begin{aligned} &Future\ Medical\ (FM)\ Reserves_{i,t} \\ &= \left[\frac{1}{3}\sum_{k=t-3}^{k=t-1}\left(Medical\ Payments_{i,t}\right)\right] \\ &\quad * \left(Life\ Expectancy_i\right) \end{aligned}$$

In this model life expectancy depends only on the age of claimant i and is independent of time t. Historical medical payments may be adjusted to remove outliers and to include costs for known future procedures, where these are expected to be greater than the historical average. Permanent Disability (PD) is defined as any lasting disability that results in a reduced earning capacity after maximum medical improvement is reached.[1] Whether a disability is considered partial or total depends on the Permanent Disability Rating, a percentage that estimates how much a job injury permanently limits the kinds of work the claimant can do. A rating of 100% implies permanent total disability; a rating less than 100% implies permanent partial disability.

The OSIP reserving methodology requires that life expectancy be calculated using the most recent U.S. Life Tables (2011 for our analysis) separately for males and females, which is provided by the CDC/NCHS National Vital Statistics System (Arias 2015). The U.S. Life Tables provide mortality rates at each age for the U.S. population, and allow the derivation of an estimate of future life expectancy in the usual actuarial way, namely: $\dot{e}_x = \int_0^\infty {}_tp_x dt$ where $\dot{e}_x$ is the complete expectation of life for an individual of age x and ${}_tp_x$ is the probability that the individual will survive for t years. (See, for example, Dickson, Hardy and Waters 2013.) Life expectancy is used in this model as a measure of duration to claim termination. A workers' compensation claim may terminate

[1] From State of California Dept. of Workers Compensation "Glossary of Workers Compensation Terms for Injured Workers." http://www.dir.ca.gov/dwc/WCGlossary.htm#p accessed July 2017.

due to death, recovery or settlement, although the latter two statuses are not common in the case of permanently disabled claimants. Because the U.S. Life Tables measure life expectancy for the population as a whole, including both healthy and disabled lives, they may not be representative of claims termination rates for PD claimants.

2. Prior use of survival models to estimate survival of permanently disabled populations

There are two major strands of research in this area: the workers' compensation actuarial literature and the health services literature. There are a number of health services studies estimating the future lifetimes of injured workers, for example, Ho, Hwang, and Wang (2006), Sears, Blanar, and Bowman (2014), Sears et al. (2013), Liss et al. (1999), Lin et al. 2012, and Wedegaertner et al. (2013). These studies cover permanently disabled workers in different countries, industries and injury types. Cox proportional hazard and Kaplan Meier models are used in some (but not all) of these studies to compare the mortality hazard with that of a comparison population. Uniformly, the studies cited found that expected lifetimes of permanently disabled workers are shorter than those of standard populations.

Workers compensation actuaries frequently estimate future liabilities by some form of chain ladder projection. The lack of long duration data makes estimation of costs in "the tail" difficult. Several studies have tackled the issue of estimation of tail liability, including Sherman and Diss (2006), Jones et al. (2013), CAS (2013), Schmid (2012), and Shane and Morelli (2013). This has led Jones et al. (2013) to find that "adverse reserve development in older accident years [is] a persistent problem . . . traditional actuarial methods typically used to project "bulk" incurred but not reported reserves often fall short." The authors go on to note that a mortality-based method of reserve setting can help address the causes of reserve misestimation. Despite some interest in the use of a mortality-based method for estimating future reserves, there is relatively little literature on this topic. Gillam (1993) tested whether injured worker mortality differed from population mortality. The Gillam study found that injured worker mortality was higher than population mortality under age 60, but equal between 60 and 74. The author calculates that the average pension of injured workers will be 1.6% lower than that calculated using the standard table, at a 6% discount rate. Gillam concludes that "higher mortality in these cases doesn't make current reserves significantly redundant." However, the study focused on the indemnity cost (effectively a disabled life pension) rather than the medical cost. Jones et al. (2013) note that medical trend is one reason for persistent reserve understatement in recent years. Unfortunately, Jones et al. do not compare their reserve estimates based on discounted contingent cash flows with traditional triangle based estimates, although they list a number of advantages of a mortality-based method.

If mortality of disabled lives is higher than that of the US population, then by using a population life table rather than a disabled life table the current methodology potentially overstates claims reserves. We tested the null hypothesis that termination rates in the claimant population are equal to the termination rates according to the current U.S. Life Table and found that experience termination rates of the sample population significantly exceed those of the population table.

3. Hypothesis

If mortality of disabled lives is higher than that of the standard population, by using a population life table rather than a disabled life table the current methodology

potentially overstates claimant longevity as well as the FM Reserves on PD claims. We tested the null hypothesis stating that termination rates in the claimant population are equal to the termination rates according to the current U.S. Life Table. Additionally, we developed a specific disabled termination table based on PD claimant data. While another table would be better than the U.S. Life Table if the null hypothesis is rejected, we demonstrate that the empirical termination table is better suited for the FM PD reserving calculation. Because our data includes a number of different variables, we have developed termination rates that depend on covariates, enabling the workers' compensation claims adjuster to estimate duration to termination more accurately for a specific claimant.

4. Dataset description

Our dataset was provided by CSAC-EIA (the excess insurance carrier) which accumulates its data from third-party administrators of workers' compensation claims as well as its own data. The data reflected detailed loss calculations for program years 1967/68 through 2015/16, evaluated annually from June 30, 1999 to June 30, 2016; there was little data prior to 1995. Although the data was provided by an excess insurer, all claims were recorded by the excess insurer are on a first dollar basis, whether or not the claim was a primary claim or an excess claim. While smaller entities may be more likely to seek excess insurance, we have no reason to suspect that this selection results in bias in terms of claimant terminations. The data included both indemnity and medical claim histories for all claim types (medical only, temporary partial, temporary total, permanent partial, and permanent total).

Our initial data set consisted of 1,124,473 claim records for 121,110 unique claimants. Each data record corresponded to a different evaluation year of the claim, so that there were multiple records for each claimant depending on the date of the initial occurrence, how many years the annual claim evaluations were performed by an adjuster and when the claim eventually "closed." The extract date was June 30, 2016. Claims remaining open at the extract date were considered "censored."

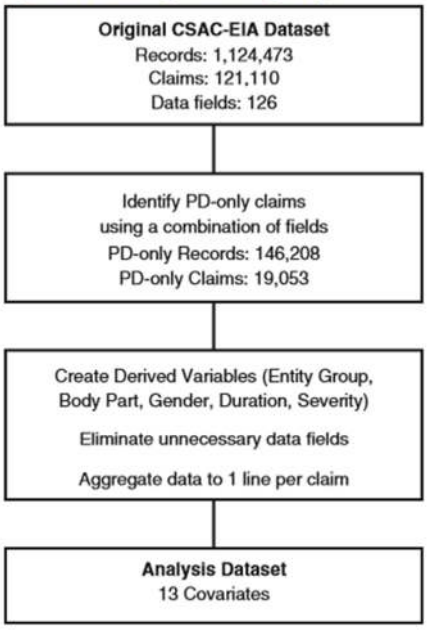
The original dataset included 126 variables. Some of these variables were duplicate columns, some had data quality issues, and many related to indemnity reserving. Table A.1 in the Appendix provides a summary of 18 variables from the original dataset that we considered for our analysis.

5. Data processing

In order to perform our survival analysis we processed the dataset to include only those variables that were necessary for our analysis, as well as creating several derived variables. The data cleaning and mapping steps are illustrated in Figure 1.

In order to use the data for our PD survival analysis, it was first necessary to identify all PD claims (both permanent partial and permanent total) and their accompanying claim histories. Some claims were identified as temporary disability (TD) while they were undergoing initial evaluation and rating,

Figure 1. Data processing steps



and later changed to permanent disability after further examination. A claim classified initially as TD and later re-classified as PD was re-classified as PD from inception. There was no single (reliable) variable indicating that a claim was a permanent disability. Therefore, we combined several variables from the original dataset (Claim Type, PD Incurred Flag, and Future Medical Award) to identify PD claims. This reduced the number of records from over 1.1 million in the original dataset to 146,208 records and 19,053 unique claims in our analysis dataset.

The quality of the data in the analysis dataset was generally good, aside from three variables: Entity Group, Body Part and Gender.

- Entity Group: Because of the large number of different occupations we started with a higher level aggregation of occupations, labeled Entity Group, in order to reduce the dimensionality of the Occupation variable. However, the Entity Group data field provided with the original data was found to have many errors in terms of its mapping from the variable Occupation; over 50% of the occupations were coded as the 'General Government' occupation class. (For example the occupation 'Police Officer' was frequently coded as the 'General Government' entity group, when it should correctly have been coded as 'Police, Corrections, and Security' entity group.) We created our own mapping using keywords found in various occupation descriptions to re-code the occupations into 15 Entity Groups.
- Body Part: The original data file contained a numeric body part code to describe the body part(s) involved in the injury, but the field was poorly coded. The original data files had a Body Part description variable, a Nature of Injury variable, and a Cause of Loss variable which allowed us to re-map the body part descriptions to the appropriate body part code.
- Gender: The Gender variable had a large percentage of missing values (19%). We tested the effect of missing values using a data imputation routine described in the next section.

In addition, we created a new variable to indicate the severity of the injury or illness in terms of the likely cost of medical treatment. The new variable, labeled "Severity," is the average annual claim amount paid during the duration of the claim. (Note that this definition of Severity is specific to our analysis. Although similar, it is not the same as the traditional general insurance definition of severity.) We also created a new variable "Duration" which is the length of time from Date of Loss (DOL) to Date Closed.

Next, we removed all variables that would not be used in our analysis in order to create our analysis dataset. This was done for ease of use as well as to improve the organization of our data. The variables in the analysis dataset are shown in Table 1.

Finally, multiple years of claims were merged into a single line per claim.

5.1. Data imputation for gender

The 'Gender' variable contained the values 'Male,' 'Female' and 'Unknown/Other.' We treated the 'Unknown/Other' values as missing. We considered two options for handling missing data: delete the rows with missing gender values, or use imputation methods to predict the gender of the individual. We found that approximately 19% of the unique claims have the 'Unknown/Other' value for gender. Deleting the claims with missing gender values would significantly reduce our sample size. We therefore imputed the missing gender values using a logistic regression-based routine in R called MICE (Multivariate Imputation by Chained Equations) (For description of the routine and its application see, for example, Van Buuren and Groothuis-Oudshoorn (2011, 2017) and Analytics Vidhya (2016)). MICE uses observed values to fill in missing values on a variable-by-variable basis using logistic models for each variable and assuming that the gender values are MCAR (missing completely at random). It then takes our predictors and data with known gender values to find the most accurate model for imputing those with missing gender values through a parametric and stochastic search algorithm. The algorithm imputes

Table 1. Analysis dataset summary

Variable	Description
Master Claim Number	• Unique alpha-numeric description of each claim • 19,053 values
Claim Status	• Closed (observed; 1) or open (censored; 0) at each evaluation date
Date of Loss (DOL)	• Date ranges from 1977 to 2016
Age at DOL	• Ages range from 16 to 89
Years Employed at DOL	• Years range from 1 to 62, or <1
Gender Indicator (Derived)	• Specifies whether Gender was imputed or provided in the dataset • Takes values 1 (Imputed) or 0 (Not Imputed)
Gender	• Male • Female
Entity Group (Derived)	• 17 Values, e.g., Education, General Government, Fire and Emergency Services, etc.
Cause of Loss Description	• 17 Values • Describes cause of injury, e.g., Burn, Fall, etc.
Body Part Description/Code (Derived)	• 56 values • Describes where on the body the injury occurred, e.g., Ankle, Brain, etc.
Nature of Injury Description	• 74 Values • Describes type of injury, e.g., Concussion, Fracture, Sprain, etc.
Duration (Derived)	• Length of time the claim was open, i.e., the time between DOL and Date Closed • Ranges from less than 1 year to 40 years
Severity (Derived)	• Average medical cost per year claim was open • Defined as Incurred Medical / Duration

incomplete values by generating 'plausible' synthetic values given other columns in the data; each incomplete column has its own specific set of predictors. The result of running the MICE algorithm is a derived Gender variable.

6. Methodology

6.1. Survival analysis

In many areas (such as biomedical, engineering, and social science), we are often interested in knowing duration until an event occurs. Statistical analysis dealing with lifetime data is known as survival analysis. What makes these lifetime data sets unique and challenging to analyze is the presence of censored information. Time until failure is not observed for all subjects during the study period, due to the fact that some subjects may be dropped out or lost to follow up. Our dataset contains right censored data, in which the event in question occurs at an unknown time after censoring. We also assume that censoring time is independent of survival time. Some important notation:

- Survival function: $S(t) = P(T > t)$, which gives the probability of surviving beyond time t.
- Failure function: $F(t) = 1 - P(T > t)$, which is the probability of failing before time t.
- Hazard function: $h(t) = f(t)/S(t)$, which is the instantaneous rate of death at time t, given that the claimant is alive at time t.
- Cumulative hazard function: $H(t) = \int_0^t h(s)ds$, which gives the cumulative rate of death up to time t, given that the claimant is alive at time t.

6.2. Kaplan-Meier estimator

Kaplan-Meier is a well-known method to estimate the survival function from given lifetime data. The

overall survival time is divided into small intervals (t_i) by ordering the distinct failure times. Within each interval, the survival probability is calculated as the number of lives surviving over the number of observed lives at risk. A simple estimate of $\Pr(T > t_i | T \geq t_i)$ is:

$$\frac{\textit{number of subjects surviving beyond } t_i}{\textit{number at risk at } t_i} = \frac{Y_i - d_i}{Y_i}$$

An estimate of $S(t)$ is $\hat{S}(t) = \prod_{j:t_j \leq t} \left(1 - \frac{d_j}{Y_j}\right)$ where Y_j is the number of subjects alive at time t_j and d_j is the number terminating at time t_j.

Subjects who have died, dropped out, or who have unobserved survival times are not at risk. Subjects that are considered as censored are counted in the denominator. Probability of surviving up to any point is estimated from the cumulative probability of surviving each of the preceding time intervals. A limitation of this method is that towards the end of the experiment, there are fewer observations, which makes the estimation less accurate than at the beginning of the study.

6.3. Cox proportional hazards model

Cox regression (proportional hazards or PH model) is an extension of regression techniques in survival analysis that allows us to examine the effect of multiple covariates on the hazard function. It is one of the most common models applied to survival data because of its flexible choice of covariates and ease of interpretation, as well as being fairly easy to fit using standard software. Let T be the continuous lifetime variable and X be a $p \times 1$ vector of fixed covariates. The hazard function for T given X takes the form:

$$h(t|X) = h_0(t) r(X; \boldsymbol{\beta})$$

In the above equation, $h_o(t)$ is a baseline hazard function. The Cox regression function does not have any specific distribution assumption. Instead, $r(X; \boldsymbol{\beta})$ is a function of known form which, if taking the natural logarithm $\ln(r)$, is assumed to be linear with coefficients $\boldsymbol{\beta}$ defined as $r(X; \boldsymbol{\beta}) = e^{\beta' X}$. This exponential form is convenient and flexible for many purposes allowing, among others, for the hazard function to have positive values (which is always the case by definition). Notice that no intercept term is included in $\beta' X$. Instead, it is subsumed in $ho(t)$. The covariates are fixed at inception of the study and do not vary with time. Hazards are always positive. The model has two separate components: the baseline hazard function and the coefficients for covariates. Values of $\boldsymbol{\beta}$ can be estimated using the partial likelihood method (Kleinbaum and Klein 2012). However, the proportional hazards and functional form (linear combination of covariates) are strong assumptions which require careful examination (diagnostics). Extensions of Cox models, such as a time-dependent model or stratified Cox regression, can be applied in cases where the PH assumption is violated. The time-dependent model is beyond the scope of this paper. However, we consider a stratified Cox regression as one of our final models.

Assume covariates $X_1, X_2, \ldots, X_p$ satisfy the PH assumption while a covariate Z does not. The stratified Cox model is given by:

$$h(t|X) = h_{og}(t) e^{\beta' X}$$

where $g = 1, \ldots, n$ are levels within covariate Z. Notice that the set of coefficients for each level is the same. The only difference is the shape of the baseline function for each level. The stratified Cox model allows the underlying baseline function to be varied across the levels by incorporating the covariate that violates the PH assumption into the baseline.

6.4. Model building and validation method

We created two different Cox models, one for imputed data and another for non-imputed data. In both cases, we randomly selected a training set consisting of 70% of observations with the remaining observations forming the validation set. The metric for model validation is the concordance index (c-index/c-statistic), which is a generalized version

of area under the Receiver Operating Characteristic curve (ROC curve). The concordance index is equivalent to rank correlation, where rank of predicted risk using the model for actual low risk observations (risk of experiencing the event) would be small while rank of predicted risk for high risk observations would be large. Therefore C > 0.5 implies good predictive power, C = 0.5 implies predictive power is equivalent to 0, and C < 0.5 implies model does a poor job at prediction.

6.5. Actuarial methods

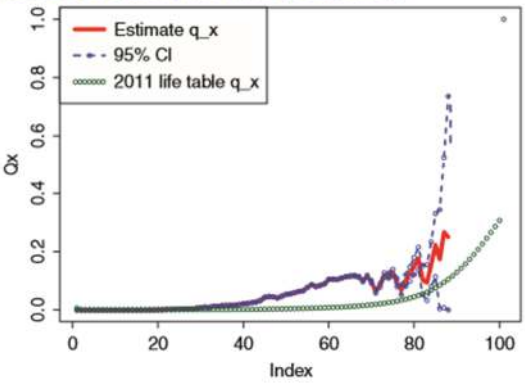
The 2011 Life Tables provide values of the one-year probability of death q_x from age x to $x + 1$. Workers compensation claims terminate for reasons other than death. The OSIP methodology requires the use of the mortality probabilities to estimate the future claim duration, so the q_x values represent all terminations, not just death. We estimate empirical values of q_x from the data as $\hat{q}_x = \frac{d_x}{l_x - 0.5(w_x)}$ where:

d_x = number of terminations between ages x and $x + 1$.
l_x = number of claimants aged x
C_n = number of censored claimants
w_x = number of claimants terminating during the year for any reason, including claims that are censored (denoted C_n), or still open at the end of the observation period.

In our model $w_x = d_x + c_x$

In order to compare directly the modeling dataset to the 2011 U.S. Life Table we iterated through every claim and created vectors tracking the number of individuals in the system, the number that were censored (open) and the number observed (closed) at every age in the range 0 to 100, in order to match the 2011 Table's range. To determine whether an individual was censored/observed and at which age, we used the indicator variable, the Age at DOL and the duration of each claim. By adding duration to the Age at DOL, it could be determined at what age every claim terminates, and by the indicator variable whether termination was censored or observed. The

Figure 2. Estimates of q_x and comparison with 2011 unisex life table (combined)



first array, denoted l_x, tracks the number of claims in the system at every age, with an initial count of 19,053 (the total number of claimants). The other two arrays, c_x and d_x respectively, count the number open (censored) and closed (observed) claimants at each age. With these arrays, it is possible to calculate estimates of $\hat{q}_x$, given that $w_x = d_x + c_x$, as defined above. $\hat{q}_x$ is now an array of probabilities of claim closure for every age from 0 to 100. Finally we reduced the age range to 17 to 88 due to the lack of data outside of this range. The U.S. Life Table exists in both sex-specific and unisex forms. Below, we tested the consistency of our estimated $\hat{q}_x$ with both the unisex table (Figure 2) and sex-distinct tables (Figure 3–4). It is clear that our estimated $\hat{q}_x$

Figure 3. Estimates of q_x and comparison with 2011 life table (female)

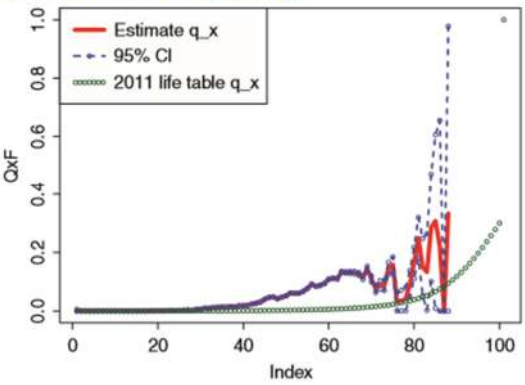
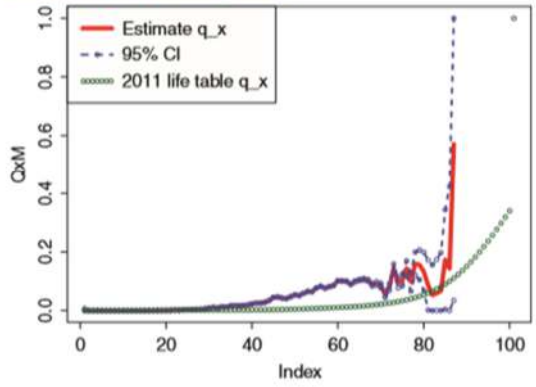


Figure 4. Estimates of q_x and comparison with 2011 life table (male)



values diverged from those of the 2011 Life Table, thus implying that termination rates are higher in our data. In order to determine whether this divergence is significant, the 95% confidence interval for each age range was calculated by using Greenwood's Approximation which estimates the variance of Kaplan Meier models, survival models equivalent to our $\hat{q}_x$ values. In Greenwood's Approximation, $\sigma_x^2 = \frac{\hat{q}_x\left(1-(\hat{q}_x/2)^2\right)}{d_x^2}$.

This approximation allowed us to calculate the 95% confidence interval for $\hat{q}_x$ as $\hat{q}_x \pm 1.96\ \sigma_x$. In Figure 2, the lower bound of the confidence interval falls above the 2011 tabular rate at all ages except the highest (above age 85) at which there are very few observations.

In Figures 3 and 4 we examined the $\hat{q}_x$ values for males and females separately. The results were similar to those of the unisex table, with the exception that some estimated $\hat{q}_x$ values are less than the tabular values at very high ages at which there are very few observations. We concluded that in the age range 35–75 termination rates for both males and females are well in excess of the 2011 tabular rates. We also performed a one-sided Kolmogorov-Smirnov goodness-of-fit test to test whether the distribution between the 2011 life table and the estimated $\hat{q}_x$ is identical. Specifically, we compared the empirical distribution function between two samples given that we do not have an assumption for the distribution of the samples. We assumed two samples are from the common distribution versus the alternative hypothesis that the CDF (cumulative density function) of the estimated $\hat{q}_x$ is greater than the CDF of the 2011 life table. Because the p-value was less than the level of significance, we rejected the null hypothesis, confirming our conclusion that termination rates for both males and females are greater than the 2011 life table rates.

6.6. Fitted actuarial models

Given that the 2011 U.S. Life Table does not represent termination rates of the workers' compensation permanently disabled population, the question arises whether we can derive a better model for q_x?

Note that all of the following regression models were tested assuming normal distribution errors and with two different types of weights included to represent the number of observations in each age interval. The two methods to determine the weights were:

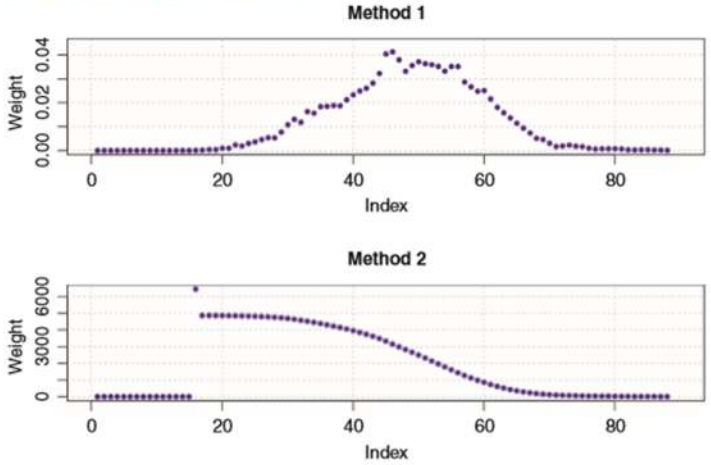
Method 1: The weight for each age interval is the proportion of the number of claims within the corresponding interval to the total number of claims in the data.

Method 2: The weight for each age interval is the inverse of the length of each 95% confidence interval of the $\hat{q}_x$ estimates.

We incorporated the weights into the regression models due to the observed pattern of heteroscedasticity (the constant variance in the errors is violated). Specifically, Method 2 allowed us to apply more weight to the observations with smaller standard errors as these observations carry more information in the data. In Figure 5 the two methods have different scales. The younger and older age intervals have relatively small weights in Method 1. For Method 2, early ages have higher weights, reflecting the lower variance at these ages, while higher ages are underweighted, reflecting their higher variance.

We first fitted a quadratic function because this form appears to fit the observed $\hat{q}_x$ values. The best

Figure 5. Weight distribution



fit quadratic model which included the set of weights in Method 2 was $\hat{q}_x = 0.0666 + 0.6289x + 0.2601x^2$, which was selected via the AIC (Akaike Information Criterion) model selection method. AIC is found by computing $2k - 2\ln\hat{L}$, where $\hat{L}$ is the Maximum Likelihood function and k is the number of free parameters to be estimated.

Next we considered fitting the Gompertz model, which is one of the most commonly used parametric survival distributions to model human mortality. The Gompertz model assumes that the hazard rates are exponentially distributed where the hazard rates are analogous to the life table values q_x and are some parametric function of age (MacDonald, Richards, and Currie 2018). In the Gompertz model the hazard rate function, μ_x, generally has the following form: $\mu_x = e^{\alpha+\beta x}$, where x denotes age of individual, and μ_x and q_x are related as follows: $q_x = \int_0^1 {}_s p_x \mu_{x+s} ds$.

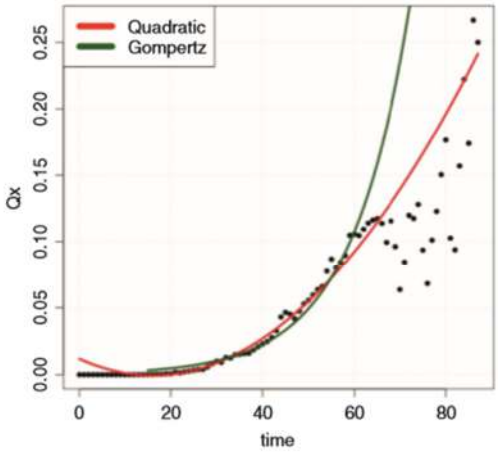
In this formula, the two parameters represent an age-dependent (β) and age-independent component (α). The log transformation of this hazard rate function is a linear function $\alpha + \beta x$. We estimated the parameters of the Gompertz model by performing linear regression on the log transformation of the $\hat{q}_x's$. The diagnostic plots of the log transformation for normality confirmed that we could proceed with the linear regression. To select the best Gompertz model, we first computed the lognormal log-likelihood for the log-transformed response, then calculated the AIC value. The resulting Gompertz model has the following form: $\hat{q}_x = e^{-6.9188+0.0782x}$, using the set of weights in Method 1.

The chosen Gompertz and quadratic models are shown in Figure 6, compared with the observed values

Table 2. AIC values of fitted models using different weights

AIC value	Method 1	Method 2
Quadratic Model	–403.0	–465.1
Gompertz Model	–296.9	–209.1

Figure 6. Gompertz and quadratic models vs. observed values



for q_x. The age range on the x-axis is determined empirically based on available data (ages 16 to 88). The y-axis contains the $\hat{q}_x$ estimates, or the probability of claim closure for a given age, x. Both the Gompertz and quadratic models fit the data reasonably well up to age 60, although, as shown in Table 2, the quadratic model fits better (lower AIC value). Thereafter, the Gompertz model significantly overestimates termination, as does the quadratic model above age 70.

7. The Cox model applied to imputed data

7.1. New grouping of entity, cause of loss, and body parts

Several covariates such as Entity Groups, Cause of Loss, and Body Parts are categorical with many levels. For example, the Body Parts variable contains 56 values that indicate the location of the injury. While the translation of the Body Part description into numeric values is convenient for coding purposes, Body Part is a nominal variable where levels do not have any natural order. A drawback of fitting Cox regression is model complexity: each covariate level costs a degree of freedom to estimate, whereas a majority of these levels are not significant. We therefore required a method to simplify the multi-level variables to a smaller number of groups. We applied the Kaplan Meier (KM) approach to re-group levels based on median survival time. We first applied KM to estimate the survival function to obtain median survival time. Second, we ranked median survival times in increasing order and re-grouped the original levels into four different groups. We then repeated this procedure for Entity, Cause of Loss, and Body Parts. Table 3 shows the new grouping of the Entity variable. (See Appendix A2 for groupings of the Cause of Loss and Body Parts variables).

The new grouping is based on the application of the KM method to the training set; we then applied the same groupings to the test set.

7.2. Stratified Cox model

The final model contains two interaction terms: interaction between Sex and Age at DOL, and between Body Parts and Cause of Loss. The Entity Group covariate did not satisfy the PH assumption, and we therefore created stratified Cox models for the different levels of Entity.

Table 3. Grouping of entity variable

Original levels	Median survival time using KM	Updated levels using KM
(1) Agriculture and farming	3.564	Group 1: (2), (13), (14), (15)
(2) Animal and vector control	3.351	
(3) Community services	4.107	
(4) Construction and building services	4.559	
(5) Education	4.507	Group 2: (1), (10), (12)
(6) Fire and emergency services	5.279	
(7) General government	4.348	
(8) Health and medical services	4.205	
(9) Police, corrections, and security	4.425	Group 3: (3), (7), (8), (11)
(10) Recreation and resource protection	3.800	
(11) Sanitation and waste collection	4.332	
(12) Transportation and transit	3.797	
(13) Unknown/Other group	2.830	Group 4: (4), (5), (6), (9)
(14) Utilities and power	3.479	
(15) Water and water conservation	3.512	

Table 4. Stratified Cox model on imputed data

Covariates	Coeff.	Hazard ratio	Std. error	P-value	95% CI of HR
Age at DOL	–0.007	0.993	0.01	0.000	0.990, 0.996
Body 2 (vs. 1)	–0.125	0.882	0.190	0.510	0.608, 1.281
Body 3 (vs. 1)	–0.572	0.565	0.191	0.003	0.389, 0.820
Body 4 (vs. 1)	–0.605	0.546	0.245	0.014	0.338, 0.883
Cause loss 2 (vs. 1)	0.040	1.041	0.147	0.786	0.781, 1.388
Cause loss 3 (vs. 1)	–0.420	0.657	0.362	0.247	0.323, 1.337
Cause loss 4 (vs. 1)	–0.231	0.794	0.149	0.121	0.593, 1.063
Severity	0.000	1.000	0.000	0.000	1.000, 1.000
Sex	–0.542	0.581	0.098	0.000	0.480, 0.704
Years employed	–0.008	0.992	0.001	0.000	0.989, 0.995
Age at DOL: Sex	0.010	1.010	0.002	0.000	1.006, 1.015
Body 2: Cause loss 2	–0.308	0.735	0.199	0.123	0.498, 1.087
Body 3: Cause loss 2	–0.087	0.917	0.197	0.658	0.623, 1.348
Body 4: Cause loss 2	–0.325	0.723	0.251	0.195	0.442, 1.181
Body 2: Cause loss 3	0.352	1.422	0.423	0.405	0.621, 3.256
Body 3: Cause loss 3	0.528	1.695	0.402	0.189	0.771, 3.730
Body 4: Cause loss 3	0.234	1.264	0.435	0.590	0.539, 2.962
Body 2: Cause loss 4	–0.079	0.924	0.197	0.689	0.628, 1.360
Body 3: Cause loss 4	0.111	1.117	0.197	0.573	0.760, 1.642
Body 4: Cause loss 4	–0.061	0.940	0.251	0.807	0.575, 1.538

The functional form of the stratified Cox model is

$$\hat{h}(t|X) = h_{og}(t) * \exp\left[\begin{array}{l} \hat{\beta}_1 age + \sum_{j=2}^{4} \hat{\tau}_j \mathbf{I}_{\{body=j\}} \\ + \sum_{j=2}^{4} \hat{\gamma}_j \mathbf{I}_{\{CL\ group=j\}} \\ + \hat{\beta}_3 severity + \hat{\beta}_4 sex \\ + \hat{\beta}_5 years + \hat{\beta}_6 sex{:}\ years \\ + \sum_{j=2}^{4} \hat{\delta}_j \mathbf{I}_{\{body=j\}} \mathbf{I}_{\{CL\ group=j\}} \end{array}\right]$$

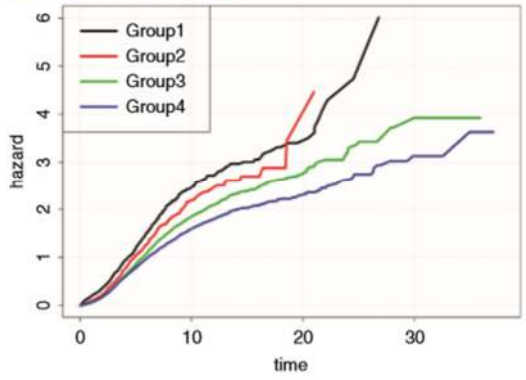
$$\text{where } \mathbf{I}_{\{CL\ group=j\}} = \begin{cases} 1, & cause\ loss\ group = j (j = 2, 3, 4) \\ 0, & otherwise \end{cases}$$

$$\mathbf{I}_{\{body=j\}} = \begin{cases} 1, & body = j (j = 2, 3, 4) \\ 0, & otherwise \end{cases}$$

$g = 1, 2, 3,$ and 4 levels within entity group.

Figure 7 shows the shapes of the baseline hazard functions for each entity group. The shapes of the cumulative baseline hazard functions for the entity levels are not always parallel; in particular the group 2 function crosses group 1, violating the PH assumption. Three different tests, the likelihood ratio test, Wald's test, and log-rank test are conducted to test

Figure 7. Baseline cumulative hazard function for each level of entity



the global hypothesis that $\boldsymbol{\beta} = \mathbf{0}$ (overall goodness-of-fit). As p-values for all three tests are close to 0, we reject the null hypothesis, indicating that the model is an appropriate fit for the data set.

7.3. Model interpretation

Coefficients of the Cox model are related to the hazard rate. For example, the coefficient value of –0.008 for Years Employed at DOL indicates that the log hazard ratio increases by a unit of –0.008 for each additional unit increase in years of employment while other variables are kept constant. In practice, it is more meaningful to interpret the result using hazard ratio (or relative risk) instead of log hazard ratio.

The hazard ratio is obtained by taking the exponential of the coefficient. Specifically, the hazard ratio of years employed is $e^{(-0.008)} = 0.992$, indicating that for each additional unit increase in duration of employment while holding other variables constant, the hazard ratio increases by a factor of 0.992. In other words, the risk of claim termination decreases by about 1% for each yearly increase in number of years employed.

The final model contained two significant interaction terms: interaction between Sex and Age at DOL (categorical vs. continuous) and interaction between Body Parts and Cause of Loss (two categorical variables). When interaction terms are significant, the interpretation of the coefficients becomes much more complex. For example, interpretation of "Sex and Age at DOL" is not as simple as Years Employed. The significant interaction between Sex and Age at DOL implies that the effect of DOL on the survival rate varies for each sex (male and female). Specifically, for each unit increase in age at DOL for a male claim, the hazard ratio increases by a factor of 1.010.

7.4. Model diagnostics

We tested the validity of the assumptions made in the model with model diagnostics.

(a) Overall fit

Cox-Snell residuals, defined as $r_i = \hat{H}_0(T_i)e^{\hat{\beta}\mathbf{x}_i}$, can be used to assess the overall fit of our Cox Proportional Hazards model. If the model is correct, a plot of the residuals of the estimated cumulative hazard rates $\hat{H}_0(r_i)$ versus r_i should follow a straight line through the origin. In Figure 8, we see the estimated cumulative hazard is close to the diagonal line for all but large values of Cox-Snell residuals.

Overall, the model fits the data well as the proportion of the observations in the early range [0,4] of Cox-Snell residuals is approximately 99.8% of the whole training set. The departure of the estimated cumulative hazard as Cox-Snell residuals get larger indicates the presence of the potential outliers in the data.

(b) Appropriateness of the proportional hazard assumption

The departure from proportionality could lead to an incorrect model. We examined the PH assumption in two ways: by plotting the Schoenfeld residuals and performing a formal hypothesis test for correlation between Schoenfeld residuals and time.

If the PH assumption is true, we should expect that the trend of $\beta(t)$ versus time to be a horizontal line

Figure 8. Cumulative hazard vs. Cox-Snell residuals for overall fit

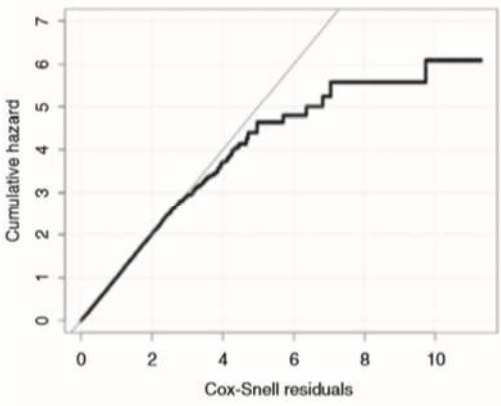
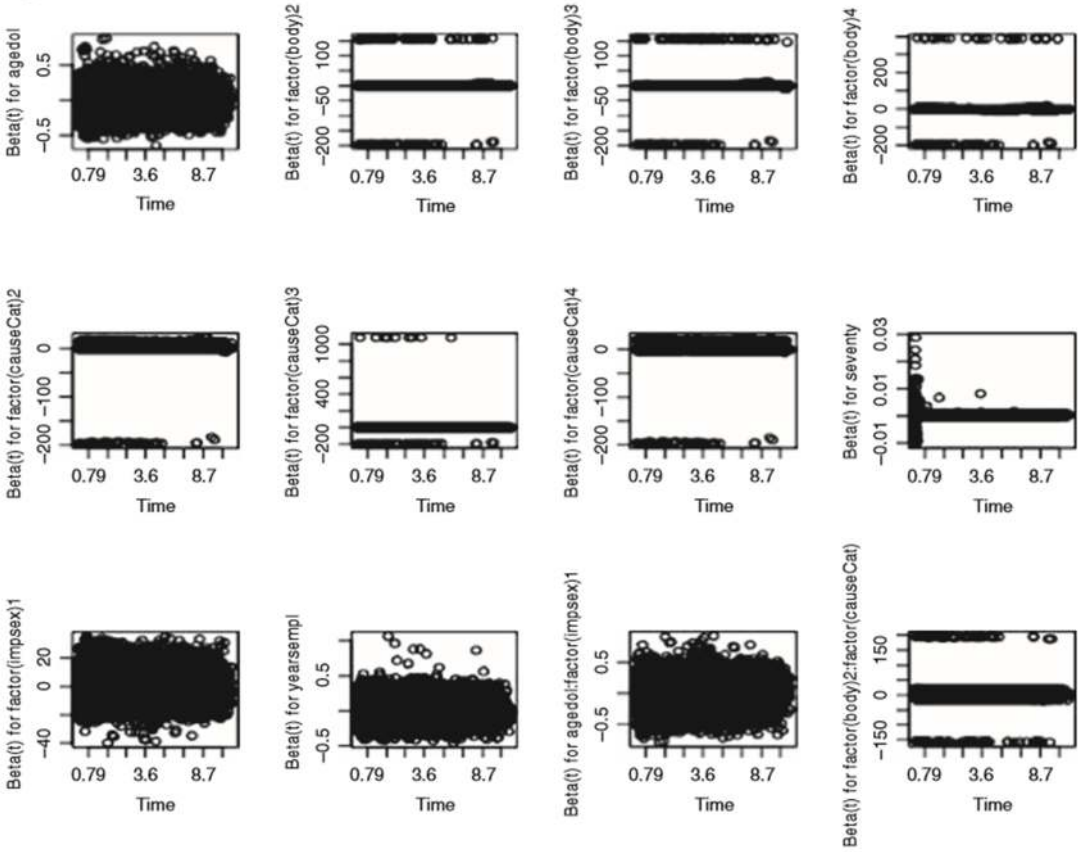


Figure 9.1. Schoenfeld residuals vs claim duration



for each covariate. As we see in Figures 9.1 and 9.2, the pattern of each plot looks horizontal around zero with little violation, implying that the PH assumption is valid.

To examine PH assumption more carefully, we performed a hypothesis test which Grambsch and Therneau (1994) proposed. Each parameter in the model is allowed to depend on time (i.e., $\beta_j(t) = \beta_i + \gamma_j g_j(t)$). We tested the value of the correlation parameter γ_j; if $\gamma_j = 0$ we would reject the hypothesis that parameters are time-dependent. We conducted this test using function *cox.zph* in R and observed that all p-values are not significant (Table 5). In summary, we did not have sufficient evidence to reject the null hypothesis that the PH assumption is valid.

(c) Linear form of covariates

We further examined whether the linear combination of covariates is the best functional form to describe the effect of the covariates on survival. To do this, we plotted the martingale residuals versus each covariate. The results in Figure 10 implied that we did not need any polynomials or transformation of the covariates.

(d) Outliers and influential points

We examined the accuracy of the model for predicting the survival of a given subject. In other words, we tried to find claims whose survival time differed significantly in comparison to their model predictions. The deviance residuals plot versus risk

Figure 9.2. Schoenfeld residuals vs. claim duration (cont'd)

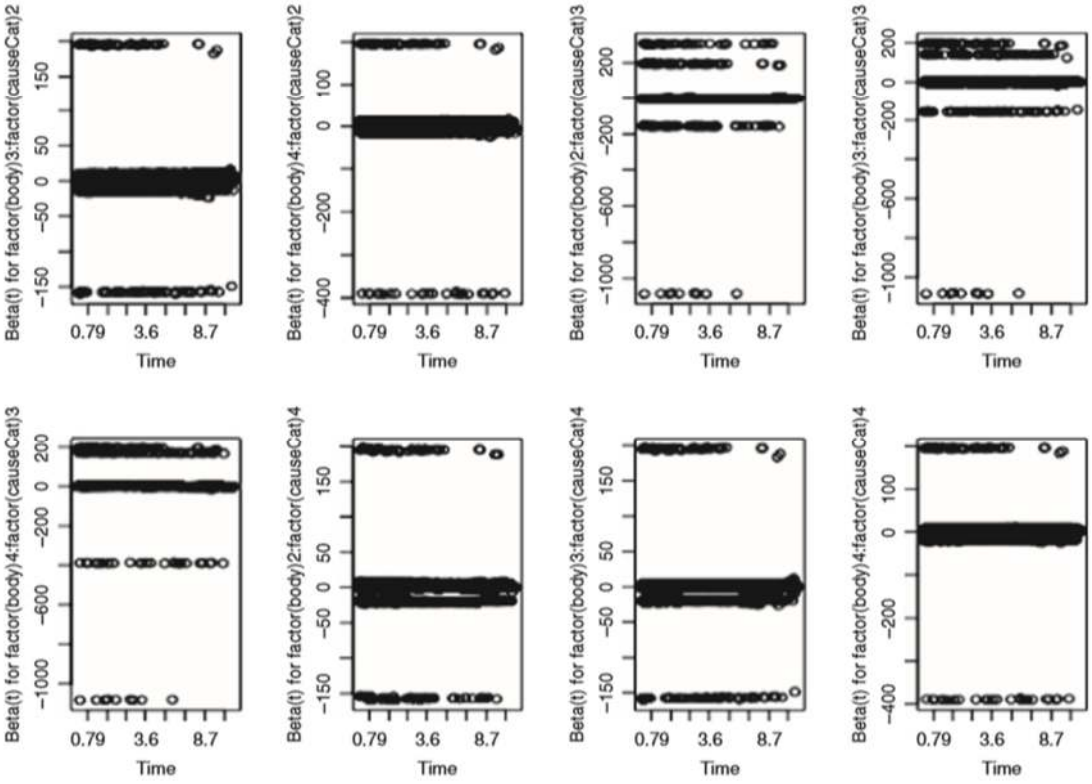
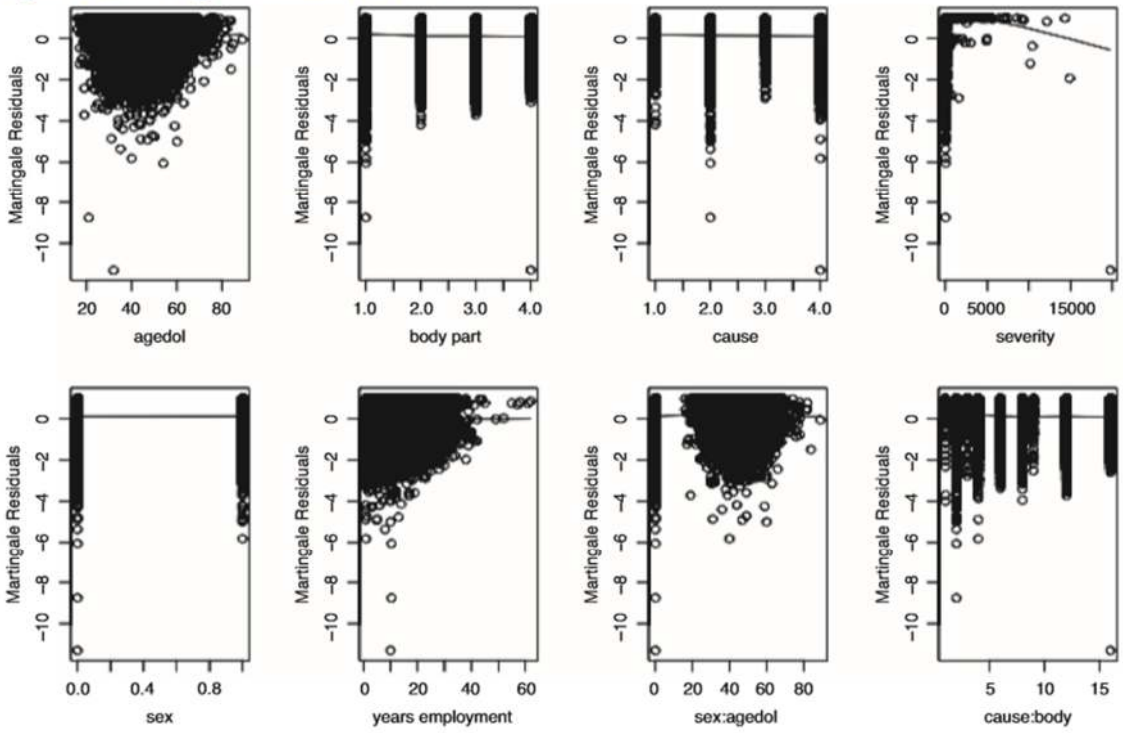


Table 5. PH Assumption hypothesis test results

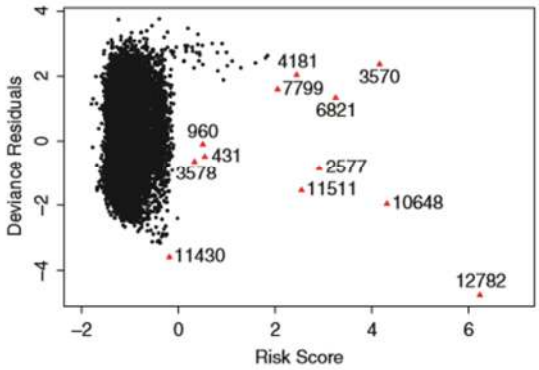
Covariates	p-value for hypothesis test	Covariates	p-value for hypothesis test
Age at DOL	0.662	Age at DOL:Sex	0.841
Body 2	0.824	Body 2: Cause of loss 2	0.751
Body 3	0.450	Body 3: Cause of loss 2	0.724
Body 4	0.185	Body 4: Cause of loss 2	0.250
Cause of loss 2	0.634	Body 2: Cause of loss 3	0.929
Cause of loss 3	0.921	Body 3: Cause of loss 3	0.527
Cause of loss 4	0.357	Body 4: Cause of loss 3	0.644
Severity	0.343	Body 2: Cause of loss 4	0.834
Sex	0.651	Body 3: Cause of loss 4	0.614
Years of employment (at DOL)	0.549	Body 4: Cause of loss 4	0.315

Figure 10. Martingale residuals vs. covariate



scores is helpful to detect which claims are potential outliers, which perhaps should be excluded from the analysis. In Figure 11, we observe that the deviance residuals are randomly scattered in the panel and some observations (marked as triangles with indices) are the detected potential outliers. "Risk Score" is defined as $\Sigma\beta x$, where β is the vector of coefficients and x is the matrix of value of covariates. We performed further sensitivity analysis by removing these outliers and refitting the model. The new fitted model is not far off from the model presented in Table 3, and predictive power for both models using c-index is similar.

Figure 11. Deviance residuals vs. risk scores

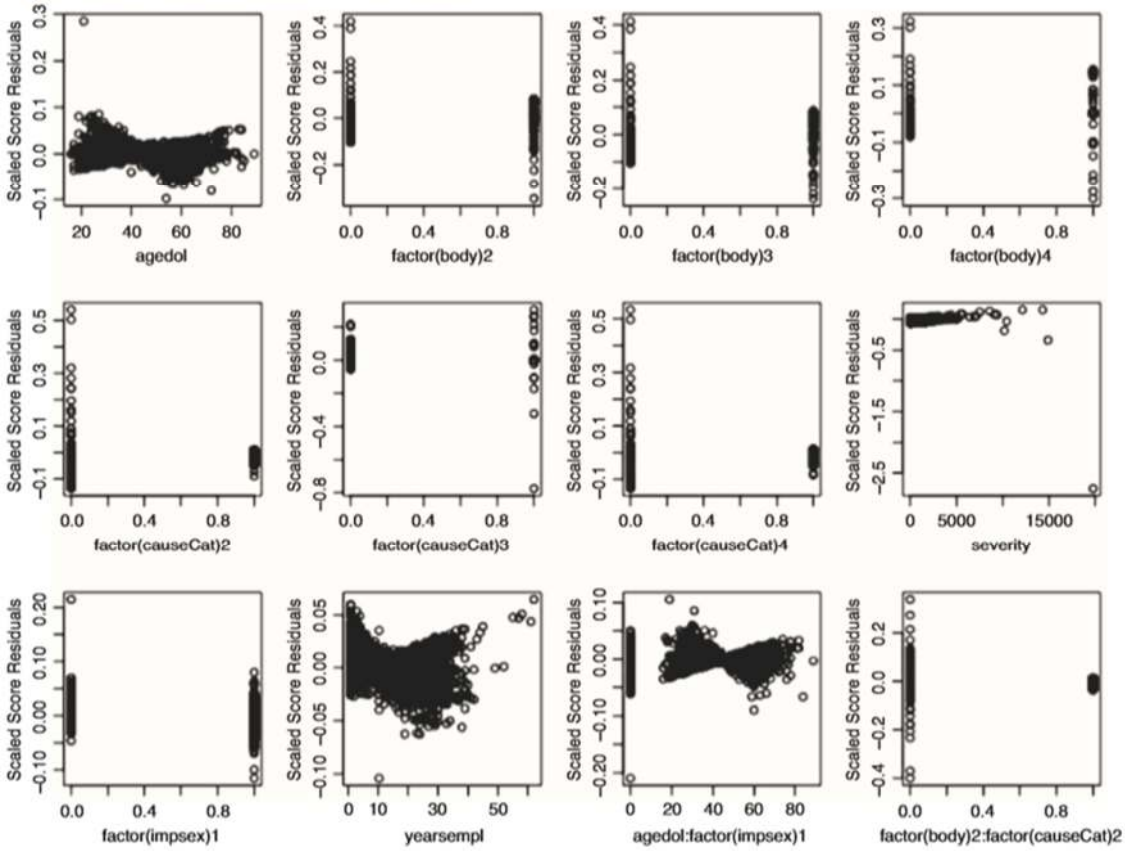


We also examined the influence of each claim on the model fit. The scaled score statistics versus covariate plot allows us to find influence points. Figure 12.1 and 12.2 show score residuals for each covariate. Using the plot between severity and the scaled score statistics, we observed several points that were further away from the majority of the observations, although this distance does not appear to be significant, suggesting that these points may be exercising influence on the fit.

7.5. Model prediction

We applied the final Cox model to the test set and calculated the concordance index. A C-index

Figure 12.1. Scaled residuals vs. covariate



of 0.58 indicates the model does a moderately good job at predicting the risk of the claim being terminated.

8. Results of Cox model on non-imputed data

We will not repeat specific details for this section as all the procedures are similar to imputed data. Table 6 presents the final form of the Cox model on the non-imputed data. It contains three interaction terms: between Sex and Age at DOL, between Entity Group and Sex, and between Body Parts and Cause of Loss. When applied to the test dataset, the C-index of 0.57 indicates that model does a good job at predicting the risk of the claim being terminated.

8.1. Discussion

Workers' compensation reserves for future medical liabilities are usually calculated in bulk using a triangle method. Although this standard method is widely used, there are examples of studies using reserving methods based on mortality projections, recognizing that explicit incorporation of injured worker mortality may reduce the potential inaccuracy in the bulk reserves. The State of California requires an explicit calculation for each permanently injured worker, assuming that termination of the claim follows the most recent U.S. Life Table. The literature shows that injured worker mortality is higher than that of the overall population, which could lead to over-reserving of future medical liabilities. We examined claims termination rates of injured workers

Figure 12.2. Scaled residuals vs. covariate (cont'd)

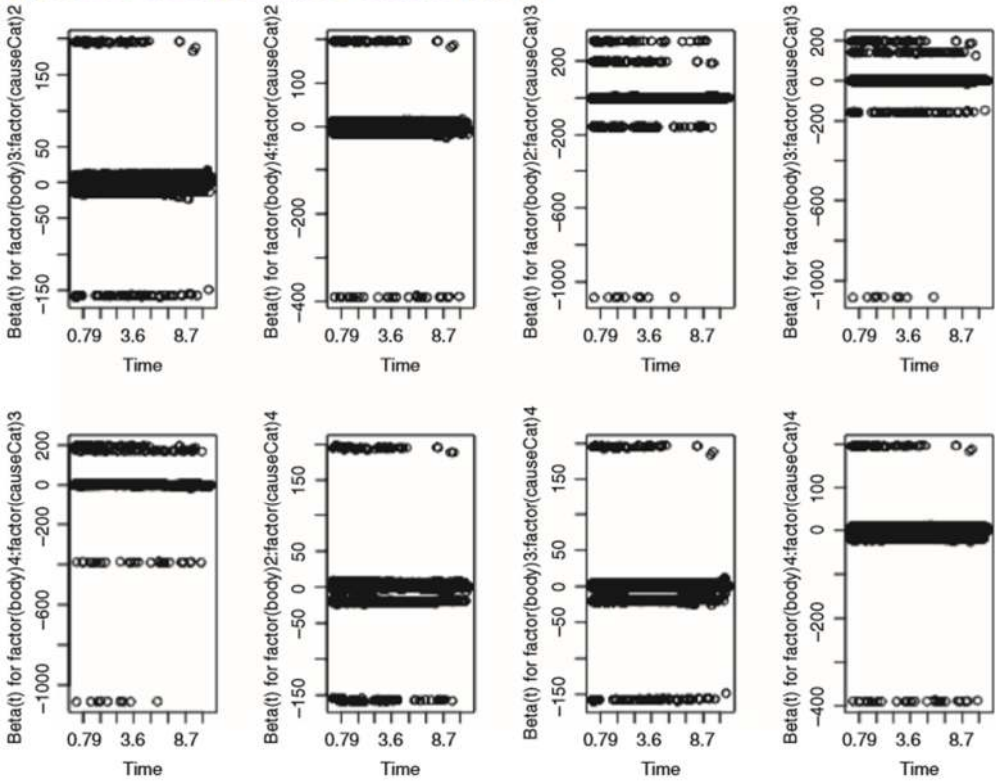


Table 6. Final Cox model on non-imputed data

Covariates	Coeff.	HR	Std. errors	P-value	95% CI of HR
Entity 2	–0.206	0.814	0.123	0.094	0.6400, 1.0358
Entity 3	–0.526	0.591	0.104	0.000	0.4817, 0.7253
Entity 4	–0.600	0.549	0.107	0.000	0.4451, 0.6772
Age at DOL	0.003	1.003	0.002	0.062	0.9998, 1.0069
Body 2	–0.581	0.560	0.140	0.000	0.4255, 0.7359
Body 3	–0.603	0.547	0.207	0.004	0.3649, 0.8204
Body 4	–0.874	0.417	0.165	0.000	0.3020, 0.5766
Cause loss 2	–0.610	0.543	0.165	0.000	0.3931, 0.7506
Cause loss 3	–0.461	0.630	0.119	0.000	0.4992, 0.7961
Cause loss 4	–0.282	0.754	0.102	0.006	0.6173, 0.9216
Severity	0.000	1.000	0.000	0.000	1.0002, 1.0002
Sex male	0.291	1.337	0.163	0.075	0.9711, 1.8421
Years employment	–0.006	0.994	0.001	0.000	0.9913, 0.9971
Severity: Sex male	–0.012	0.988	0.002	0.000	0.9833, 0.9921

Table 6. Final Cox model on non-imputed data (cont'd)

Covariates	Coeff.	HR	Std. errors	P-value	95% CI of HR
Entity 2: Sex male	0.280	1.324	0.155	0.070	0.9777, 1.7918
Entity 3: Sex male	0.416	1.515	0.130	0.001	1.1750, 1.9537
Entity 4: Sex male	0.298	1.348	0.132	0.023	1.0412, 1.7444
Body 2: Cause loss 2	0.672	1.958	0.216	0.002	1.2825, 2.9902
Body 3: Cause loss 2	0.539	1.714	0.299	0.071	0.9543, 3.0787
Body 4: Cause loss 2	0.417	1.517	0.243	0.087	0.9413, 2.4440
Body 2: Cause loss 3	0.401	1.493	0.162	0.013	1.0875, 2.0489
Body 3: Cause loss 3	0.255	1.291	0.226	0.259	0.8284, 2.0120
Body 4: Cause loss 3	0.394	1.482	0.183	0.032	1.0354, 2.1223
Body 2: Cause loss 4	0.247	1.281	0.145	0.088	0.9637, 1.7020
Body 3: Cause loss 4	0.058	1.060	0.212	0.784	0.6997, 1.6054
Body 4: Cause loss 5	0.117	1.125	0.170	0.490	0.8062, 1.5685

using the experience of the California Association of Counties-Excess Insurance Authority (CSAC-EIA). We applied a number of different methods, including direct calculation of the termination rates ($\hat{q}_x$) (both raw and fitted to polynomials) to compare with the tabular rates, and found that for most ages, termination rates are in excess of those implied by the tabular rates. Finally, we applied Cox Proportional Hazards modeling to develop termination hazard rates based on our dataset. The Cox PH model is powerful in that it allows us to incorporate covariates and to assess the influence of individual covariates on the termination hazard. Tests of the proportional hazard assumptions show that the Cox model fits the data well, and that we can have confidence in the derived model.

8.2. Conclusion

Analysis of the CSAC-EIA data shows that the use of the standard population mortality table as the basis for permanent disability claim projections may be inappropriate because the table overestimates injured worker survival. However, it is important to remember that the life expectancy of the injured worker is only one component of the reserve calculation; the other component is the average 3-year cost of medical claims. Because the claims cost component excludes a provision for medical trend, it may underestimate the future medical cost component. The result of combining an overestimate of survival with an underestimate of future medical costs may well result in reasonable reserves in total; however, if the intention is to produce accurate reserves for future medical claims, more accurate methods of estimating both life expectancy and future medical claims would be appropriate.

We applied Cox Proportional Hazards modeling to develop termination hazard rates based on our dataset. The Cox PH model is powerful because it allows us to incorporate covariates and to assess the influence of individual covariates on the termination hazard. Tests of the proportional hazard assumptions show that the Cox model fits the data well, and that we can have confidence in the derived model. The effect of covariates on the hazard rates provides more information to claims managers about the likely survival of specific claimants than the standard table.

8.3. Limitations

This study was performed on the experience of one

pool, incorporating a number of different third-party administrators. Changes in reporting requirements and administrators over time may affect the accuracy of the data. As noted in our conclusion, life expectancy is only one component of the reserving calculation, and reserves calculated according to the State of California methodology may be appropriate because different components of the calculation offset each other.

Acknowledgments

The authors acknowledge with gratitude the collaboration of CSAC-EIA and its chief actuary, John Alltop FCAS MAAA, in the preparation of this study, as well as UCSB students Shannon Nicponski, MS; Elizabeth Riedell, BS; and Jerrick Zhang, BS, who performed the initial analysis. This work was supported in part by a CAE 2016 grant from the Society of Actuaries.

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Appendix. Data Summary

Table A.1. Original variables

Variable	Description
Original Excel #	• The row number in original dataset (1,124,473 rows total)
Gender	• Female • Male • Unknown/Blank
Master Claim Number	• Unique alpha-numeric description of each claim • 121,110 values
Claim Type	• Dupe/Delete • First Aid • Future Medical • Indemnity • Info Only • Medical Only • Other • Temporary Disability
Date of Loss (DOL)	• Dates range from 1967 to 2016 • 3.5% of records relate to accident years 1994 & prior
Age at DOL	• Ages range from 1 to 97 • Missing Values (fewer than 2%)
Claim Status at 6–30–2016	• Open • Closed • ReOpened-Closed • Blank
Occupation	• 2,624 occupational descriptions • e.g. Firefighter, Teacher, Accountant, Electrician
Entity Group	• 17 Departments e.g. Education, General Government, Fire and Emergency Services, etc.
Date Closed	• Date ranges from 8/1/77 to 6/30/2016
Average Weekly Wages	• Ranges from $0.00 to $33,446.40 • Missing Values (over 50% of data)
Nature of Injury Description/Code	• 74 values, e.g. Sprain, Fracture, Hearing Loss, Concussion, etc.
Future Medical Award	• TRUE or FALSE
PD Incurred Flag	• TRUE or FALSE
Incurred Medical	• Incurred Medical = Total dollar amounts of medical payments paid plus reserves for future medical costs
Incurred PD	• Numeric values ranging from $0.30 to $1.8 million • Incurred PD = Paid PD + Reserved PD • Refers to indemnity benefits (paid to worker to compensate for lost wages) on PD claims, not medical benefits
Years Employed at DOL	• Years range from 1 to 62, or <1 • Missing values (approx 4.5%)
Cause of Loss Description/Code	• 143 values, e.g., Animal or Insect Bite, Broken Glass, Burn, Fall, etc.
Body Part Description/Code	• 69 values, e.g., Abdomen, Ankle, Brain, Buttocks, Chest, etc.

Table A.2. New grouping of cause of loss in imputed data

Original level	Median survival time using KM	New grouping
(1) CL1: Absorption, ingestion, or inhalation	4.211	Group 1: (5), (12), (14), (15)
(2) CL2: Animal or insect	4.893	
(3) CL3: Burn	4.192	
(4) CL4: Caught	3.493	
(5) CL5: Cut	3.455	Group 2: (4), (8), (10), (11)
(6) CL6: Explosion or flare back	5.178	
(7) CL7: Fall	4.274	
(8) CL8: Fellow worker, patient, or other person	3.597	
(9) CL9: Machine or tool	4.181	Group 3: (1), (3), (9)
(10) CL10: Miscellaneous	4.090	
(11) CL11: Motor vehicle	3.978	
(12) CL12: Natural disasters	1.268	
(13) CL13: Person in act of a crime	4.274	Group 4: (2), (6), (7), (13), (16), (17)
(14) CL14: Rubbed	2.745	
(15) CL15: Slipped	3.332	
(16) CL16: Strain	4.474	
(17) CL17: Strike	4.356	

Table A.3. New grouping of body parts in imputed data

Original level (description with numeric code)	Median survival time using KM	New grouping
(1) other –9	3.074	Group 1: (9), (12), (14), (16), (24), (36), (37), (52), (54), (58), (62), (64), (66), (99).
(2) multiple head injury –10	5.063	
(3) skull –11	3.816	
(4) brain –12	2.773	
(5) ear(s) –13	5.132	
(6) eye(s) –14	2.964	
(7) nose –15	5.267	
(8) teeth –16	1.996	
(9) mouth –17	3.830	
(10) other facial soft tissue -18	5.405	
(11) facial bones –19	9.266	
(12) multiple neck injury –20	4.668	
(13) vertebrae –21	4.600	
(14) disk (neck) –22	5.458	

Table A.3. New Grouping of Body Parts in Imputed Data (cont'd)

Original level (description with numeric code)	Median survival time using KM	New grouping
(15) spinal cord –23	4.429	Group 2: (11), (17), (31), (32), (33), (35), (38), (39), (44), (46), (55), (56), (61), (65), (11), (17), (31), (32), (33), (35), (38), (39), (44), (46), (55), (56), (61), (65).
(16) larynx –24	1.956	
(17) soft tissue neck –25	5.044	
(18) multiple upper extremities –30	4.375	
(19) upper arm incl. clavicle and scapula –31	3.644	
(20) elbow –32	3.438	
(21) lower arm –33	3.658	
(22) wrist –34	4.274	
(23) hand –35	4.060	
(24) finger(s) –36	2.803	
(25) thumb –37	3.096	
(26) shoulder(s) –38	3.929	
(27) wrist(s) and hand(s) –39	4.195	
(28) multiple trunk –40	4.532	
(29) upper back area –41	5.219	Group 3: (20), (21), (23), (30), (34), (40), (42), (45), (48), (50), (51), (53), (57), (91).
(30) lower back area –42	4.877	
(31) disc trunk –43	5.266	
(32) chest –44	3.534	
(33) sacrum and coccyx –45	4.359	
(34) pelvis –46	3.868	
(35) spinal cord –47	6.888	
(36) internal organs –48	4.753	
(37) heart –49	8.932	
(38) multiple lower extremities -50	4.348	
(39) hip –51	4.932	
(40) upper hip –52	3.066	
(41) knee –53	4.249	
(42) lower hip –54	2.921	
(43) ankle –55	3.501	Group 4: (10), (13), (15), (18), (19), (22), (25), (41), (43), (47), (49), (60), (63), (90).
(44) foot –56	3.674	
(45) toe(s) –57	4.258	
(46) great toe –58	1.508	
(47) lung –60	5.501	
(48) abdomen incl. groin -61	3.321	
(49) buttocks –62	2.992	
(50) lumbar and/or sacral vertebrae –63	5.638	
(51) artificial appliances (braces, etc.) –64	2.452	
(52) insufficient info to identify/unclass –65	4.085	
(53) no physical injury –66	2.721	
(54) multiple body parts –90	5.227	
(55) body system and mult. body systems –91	4.611	
(56) whole body –99	2.978	

Chapter 3: Addendum

This addendum is intended to supplement the published work in the main part of Chapter 3.

A.1 Missing Data

A problem in any study is that of missing data. Several methods exist to address missing data; because the sample in this case was relatively small and the missing values for gender were a non-trivial percentage of all observations, we did not remove observations. Methods for addressing missing data when observations are not removed include replacement by the mean, median or mode, or imputation with the last (or next) value of the missing variable. For this study we focus on values of one missing variable, gender, and apply an imputation method.

Multiple imputation has become increasingly popular for handling missing data in epidemiologic analysis. Initially, statistical models are used to obtain plausible substitutes for missing values, with the imputation process being repeated several times to allow for the uncertainty in the missing values. Analytic results are then obtained by combining the results of standard complete-data analyses across the multiple completed data sets in an appropriate manner (Lee and Carlin, [24]). Missing values are imputed based on observed values for an individual and relations observed in other data for other participants. (Azur et al. [25]). Multiple imputation involves creating multiple predictions for each missing value on a variable-by-variable basis using logistic models for each variable and assuming that the gender values are MCAR (missing completely at random). The R package used for this analysis performs five iterations of the routine [26]and combines estimates using Rubin's rules [27]. Table AA3.1 shows a comparison of gender distribution before and after imputation.

	Missing Values	**Females**	**Males**
Without imputation	19%	32%	49%
With imputation		59%	41%

Table AA 3.1 Gender Distribution Before and After Imputation

A.2 Data

Imputation has led to a higher number of female claimants than males; with imputation, females are now 60% of the group. This change in gender distribution as a result of imputation helps to explain the differences between Cox regression models applied to the non-imputed and imputed datasets.

At the suggestion of a reviewer Table 3.3 (Grouping of entity variables) has been re-sorted according to median survival time. There is some similarity between entities at different levels: for example level 4 (longest median survival time) consists of a number of heavy manual occupations (fire, emergency, construction). These entities have the longest median survival time, possibly because they claim at an earlier age.

Original levels	Median survival time using KM	Updated levels using KM
(6) Fire and emergency services	5.279	4
(4) Construction and building services	4.559	4
(5) Education	4.507	4
(9) Police, corrections, and security	4.425	4
(7) General government	4.348	3
(11) Sanitation and waste collection	4.332	3
(8) Health and medical services	4.205	3
(3) Community services	4.107	3
(10) Recreation and resource protection	3.800	2
(12) Transportation and transit	3.797	2
(1) Agriculture and farming	3.564	2
(15) Water and water conservation	3.512	1
(14) Utilities and power	3.479	1
(2) Animal and vector control	3.351	1
(13) Unknown/Other group	2.830	1

Table AA3.2: Grouping of Entity Variables

Grouping of Cause of Loss

There does not appear to be a natural grouping of causes of loss. Therefore in table AA3.3 we group cause of loss by median survival time.

Original level	Median survival time using KM	Group
(6) CL6: Explosion or flare back	5.178	4
(2) CL2: Animal or insect	4.893	4
(16) CL16: Strain	4.474	4
(17) CL17: Strike	4.356	4
(7) CL7: Fall	4.274	4
(13) CL13: Person in act of a crime	4.274	4
(1) CL1: Absorption, ingestion, or inhalation	4.211	3
(3) CL3: Burn	4.192	3
(9) CL9: Machine or tool	4.181	3
(10) CL10: Miscellaneous	4.090	2
(11) CL11: Motor vehicle	3.978	2
(8) CL8: Fellow worker, patient, or other person	3.597	2
(4) CL4: Caught	3.493	2
(5) CL5: Cut	3.455	1
(15) CL15: Slipped	3.332	1
(14) CL14: Rubbed	2.745	1
(12) CL12: Natural disasters	1.268	1

Table AA3.3: Grouping of Cause of Loss

Grouping of body parts

There are different ways to group body parts; they can be grouped by body system (e.g. body parts involving the head and neck could be clustered). However, inspection of the median survival time by body part indicates different survival times for related body parts, and similar survival time for disparate parts. We therefore elected to group by median survival time.

Original level (description with numeric code)	Median survival time using KM	Grouping
(11) facial bones -19	9.266	4
(37) heart -49	8.932	4
(35) spinal cord -47	6.888	4
(50) lumbar and/or sacral vertebrae -63	5.638	4
(47) lung -60	5.501	4
(14) disk (neck) -22	5.458	4
(10) other facial soft tissue -18	5.405	4
(7) nose -15	5.267	4
(31) disc trunk -43	5.266	4
(54) multiple body parts -90	5.227	4
(29) upper back area -41	5.219	4
(5) ear(s) -13	5.132	4
(2) multiple head injury -10	5.063	4
(17) soft tissue neck -25	5.044	4
(39) hip -51	4.932	3
(30) lower back area -42	4.877	3
(36) internal organs -48	4.753	3
(12) multiple neck injury -20	4.668	3
(55) body system and multi. body systems -91	4.611	3
(13) vertebrae -21	4.600	3
(28) multiple trunk -40	4.532	3
(15) spinal cord -23	4.429	3
(18) multiple upper extremities -30	4.375	3
(33) sacrum and coccyx -45	4.359	3
(38) multiple lower extremities -50	4.348	3
(22) wrist -34	4.274	3
(45) toe(s) -57	4.258	3
(41) knee -53	4.249	3
(27) wrist(s) and hand(s) -39	4.195	2
(52) insufficient info to identify/unclass -65	4.085	2
(23) hand -35	4.06	2
(26) shoulder(s) -38	3.929	2
(34) pelvis -46	3.868	2
(9) mouth -17	3.83	2
(3) skull -11	3.816	2
(44) foot -56	3.674	2
(21) lower arm -33	3.658	2
(19) upper arm incl. clavicle and scapula -31	3.644	2

(32)	chest -44	3.534	2
(43)	ankle -55	3.501	2
(20)	elbow -32	3.438	2
(48)	abdomen incl. groin -61	3.321	2
(25)	thumb -37	3.096	1
(1)	other -9	3.074	1
(40)	upper hip -52	3.066	1
(49)	buttocks -62	2.992	1
(56)	whole body -99	2.978	1
(6)	eye(s) -14	2.964	1
(42)	lower hip -54	2.921	1
(24)	finger(s) -36	2.803	1
(4)	brain -12	2.773	1
(53)	no physical injury -66	2.721	1
(51)	artificial appliances (braces, etc.) -64	2.452	1
(8)	teeth -16	1.996	1
(16)	larynx -24	1.956	1
(46)	great toe -58	1.508	1

Table AA3.5: New Grouping of Body Parts in Imputed Data

Final Model Selection

ANOVA tables are provided to display the sequential analysis of the deviance of our final models. That is, we test the significance of the reduction in the model log-likelihood when the covariates are added sequentially to the model. The likelihood ratio test is employed as the models are nested. Note that the NULL covariates within a model mean that that model does not have covariates and that the predicted values are simply the average within the data.

Covariates	Log-likelihood	Chi-squared Statistics	Degrees of freedom	p-value
Null	-73030			
Age at Date of Loss	-73011	38.2591	1	0.000
Body	-72736	548.0979	3	0.000
Cause of Loss	-72727	18.5789	1	0.000
Severity	-72635	177.6585	1	0.000
Sex	-72635	7.3075	1	0.007
Years employed	-72616	38.2910	1	0.000
Age at DOL: Sex	-72604	23.4909	1	0.000
Body: Cause of Loss	-72595	18.2113	9	0.033

Table AA 3.6: ANOVA for the final model with imputed data

Covariates	Log-likelihood	Chi-squared Statistics	Degrees of freedom	p-value
Null	-75694			
Entity	75631	-127.1092	3	0.000
Age at Date of Loss	-75610	40.7316	1	0.000
Body	-75373	474.8634	3	0.000
Cause of Loss	-75296	10.7016	3	0.000
Severity	-75296	143.1253	1	0.000
Sex	-75292	7.3213	1	0.007
Years employed	-75280	23.7520	1	0.000
Severity: Sex	-75267	27.7000	1	0.000
Entity: Sex	-75259	14.0961	3	0.003
Body: Cause of Loss	-75249	21.6641	9	0.010

Table AA 3.7 ANOVA for the final model without imputed data

A.3 Model Interpretation

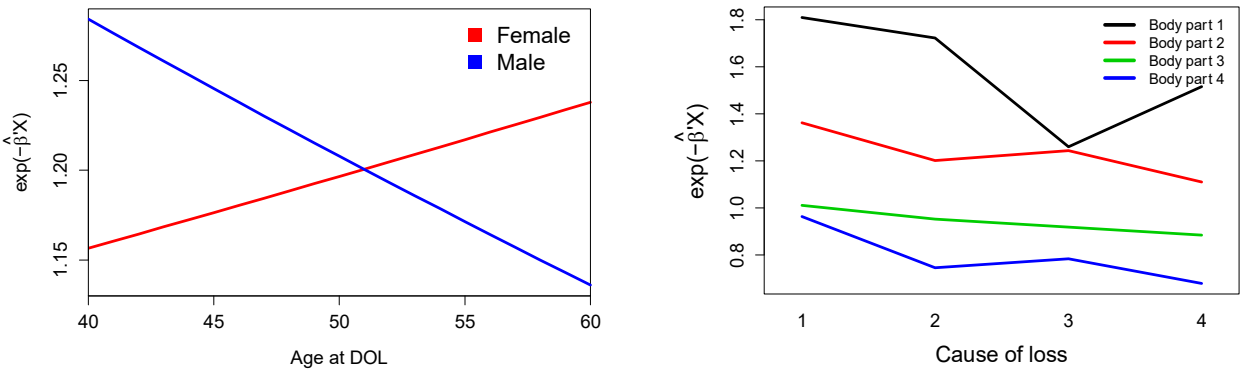

Figure AA 3.1 Effect of the Interaction Terms in the Final Model with Imputed Data

We provide examples to understand the effect on the hazard rates of interaction terms between covariates.

Example 1: Interpret the interaction between Age at DOL and Sex (continuous vs. categorical). We fix the value for Years Employed (0.9), Severity (17.46), Entity group (3) Cause of Loss (4), Body Part (2) while letting Age at DOL vary between 40 and 60. Furthermore we compute $exp^{(-\widehat{\beta}'X)}$ separately for Males and Females. The interaction between Age at DOL and Sex suggests that the effect of Age at DOL on the hazards depends on the status of Sex. Figure AA 3.1 shows that as we increase values of Age at DOL hazard decreases for Males but increases for Females.

Example 2: Interpret the interaction between Body Part and Cause of Loss (categorical vs. categorical). Similar to Example 1, we fix the value for Years Employed (0.9), Severity (17.46), Entity Group (3), Age at DOL (28), Sex (Female) while computing $exp^{(-\widehat{\beta}'X)}$ for each level of Body Part and Cause of Loss. The second figure in AA 3.1 confirms that the effect of each level of Body Part on the hazard rate depends on which category of Cause of Loss to which the claim belongs.

CHAPTER 4 - MEDICARE COST AT END-OF-LIFE

4.1 Health Coverage for the Elderly in the United States

This chapter serves as an introduction to the hospice setting of care, the experience of patients at end of life, and the cost of such patients to the healthcare system. We are concerned with the cost of patients at the end of life, as paid by the United States (U.S.) Medicare system. Elderly patients, 65 and older, are the responsibility, financially, of the Medicare system, administered by the U.S. Centers for Medicare and Medicaid Services (CMS).[4] Although CMS is responsible for payment, care is actually delivered by private providers (doctors, hospitals, pharmacies, hospices etc.). Medicare members may choose, on an annual basis, to be covered by traditional Medicare, which consists of Parts A (hospital), B (outpatient and professional), and D (prescription drugs), or by a managed care plan under Medicare Part C (Medicare Advantage). Approximately one-third of Medicare-eligible persons elect Medicare Advantage coverage. Traditional Medicare allows choice of provider, and providers are reimbursed on a fee-for-service basis. Medicare Part C consists of contracting Health Maintenance Organizations (HMOs), insurers that are reimbursed on the basis of a risk-adjusted premium per member per month. Risk adjustment results in modified payments, according to the expected costs of a patient's long-term conditions. Because the HMO takes risk for all services for its members, choice of providers is limited and often additional steps are required before medical services are obtained (a referral from a gate-keeping provider, for example). For more information, see, for example, Kaiser Family Foundation [28].

The dataset on which the analysis in the accompanying paper is based is known as the Medicare 5% Limited Data Set (LDS) Analytical File or the "Medicare 5% file," because it consists of a sample of 5% of all of Medicare's reimbursed claims. Researchers may purchase annual LDS files; patients are included, longitudinally, in the samples, so that patient experience may be followed over time. Despite its name, the 5% LDS "file" actually consists of eight separate files: a denominator file that contains eligibility and demographic data and seven claims files, together with files for services performed in different facilities, reported separately (inpatient hospital, outpatient, skilled-nursing

[4] In addition certain persons under age 65 who are deemed permanently disabled in terms of the Social Security Act are also eligible for Medicare coverage.

facility (SNF), home health, and hospice). Finally, one file contains professional claims. The claim files consist of the clinical files (containing for example diagnoses and procedure codes) and revenue files, containing cost of care information. We have integrated all files into an analysis dataset. In addition, there is an eligibility file (the "denominator" file), containing information on eligibility dates and demographics of sample members.

Our available data consists of samples for 2015 and 2016. Total Medicare enrolment in these two years was 55.3 million and 57.1 million, respectively [29]. Our analytical dataset consists of a random sample of Medicare's claims for the two years, containing experience of approximately 2.9 million patients for each year, or approximately 5% of Medicare's total enrolment. Approximately 30% of these patients are enrolled in managed care plans (Medicare Advantage Health Maintenance Organizations (HMOs, or pre-paid, capitated health insurance) and Preferred Provider Organizations, (PPOs, or groups of providers paid on a discounted fee-for-service basis)), leaving approximately 2.1 million beneficiaries enrolled in "traditional Medicare[5]" and available for analysis. We exclude members who have less than six months of eligibility in any year. Our sample shows that 259,000 of the 5.8 million total patients (including Medicare Advantage patients) died in 2015-6, or 4.47%, a rate that is consistent with the Krumholz study [30] and Medicare's published rate.

4.2 End-of-Life Care in the United States

The topic of care at the end of life is not a happy one. It is too often expensive, painful, and fraught with complications involving medical practitioners, patients, their families, and caregivers. In addition, in the United States, because patients are invariably elderly and covered by the Medicare system, these decisions affect the cost and financing of care. Table 4.1 shows the number of deaths in the U.S. in 2013, with the distribution by age. The total budget for Medicare, net of premiums, and other expenses paid by beneficiaries in 2016 was $685 billion U.S.[6] The cost of care provided by Medicare for medical services of

[5] Unlike Medicare Managed Care plans which impose varying degrees of managed care techniques such as pre-authorization, restricted networks, etc., patients in traditional Medicare are free to seek care from any willing provider, who is then reimbursed on a fee-for-service basis.

[6] https://www.hhs.gov/about/budget/budget-in-brief/cms/medicare/index.html#overview; accessed March 2017.

patients in the last six months of life is believed to account for 25% to 30% of Medicare's total spending.[7]

Total no. deaths (US) 2013	2.6 million
Deaths over 65	1.9 million
Number of deaths in hospice[8], 2013	1.1 million (42%)
Deaths per 100,000 of population by age group	
65-74	1,802.1
75-84	4,648.1
85 and over	13,660.4

Table 4. 1 U.S. Mortality

With mortality heavily skewed toward elderly patients, and given the increased prevalence of different medical conditions as patients age, cost of care is likely to increase with increased age, and with increased proportions of "old-old" seniors in the population. Table 4.2 shows the cause of death for patients dying in the U.S. in 2013. Slightly fewer than one-quarter of patients die from diseases of the heart and malignant neoplasms, both of which are conditions that can be chronic and require expensive treatment over time.
As noted in the attached paper, the last six months of care for patients that die accounts for approximately 25% of Medicare's expense in the last year of life. Interestingly, these patients account for 13% of cost in the year prior to the last year of life, indicating that patients nearing the end of life account for a significant portion of Medicare's total expense, particularly when we consider that fewer than 5% of Medicare members die annually. According to Krumholz [30], the mortality rate of Medicare members was 4.45% in 2013. In the attached paper, we report the mortality rate of the Medicare sample database.

[7] Our paper, reproduced in this chapter, examines this belief and finds that it is an over-estimate of actual cost.
[8] In the United States "hospice" refers both to a type of service and a place of service. As we discuss in Chapter 5, approximately two-thirds of patients receive hospice benefits in their own homes.

Rank	Cause of death (based on ICD-10)	Number	Percent of total deaths	2014 crude death rate
	All causes	2,626,418	100.0	823.7
1	Disease of heart ……...(|00-|09,|11,|13,|20-|51)	614,348	23.4	192.7
2	Malignant neoplasms…….....(C00-C97)	591,699	22.5	185.6
3	Chronic lower respiratory diseases……(J40-J47)	147,101	5.6	46.1
4	Accidents (unintentional injuries)……...(V01-X59,Y85-Y86)	136,053	5.2	42.7
5	Cerebrovascular diseases…….(|60-|69)	133,103	5.1	41.7
6	Alzheimer's disease…….(G30)	93,541	3.6	29.3
7	Diabetes mellitus……..(E10-E14)	76,488	2.9	24.0
8	Influenza and pneumonia……...(J09-J18)	55,227	2.1	17.3
9	Nephritis, nephrotic syndrome, and nephrosis…….(N00-N07, N17-N19,N25-N27	48,146	1.8	15.1
10	Intentional self-harm (suicide)…….....(*U03,X60-X84,Y87.0)	42,773	1.6	13.4
11	Septicaemia……...(A40-A41)	38,940	1.5	12.2
12	Chronic liver disease and cirrhosis…….....(K70,K73-K74)	38,170	1.5	12.0
13	Essential hypertension and hypertensive renal disease…..(|10,|12,|15)	30,221	1.2	9.5
14	Parkinson's disease……..(G20-G21)	26,150	1.0	8.2
15	Pneumonitis due to solids and liquids……...(J69)	18,792	0.7	5.9
	All other causes……..(residual)	535,666	20.4	168.0

Table 4. 2 Cause of Death 2014 [31]

It is usual, in the United States, to report medical costs on the basis of net paid claims cost per member, per month (abbreviated to PMPM).[9] Each patient ("member") in the dataset has a record of the beginning and end of the member's exposure during the year. These dates could be the first of the year and the last day of the year for those members who were enrolled prior to the start of the year and did not leave during the year. All exposure is incremented in months (because eligibility at the start of the month entitles the member to a full month of coverage). For those members who "exit" the exposure is slightly over-stated.[10] The numerator of the calculation is the total costs incurred by the members during the period (usually a year).

Table 3, in the attached paper, contains the cost, per member, per month, of different types of medical service, incurred and reimbursed by Medicare, in the last three

[9] In Medicare, as in other forms of U.S. insurance, all services that are to be reimbursed require the submission and adjudication of a claim. "Net Paid Claims" represent the portion of the approved claim that is the responsibility of the payer (in this case, Medicare), after exclusion of any ineligible services and deduction of patient responsibility (deductible and coinsurance).

[10] Exits during the year, other than by death are relatively infrequent. Members may change between traditional Medicare and Medicare Advantage, but except in rare circumstances (such as a geographical move) this occurs at the start of the year. A small fraction of members may leave the United States or otherwise lose their coverage during the year.

and six months of life. The paper reports numbers only. Figures 4.1 and 4.2 report costs, per member, per month, by place of death and by type of service. Patients dying in an inpatient setting, unsurprisingly, incur the highest costs, while hospital costs are the most significant component of overall costs, even among patients who die in settings other than hospital.

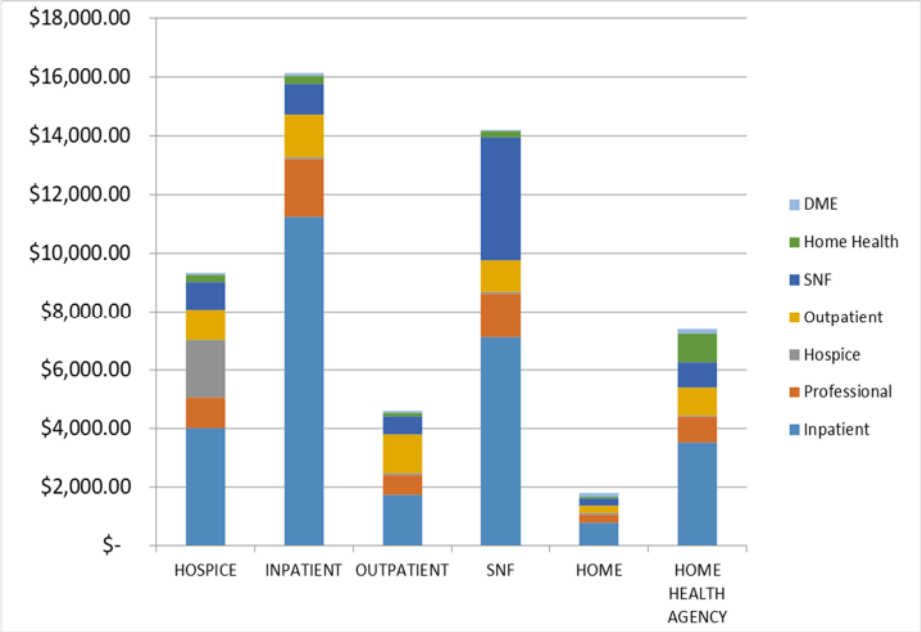

Figure 4. 1 Cost by Place of Death and Type of Service for Patients in Last Three Months of Life

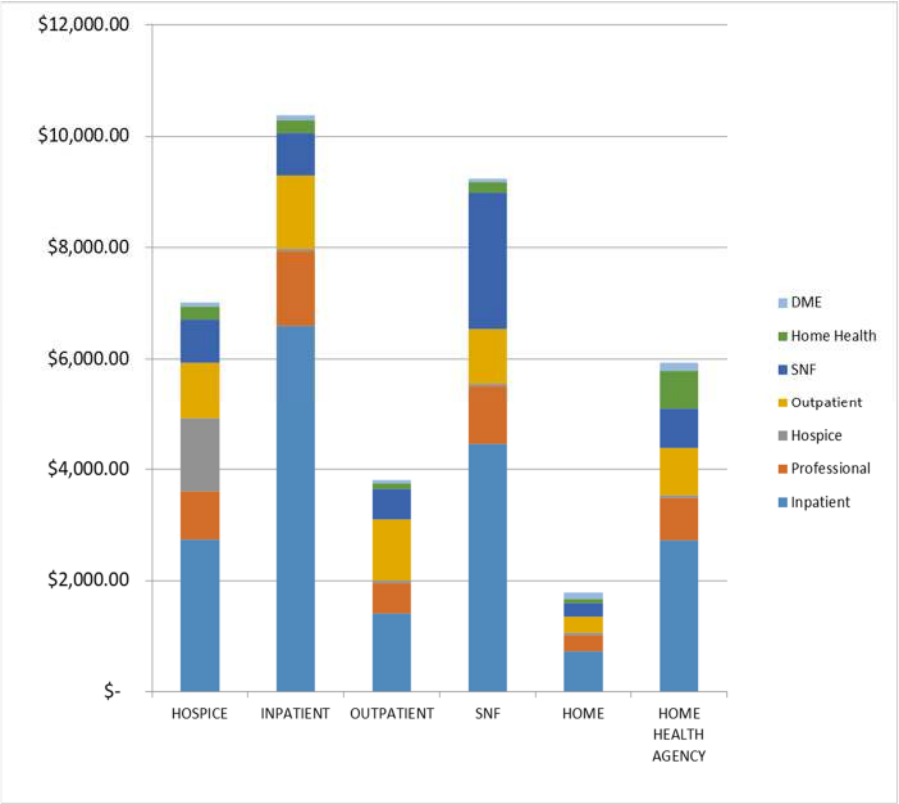

Figure 4. 2 Cost by Place of Death and Type of Service for Patients in Last Six months of life

4.3 Hospice

As we saw above, about 40% of all deaths of Medicare-age persons in the United States take place in hospice. In this section, we discuss the purpose and some of the benefits of hospice. Beginning with the work of Dame Cecily Saunders in London, hospice is considered the model for compassionate care for people facing a life-limiting illness. Hospice provides palliative medical care, pain management, and emotional and spiritual support, tailored to the patient's needs and wishes, as well as support to the patient's family. Hospice focuses on palliative, rather than curative care. In most cases (about 60%), care is provided in the patient's home, but may also be provided in freestanding hospices, inpatient hospitals, nursing homes, and other long-term care facilities. Hospice services are available to patients with any terminal illness, although the most frequent diagnoses are cancer and heart disease.

One important feature of hospice care is that it is palliative, rather than curative. The hospice team develops a care plan that meets each patient's individual needs for pain

management and symptom control. This interdisciplinary team usually consists of the patient's personal physician, hospice physician, or medical director, nurses, hospice aides, social workers, bereavement counsellors, clergy, or other spiritual counsellors, trained volunteers, and speech, physical, and occupational therapists, if needed. In the United States in 2014, an estimated 1.6 to 1.7 million patients received services from hospice. As shown in Figure 4.1, the number of patients and families served by hospice has steadily increased over the past several years. The National Hospice and Palliative Care Organization (NHPCO) estimates that approximately 1,200,000 deaths occurred in the U.S. while under the care of hospice, or approximately 46% of all U.S. deaths.

The total number of days that a hospice patient receives care is referred to as the length of stay or length of service. Length of stay can be influenced by a number of factors, including disease course, timing of referral, and access to care. According to NHCPO, the median (50th percentile) length of stay in 2014 was 17.4 days. This means that about half of hospice patients received care for fewer than 17 days and half received care for more than 17 days. Because of long stays among a minority of patients, average length of stay was 71.3 days in 2014. In 2014, 35.5% died or were discharged within seven days of admission, while 10.3% of patients had a length of stay of 180 days or more.

A goal of caregivers and, to some degree, CMS, (the payer for much of the care delivered in hospice for patients 65 and older) is to encourage earlier admission to hospice, because this reduces potentially futile care in inpatient and outpatient settings for patients who, otherwise, are at risk of early death. At the same time, CMS has strict eligibility requirements for admission to hospice (see Appendix 4.1). About 35% of patients are only in hospice less than one week, and, often, while the patient is actively dying and the family is in crisis. Earlier encouragement of admission would result in longer median and average lengths of stay in hospice. For hospice providers, more accurate estimates of life expectancy, for newly admitted patients, would allow the hospice to better plan for staffing, medication, and other needs of patients. The prediction of life expectancy of hospice patients and, in particular, how their changing prescription drug use is a predictor of termination is one of the purposes of this study and is covered in Chapter 8.

The hospice movement provides quality compassionate care at the end of life. Hospice services consist of:

- Pain and symptom management

- Maintenance of quality of life.
- Emotional, psychosocial, and spiritual support.
- Maintenance drugs, medical supplies, and equipment for palliation, but not acute drugs or equipment necessary to prolong life.
- Speech or physical therapy, if needed.
- Short-term inpatient care available, if needed (patient can be transferred back to the inpatient setting when acute services are required).
- Instruction for the family on how to care for the patient.
- Bereavement care and counselling

There are generally four levels of hospice care:

- Home-based care ("hospice at home").
    - Routine home care: patient receives care at the patient's home.
    - Continuous home care: care consisting predominantly of licensed nursing care on a continuous basis at home. This is only for brief periods of crisis and only as necessary.
- Inpatient care
    - General inpatient care: patient receives care in an inpatient facility for pain or acute/complex symptom control that cannot be managed in the home or nursing home setting.
    - Inpatient respite care: patient receives care in an approved facility on a short-term basis in order to give respite to the caregiver.

Hospice utilization in the U.S. is growing at a rate of about 5%, annually. Figure 4.3 shows the growth in the number of patients served, by year, since 2009.

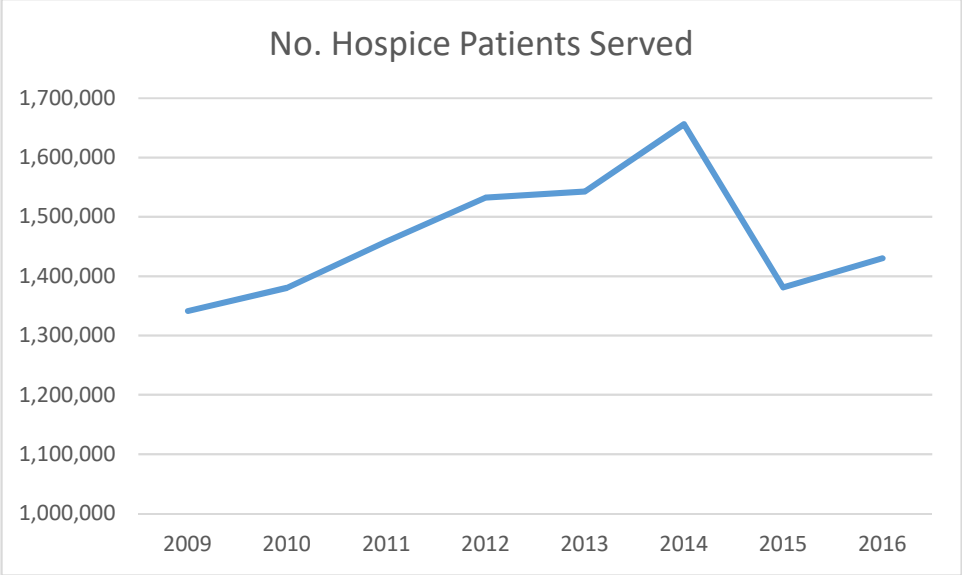

Figure 4. 3 Growth in Hospice Utilization by Year. Source: NHPCO [32]. Admissions in 2016 are the most recently-available.

The length of stay in hospice is also highly skewed, with the median length of stay equal to 17.4 days in 2014. The mean length of stay is 71.3 days, indicating the effect of outliers. Over one-third of patients stay for less than seven days. Figure 4.4 shows the distribution of hospice stay duration.

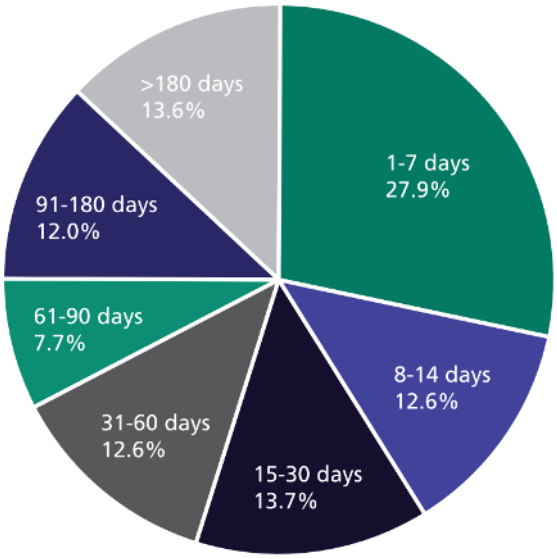

Figure 4. 4 Distribution of Hospice Stay Durations in 2016. Source: NHCPO [32].

In summary, hospice provides palliative care for patients near the end of life. Patients who would do well in hospice tend to receive acute and invasive care, rather than palliative care. How to provide education for patients and their families about the benefits of hospice remains a significant issue within a system in which patients are accustomed to receiving unlimited access to world-class care.

4.4 End of Life Costs

As we discuss in the following paper, care delivered to patients at end of life is often costly (particularly when delivered in an inpatient setting) and frequently futile. Our analysis of the Medicare LDS data shows that patients who die in hospital cost on average nearly $6,000 per day, compared with $231 per day, if the patient were to die in hospice (paper, Table 5). Encouraging greater use of hospice would result in better-quality care for the patient and reduced costs for Medicare.

4.5 Author Contributions to this paper

Ian Duncan: conception; data acquisition; analysis design; paper drafting.

Terri Maxwell: hospice and palliative care technical details

Henry Dove: literature review

Tamim Ahmed: programming and analysis of the Medicare LDS file.

Original Article

Medicare Cost at End of Life

American Journal of Hospice & Palliative Medicine®
1-6

DOI: 10.1177/1049909119836204
journals.sagepub.com/home/ajh
SAGE

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Abstract

As the Medicare program struggles to control expenditures, there is increased focus on opportunities to manage patient populations more efficiently and at a lower cost. A major source of expense for the Medicare program is beneficiaries at end of life. Estimates of the percentage of Medicare costs that arise from patients in the last year of life differ, ranging from 13% to 25%, depending on methods and assumptions. We analyze the most recently available Medicare Limited Data Set to update prior studies of end-of-life costs and examine different methods of performing this calculation. Based upon these findings, we conclude that higher estimates that take into account the spending over the 12 months leading up to death more accurately reflect the full cost of a patient's last year of life. Comparing current year costs of decedents with Medicare's current year costs understates the full budgetary impact of end-of-life patients. Because risk-taking entities such as Medicare Advantage plans and Accountable Care Organizations (ACOs) need to reduce costs while improving the quality of care, they should initiate programs to better manage the care of patients with serious or advanced illness. We also calculate costs for beneficiaries dying in different settings and conclude that more effective use of palliative care and hospice benefits offers a lower cost, higher quality alternative for patients at end of life.

Keywords

medicare, end-of-life costs, hospice, palliative care, population management, inpatient

Background

As the Medicare program struggles to control expenditures, there is increased focus on opportunities to manage patient populations more efficiently and at a lower cost. Patients at end of life (EOL) represent a disproportionate share of Medicare's costs, implying that these patients are an appropriate population for management by risk-taking Medicare entities such as Medicare Advantage plans and Accountable Care Organizations (ACOs), whose mission is to reduce cost as well as improve the quality of care. Because risk-taking entities need to reduce costs to share savings, they seek opportunities for more intense patient engagement and management. Actuaries, health economists, policy analysts, and health services researchers have studied expenditures at the EOL for Medicare decedents for more than 30 years. What is important from the perspective of managing patients and costs is that for patients at the EOL, alternative care pathways that involve palliative care are available which can result in higher quality of life at less cost.

The objectives of this article are 4-fold:

1. To summarize some of the main findings of previously published research articles on EOL expenditures and utilization patterns.
2. To propose an appropriate methodology for estimating the proportion of Medicare spending accounted for by patients at EOL that takes into account spending during the final year of life, not just at the time of death.
3. To investigate recent Medicare EOL expenditures using the most recent Medicare Limited Data Set (LDS) data for calendar year (CY) 2015 to 2016.
4. To model the opportunity for Medicare Advantage plans and Medicare Shared-savings Program (MSSP) ACOs to reduce cost of care for members in their final year of life while maintaining or improving care quality.

Literature Review on EOL Costs

There is a considerable literature about EOL costs, delivery, and financing from different disciplines. To better understand

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EOL costs and utilization patterns, we summarize examples of different aspects, as well as some recent developments in palliative care, quality, and futile care.

Numerous articles on EOL costs show that a large proportion of Medicare expenditures occur during the last 6 months of life.[1-9] This phenomenon has continued for many years as the number of Medicare decedents has increased with the aging American population. Medicare expenditures for EOL have increased dramatically from 1983 to 2016, primarily because of the increase in the number of decedents. Other articles compare EOL expenditures in the United States to other countries[10,11] or focus on Medicare expenditures for specific diseases.[12-14] A recent development in the literature challenges the idea that EOL costs are responsible for a high percentage of health-care costs.[15] Below, we discuss methodological differences that could account for differences in estimated proportions. Utilization trends also affect Medicare expenditures and utilization patterns at the EOL, including a higher proportion of Medicare decedents electing hospice. In addition, an increasing proportion of Medicare decedents electing hospice are living longer than 6 months, and noncancer patients now constitute the majority of hospice patients.

Cost Savings

Several researchers have studied the hypothesis that hospice care reduces Medicare expenditures.[16-18] Although the evidence is mixed, recent research challenges this hypothesis, although methodological issues make testing difficult.[19] Hospice eligibility is based upon a prognosis of 6 months or less, but predicting the remaining length of life for most terminally ill patients is difficult, especially for those with noncancer diagnoses. The Centers for Medicare and Medicaid Services (CMS) reimburses hospices on a per diem basis for all care related to the terminal prognosis, including nursing care, social services, spiritual care, medications, medical equipment, personal aides, volunteers, and bereavement services. Based upon a per diem payment system, patients with long lengths of stay in hospice are less likely to create savings.[20] The patient's diagnosis is an important variable.[21-25] Several innovative programs have been tried to alter the payment methods for the delivery of hospice services designed to improve the coordination of EOL care and better control of EOL costs. Descriptions of experimental and successful palliative care programs are provided in the March 2018 MedPAC report and several other references.[19,26-30] Finally, physicians have noted that some care, particularly in acute hospitals, is futile. Attempts to define, identify, and address such care is in its infancy.[26,31]

Data/Methods

The Medicare 5% LDS Analytical File ("Medicare 5% File")

For the purpose of understanding cost of care at the EOL, we perform analysis of the Medicare 5% file for the years 2015 and 2016. This file is a random sample of Medicare's claims for the 2 years, containing experience of approximately 2.9 million patients for each year. Approximately 30% of these patients are enrolled in managed care plans (Medicare Advantage Health Maintenance Organization [HMOs] and Preferred Provider Organization [PPOs]), leaving approximately 2.1 million beneficiaries enrolled in "traditional Medicare" and available for analysis. We exclude members who have <6 months of eligibility in any year. Our sample shows 259 000 of the 5.8 million total patients (including Medicare Advantage patients) died in 2015 to 2016, or 4.47%, a rate that is consistent with the Krumholz et al's study[32] and Medicare's published rate.

Deaths are assigned to a particular place of death based on the last service date. For deaths reported in the eligibility file, the service with the latest reported date determines the place of death. We calculated the Medicare expenditures for inpatient, outpatient, professional, emergency department, physician office visits, hospital outpatient visits, hospice, skilled nursing facility, home health, and durable medical supplies. Outpatient pharmaceutical data are not included in the 5% files, although inpatient and outpatient infused drugs are paid under Medicare Part B and are included.

Results

Medicare Costs at EOL

The share of Medicare's total costs represented by subpopulations helps identify areas of opportunity for program management. There is some controversy over the share of Medicare's cost that Medicare decedents represent. A defined period, usually the last 12 months of life, is essential for assessing the cost of EOL patients because of the exponential increase in cost in the last months of life (see, eg, Table 1). However, some comparisons are made on a calendar period basis, which (by definition) includes patients with differing life expectancies. A typical statistic is that 25% of all Medicare's annual costs are accounted for by decedents (Riley and Lubitz[1] based on 2006 Medicare payments). Cubanski et al in a 2016 Kaiser Family Foundation Data Note[33] report that "in 2014, beneficiaries who died at some point during the year accounted for 4% of all beneficiaries in traditional Medicare, but 13.5% of traditional Medicare spending . . . This estimate is lower than the 25% estimate cited earlier because it is based on Medicare spending for people who died at some point in a given CY (in this case, 2014), rather than the last 12 months of spending for people who died." Aldridge and Kelley[15] also challenge the traditional estimate from the perspective of total EOL spending in the population (not restricted to Medicare patients). They report 13% of total spending due to patients in the last year of life. French et al[34] compare international costs at EOL, reporting 8.5% for the United States. Finally, a recent article by Finkelstein et al,[35] using Medicare data from 2007 to 2008, reports that patients dying in 2008 accounted for 15% of total Medicare cost for that year. Whether total spending on EOL patients is 13% or closer to 25% matters in terms of the priority given to managing this subpopulation.

Table 1. Average Medicare Expenditures Prior to Death.

Year	Place of Death	Place of Service									% Place of Death
		Inpatient	Carrier	Hospice	Outpatient	SNF	HHA	DME	Total	Members	
Average Medicare expenditures 90 days prior to death (per decedent, per month)											
2015	Home	$807.95	$410.63	$30.13	$311.63	$248.71	$88.67	$117.01	$2014.72	2592	4.5%
2015	Home health agency	$3541.09	$1129.44	$65.01	$1064.56	$962.87	$1039.89	$180.12	$7982.98	1251	2.2%
2015	Hospice	$3984.60	$1272.44	$2048.64	$1062.14	$986.45	$287.67	$63.14	$9705.09	26 924	46.6%
2015	Inpatient	$11 231.53	$2476.00	$61.66	$1530.73	$1072.00	$286.44	$88.30	$16 746.66	14 462	25.0%
2015	Outpatient	$1712.01	$852.84	$47.11	$1382.93	$628.29	$120.87	$55.62	$4799.68	9593	16.6%
2015	SNF	$7485.28	$1905.60	$63.02	$1164.98	$4134.56	$231.27	$37.75	$15 022.45	2945	5.1%
2015	Subtotal	$5447.80	$1494.59	$984.06	$1204.35	$1075.27	$264.15	$71.84	$10 542.06	57 767	100.0%
2016	Home	$711.86	$364.74	$39.86	$285.47	$228.63	$78.15	$106.93	$1815.63	2332	4.1%
2016	Home health agency	$3533.62	$1077.95	$26.56	$1000.65	$856.60	$1029.46	$111.59	$7636.43	1249	2.2%
2016	Hospice	$4148.12	$1306.42	$2176.84	$1109.27	$942.44	$293.76	$57.56	$10 034.41	26 989	48.0%
2016	Inpatient	$11 615.17	$2527.64	$73.58	$1598.92	$1078.33	$287.51	$90.01	$17 271.17	13 816	24.6%
2016	Outpatient	$1607.58	$828.37	$51.47	$1388.16	$574.70	$127.75	$49.15	$4627.18	9201	16.4%
2016	SNF	$7281.36	$1885.30	$49.01	$1276.51	$4444.66	$239.22	$35.88	$15 211.95	2674	4.8%
2016	Subtotal	$5559.16	$1511.54	$1075.31	$1246.51	$1050.63	$269.88	$66.37	$10 779.41	56 261	100.0%
Average Medicare expenditures 180 days prior to death (per decedent, per month)											
2015	Home	$806.06	$397.52	$29.20	$329.83	$263.06	$89.55	$106.04	$2021.24	2592	4.5%
2015	Home health agency	$2784.61	$967.75	$66.15	$956.38	$753.71	$736.66	$160.65	$6425.93	1251	2.2%
2015	Hospice	$2723.59	$1046.77	$1331.48	$1079.11	$794.01	$244.16	$65.16	$7284.28	26 924	46.6%
2015	Inpatient	$6596.72	$1700.23	$50.03	$1368.61	$802.04	$230.94	$86.65	$10 835.21	14 462	25.0%
2015	Outpatient	$1404.19	$706.89	$41.93	$1132.55	$542.94	$104.69	$53.64	$3986.84	9593	16.6%
2015	SNF	$4665.84	$1346.00	$48.70	$1035.39	$2449.90	$206.48	$45.15	$9797.46	2945	5.1%
2015	Subtotal	$3488.42	$1138.34	$645.29	$1121.95	$814.05	$219.50	$71.51	$7499.06	57 767	100.0%
2016	Home	$724.97	$359.45	$39.18	$325.86	$238.44	$84.94	$99.91	$1872.74	2332	4.1%
2016	Home health agency	$2686.65	$934.45	$27.81	$921.75	$674.89	$738.28	$110.31	$6094.14	1249	2.2%
2016	Hospice	$2826.87	$1079.75	$1407.14	$1122.95	$770.13	$249.25	$60.29	$7516.38	26 989	48.0%
2016	Inpatient	$6810.05	$1727.88	$58.56	$1444.93	$800.33	$229.60	$91.13	$11 162.49	13 816	24.6%
2016	Outpatient	$1292.79	$684.30	$43.57	$1163.83	$483.42	$109.32	$49.44	$3826.66	9201	16.4%
2016	SNF	$4563.45	$1343.12	$43.92	$1149.66	$2593.48	$215.89	$44.30	$9953.83	2674	4.8%
2016	Subtotal	$3546.43	$1153.67	$700.86	$1172.47	$793.16	$224.00	$68.08	$7658.68	56 261	100.0%

[a]Places of death of home includes professional and DME claims.
Abbreviations: SNF, skilled-nursing Facility; HHA, home health Agency; DME, durable medical equipment.

Table 3. Average Medicare Expenditures—Outliers Removed.

Year	Inpatient	Carrier	Hospice	Outpatient	SNF	HHA	DME	Total	Members
PMPM 90 days prior to death—outliers removed									
2015	$5290.62	$1465.97	$983.70	$1054.72	$1072.38	$264.04	$50.26	$10 181.71	57 767
2016	$5400.69	$1485.45	$1075.28	$1094.30	$1045.47	$269.72	$42.80	$10 413.72	56 261
PMPM 180 days prior to death—outliers removed									
2015	$3378.66	$1102.26	$644.64	$935.67	$812.92	$219.29	$50.86	$7144.31	57 767
2016	3440.19	$117.98	$700.80	$980.45	$790.83	$223.73	$45.92	$7299.90	56 261

Abbreviations: SNF, skilled-nursing Facility; HHA, home health Agency; DME, durable medical equipment; PMPM, per member per month.

is 13.4%; adding the full 12 months of costs, the percentage rises to 19.7%.

2. In addition to adjusting the numerator of the percentage calculation, we also need to adjust the denominator. The cost of all members in 2015 is US$19.0 billion. At some point in 2016, some of those costs will be attributed to members who die in 2016. It is therefore appropriate to deduct the 2015 cost of 2016 decedents from the 2015 costs. We reduce the 2015 costs by this amount to reflect the total cost incurred by 2015 decedents and survivors.

With these 2 adjustments, the percentage of Medicare's cost represented by 2015 decedents rises to 21%. This percentage is somewhat lower than that reported by Riley and Lubitz based upon Medicare data between 1978 and 2006,[1] although these authors report a decreasing trend in EOL costs. The percentage is higher than that reported by other authors, likely because we include a full 12 months of final year expenses for decedents and defer the current year's final 12-month costs for those members who die in the following year.

Table 4. Study Population.[a]

Sample Size Description	Member Count
1. All members	3 114 712
2. Non-Medicare advantage members	2 129 432
3. Parts A and part B With >5 months of eligibility	1 668 000
4. Final sample—Members dying between January 1, 2015, and December 31, 2016	114 028

Table 5. Average Cost per Day for Patients Dying in Hospital Compared with Cost per Day in Hospice.

Days Prior to Death	Hospital Cost Per day	Hospice Cost Per day
1-3	$5983	$230.74
4-7	638	230.74
8-20	493	190.55
21-40	349	190.55
41-60	267	190.55
60-90	220	190.55
90-130	184	190.55
130-180	156	190.55

hospice earlier. An additional challenge is educating patients and families about hospice benefits.

Discussion

Numerous innovative programs and interventions are attempting to help CMS contain Medicare costs. One important statistic for program planning, however, is the ratio between the cost of a patient subpopulation and the number of patients. A relatively high ratio indicates a possible opportunity to reduce overall cost (subject to maintaining quality). Whether the ratio for EOL patients is 2.9 (13.0/4.5), 4.7 (21/4.5), or 5.6 (25/4.5) matters from the perspective of those who are responsible for managing the cost of the program (and particularly risk-taking entities such as MA plans and ACOs). Patients, clinicians, policy analysts, and administrators agree that the most important goal of EOL is to provide services that respect the wishes of the patient and his or her family. Palliative or hospice care can help to ensure that care is concordant with the preferences of patients and their caregivers while at the same time reducing Medicare expenditures. One critical challenge is to provide information to patients and caregivers at an appropriate juncture in a patient's care. A related challenge is to have a discussion between patients and families and providers about treatment options most likely to meet their EOL preferences.

Medicare expenditures increase sharply in the last few days of life, particularly for patients who die in hospital. Recent developments in hospice and palliative care offer the possibility of higher quality care at lower cost to Medicare if patients enter hospice earlier. Finding a lower cost site of care that does not jeopardize patients' wishes is a realistic, worthy goal. Expensive, futile care—especially given in an intensive care unit of an acute hospital—probably does not meet the preferences of most people at the end of life. Identifying those who will benefit from intensive care from those in which aggressive care is likely to be futile and burdensome is a challenge for providers, patients, and families. Published studies show that palliative care services can have a moderating effect on cost while improving quality of care. Examples of studies include the study by Lustbader et al, Center to Advance Palliative Care, and Pham and Krahn, and Smith et al.[37-40] The increased existence of hospital-based palliative care services and the recent development of community-based palliative care programs may help to ensure that care at the EOL is concordant with patient and family goals, while at the same reducing the cost of care.

Conclusion

Beneficiaries at EOL account for a significant portion of Medicare spending. Comparing current year cost of decedents with Medicare's current year costs understates the full budgetary impact of EOL patients. Greater use of hospice and palliative care, with their lower cost per patient, offers the possibility of expense reduction to the Medicare program while also improving quality of life outcomes.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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CHAPTER 5 - HOSPICE DATA SET

This chapter covers the hospice dataset on which the modelling, in this part of the thesis, is based. Our objective, in this part of the thesis, is two-fold: to model the rate at which drugs are deprescribed (patient weaning) and to predict expected future length of stay (or expected future lifetime) of patients admitted to hospice, as a function of admitting diagnosis, co-morbidities, drug regimens, and changes in regimen (drug/dosage/drug form). These problems are appropriate for survival modelling, as discussed, in theory, in Chapter 2.

The source of the data is Enclara Pharmacia Inc. a large national hospice pharmacy benefit manager (PBM). In the United States, because there is neither a national formulary[11], nor regulated drug prices, PBMs play an intermediary role between payers (insurers, employers or, in this case, Medicare) providers, and patients. PBMs define formularies for payers and negotiate pricing with drug companies. They will often supply the drugs as well, through a mail-order facility. The PBM is also the intermediary through which all drug-related financial transactions flow, resulting in a unique database of complete prescription records for hospice patient drugs.

5.1 Data Source

Data used for this study come from a single-source clinical and administrative database, provided by Enclara Pharmacia Inc. (EP) that contains information about clinical outcomes and medical resource use for persons who receive hospice care. EP is a Philadelphia, Pennsylvania-based company that provides telephonic support and pharmacy services to hospice patients. EP currently provides service to over 800 hospices in 49 states, overseeing medication therapy for more than 85,000 patients daily. EP maintains a comprehensive and continuously updated administrative database for all patients. Data are routinely collected as part of the pharmacy care process, including demographic variables, drug prescription information, and characteristics of hospice programs rendering services. Permission to use the EP data for this study was given by the Executive Vice President and

[11] A formulary is a listing of approved drugs; in the U.S. PBMs construct different formularies. While the inclusion of a drug on the formulary means that the drug will be reimbursed by insurance, formularies also have different “tiers” that determine the level of patient cost-sharing for each drug.

Chief Development officer of EP. Ethics approval for this study was given by Heriot-Watt's Ethics committee.

5.2 Data Source

A nurse, or hospice representative, records the data, including all medication information, in a patient profile in EP's computer system. This study includes patient demographic data recorded during telephone calls, such as date of birth, sex, race, diagnosis, select medication information, and discharge status. Data are collected for all patients during each telephone encounter between pharmacists and nurses, including all patient demographic information, any changes in medication or care setting, clinical assessment information, and discharge status, beginning with the hospice admission and continuing until the patient is either discharged from hospice or dies. In general, a hospice nurse visits the patient every few days, or more often, as the patient's condition warrants.

Validation of the dataset has been demonstrated in published studies [33, 34]. These studies of patients in the EP dataset (N = 356,760), between February 1, 2000 and July 26, 2004, found a high level of accuracy in the data: 0.1% of patients were listed with a negative age on admission, 0.2% with a discharge date before admission date, 0.2% missing an admission date, and 0.1% with a negative length of stay. Because patient records are matched to billing data, variables such as admission date, discharge status (died vs. discharged and associated dates), hospice affiliation, and hospice location (state and zip code) are reliable. Internal quality checks at EP have found medication-related information to be very reliable; however, these data are dependent upon the nurse communicating a complete medication profile for each patient, otherwise drug use could be underestimated. If the hospice nurse fails to provide a complete list of medications to the EP pharmacist, medications will be missing from the patient profile, which is a potential limitation of the study. Raw data files were provided by EP in MS Excel. Analysis was performed in Excel and R. After being reformatted, the data were checked by performing descriptive and summary statistics, such as ranges, means, and frequency distributions, to identify outliers, such as negative age, age > 110, negative length of stay, and duplicate identifiers.

Representatives of EP also assisted with data validation, interpretation, and mapping of drug classes. The comparability of the EP dataset to other national estimates from the National Home and Hospice Care Survey (NHCCS) and the National Hospice and

Palliative Care Organization (NHPCO), indicates that this dataset is a generally representative sample of persons who receive hospice care.

5.3 Patient variables

The patient's age was calculated from the date of birth at the time of admission. Sex was recorded as either male or female and was provided by the hospice staff at the time of admission to hospice. The patient's diagnosis was the medical diagnosis responsible for the admission of the patient on hospice, recorded as ICD-9 or ICD-10 codes, depending whether date of admission was prior to, or after, October 1st 2015[12]. There is no missing demographic data, although it is possible that there is missing drug data (for example, for any prescription medications in possession of the patient at the time of admission). Prescriptions ordered and filled after admission must be recorded as a requirement of patient care.

Patient status was indicated as "active" at the time of admission and remained active until the patient was reported as "discharged" or "deceased," and recorded accordingly. Hospice length of stay described the total number of continuous days of service from admission to discharge, including both the admission and discharge days. The length of hospice stay was calculated as the number of days from when the patient was accepted for coverage by the hospice organization (start coverage date) to the date when the hospice organization was no longer responsible for the patient services (stop coverage date). Length of stay was calculated as a continuous variable.

The patient profile contained a list of all medications, regardless of whether or not EP supplied them; therefore, drugs from other sources (such as a local pharmacy), outside of EP were included.

5.4 Dataset

Our dataset consists of three main categories of data: demographic, clinical, and drug data. Demographic data includes age and sex, as well as date of admission to hospice and date of death. Clinical data includes admitting diagnosis and co-morbidities. Finally, the drug data includes all prescriptions with drug name, dose, days' supply, and average wholesale price of the drug.

[12] The U.S. adopted the ICD-10 classification system with effect from October 1, 2015.

5.4.1 Demographic data

Data were available from 2014 to 2017, inclusive of 499,277 participants. Table 5.1 shows the distribution of members, by year of admission, together with numbers of patients alive and deceased. Designation of "active" status (alive) is made at May 5, 2018. All members are recorded at first admission to hospice, so there is no issue with left truncation of the observations. Some right censoring of observations occurs; of the 499,264 admitted patients, 26,463 remain alive at the extract date of the data (May 2018).

Year	**Female**		**Male**		**Total**		**Subtotal by Year**
	Active[13]	Deceased	Active	Deceased	Active	Deceased	
2014	40	39,671	19	27,582	59	67,253	67,312
2015	140	42,730	55	31,350	195	74,080	74,275
2016	3,041	63,949	1,149	44,490	4,109	108,439	112,629
2017	14,957	124,848	7,062	98,181	22,019	223,029	245,048
Subtotal by Year, Sex, and Status	18,178	271,198	8,285	201,603	26,463	472,801	499,264

Table 5. 1 Patients in Hospice by Year of Admission

Patients in table 5.1 represent those 499,264 patients for whom we have demographic data, as well as drug data, in their records. In the data summary, in table 5.1, years prior to 2016 have relatively few surviving patients, as of May 2018. The fact that 2015-6 admission years still have patients who are alive is somewhat problematic, although it is not uncommon for hospice patients to survive more than six months, despite the expectation of a stay of 180 days or fewer in hospice. Patients with hospice benefits are confined in different settings (home, nursing home, assisted living facility (ALF), and hospital inpatient). Table 5.2 shows the number and distribution of patients by setting of care.

[13] Still alive at May 5th, 2018.

Year	Assisted Living	Homecare	Inpatient	Long-Term Care[14]	Total
2014	429	47,956	2,133	16,777	67,295
2015	354	53,352	2,238	18,317	74,261
2016	3,129	72,865	3,344	33,282	112,620
2017	8,696	153,648	7,597	75,109	245,050
Total	12,608	327,821	15,312	143,485	499,226
Year	**Assisted Living**	**Homecare**	**Inpatient**	**Long-Term Care**	**Total**
2014	0.6%	71.3%	3.2%	24.9%	100.0%
2015	0.5%	71.8%	3.0%	24.7%	100.0%
2016	2.8%	64.7%	3.0%	29.6%	100.0%
2017	3.5%	62.7%	3.1%	30.7%	100.0%
Total	2.5%	65.7%	3.1%	28.7%	100.0%

Table 5. 2 Distribution of Patients by Care Setting

The majority of patients receive hospice care, either in their own home or in a nursing home (care home, or other long-term care facility). Only a very small proportion of all hospice patients receive benefits while in an inpatient hospital or assisted-living facility. The small number of patients receiving hospice care in the inpatient setting may appear contradictory with the literature that shows the scope of futile care delivered in the inpatient setting. However, it should be remembered that patients receiving inpatient critical care are almost invariably covered by traditional Medicare (even if the care represents services at end of life). It is very rare for a patient who has been accepted for Medicare hospice benefits to be re-admitted to an acute inpatient setting.

5.4.1.1 Patient age

Patient age at admission is, as one would expect, heavily skewed to older ages. Table 5.3 shows the distribution of age at admission for 2015 admissions.

[14] Long-term Care settings are care homes that include assisted-living and nursing care. Assisted living facilities are generally step-down facilities where ambient patients receive assistance with daily activities.

Age at Admission	Female Active	Deceased	Male Active	Deceased	Total Active	Deceased	Total
Age < 5	0	66	0	66	0	132	132
6 < Age < 21	1	71	0	115	1	186	187
22 < Age < 34	1	130	0	148	1	278	279
35 < Age < 50	2	1,100	2	906	4	2,006	2,010
51 < Age < 64	9	4,670	9	4,986	18	9,656	9,674
65 < Age < 74	14	6,874	18	6,774	32	13,648	13,680
75 < Age < 79	17	4,530	9	4,007	26	8,537	8,563
80 < Age < 84	23	5,950	4	4,659	27	10,609	10,636
85 < Age < 89	31	7,797	8	4,968	39	12,765	12,804
Age > 89	42	11,542	5	4,721	47	16,263	16,310
Subtotal by Age and Sex	140	42,730	55	31,350	195	74,080	74,275
Age at Admission	**Female Active**	**Deceased**	**Male Active**	**Deceased**	**Total Active**	**Deceased**	**Total**
Age < 5	0.0%	0.1%	0.0%	0.1%	0.0%	0.2%	0.2%
6 < Age < 21	0.0%	0.1%	0.0%	0.2%	0.0%	0.3%	0.3%
22 < Age < 34	0.0%	0.2%	0.0%	0.2%	0.0%	0.4%	0.4%
35 < Age < 50	0.0%	1.5%	0.0%	1.2%	0.0%	2.7%	2.7%
51 < Age < 64	0.0%	6.3%	0.0%	6.7%	0.0%	13.0%	13.0%
65 < Age < 74	0.0%	9.3%	0.0%	9.1%	0.0%	18.4%	18.4%
75 < Age < 79	0.0%	6.1%	0.0%	5.4%	0.0%	11.5%	11.5%
80 < Age < 84	0.0%	8.0%	0.0%	6.3%	0.0%	14.3%	14.3%
85 < Age < 89	0.0%	10.5%	0.0%	6.7%	0.1%	17.2%	17.2%
Age > 89	0.1%	15.5%	0.0%	6.4%	0.1%	21.9%	22.0%
Subtotal by Age and Sex	0.2%	57.5%	0.1%	42.2%	0.3%	99.7%	100.0%

Table 5. 3 Distribution of Age and Sex at Admission: 2015 Admissions

Age at Admission	Female Active	Deceased	Male Active	Deceased	Total Active	Deceased	Total
Age < 5	6	64	6	72	12	136	148
6 < Age < 21	7	77	6	118	13	195	208
22 < Age < 34	6	150	7	156	13	306	319
35 < Age < 50	23	1,168	21	956	44	2,124	2,168
51 < Age < 64	127	5,710	114	5,933	241	11,643	11,884
65 < Age < 74	248	8,732	208	9,046	456	17,778	18,234
75 < Age < 79	285	6,439	137	5,686	422	12,125	12,547
80 < Age < 84	459	8,889	189	6,870	648	15,759	16,407
85 < Age < 89	699	12,093	223	7,621	922	19,714	20,636
Age > 89	1,181	20,627	238	8,032	1,419	28,659	30,078
Subtotal by Age and Sex	3,041	63,949	1,149	44,490	4,190	108,439	112,629
Age at Admission	**Female Active**	**Deceased**	**Male Active**	**Deceased**	**Total Active**	**Deceased**	**Total**
Age < 5	0.0%	0.1%	0.0%	0.1%	0.0%	0.1%	0.1%
6 < Age < 21	0.0%	0.1%	0.0%	0.1%	0.0%	0.2%	0.2%
22 < Age < 34	0.0%	0.1%	0.0%	0.1%	0.0%	0.3%	0.3%
35 < Age < 50	0.0%	1.0%	0.0%	0.8%	0.0%	1.9%	1.9%
51 < Age < 64	0.1%	5.1%	0.1%	5.3%	0.2%	10.3%	10.6%
65 < Age < 74	0.2%	7.8%	0.2%	8.0%	0.4%	15.8%	16.2%
75 < Age < 79	0.3%	5.7%	0.1%	5.0%	0.4%	10.8%	11.1%
80 < Age < 84	0.4%	7.9%	0.2%	6.1%	0.6%	14.0%	14.6%
85 < Age < 89	0.6%	10.7%	0.2%	6.8%	0.8%	17.5%	18.3%
Age > 89	1.0%	18.3%	0.2%	7.1%	1.3%	25.4%	26.7%
Subtotal by Age and Sex	2.7%	56.8%	1.0%	39.5%	3.7%	96.3%	100.0%

Table 5. 4 Distribution of Age and Sex at Admission: 2016 Admissions

5.4.1.2 Age at death

Consistent with age at admission and length of stay, age at death is also heavily skewed to older ages. Figures 5.1 and 5.2 show age at death for 2015-2016 admissions.

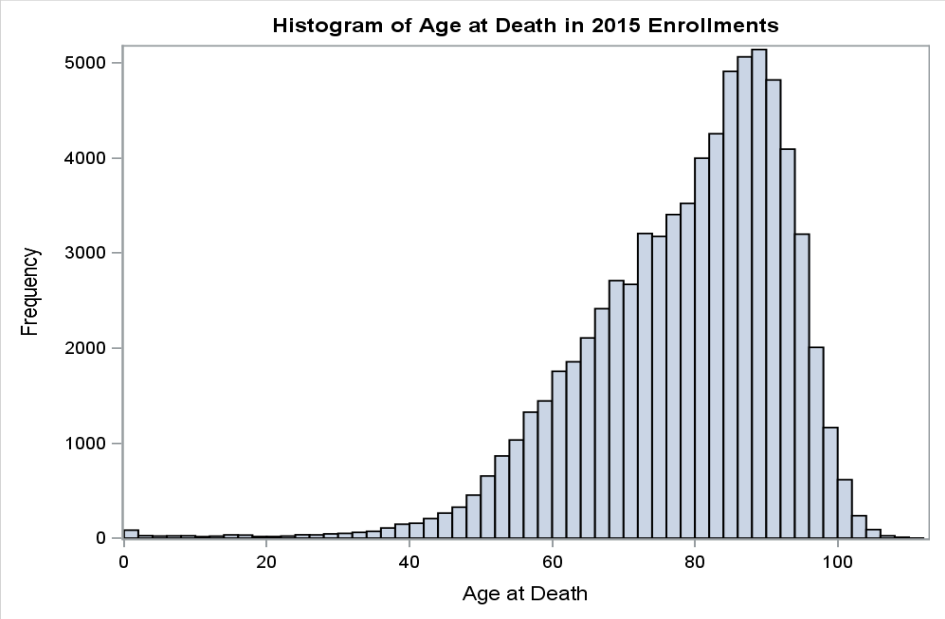

Figure 5. 1 Age of Death: 2015 Admissions

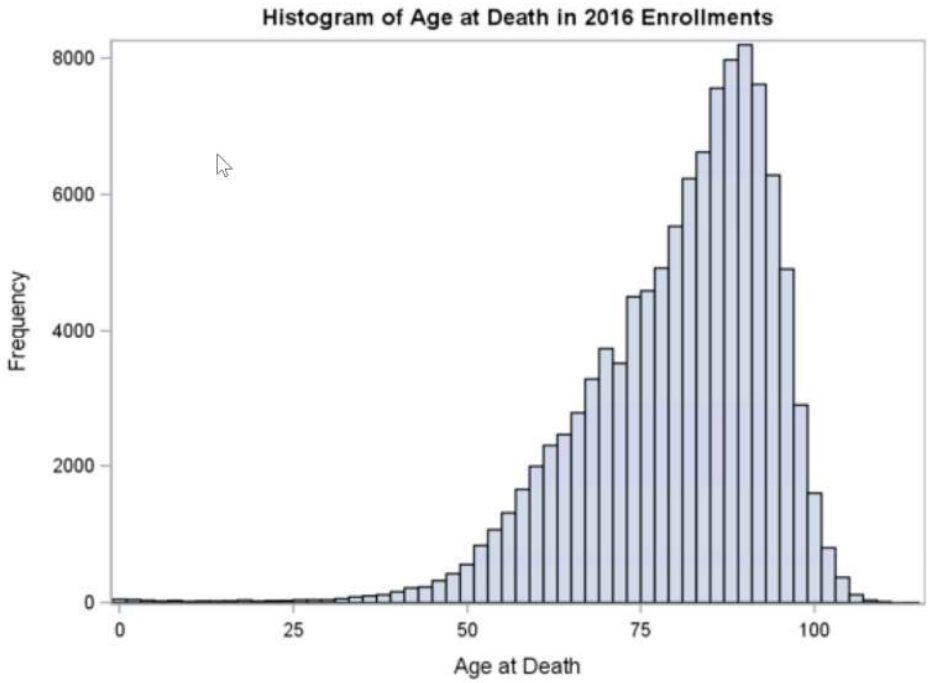

Figure 5. 2 Age at Death: 2016 Admissions

5.4.2 Clinical data

5.4.2.1 Cause of admission

Approximately 74% of patients are admitted with a primary diagnosis of one of ten conditions, primarily dementia, cancer, and heart disease. Stroke, COPD, and Parkinson's diseases are also prevalent. Table 5.5 shows the distribution of the ten most common admitting conditions. Diagnoses, both admitting (primary) diagnoses and co-morbidities, are recorded as part of the hospice patient record. Diagnoses are coded using the ICD-9 system (until September 30, 2015) and ICD-10 system (October 1, 2015 and later). We address the large number of diagnosis codes (approximately 15,000 in the ICD-9 system and 80,000 in the ICD-10 system) by grouping conditions into diagnostic categories, called hierarchical condition categories (HCCs). The HCC system[15] was developed for CMS and is used by CMS, and most commercial health plans, for (among other purposes) reimbursement in a risk adjusted revenue transfer system. For a detailed discussion about the development, structure, and use of the HCC system, see Duncan [35]. In total, there is provision for 189 HCCs (although CMS only uses 86 of these) and the system provides a simple way of aggregating and displaying patient records, according to their primary diagnoses, without having to create and maintain algorithms to group multiple diagnosis codes. In addition to grouping by HCCs we also group HCCs into "super" condition categories for some analyses; the HCC mapping into these categories is described in Appendix 6.8.

[15] See Appendix 5.6 for a detailed discussion of CMS's HCC grouper model.

	2015			2016		
Diagnosis	**Female**	**Male**	**Total**	**Female**	**Male**	**Total**
Lung and Other Severe Cancers[16]	6,881	6,779	13,660	8,712	9,222	17,934
Dementia without Complication	5,878	2,306	8,184	12,631	4,608	17,239
Congestive Heart Failure	4,030	2,948	6,978	7,615	5,447	13,062
Breast, Prostate, and Other Cancers and Tumours	3,609	2,438	6,047	4,309	3,241	7,550
Colorectal, Bladder, and Other Cancers	2,282	2,419	4,701	3,519	3,678	7,197
COPD	3,002	2,017	5,019	4,493	3,038	7,531
Cerebrovascular Disease	1,578	744	2,322	4,999	1,908	6,907
Lymphoma and Other Cancers	1,778	967	2,745	2,855	1,764	4,619
Ischaemic and Unspecified Stroke	1,580	772	2,352	2,585	1,298	3,883
Heart Disease	1,094	720	1,814	1,570	1,098	2,668
Subtotal by condition	31,712	22,110	53,822	53,288	35,302	88,590
Total (all conditions)	42,870	31,405	74,275	66,990	45,639	112,629
Top 10 Dx as % of all patients	74.0%	70.4%	72.5%	79.5%	77.4%	78.7%
	2015			**2016**		
Diagnosis	**Female**	**Male**	**Total**	**Female**	**Male**	**Total**
Lung and Other Severe Cancers	16.1%	21.6%	18.4%	13.0%	20.2%	15.9%
Dementia without Complication	13.7%	7.3%	11.0%	18.9%	10.1%	15.3%
Congestive Heart Failure	9.4%	9.4%	9.4%	11.4%	11.9%	11.6%
Breast, Prostate, and Other Cancers and Tumours	8.4%	7.8%	8.1%	6.4%	7.1%	6.7%
Colorectal, Bladder, and Other Cancers	5.3%	7.7%	6.3%	5.3%	8.1%	6.4%
COPD	7.0%	6.4%	6.8%	6.7%	6.7%	6.7%
Cerebrovascular Disease	3.7%	2.4%	3.1%	7.5%	4.2%	6.1%
Lymphoma and Other Cancers	4.1%	3.1%	3.7%	4.3%	3.9%	4.1%
Ischaemic and Unspecified Stroke	3.7%	2.5%	3.2%	3.9%	2.8%	3.4%
Heart Disease	2.6%	2.3%	2.4%	2.3%	2.4%	2.4%
Subtotal by condition	74.0%	70.4%	72.5%	79.5%	77.4%	78.7%
Total (all conditions)	42,870	31,405	74,275	66,990	45,639	112,629

Table 5. 5 Patients by Top 10 Primary Diagnosis in 2015 and 2016

For some later analysis, the relative distribution of primary diagnosis, by sex, will be important. Table 5.6 shows the distribution of some major diagnostic categories, by sex.

[16] "Other Cancers" is a collective term used by the developer of the HCCs (CMS) because of the number of different diagnoses included. More detail is provided in Appendix B.

A key implication of these tables is that males are more likely to suffer from cancers and less likely to suffer from stroke or dementia than females.

Condition	Female Active	Deceased	Male Active	Deceased	Total Active	Deceased	Total
Cancers	13.8%	46.0%	36.6%	57.0%	20.0%	50.5%	50.4%
Dementia	63.3%	18.4%	26.8%	10.4%	53.3%	15.1%	15.2%
Cardiac	8.3%	16.2%	22.0%	16.6%	12.0%	16.3%	16.3%
Lung	5.5%	9.5%	9.8%	9.1%	6.7%	9.3%	9.3%
Cerebrovascular and Stroke	9.2%	10.0%	4.9%	6.9%	8.0%	8.7%	8.7%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Condition	**Female Active**	**Deceased**	**Male Active**	**Deceased**	**Total Active**	**Deceased**	**Total**
Cancers	9.6%	37.7%	23.4%	51.4%	13.2%	43.2%	42.1%
Dementia	35.7%	23.1%	19.5%	12.9%	31.4%	19.0%	19.5%
Cardiac	15.9%	17.3%	22.0%	18.5%	17.5%	17.8%	17.8%
Lung	7.9%	8.5%	12.1%	8.5%	9.0%	8.5%	8.5%
Cerebrovascular and Stroke	31.0%	13.4%	23.0%	8.7%	28.9%	11.5%	12.2%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 5. 6 Distribution of Major Diagnostic Categories by Sex, 2015 and 2016

Condition Category	Diagnosis(es)
HCC52	Dementia Without Complication
HCC85	Congestive Heart Failure
HCC111	Chronic Obstructive Pulmonary Disease
HCC9	Lung and Other Severe Cancers
HCC8	Metastatic Cancer and Acute Leukaemia
HCC96	Specified Heart Arrhythmias
HCC19	Diabetes without Complication
HCC100	Ischemic or Unspecified Stroke
HCC12	Breast, Prostate, and Other Cancers and Tumours
HCC11	Colorectal, Bladder, and Other Cancers
HCC10	Lymphoma and Other Cancers
HCC78	Parkinson's and Huntington's Diseases
HCC21	Protein-Calorie Malnutrition
HCC48	Coagulation Defects and Other Specified Haematological Disorders
HCC141	Nephritis
HCC108	Vascular Disease
HCC79	Seizure Disorders and Convulsions
HCC28	Cirrhosis of Liver
HCC2	Septicaemia, Sepsis, Systemic Inflammatory Response Syndrome/Shock
HCC18	Diabetes with Chronic Complications

Table 5. 7 Diagnoses and Hierarchical Condition Categories (HCCs)

Tables 5.8 through 5.11 show distributions, by sex, and admitting diagnosis of frequencies of duration, from admission to death.

	Female								
Condition Categories	**0-3**	**4-7**	**8-14**	**15-29**	**30-59**	**60-89**	**90-179**	**≥ 180**	**Total**
Dementia Without Complication	243	544	755	842	891	546	834	1,223	5,878
Lung and Other Severe Cancers	391	880	1,161	1,512	1,422	652	607	256	6,881
Congestive Heart Failure	286	489	570	672	688	334	523	468	4,030
Breast, Prostate, and Other Cancers and Tumours	216	445	606	743	689	335	372	203	3,609
COPD	240	360	384	438	500	276	428	376	3,002
Cerebrovascular Disease	59	159	246	256	261	149	240	208	1,578
Colorectal, Bladder, and Other Cancers	122	244	359	483	499	200	248	127	2,282
Lymphoma and Other Cancers	97	192	307	391	364	168	170	89	1,778
Ischemic or Unspecified Stroke	123	256	267	248	217	101	190	178	1,580
Heart Disease	74	110	148	174	167	103	150	168	1,094
Protein-Calorie Malnutrition	21	61	97	93	85	51	70	54	532
Parkinson's and Huntington's Diseases	8	20	23	47	45	19	40	51	253
Metastatic Cancer and Acute Leukaemia	39	59	84	83	83	28	37	18	431
Cirrhosis of Liver	20	52	85	65	58	34	29	19	362
Unspecified Renal Failure	44	89	87	59	48	20	22	26	395
Chronic Kidney Disease	6	13	9	8	7	1	5	9	58
Lung Disease	37	41	37	36	19	17	12	17	216
Neoplasm	15	27	44	72	80	33	36	9	316
Septicaemia, Sepsis, Systemic Inflammatory Response Syndrome/Shock	42	39	36	29	22	15	7	12	202
Fibrosis of Lung and Other Chronic Lung Disorders	21	35	33	41	39	37	40	42	288
Subtotal by Condition	2,669	5,219	6,624	7,721	7,542	3,778	4,979	4,338	42,870
Discrete Mortality Frequency	6.2%	12.2%	15.5%	18.0%	17.6%	8.8%	11.6%	10.1%	100%
Cumulative Mortality Frequency	6.2%	18.4%	33.9%	51.9%	69.5%	78.3%	89.9%	100%	100%

Table 5. 8 Distribution of Duration (days) from Hospice Admission to Death in 2015 (Female)

Condition Categories	Female								
	0-3	4-7	8-14	15-29	30-59	60-89	90-179	≥ 180	Total
Dementia Without Complication	432	836	1,069	1,362	1,488	1,026	2,006	4,412	12,631
Lung and Other Severe Cancers	545	1,077	1,424	1,718	1,663	795	876	614	8,712
Congestive Heart Failure	447	775	934	1,046	1,112	640	1,083	1,578	7,615
Breast, Prostate, and Other Cancers and Tumours	247	503	722	798	762	392	470	415	4,309
COPD	268	425	461	556	639	403	697	1,044	4,493
Cerebrovascular Disease	120	282	350	486	509	350	776	2,126	4,999
Colorectal, Bladder, and Other Cancers	188	407	550	688	654	322	397	313	3,519
Lymphoma and Other Cancers	136	321	508	569	538	250	285	248	2,855
Ischemic or Unspecified Stroke	178	378	351	308	282	180	337	571	2,585
Heart Disease	57	113	166	181	200	124	236	493	1,570
Protein-Calorie Malnutrition	36	75	126	176	166	96	208	310	1,193
Parkinson's and Huntington's Diseases	34	83	93	155	181	128	252	552	1,478
Metastatic Cancer and Acute Leukaemia	67	102	129	153	110	54	51	56	722
Cirrhosis of Liver	41	66	57	71	70	28	29	23	385
Unspecified Renal Failure	54	68	83	74	58	36	36	40	449
Chronic Kidney Disease	13	24	39	44	30	15	23	36	224
Lung Disease	11	14	16	16	20	12	13	19	121
Neoplasm	21	55	70	103	76	46	57	43	471
Septicaemia, Sepsis, Systemic Inflammatory Response Syndrome/Shock	55	65	63	57	42	20	29	28	359
Fibrosis of Lung and Other Chronic Lung Disorders	30	37	44	58	59	37	66	88	419
Subtotal by Condition	3,592	6,669	8,255	9,770	9,718	5,540	8,858	14,588	66,990
Discrete Mortality Frequency	5.4%	10.0%	12.3%	14.6%	14.5%	8.3%	13.2%	21.8%	100.0%
Cumulative Mortality Frequency	5.4%	15.3%	27.6%	42.2%	56.7%	65.0%	78.2%	100.0%	100.0%

Table 5. 9 Distribution of Duration (days) from Hospice Admission to Death in 2016 (Female)

	Female								
Condition Categories	**0-3**	**4-7**	**8-14**	**15-29**	**30-59**	**60-89**	**90-179**	**≥ 180**	**Total**
Dementia Without Complication	4.1%	9.3%	12.8%	14.3%	15.2%	9.3%	14.2%	20.8%	100%
Lung and Other Severe Cancers	5.7%	12.8%	16.9%	22.0%	20.7%	9.5%	8.8%	3.7%	100%
Congestive Heart Failure	7.1%	12.1%	14.1%	16.7%	17.1%	8.3%	13.0%	11.6%	100%
Breast, Prostate, and Other Cancers and Tumours	6.0%	12.3%	16.8%	20.6%	19.1%	9.3%	10.3%	5.6%	100%
COPD	8.0%	12.0%	12.8%	14.6%	16.7%	9.2%	14.3%	12.5%	100%
Cerebrovascular Disease	3.7%	10.1%	15.6%	16.2%	16.5%	9.4%	15.2%	13.2%	100%
Colorectal, Bladder, and Other Cancers	5.3%	10.7%	15.7%	21.2%	21.9%	8.8%	10.9%	5.6%	100%
Lymphoma and Other Cancers	5.5%	10.8%	17.3%	22.0%	20.5%	9.4%	9.6%	5.0%	100%
Ischemic or Unspecified Stroke	7.8%	16.2%	16.9%	15.7%	13.7%	6.4%	12.0%	11.3%	100%
Heart Disease	6.8%	10.1%	13.5%	15.9%	15.3%	9.4%	13.7%	15.4%	100%
Protein-Calorie Malnutrition	3.9%	11.5%	18.2%	17.5%	16.0%	9.6%	13.2%	10.2%	100%
Parkinson's and Huntington's Disease	3.2%	7.9%	9.1%	18.6%	17.8%	7.5%	15.8%	20.2%	100%
Metastatic Cancer and Acute Leukaemia	9.0%	13.7%	19.5%	19.3%	19.3%	6.5%	8.6%	4.2%	100%
Cirrhosis of Liver	5.5%	14.4%	23.5%	18.0%	16.0%	9.4%	8.0%	5.2%	100%
Unspecified Renal Failure	11.1%	22.5%	22.0%	14.9%	12.2%	5.1%	5.6%	6.6%	100%
Chronic Kidney Disease	10.3%	22.4%	15.5%	13.8%	12.1%	1.7%	8.6%	15.5%	100%
Lung Disease	17.1%	19.0%	17.1%	16.7%	8.8%	7.9%	5.6%	7.9%	100%
Neoplasm	4.7%	8.5%	13.9%	22.8%	25.3%	10.4%	11.4%	2.8%	100%
Septicaemia, Sepsis, Systemic Inflammatory Response Syndrome/Shock	20.8%	19.3%	17.8%	14.4%	10.9%	7.4%	3.5%	5.9%	100%
Fibrosis of Lung and Other Chronic Lung Disorders	7.3%	12.2%	11.5%	14.2%	13.5%	12.8%	13.9%	14.6%	100%

Table 5. 10 Distribution of Duration (days) from Hospice Admission to Death in 2015 (Female)

	Female								
Condition Categories	**0-3**	**4-7**	**8-14**	**15-29**	**30-59**	**60-89**	**90-179**	**≥180**	**Total**
Dementia without Complication	3.4%	6.6%	8.5%	10.8%	11.8%	8.1%	15.9%	34.9%	100%
Lung and Other Severe Cancers	6.3%	12.4%	16.3%	19.7%	19.1%	9.1%	10.1%	7.0%	100%
Congestive Heart Failure	5.9%	10.2%	12.3%	13.7%	14.6%	8.4%	14.2%	20.7%	100%
Breast, Prostate, and Other Cancers and Tumours	5.7%	11.7%	16.8%	18.5%	17.7%	9.1%	10.9%	9.6%	100%
COPD	6.0%	9.5%	10.3%	12.4%	14.2%	9.0%	15.5%	23.2%	100%
Cerebrovascular Disease	2.4%	5.6%	7.0%	9.7%	10.2%	7.0%	15.5%	42.5%	100%
Colorectal, Bladder, and Other Cancers	5.3%	11.6%	15.6%	19.6%	18.6%	9.2%	11.3%	8.9%	100%
Lymphoma and Other Cancers	4.8%	11.2%	17.8%	19.9%	18.8%	8.8%	10.0%	8.7%	100%
Ischemic or Unspecified Stroke	6.9%	14.6%	13.6%	11.9%	10.9%	7.0%	13.0%	22.1%	100%
Heart Disease	3.6%	7.2%	10.6%	11.5%	12.7%	7.9%	15.0%	31.4%	100%
Protein-Calorie Malnutrition	3..0%	6.3%	10.6%	14.8%	13.9%	8.0%	17.4%	26.0%	100%
Parkinson's and Huntington's Disease	2.3%	5.6%	6.3%	10.5%	12.2%	8.7%	17.1%	37.3%	100%
Metastatic Cancer and Acute Leukaemia	9.3%	14.1%	17.9%	21.2%	15.2%	7.5%	7.1%	7.8%	100%
Cirrhosis of Liver	10.6%	17.1%	14.8	18.4%	18.2%	7.3%	7.5%	6.0%	100%
Unspecified Renal Failure	12.0%	15.1%	18.5%	16.5%	12.9%	8.0%	8.0%	8.9%	100%
Chronic Kidney Disease	5.8%	10.7%	17.4%	19.6%	13.4%	6.7%	10.3%	16.1%	100%
Lung Disease	9.1%	11.6%	13.2%	13.2%	16.5%	9.9%	10.7%	15.7%	100%
Neoplasm	4.5%	11.7%	14.9%	21.9%	16.1%	9.8%	12.1%	9.1%	100%
Septicamia, Sepsis, Systemic Inflammatory Response Syndrome/Shock	15.3%	18.1%	17.5%	15.9%	11.7%	5.6%	8.1%	7.8%	100%
Fibrosis of Lung and Other Chronic Lung Disorders	7.2%	8.8%	10.5%	13.8%	14.1%	8.8%	15.8%	21.0%	100%

Table 5. 11 Distribution of Duration (days) from Hospice Admission to Death in 2016 (Female)

	Male								
Condition Categories	**0-3**	**4-7**	**8-14**	**15-29**	**30-59**	**60-89**	**90-179**	**≥ 180**	**Total**
Dementia Without Complication	125	244	341	368	353	207	327	341	2,306
Lung and Other Severe Cancers	481	955	1,314	1,505	1,278	527	496	223	6,779
Congestive Heart Failure	233	426	413	508	500	280	320	268	2,948
Breast, Prostate, and Other Cancers and Tumours	152	295	385	483	535	218	248	122	2,438
COPD	159	249	288	296	312	173	287	253	2,017
Cerebrovascular Disease	31	85	112	131	121	72	110	82	744
Colorectal, Bladder, and Other Cancers	134	306	409	544	501	197	228	100	2,419
Lymphoma and Other Cancers	55	114	170	235	197	78	82	36	967
Ischemic or Unspecified Stroke	69	109	135	114	100	58	94	93	772
Heart Disease	55	74	93	110	124	63	102	99	720
Protein-Calorie Malnutrition	9	27	34	31	43	16	26	16	202
Parkinson's and Huntington's Diseases	19	31	47	59	64	33	53	34	340
Metastatic Cancer and Acute Leukaemia	36	66	61	79	59	25	34	10	370
Cirrhosis of Liver	49	101	87	73	77	33	38	24	482
Unspecified Renal Failure	56	75	92	50	32	20	24	14	363
Chronic Kidney Disease	4	4	5	6	8	2	3	2	34
Lung Disease	31	32	18	16	20	15	13	8	153
Neoplasm	15	27	44	57	62	30	15	12	262
Septicaemia, Sepsis, Systemic Inflammatory Response Syndrome/Shock	18	35	29	26	18	7	6	7	146
Fibrosis of Lung and Other Chronic Lung Disorders	18	29	32	49	53	35	39	25	280
Subtotal by Condition	2,302	4,288	5,261	5,902	5,520	2,579	3,248	2,305	31,405
Discrete Mortality Frequency	7.3%	13.7%	16.8%	18.8%	17.6%	8.2%	10.3%	7.3%	100.0%
Cumulative Mortality Frequency	7.3%	21.0%	37.7%	56.5%	74.1%	82.3%	92.7%	100.0%	100.0%

Table 5. 12 Distribution of Duration (days) from Hospice Admission to Death in 2015 (Male)

	Male								
Condition Categories	**0-3**	**4-7**	**8-14**	**15-29**	**30-59**	**60-89**	**90-179**	**≥ 180**	**Subtotal**
Dementia Without Complication	217	410	527	566	593	389	734	1,172	4,608
Lung and Other Severe Cancers	770	1,366	1,564	1,906	1,656	693	777	490	9,222
Congestive Heart Failure	405	682	723	842	759	412	691	933	5,447
Breast, Prostate, and Other Cancers and Tumours	172	412	488	595	614	291	396	273	3,241
COPD	220	322	337	392	424	278	441	624	3,038
Cerebrovascular Disease	57	149	191	205	204	152	310	640	1,908
Colorectal, Bladder, and Other Cancers	240	486	626	723	625	331	390	257	3,678
Lymphoma and Other Cancers	116	228	302	373	298	149	175	123	1,764
Ischemic or Unspecified Stroke	95	173	169	173	146	86	173	283	1,298
Heart Disease	49	103	144	139	168	89	148	258	1,098
Protein-Calorie Malnutrition	26	50	56	76	65	59	75	88	495
Parkinson's and Huntington's Disease	64	123	173	210	223	132	304	462	1,691
Metastatic Cancer and Acute Leukaemia	73	114	139	139	104	32	40	39	680
Cirrhosis of Liver	48	85	99	94	89	32	45	42	534
Unspecified Renal Failure	49	95	67	52	42	12	35	34	386
Chronic Kidney Disease	16	29	25	30	21	17	23	17	178
Lung Disease	8	14	16	9	11	9	6	12	85
Neoplasm	28	49	65	77	62	35	37	38	391
Septicaemia, Sepsis, Systemic Inflammatory Response Syndrome/Shock	44	59	50	32	30	12	15	18	260
Fibrosis of Lung and Other Chronic Lung Disorders	28	34	34	51	61	46	62	65	381
Subtotal by Condition	3,230	5,749	6,535	7,432	6,848	3,670	5,444	6,731	45,639
Discrete Mortality Frequency	7.1%	12.6%	14.3%	16.3%	15.0%	8.0%	11.9%	14.7%	100.0%
Cumulative Mortality Frequency	7.1%	19.7%	34.0%	50.3%	65.3%	73.3%	85.3%	100.0%	100.0%

Table 5. 13 Distribution of Duration (days) from Hospice Admission to Death in 2016 (Male)

Condition Categories	Male 0-3	4-7	8-14	15-29	30-59	60-89	90-179	≥ 180	Subtotal
Dementia Without Complication	5.4%	10.6%	14.8%	16.0%	15.3%	9.0%	14.2%	14.8%	100.0%
Lung and Other Severe Cancers	7.1%	14.1%	19.4%	22.2%	18.9%	7.8%	7.3%	3.3%	100.0%
Congestive Heart Failure	7.9%	14.5%	14.0%	17.2%	17.0%	9.5%	10.9%	9.1%	100.0%
Breast, Prostate, and Other Cancers and Tumours	6.2%	12.1%	15.8%	19.8%	21.9%	8.9%	10.2%	5.0%	100.0%
COPD	7.9%	12.3%	14.3%	14.7%	15.5%	8.6%	14.2%	12.5%	100.0%
Cerebrovascular Disease	4.2%	11.4%	15.1%	17.6%	16.3%	9.7%	14.8%	11.0%	100.0%
Colorectal, Bladder, and Other Cancers	5.5%	12.6%	16.9%	22.5%	20.7%	8.1%	9.4%	4.1%	100.0%
Lymphoma and Other Cancers	5.7%	11.8%	17.6%	24.3%	20.4%	8.1%	8.5%	3.7%	100.0%
Ischemic or Unspecified Stroke	8.9%	14.1%	17.5%	14.8%	13.0%	7.5%	12.2%	12.0%	100.0%
Heart Disease	7.6%	10.3%	12.9%	15.3%	17.2%	8.8%	14.2%	13.8%	100.0%
Protein-Calorie Malnutrition	4.5%	13.4%	16.8%	15.3%	21.3%	7.9%	12.9%	7.9%	100.0%
Parkinson's and Huntington's Disease	5.6%	9.1%	13.8%	17.4%	18.8%	9.7%	15.6%	10.0%	100.0%
Metastatic Cancer and Acute Leukaemia	9.7%	17.8%	16.5%	21.4%	15.9%	6.8%	9.2%	2.7%	100.0%
Cirrhosis of Liver	10.2%	21.0%	18.0%	15.1%	16.0%	6.8%	7.9%	5.0%	100.0%
Unspecified Renal Failure	15.4%	20.7%	25.3%	13.8%	8.8%	5.5%	6.6%	3.9%	100.0%
Chronic Kidney Disease	11.8%	11.8%	14.7%	17.6%	23.5%	5.9%	8.8%	5.9%	100.0%
Lung Disease	20.3%	20.9%	11.8%	10.5%	13.1%	9.8%	8.5%	5.2%	100.0%
Neoplasm	5.7%	10.3%	16.8%	21.8%	23.7%	11.5%	5.7%	4.6%	100.0%
Septicaemia, Sepsis, Systemic Inflammatory Response Syndrome/Shock	12.3%	24.0%	19.9%	17.8%	12.3%	4.8%	4.1%	4.8%	100.0%
Fibrosis of Lung and Other Chronic Lung Disorders	6.4%	10.4%	11.4%	17.5%	18.9%	12.5%	13.9%	8.9%	100.0%

Table 5. 14 Distribution of Duration (days) from Hospice Admission to Death in 2015 (Male)

Condition Categories	Male 0-3	04-07	08-14	15-29	30-59	60-89	90-179	≥ 180	Subtotal
Dementia Without Complication	4.7%	8.9%	11.4%	12.3%	12.9%	8.4%	15.9%	25.4%	100.0%
Lung and Other Severe Cancers	8.3%	14.8%	17.0%	20.7%	18.0%	7.5%	8.4%	5.3%	100.0%
Congestive Heart Failure	7.4%	12.5%	13.3%	15.5%	13.9%	7.6%	12.7%	17.1%	100.0%
Breast, Prostate, and Other Cancers and Tumours	5.3%	12.7%	15.1%	18.4%	18.9%	9.0%	12.2%	8.4%	100.0%
COPD	7.2%	10.6%	11.1%	12.9%	14.0%	9.2%	14.5%	20.5%	100.0%
Cerebrovascular Disease	3.0%	7.8%	10.0%	10.7%	10.7%	8.0%	16.2%	33.5%	100.0%
Colorectal, Bladder, and Other Cancers	6.5%	13.2%	17.0%	19.7%	17.0%	9.0%	10.6%	7.0%	100.0%
Lymphoma and Other Cancers	6.6%	12.9%	17.1%	21.1%	16.9%	8.4%	9.9%	7.0%	100.0%
Ischemic or Unspecified Stroke	7.3%	13.3%	13.0%	13.3%	11.2%	6.6%	13.3%	21.8%	100.0%
Heart Disease	4.5%	9.4%	13.1%	12.7%	15.3%	8.1%	13.5%	23.5%	100.0%
Protein-Calorie Malnutrition	5.3%	10.1%	11.3%	15.4%	13.1%	11.9%	15.2%	17.8%	100.0%
Parkinson's and Huntington's Disease	3.8%	7.3%	10.2%	12.4%	13.2%	7.8%	18.0%	27.3%	100.0%
Metastatic Cancer and Acute Leukaemia	10.7%	16.8%	20.4%	20.4%	15.3%	4.7%	5.9%	5.7%	100.0%
Cirrhosis of Liver	9.0%	15.9%	18.5%	17.6%	16.7%	6.0%	8.4%	7.9%	100.0%
Unspecified Renal Failure	12.7%	24.6%	17.4%	13.5%	10.9%	3.1%	9.1%	8.8%	100.0%
Chronic Kidney Disease	9.0%	16.3%	14.0%	16.9%	11.8%	9.6%	12.9%	9.6%	100.0%
Lung Disease	9.4%	16.5%	18.8%	10.6%	12.9%	10.6%	7.1%	14.1%	100.0%
Neoplasm	7.2%	12.5%	16.6%	19.7%	15.9%	9.0%	9.5%	9.7%	100.0%
Septicaemia, Sepsis, Systemic Inflammatory Response Syndrome/Shock	16.9%	22.7%	19.2%	12.3%	11.5%	4.6%	5.8%	6.9%	100.0%
Fibrosis of Lung and Other Chronic Lung Disorders	7.3%	8.9%	8.9%	13.4%	16.0%	12.1%	16.3%	17.1%	100.0%
Subtotal by Condition	7.1%	12.6%	14.3%	16.3%	15.0%	8.0%	11.9%	14.7%	100.0%

Table 5. 15 Distribution of Duration (days) from Hospice Admission to Death in 2016 (Male)

In the next section, we will analyse the prescription data in our database.

5.4.3 Hospice drug coverage

The United States Congress created a Medicare hospice benefit, in 1982, for beneficiaries, certified as having a life expectancy of six months or less. Medicare hospice providers are paid a per diem rate that is designed to cover all services necessary for the palliation and management of the terminal illness and related conditions, including the cost of

medications related to the terminal illness. When Medicare beneficiaries elect the hospice benefit, they forego Medicare coverage for curative treatment related to their terminal illness, but are still eligible for Medicare coverage for all other covered care. For example, if a Medicare beneficiary with liver cancer elects the hospice benefit, Medicare will no longer pay for treatment to cure the cancer, but it will continue to pay for care related to other illnesses, like diabetes and hypertension.

Federal regulations at 42 CFR § 418.202(f) stipulate that the Medicare Hospice Benefit must cover all medications and biologicals used primarily for the relief of pain and symptom control for the terminal illness and related conditions. This includes both prescription and over-the-counter drugs, as defined in §1861(t) of the Social Security Act. There is widespread agreement in the clinical literature about the classes of palliative drugs appropriate and necessary for patients at end of life [36-38]. In 2014, CMS [39] issued guidance on coverage of prescription drugs for patients in hospice, reiterating that drugs and biologicals, covered under the Medicare Part A per diem payments to a Medicare hospice program, are excluded from coverage under Medicare Part D[17]. This guidance states that CMS "expects that Medicare hospice providers will continue to provide all of the medications that are reasonable and necessary for the palliation and management of a beneficiary's terminal illness and related conditions. We expect that this will routinely include, but is not limited to, the drugs in the four categories highlighted by the OIG[18]:

1. Analgesics (opioids and non-opioid pain medications)
2. Anti-nauseants (anti-emetics)
3. Anti-cholinergic (laxatives and drugs prescribed for dizziness, vertigo, nausea, vomiting, diarrhoea, and symptoms of anti-psychotic medications).
4. Anxiolytics (anti-anxiety drugs).

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[17] Medicare Part D: the component of Medicare coverage introduced in 2006 to cover outpatient drugs (infusion and other specialty drugs were already covered under Part B of Medicare). The benefit is insured and administered by insurers, separately from Parts A and B (hospital and major medical) coverage, unless the member is part of a Medicare Part C (Medicare Advantage) plan (which covers all services, including outpatient drugs). However, on entry to hospice, Medicare Advantage members revert to Parts A/B traditional Medicare.

[18] OIG: Office of the Inspector General, or the Medicare Program Auditor-General, responsible for ensuring the financial integrity of the program.

Hospices must complete a prior authorization form if they determine that a medication from these four classes is for a condition unrelated to the terminal illness or related conditions. CMS recognizes that many maintenance drugs, as well as drugs to treat or cure a condition, are typically discontinued, as the focus of care shifts to palliation. Maintenance drugs, beyond the four classes noted above, that are appropriate to continue, as they may offer symptom relief, should be covered under the hospice benefit.

5.4.3.1 Analysis of drug prevalence

Table 5.16 shows the distribution of the four CMS drug classes, by patient, in 2015, and table 5.17 shows the distribution of the four CMS drug classes, by patient, in 2016.

Analgesics	**Laxatives**	**Anti-nauseants**	**Anxiolytics**	**Total**
69,335	54,984	25,971	59,669	209,959
Number of patients with at least one of 4 drug types				73,068
Number of patients without any of 4 drug types (1.63%)				1,207
			Total	74,275
93.4%	74.0%	35.0%	80.3%	282.7%

Table 5. 16 Prevalence of Four (CMS) Drug Classes: 2015 Admissions

Analgesics	**Laxatives**	**Anti-nauseants**	**Anxiolytics**	**Total**
103,911	79,688	35,614	88,972	308,185
Number of patients with at least one of 4 drug types				110,476
Number of patients without any of 4 drug types (1.91%)				2,153
			Total	112,629
92.3%	70.8%	31.6%	79.0%	273.6%

Table 5. 17 Prevalence of Four (CMS) Drug Classes: 2016 Admissions

Of CMS's four major drug classes (analgesics, laxatives, anti-nausea, and anxiolytic drugs), most patients have prescriptions for at least one drug class. Most patients have

prescriptions for multiple drug types; only 2.6% of 2015 admissions and 3.2% of 2016 admissions do not have at least one of the four drug classes. The most frequently prescribed drug class is analgesics (93.4% in 2015 and 92.3% in 2016), with other drug classes having lower incidence. On average, each patient with one or more prescriptions has a prescription for 2.8 (2015) and 2.7 (2016) drugs of the four drug types.

Tables 5.18 and 5.19 show the prevalence of different combinations of the four drug types by patient; frequencies of combinations are roughly, uniformly, distributed, with approximately one-quarter of patients having one, two, three, or four of the different drug types. These two tables do not distinguish the timing of the prescription, nor the strength or dosage, and simply present the frequencies of different combinations, at some time during hospice stay. It is frequently possible that a patient will have simultaneous prescriptions of more than one drug from a class. This observation has implications for other analysis, as we shall see shortly.

Tables 5.18 and 5.19 show the distribution of different drug classes. Ninety percent of patients have two or more classes of drugs.

All possible combinations of four drug classes	Female	Male	Number of patients	Group % of Total
Analgesics	2,882	1,900	4,782	
Laxatives	513	385	898	
Anti-nauseants	146	76	222	
Anxiolytics	693	615	1,308	9.9
Analgesics & Laxatives	2,847	2,166	5,013	
Analgesics & Anti-nauseants	430	246	676	
Anti-nauseants & Anxiolytics	4,974	3,685	8,659	
Analgesics & Anxiolytics	61	35	96	
Laxatives & Anti-nauseants	456	405	861	
Laxatives & Anxiolytics	1,046	666	1,712	23.3
Analgesics & Laxatives & Anti-nauseants	14,237	11,339	25,576	
Analgesic & Laxatives & Anxiolytic	1,429	865	2,294	
Analgesic & Anti-nausea & Anxiolytics	130	75	205	
Laxatives & Anti-nauseants & Anxiolytics	12,225	8,398	20,623	66.7
Analgesics & Laxatives & Anxiolytics & Anti-nauseants	90	53	143	0.2
Total	42,159	30,909	73,068	100.0

Table 5. 18 Frequency of Drug Classes: 2015 Admissions

All possible combinations of four drug classes	Female	Male	Number of patients	Group % of Total
Analgesics	4,588	3,067	7,655	
Laxatives	1,067	662	1,729	
Anti-nauseants	213	123	336	
Anxiolytics	1,312	992	2,304	10.9%
Analgesics & Laxatives	4,820	3,350	8,170	
Analgesics & Anti-nauseants	694	370	1,064	
Anti-nauseants & Anxiolytics	9,140	6,285	15,425	
Analgesics & Anxiolytics	118	71	189	
Laxatives & Anti-nauseants	809	622	1,431	
Laxatives & Anxiolytics	1,436	925	2,361	25.9%
Analgesics & Laxatives & Anti-nauseants	22,146	16,002	38,148	
Analgesisc & Laxatives & Anxiolytic	2,337	1,408	3,745	
Analgesic & Antinausea & Anxiolytics	198	119	317	
Laxatives & Anti-nauseants & Anxiolytics	16,704	10,639	27,343	63.0%
Analgesics & Laxatives & Anxiolytics & Anti-nauseants	153	106	259	0.2%
Total	65,735	44,741	110,476	100.0%

Table 5. 19 Frequency of Drug Classes: 2016 Admissions

5.4.3.2 Mapping drug class, strength, form, and dosage

5.4.3.2.1 Drug Classes

Within the four major drug classes, we group individual drugs into sub-classes. In the United States, individual drugs are coded with a National Drug Code (NDC). The NDC is a 10 or 11-digit code that provides information about the drug, manufacturer, form (capsule, pill, or liquid), formulation (active ingredient), and packaging (package size and type). The NDC code allows grouping by manufacturer or packager. For therapeutic studies, we need a classification by function. Our data did not contain NDC codes for individual drugs. Instead, the data consists of GCN codes, or generic code numbers, a numbering system developed by the First Data Bank Company. The GCN is a five-digit

code representing a clinical formulation. It is specific to active ingredient, strength, form, and route of administration. Most importantly, it is constant across manufacturers and/or package size, allowing the grouping of pharmaceutically equivalent products. Every drug has a hierarchical ingredient code ("HIC"). Because the coding is hierarchical, the codes may be used to group different drugs into therapeutic classes and sub-classes. This grouping of NDC codes into hierarchical ingredient codes is analogous to the condition grouping that is performed by the hierarchical condition categories for diagnosis codes, and greatly simplifies analysis of multiple drugs. Table 5.20 provides an example of the coding and mapping.

Characters	Information	Example
1	Organ system	nervous system
2	Pharmacological class	analgesics
3	Therapeutic class	narcotic analgesics
4	Ingredient (base)	morphine
5-6	Ingredient (specific); characters 5-6 indicate the salt or ester when applicable and are blank otherwise	morphine sulfate

Table 5. 20 Example of HIC Coding

First DataBank's specific therapeutic class consists of the first three digits of the hierarchical ingredient code, and, therefore, is referred to as HIC-3. For our study, we used the HIC-3 code to map drugs to the therapeutic class. The GTC description is also listed in the database and provides a plain-language description of the drug class. It is not used in the study.

An important part of data preparation is the creation, from raw drug data, of a number of derived variables. These include drug strength, form, and dosage. These variables, and particularly changes in them, will form the time-dependent covariates in later analysis. An example of the drug class coding is provided in table 5.21.

GCN Sequence Number	Generic Name	Label Name	HIC3_DESC	GTC_DESC	Class
3767	Diazepam	Diazepam 2 mg tablet	Anti-anxiety drugs	Psychotherapeutic Drugs	Anxiolytics
3767	Diazepam	Diazepam 2 mg tablet	Anti-anxiety drugs	Psychotherapeutic Drugs	Anxiolytics
3768	Diazepam	Diazepam 5 mg tablet	Anti-anxiety drugs	Psychotherapeutic Drugs	Anxiolytics
3766	Diazepam	Diazepam 10 mg tablet	Anti-anxiety drugs	Psychotherapeutic Drugs	Anxiolytics
3766	Diazepam	Diazepam 10 mg tablet	Anti-anxiety drugs	Psychotherapeutic Drugs	Anxiolytics
3736	Chlordiazepoxide HCL	Librium 5 mg capsule	Anti-anxiety drugs	Psychotherapeutic Drugs	Anxiolytics
3767	Diazepam	Diazepam 2 mg tablet	Anti-anxiety drugs	Psychotherapeutic Drugs	Anxiolytics
3766	Diazepam	Diazepam 10 mg tablet	Anti-anxiety drugs	Psychotherapeutic Drugs	Anxiolytics
4732	Meclizine HCL	Antivert 25 mg tablet	Antiemetic/ Antivertigo agents	Gastrointestinal	Anti-nauseants
3746	Clorazepate Dipotassium	Clorazepate 7.5 mg tablet	Anti-anxiety drugs	Psychotherapeutic Drugs	Anxiolytics
4682	Trimethobenzamide HCL/B-Caine	Trimethobenzamide 100MG	Antiemetic/ Antivertigo agents	Gastrointestinal	Anti-nauseants
4731	Meclizine HCL	Antivert 12.5 mg tablet	Antiemetic/ Antivertigo agents	Gastrointestinal	Anti-nauseants
4731	Meclizine HCL	Meclizine 12.5 mg tablet	Antiemetic/ Antivertigo agents	Gastrointestinal	Anti-nauseants
4683	Trimethobenzamide HCL/B-Caine	Trimethobenzamide 200MG	Antiemetic/ Antivertigo agents	Gastrointestinal	Anti-nauseants
3767	Diazepam	Diazepam 2 mg tablet	Anit-anxiety drugs	Psychotherapeutic Drugs	Anxiolytics

Table 5. 21 Example of Drug Class Coding

5.4.3.3 Coding drug strength

An important requirement of this study is the need to reduce the multiplicity of different drugs, drug strengths, dosage, and route of administration, in such a way that they may be incorporated as variables into a model. We do this by mapping drugs to relative strengths. For analgesics, this is largely straightforward because there is a clinical conversion of analgesics of the opioid type to equivalent units of morphine. For other drug classes, instead of strength and dosage, we record whether the patient had a prescription for the

drug at a particular point in time, and (cumulatively) the number of prescriptions that the patient has had within the class during the stay.

Table 5.22 shows examples of mappings of opioid (analgesic) drugs. Opioids are mapped to their equivalent, in terms of oral morphine using their morphine conversion factor. Intravenous hydromorphone is the strongest opioid drug; all other drug strengths are expressed as a percentage of hydromorphone's (maximum) strength. For example, morphine, OxyContin, and oxymorphone all have equivalent strengths, in terms of morphine equivalence, although tablet strengths are 60, 40, and 30 mg, respectively.

Form	**Drug**	**Strength**	**Unit**	**Oral morphine equivalent per dose**	**Relative Strength**
Capsule	Morphine Sulfate	60	MG	60	18%
Tablet	Morphine LA	60	MG	60	18%
Tablet	OxyContin CR	40	MG	60	18%
Tablet	Oxymorphone HCL	30	MG	60	18%
Tablet	Hydromorphone	16	MG	64	19%
Capsule	Morphine Sulfate	80	MG	80	24%
Capsule	Morphine Sulfate	90	MG	90	27%
Tablet	OxyContin CR	60	MG	90	27%
Capsule	Morphine Sulfate	100	MG	100	30%
Liquid	Morphine Sulfate	100	MG/5ML	100	30%
Tablet	Morphine LA	100	MG	100	30%
Tablet	OxyContin CR	80	MG	120	36%
Tablet	Morphine LA	200	MG	200	60%
Intravenous	Hydromorphone	10	MG/ML	333.33	100%

Table 5. 22 Example of Strength Coding – Analgesic drugs

An important consideration, which will become apparent below, is that it is possible for a patient to have a drug dosage that exceeds 100%, or more than one prescription at a time (non-analgesic drugs). This phenomenon occurs when a patient has overlapping prescriptions within the same drug class. For example, it is possible for a patient to be

prescribed two different analgesics of maximum strength at the same time. The U.S. Centers for Disease Control and Prevention (CDC), the body that makes recommendations for drug use, recommends a daily dosage of no more than 90 milligrams of morphine equivalent (MME). Patients in hospice regularly exceed this dosage, often by multiples. Analysis of a sample of 152,094 deceased patients from our database indicates that 98,204 had at least one prescription day in excess of 90 mg; 60% of deceased patients had a prescription in excess of two times the CDC's recommended daily dose (slightly fewer than 40% of all deceased patients). Table 5.23 shows the number and percentage of patients who had at least one day of opioid prescription, in excess of the recommended daily dose; table 5.24 shows the use of opioids for the number of days, continuously, prior to death. For example, 37% of deceased patients, with prescriptions in excess of 90 mg morphine equivalent, used at least twice the recommended dose of opioids for between one and seven days prior to death.

MME ≥ 90 mg	**Patients**	**% ≥ 90 mg***	**% all patients**
90 – 150 mg	33,363	34.0%	21.9%
150^{+} - 180 mg	5,637	5.7%	3.7%
180 mg +	59,204	60.3%	38.9%
Total Patients	98,204	100.0%	64.6%

* Patients are classified in the highest dosage category during their stay

Table 5. 23 Patients with Prescriptions in Excess of the Recommended Maximum Daily Dose of Opioids.

While many drugs are titrated by body mass, opioids are not. The dosage of opioids depends instead on pain level. Patients (particularly cancer patients) lose so much weight during treatment that dosage would not vary much. The authoritative source for Cancer Treatment in the US is National Comprehensive Cancer Network, which provides dosage instructions for pain control and side effect limitation, with no relation to patient weight. See for example [40].

MME ≥ 90 mg	1 - 7 days (%)	8 - 30 days (%)	31 - 90 days (%)	90+ days (%)	Subtotal	Total
90 – 150 mg	15,523 (47%)	670 (2%)	1 (0%)	0 (0%)	16,194 (49%)	33,363
150 mg^{+} - 180 mg	2,413 (43%)	97 (2%)	0 (0%)	0 (0%)	2,510 (45%)	5,637
180 mg+	21,872 (37%)	2,625 (4%)	338 (1%)	45 (0%)	24,880 (42%)	59,204
Total	39,808 (41%)	3,392 (3%)	339 (0%)	45 (0%)	43,584 (44%)	98,204

Table 5. 24 Patients with Continuous Prescriptions in Excess of the Recommended Maximum Daily Dose of Opioids for Days until Death

5.4.3.4 Treatment of ComfortPak drugs

ComfortPaks are packages that contain small supplies of all four classes of drugs. They are provided for use by the patient in an emergency, for example, when a supply of a specific drug has been used up, and the patient is waiting for the delivery of a new prescription. Use of drugs from the package is not recorded; therefore, we developed an algorithm to proxy the use of these drugs from the packs.

ComfortPak (CP) drugs are included in the study, subject to the rules illustrated in figure 5.3. Certain CP drug records contain no date; these records are ignored because a blank date implies that the ComfortPak prescription was never dispensed. A prescription record for a regular drug is always included in the analysis.

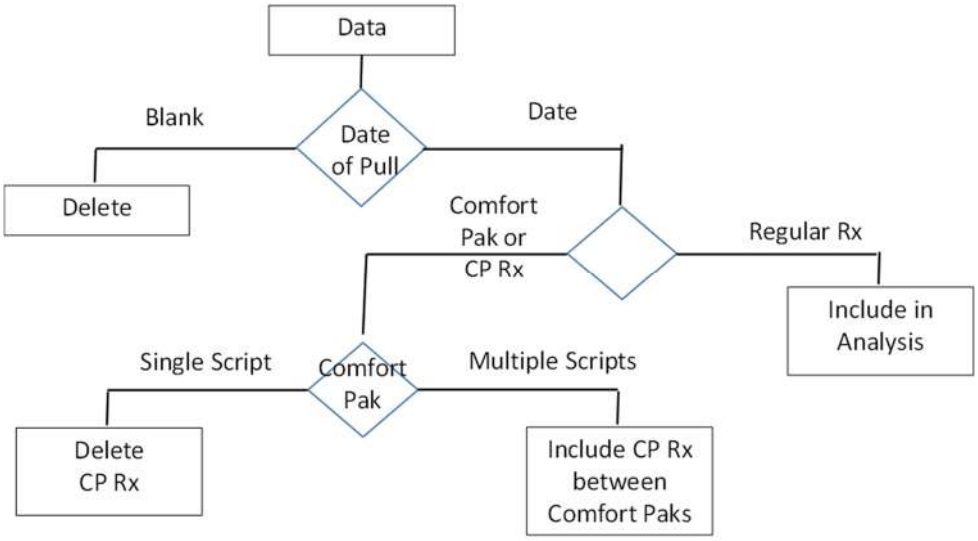


Figure 5. 3 Treatment of ComfortPak Drugs

ComfortPak drugs are excluded from the analysis if there is a single occurrence of a ComfortPak for that patient during the stay, assuming that the absence of a second ComfortPak prescription implies that the first pack was not exhausted. (This assumption potentially undercounts ComfortPak drugs by ignoring ComfortPak drugs used from the first pack when a second pack may not have been ordered. However, the ComfortPak contains only a two-day supply of the drug, implying that even if the drug is included or excluded erroneously, the potential error is minor.) Only in the case of multiple ComfortPak prescriptions is the drug included in analysis; only prescriptions up to, and including, the penultimate CP supply are included (because with no further CP prescription, there is no indication that earlier ComfortPaks were used). All drugs in the ComfortPak are included in the analysis, where the ComfortPak is deemed to have been used.

5.4.3.5 Investigation of drug dosage

An important aspect of this thesis is the predictive value of time-dependent variables, such as number of prescriptions and drug strength. In this section, we discuss prescribing patterns of the four palliative drug classes.

We investigated the prescribing pattern, particularly the dosage of analgesic drugs, and of the number of prescriptions of the other three drug classes, toward the end of life. The scale of relative dosage graphs is 0-1 (0% to 100% of the maximum dosage of oral equivalent morphine; refer to Table 5.22 for an example of the coding of relative strength of different drugs). The measure in the analgesic charts is the average and median cumulative dosage of morphine equivalent. The average cumulative drug dosage is calculated as $\hat{d} = \frac{\sum_{t=1}^{T} d_t}{T}$, where d_t is the daily analgesic dose (calculated as the strength per pill, multiplied by the number of pills per day, or equivalent when the drug form is not pills) and T is the number of days over which the dose is averaged. Because a patient may be prescribed more than one opioid at a time, it is possible for a patient to have a total morphine equivalent dose that exceeds 100% (> 1.0 in Figure 5.4). Tables 5.23 and 5.24 indicate that this is possible because of the number of patients whose prescriptions exceed the recommended maximum daily dosage. Figure 5.4 shows the progression of the cumulative average and median dosage of analgesic drugs from admission to death.

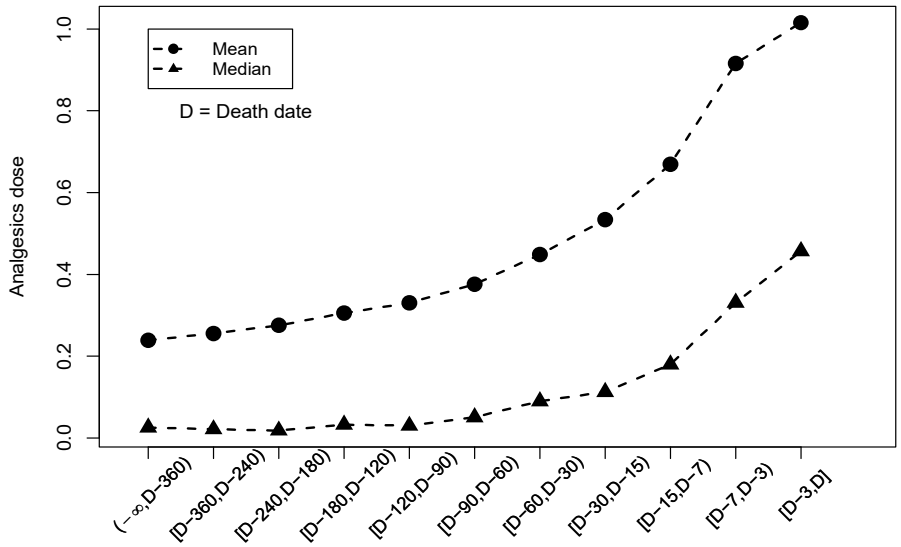


Figure 5. 4 Cumulative Dosage of Analgesic Drugs at End of Life

Prescription strength is highly variable by patient, as the difference between average and median drug strength in figure 5.4 shows. Both median and average doses of analgesics increase exponentially over the length of stay in hospice. For the remaining drug categories (anti-nausea, laxatives, and anxiolytics), we report the average and median number of prescriptions, per patient, at different times during the hospice stay.

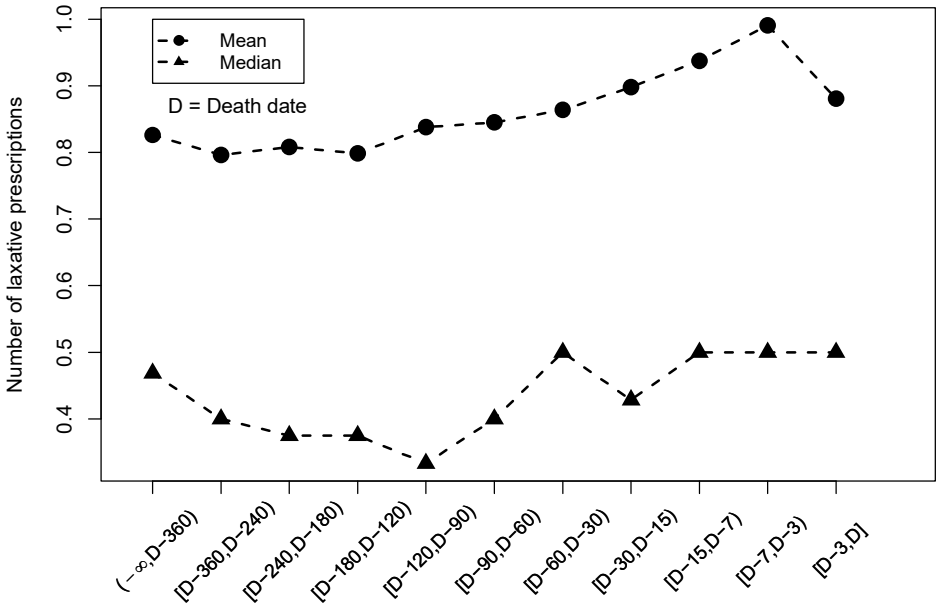


Figure 5. 5 Number of Laxative Prescriptions at End of Life

For non-analgesic drugs, on advice of a clinical pharmacist, we record the number of prescriptions, rather than the dose, because (unlike in the case of analgesics) there is no common measure to which to reduce all drugs within a class. For example, figure 5.5 shows the average and median number of laxative prescriptions, per patient, at different times in the patient's stay. On average, patients have 0.8 prescriptions early in the stay, increasing to an average of 1.0 prior to death, with a reduction in the average number of prescriptions in the last three days. The number of patients who die shortly after admission contributes to the downturn in the average number of prescriptions. The median number of prescriptions is roughly level throughout the stay at about 0.5, implying that one in two patients have a laxative prescription throughout the stay.

"Anti-cholinergic burden" is defined as the cumulative effect of taking one or more drugs that are capable of developing anti-cholinergic adverse effects. Peripheral manifestations may occur such as urinary retention, constipation, decreased secretions, amongst others and central manifestations, such as delirium, cognitive, and functional disorders. Anti-cholinergic burden is associated with loss of function and prognosis [41]. More work is required to understand the role of multiple medications in contributing to the anticholinergic burden, vs. the use of anticholinergic drugs.

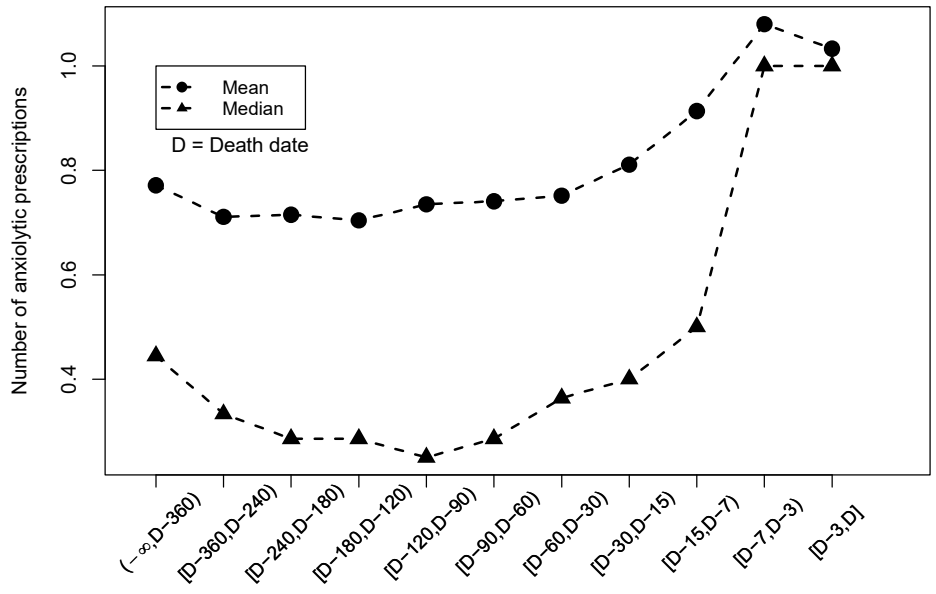


Figure 5. 6 Number of Anxiolytic Prescriptions at End of Life

Anxiolytic drugs are often prescribed together with analgesics, as tables 5.16 and 5.17 indicate. Both the mean and median numbers of anxiolytic prescriptions increase during the hospice stay, again with a small decline in the last seven days (figure 5.6).

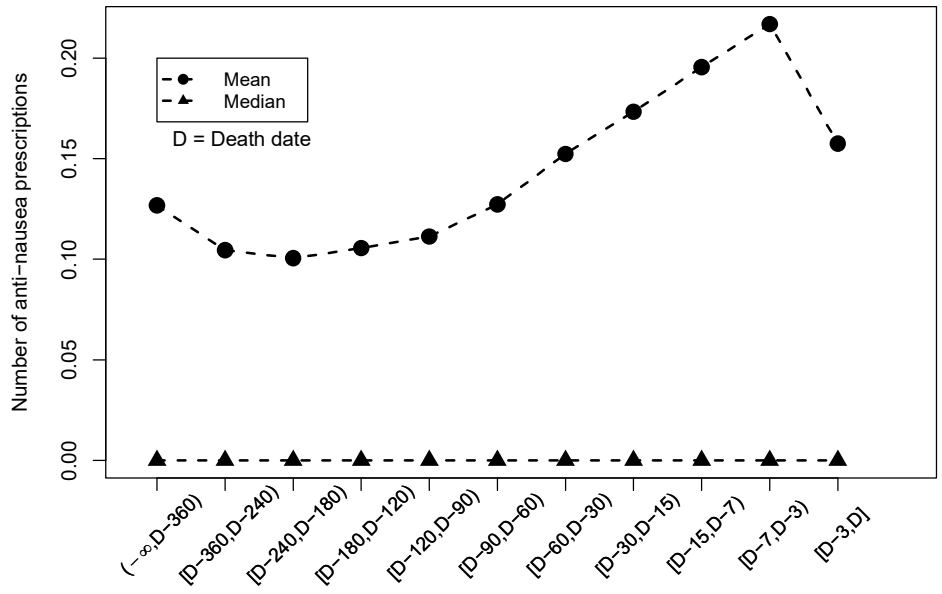


Figure 5. 7 Number of Anti-Nausea Prescriptions at End of Life

On average, few patients have a prescription for an anti-nausea drug, although there is some increase in the average number of prescriptions during the stay, with a decline in the last few days of life, possibly because patients' method of nutrition changes from solid to liquid form (see figure 5.7).

5.4.3.6 Relationship of drug strength and diagnosis

Figures 5.8 through 5.11 are similar to figures 5.4 through 5.7, except that here we show the pattern of prescribing by diagnostic group. We compare drug strength and prescription prevalence during the patient's stay with diagnosis, grouping the top ten admitting diagnoses into five categories as follows:

1. Cancer: Metastatic cancer and acute leukemia, lung and other severe cancers, colorectal, bladder, and other cancers, and breast, prostate, and other cancers and tumours (Sum of the HCC categories HCC 8-12).
2. Heart: Congestive heart failure, acute myocardial infarction, unstable angina and acute ischemic heart disease, and specified heart arrhythmias (HCCs 85-88 and 96).
3. Kidney: Dialysis, acute renal disease, and chronic kidney disease (HCC 134-141).

4. Lung: COPD (HCC 82-84).
5. Dementia and Psych conditions, such as drug/alcohol psychosis, schizophrenia, and major depressive, bipolar, and paranoid disorders (HCC 51-58).

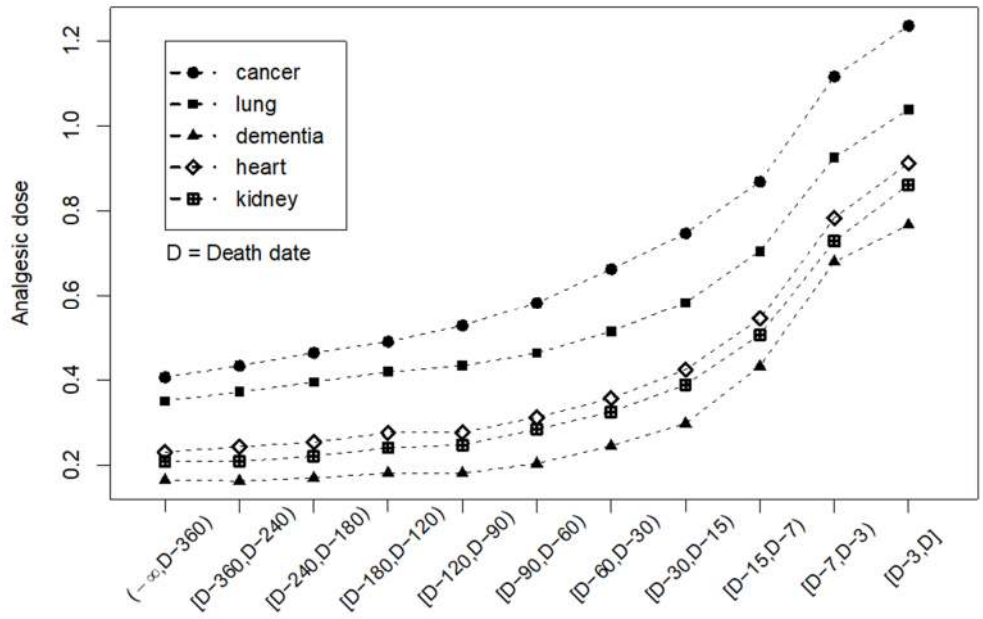


Figure 5. 8 Cumulative Analgesic Dose at End of Life by Diagnostic Category

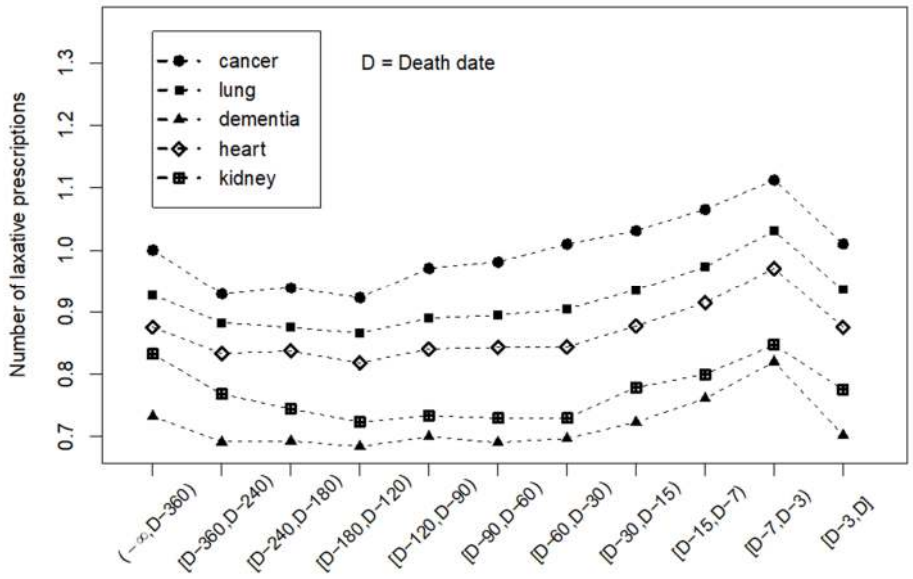


Figure 5. 9 Number of Laxative Prescriptions at End of Life by Diagnostic Category

There is clear separation between cancer and lung diagnoses and other diagnoses, in terms of the analgesic prescription dosage throughout the patient's hospice stay (figure 5.8). Average dosages of analgesics for cancer patients increase from 0.4 initially, to an amount

in excess of 100% (reflecting the prescriptions of multiple analgesic drugs). The average dosage of dementia patients is conversely low, but not non-zero. All diagnoses, however, experience sharp increases in drug strength in the last 30 days of life.

Cancer patients experience the highest frequency of laxative prescriptions throughout their stays (figure 5.9), with lung (COPD) patients and heart patients experiencing lower, but similar, patterns of prescription frequency. Although dementia and kidney patients experience relatively lower prescription frequency, the frequency within these diagnoses remains high. Patients with all diagnoses, except cancer, experience reductions in laxative prescriptions in their last few days.

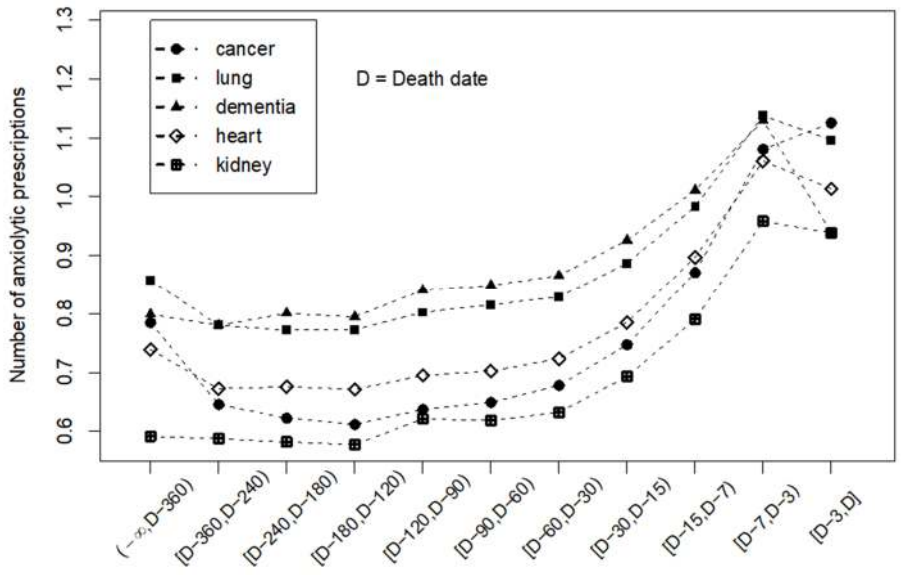


Figure 5. 10 Number of Anxiolytic Prescriptions at End of Life by Diagnostic Category

Figure 5.11 shows that the average frequency of anti-nausea drugs is relatively low (compared with other drug classes) throughout the hospice stay. The frequency increases modestly during the stay, with a decline in the last few days of life.

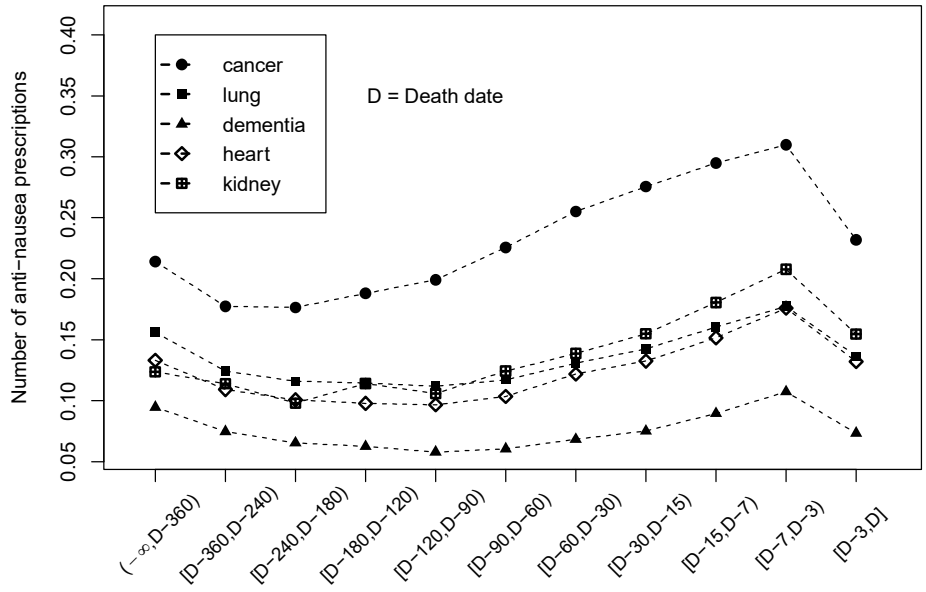


Figure 5. 11 Anti-nausea Prescriptions at End of Life by Diagnostic Category

As the analysis in this section shows, the prescribing patterns of different drugs vary during a patient's hospice stay, both over time and by diagnosis, providing potential information for estimating a patient's survival as prescriptions change.

5.4.3.7 Relationship of drug strength and other variables

Drug strength and number of prescriptions vary by a number of variables, implying that we will need to account for this variation in any time-dependent survival model. In addition to time, age at admission has a significant effect on prescription strength. Specifically, drug strength first increases and then decreases, with an increase in age at admission. Figure 5.12 shows the distribution of strength within each age group. We first observe the increasing trend (moving from age group one and two to other groups) and then the decreasing trend (from group three towards the end). However, the percentage of hospice in these two young-age groups is low and we can omit the initial increasing trend and focus only on the decreasing trend. It may appear counter-intuitive that drug strength decreases with patient age at admission. However, this finding is consistent with the clinical observation that older patients have a higher pain threshold and tolerance for pain than younger patients.

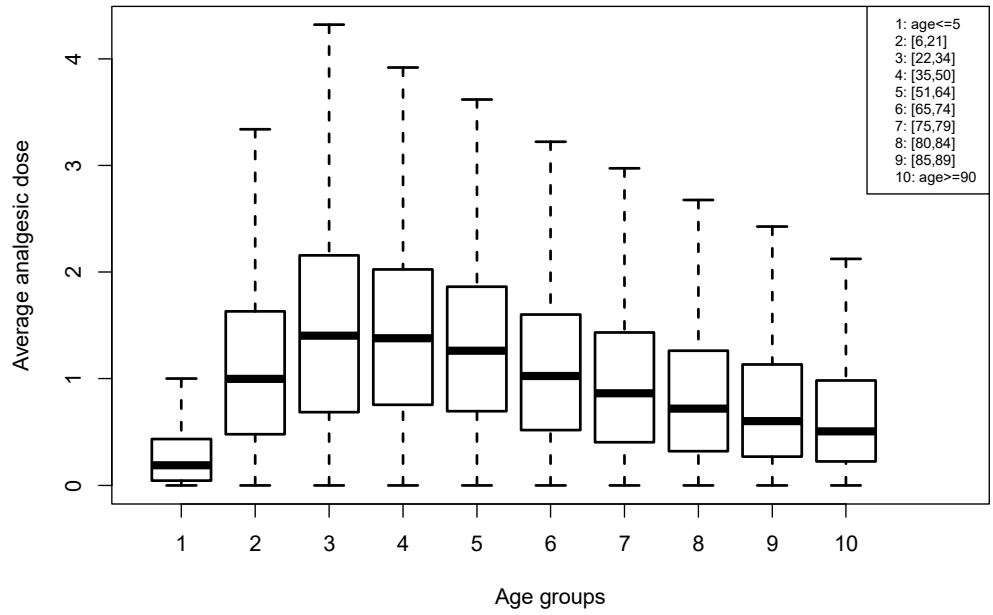


Figure 5. 12 Decreasing Trend in Analgesic Dose as Age Increases

Figure 5.13 shows that males have, on average, a higher dose of analgesic drugs than females. This is due, in part, to the difference in primary diagnoses. As table 5.6 shows, male hospice patients are more likely to suffer from cancer than females, while the prevalence of stroke and dementia is considerably higher in females.

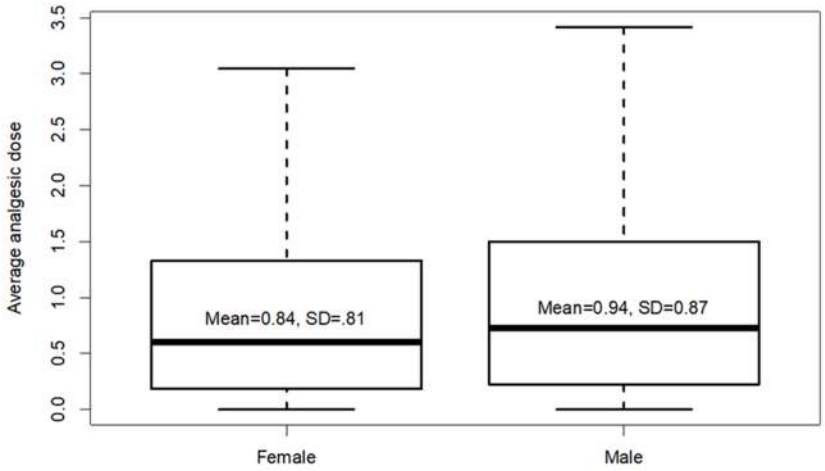


Figure 5. 13 Males Have a Higher Analgesic Dose on Average Compared to Females

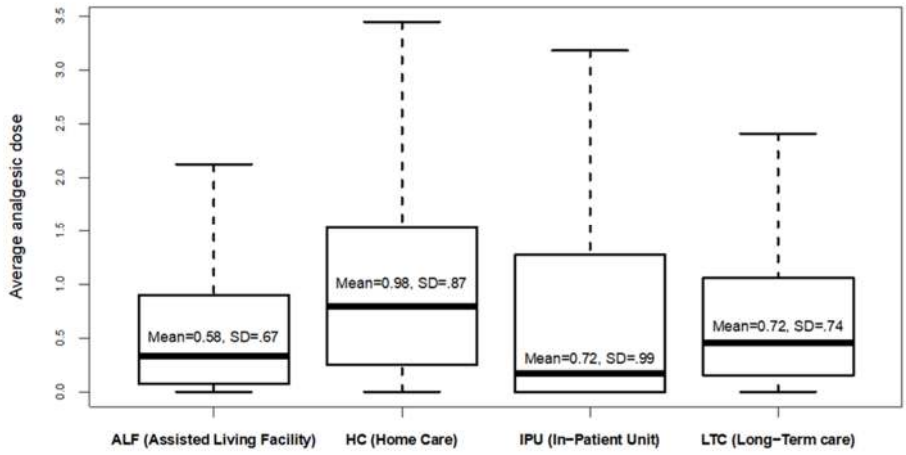


Figure 5. 14 Home Care has Highest Analgesic Dose, on Average, Compared to Other Settings

The drug strength variable constructed and analysed in this chapter will form an input variable in the survival models developed later.

5.5 Summary

This chapter covered the demographic, clinical, and drug data available in our database. Variables, particularly diagnostic and drug variables, have been developed that will be used as inputs to the survival models in succeeding chapters.

5.6 Appendix A: CMS's Hierarchical Condition Categories (HCCs)

HCCs are a very useful set of algorithms for mapping diagnoses to higher-level condition categories, enabling us to reduce the number of independent variables in an analysis. The HCC system has the additional benefit that it was developed and is maintained by CMS. The (CMS) HCC system was developed in the late 1990s as a health risk adjuster for HMOs that enrol Medicare populations (now called Medicare Advantage). Initially, the system focused only on inpatient diagnoses (PIP-DCG), but was later extended to all services. The HCC system has been extensively evaluated and reported in the literature [42]. The fundamental concept of the HCC system is that diagnoses (approximately 15,000 different ICD-9 codes and 80,000 ICD-10 codes) may be mapped to a set of condition categories (the HCCs). The HCCs are, however, hierarchical; a patient with an uncomplicated diagnosis, as well as a diagnosis with complications, will trigger only one HCC, the highest severity within that condition category.

The HCC model is used for risk adjustment by assigning a weight to each HCC. The weights are developed by a linear regression model, where the dependent variable is claims cost and independent variables include the HCCs, demographic variables and a few interaction terms. Figure A5.1 shows the distribution of the CMS HCC risk scores of patients in this study.

More information may be found in Duncan [35].

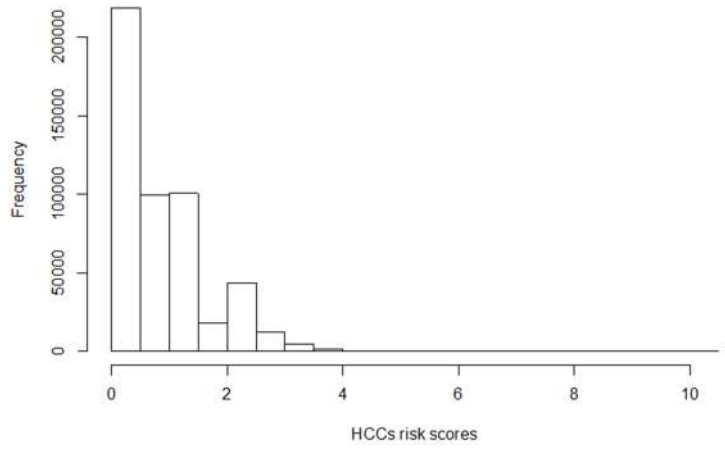


Figure A5.1 Distribution of HCC Risk Scores for Hospice Population

5.7 Appendix B: Cancer diagnoses included in CMS's Hierarchical Condition Categories

The CMS HCCs group a number of different cancer diagnoses into categories denoted by Lung, Breast, Colorectal and Lymphatic cancers. Within each of these groups are a number of other, less-prevalent cancers. The following provides examples of the mapping of other cancers:

Breast, Prostate and other cancers

In addition to breast cancer this category includes cancer of the prostate, face, neck, genitals, etc.

Lung and other severe cancers

In addition to lung cancer, this category includes cancer of the esophagus, stomach, pancreas and leukemia.

Colorectal, bladder and other cancers

In addition to colorectal and bladder cancers, this category includes cancers of the mouth, tongue and kidneys.

Lymphoma and other cancers

In addition to cancers of the lymphatic system this category includes brain and ovarian cancers.

CHAPTER 6 – POLYPHARMACY, MEDICATION POSSESSION AND DEPRESCRIBING OF PREVENTATIVE DRUGS IN HOSPICE PATIENTS

6.1 Background

6.1.1 Introduction

This chapter applies the principles of survival models to a problem frequently encountered in hospice: patients are prescribed drugs of limited efficacy that may also be potential sources of adverse drug events (ADEs). We study the prevalence of drugs that are prescribed for preventive purposes, but which are no longer likely to be beneficial and could result in ADEs in a population with terminal illness, as well as the rate at which these drugs are withdrawn from patients (deprescribed).

Patients receiving hospice and palliative care frequently have a number of co-morbidities, in addition to the terminal illness that qualifies the patient for hospice. Because they often continue to require treatment for their underlying medical conditions, in addition to the medications prescribed for palliation, hospice patients frequently are at risk for polypharmacy. Polypharmacy may be defined as the presence of five to nine different classes of medication; however, some definitions include taking a medication that lacks an indication, is ineffective, or duplicates treatment provided by another drug [43]. Polypharmacy is associated with multiple negative consequences, including an increased risk for adverse drug events, drug-drug and drug-disease interactions, reduced functional capacity, multiple geriatric syndromes, medication non-adherence, and increased mortality. Polypharmacy also contributes to increased health care costs for both the patient and the health care system [43].

Deprescribing is defined as the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits, within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences [44]. After hospice election, many maintenance drugs, as well as drugs used to treat or cure a condition, should be considered for discontinuation, unless they are offering symptom relief.

The Centers for Medicare and Medicaid Services (CMS, the administrator of the Medicare program for the elderly) pays hospices a *per diem* rate to include all medications,

services, and supplies related to the conditions affecting prognosis. CMS expects that hospices provide "virtually all of the care needed by terminally ill individuals," including related prescription drugs [45], p.2. CMS requires hospices to cover the cost of these medications as part of the *per diem* payment. In addition to the importance of deprescribing non-beneficial and over-used medications to decrease risk to patients, hospices should also take steps to deprescribe medications that are no longer needed by the patient, to avoid paying for treatment that is not medically necessary. Studies of deprescribing in hospice patients are rare, and to our knowledge, this is the first study of medication possession and deprescribing rates in a large national database of hospice prescription drug data.

6.2 Prior Studies

As noted by Van Nordennen and colleagues [46], there is a lack of data regarding medication prescribing at the end of life. Prior studies fall, generally, into three categories: principles of prescribing and consensus criteria [47, 48], reviews of the literature [49-54], or cohort studies of specific populations [37, 46, 55-60]. Although authors have studied institutionalized populations, studies of hospice patients are rare. A frequent conclusion from review articles is that "patients with life-limiting illnesses are prescribed preventative medications considered inappropriate in the context of diminished life," particularly lipid-regulating drugs, antihypertensive, and antidiabetic medications ([53], abstract p.1). Cohort studies reach similar conclusions. For example, Currow and colleagues studied 260 Australian end-of-life patients and concluded that "medications for co-morbid conditions especially for secondary prevention may be continued for longer than clinically indicated….there may be opportunities to prevent morbidity and even premature mortality in a person with a life-limiting illness, especially in older people, if medications for comorbid conditions are more actively managed" ([37], p. 593). In a Dutch study, examining 155 patients with life expectancy of 3 months or less, Van Nordennen and colleagues observed that "all other [non-palliative] drug classes decreased between admission and date of death...including anti-coagulants, beta-blocking agents, drugs used in diabetes and lipid-modifying agents…. there are still patients dying with medication not used for symptom control" ([61], p.514) Although several cohort studies report medication prevalence at admission and at death, ours is the first study that reports the observed rate at

which terminal patients are weaned from curative drugs, and the persistency of such drugs in the hospice population.

6.3 Methods

6.3.1 Design

This is a historical cohort observational study that applies Cumulative Incidence Competing Risk survival models to our hospice database to estimate the rate of deprescribing of different drug classes. Because patients survive in hospice for different durations, we also calculate patient medication possession ratios to estimate the percentage of a patient's stay during which the patient had a prescription for each drug class.

6.3.2 Potentially ineffective drug classes

Our hospice population uses a wide range of drugs, classified by therapeutic class. For this study, a professional pharmacist was consulted and has identified, for hospice patients at end of life, ten classes of potentially ineffective drugs. The specific drugs that make up these classes number in the thousands; the actual drugs are available as supplementary material from the author. Drug classes that consist of potentially ineffective drugs that show evidence of a high rate of prescribing within our database are antibiotics, anti-hypertensives, proton pump inhibitors, inhalers, anti-coagulants, dementia medications, anti-virals, diabetes medications, statins and other lipid-lowering agents, appetite stimulants, and vitamins and supplements.

6.4 Data

In total, our data cover 186,904 patients admitted to hospice in 2015-2016, of whom 4,385 remained alive at the date of extraction (May 2018). See table 6.1.

Year	Female		Male		Total		Subtotal
	Alive	Deceased	Alive	Deceased	Alive	Deceased	By Year
2015	140	42,730	55	31,350	195	74,080	74,275
2016	3,041	63,949	1,149	44,490	4,190	108,439	112,629
Subtotal by Year, Sex, and Status	3,181	106,679	1,204	75,840	4,385	182,519	186,904

Table 6. 1 Hospice Population by Age, Sex, Status, and Year of Admission

Study patients have a wide variety of primary conditions; for analysis, we grouped diagnoses using the Medicare hierarchical condition categories (HCCs) [35, 62]. We then aggregated Medicare HCCs into categories of conditions. The aggregation of HCCs is described in Appendix 6.1.

In table 6.2, we report patients by primary condition, grouped into seven primary condition categories. In addition, for completeness (and because many published studies do not distinguish between palliative and therapeutic drug classes), we report both palliative and therapeutic drugs. Palliative drugs make up a high percentage of all prescriptions, although the data also show significant therapeutic drug prescribing. In the analysis that follows, we focus on other therapeutic and potentially ineffective classes that are often prescribed for maintenance rather than palliative care and omit the four palliative drug classes, because these classes are considered required for hospice patients and not a target for deprescribing.

Overall, in Table 6.2, aggregating patients over the two years, 2015-2016, 173,246 or 92.7% of all patients have an analgesic prescription (Table 6.3). In table 6.2, cancer patients represent 66,656, or 35.7% of patients, out of the total patient population of 186,904. These patients account for 36.2% of all analgesic prescriptions (table 6.3), indicating that analgesic drug use is widely distributed by diagnosis and is not confined to cancer patients. Of all cancer patients (66,656), 62,690, or 94.1%, have an analgesic prescription (table 6.4).

The remainder of this chapter focuses on therapeutic or potentially ineffective drugs. Patients with an antibiotic prescription number 43,316, or 23.2% of all patients. Cancer patients with an antibiotic prescription number 11,474. Cancer patients represent 26.5% of all patients with an antibiotic prescription (table 6.3) and 17.2% of all cancer patients have an antibiotic prescription (table 6.4). It is important to note that tables 6.2 and 6.3 show drug possession numbers and percentages for different diagnoses at some point during the hospice stay; they do not indicate the possession of these drugs over time. Because therapeutic drugs may have been prescribed at entry to hospice, they could be deprescribed during the patient's stay. Some patients will not have therapeutic prescriptions at admission to hospice because they have unused supplies of drugs from prior to admission; drugs will, however, be prescribed once supplies are exhausted. We will study possession of drugs over time later in this chapter.

Drug Class	Cancer	Dementia	Heart	Lung	Gastro-intestinal	Kidney	Liver	Other	Row total	All patients within drug class
Palliative Drugs										
Analgesics	62,690	23,565	18,841	14,829	2,482	2,161	1,853	1,891	128,312	173,246
Anxiolytics	53,292	20,442	16,353	13,145	2,043	1,823	1,634	1,566	110,298	134,672
Laxatives	49,030	18,044	14,629	11,568	1,781	1,543	1,497	1,383	99,475	148,641
Anti-nauseants	27,090	6,188	6,323	4,710	806	767	818	584	47,286	61,585
Sub-total	192,102	68,239	56,146	44,252	7,112	6,294	5,802	5,424	385,371	518,144
Other Drugs										
Antibiotics	11,474	6,922	5,245	5,196	612	360	349	408	30,566	43,316
Antihypertensives	6,963	3,610	8,728	3,215	358	594	257	278	24,003	36,219
Proton pump inhibitors	13,459	2,587	3,643	3,494	394	302	498	256	24,633	31,934
Inhalers	5,019	524	1,681	4,413	68	91	115	68	11,979	14,136
Anticoagulants	1,717	293	1,880	524	55	50	6	34	4,559	6,211
Antifungals	1,649	599	484	527	60	41	42	62	3,464	4,720
Diabetes medications	987	307	430	288	20	41	34	24	2,131	3,072
Dementia medications	76	793	69	40	17	6	1	8	1,010	1,568
Antivirals	394	147	104	102	12	4	8	23	794	1,109
Statins and other lipid-lowering agents	68	40	140	42	1	3	2	-	296	532
Appetite stimulant	5	2	1	1	1	-	-	-	10	12
Vitamins & supplements	1	1	1	1	-	-	1	-	5	8
Sub-total	41,812	15,825	22,406	17,843	1,598	1,492	1,313	1,161	103,450	141,766
Total prescriptions	1,008,888	508,091	350,217	364,447	39,531	24,984	25,699	13,397	2,335,254	
Total patients with primary diagnosis	66,656	25,861	20,522	15,870	2,710	2,371	2,045	2,040	138,075	186,904
Prescriptions per patient	15.14	19.65	17.07	22.96	14.59	10.54	12.57	6.57	16.91	

Table 6. 2 Distribution of Patients by Drug Class and Primary Condition (2015-2016)

Drug Class	Cancer	Dementia	Heart	Lung	Gastro-intestinal	Kidney	Liver	Other	Row total	All patients within drug class
Palliative Drugs										
Analgesics	0.362	0.136	0.109	0.086	0.014	0.012	0.011	0.011	0.741	0.927
Anxiolytics	0.396	0.152	0.121	0.098	0.015	0.014	0.012	0.012	0.819	0.721
Laxatives	0.330	0.121	0.098	0.078	0.012	0.010	0.010	0.009	0.669	0.795
Anti-nauseants	0.440	0.100	0.103	0.076	0.013	0.012	0.013	0.009	0.768	0.330
Other Drugs										
Antibiotics	0.265	0.160	0.121	0.120	0.014	0.008	0.008	0.009	0.706	0.232
Antihypertensives	0.192	0.100	0.241	0.089	0.010	0.016	0.007	0.008	0.663	0.194
Proton pump inhibitors	0.421	0.081	0.114	0.109	0.012	0.009	0.016	0.008	0.771	0.171
Inhalers	0.355	0.037	0.119	0.312	0.005	0.006	0.008	0.005	0.847	0.076
Anticoagulants	0.276	0.047	0.303	0.084	0.009	0.008	0.001	0.005	0.734	0.033
Antifungals	0.349	0.127	0.103	0.112	0.013	0.009	0.009	0.013	0.734	0.025
Diabetes medications	0.321	0.100	0.140	0.094	0.007	0.013	0.011	0.008	0.694	0.016
Dementia medications	0.048	0.506	0.044	0.026	0.011	0.004	0.001	0.005	0.644	0.008
Antivirals	0.355	0.133	0.094	0.092	0.011	0.004	0.007	0.021	0.716	0.006
Statins and other lipid-lowering agents	0.128	0.075	0.263	0.079	0.002	0.006	0.004	-	0.556	0.003
Appetite stimulant	0.417	0.167	0.083	0.083	0.083	-	-	-	0.833	0.000
Vitamins & supplements	0.125	0.125	0.125	0.125	-	-	0.125	-	0.625	0.000

Table 6. 3 Distribution of Primary Condition within Drug Class (2015-2016)

Table 6.4 shows the prevalence of different classes of prescriptions within each condition category. For example, 94.1% of cancer patients have a prescription for an analgesic. Columns in table 6.4 sum to more than 100% because patients may have prescriptions from a number of drug classes.

Drug Class	Cancer	Dementia	Heart	Lung	Gastro-intestinal	Kidney	Liver	Other	% Patients within Drug Class
Palliative Drugs									
Analgesics	0.941	0.911	0.283	0.934	0.916	0.911	0.906	0.927	0.929
Anxiolytics	0.800	0.790	0.245	0.828	0.754	0.769	0.799	0.768	0.799
Laxatives	0.736	0.698	0.219	0.729	0.657	0.651	0.732	0.678	0.720
Anti-nauseants	0.406	0.239	0.095	0.297	0.297	0.323	0.400	0.286	0.342
Other Drugs									
Antibiotics	0.172	0.268	0.256	0.327	0.226	0.152	0.171	0.200	0.221
Antihypertensives	0.104	0.140	0.425	0.203	0.132	0.251	0.126	0.136	0.174
Proton pump inhibitors	0.202	0.100	0.178	0.220	0.145	0.127	0.244	0.125	0.178
Inhalers	0.075	0.020	0.082	0.278	0.025	0.038	0.056	0.033	0.087
Anticoagulants	0.026	0.011	0.092	0.033	0.02	0.021	0.003	0.017	0.033
Antifungals	0.025	0.023	0.024	0.033	0.022	0.017	0.021	0.030	0.025
Diabetes medications	0.015	0.012	0.021	0.018	0.007	0.017	0.017	0.012	0.015
Dementia medications	0.001	0.031	0.003	0.003	0.006	0.003	0.000	0.004	0.007
Antivirals	0.006	0.006	0.005	0.006	0.004	0.002	0.004	0.011	0.006
Statins (HMG CoA Reductase Inhibitors)	0.001	0.002	0.007	0.003	0.000	0.001	0.001	-	0.002
Appetite stimulant	0.000	0.000	0.000	0.000	0.000	-	-	-	0.000
Vitamins & supplements	0.000	0.000	0.000	0.000	-	-	0.000	-	0.000

Table 6. 4 Prevalence of Drug Classes by Primary Condition (2015-2016)

Tables 6.5 through 6.12 report the prevalence of potentially ineffective drugs by year, drug class, sex, and seven diagnosis categories.

Drug classes	All diagnoses		All diagnoses		Row total
	Female	Male	Female	Male	
Antibiotics	9,545	6,620	28.9%	28.0%	16,165
Antihypertensives	8,243	5,430	25.0%	23.0%	13,673
Proton pump inhibitors	7,821	5,790	23.7%	24.5%	13,611
Inhaler	3,544	2,996	10.7%	12.7%	6,540
Anticoagulants	1,529	1,313	4.6%	5.6%	2,842
Antifungals	1,342	592	4.1%	2.5%	1,934
Diabetes medications	573	546	1.7%	2.3%	1,119
Antivirals	259	189	0.8%	0.8%	448
Statins (HMG CoA reductase inhibitors)	80	96	0.2%	0.4%	176
Dementia medications	54	25	0.2%	0.1%	79
Appetite stimulant	3	6	0.0%	0.0%	9
Vitamins & supplements	4	1	0.0%	0.0%	5
Total column	32,997	23,604	100.0%	100.0%	56,601
Total patients	20,740	15,005			
Prescription per patient	1.59	1.57			

Table 6. 5 Number and Percentage of Patients with Potentially Ineffective Drugs (2015)

Drug classes	All diagnoses		All diagnoses		Row total
	Female	Male	Female	Male	
Antibiotics	16,872	10,279	32.5%	31.0%	27,151
Antihypertensives	14,118	8,428	27.2%	25.4%	22,546
Proton pump inhibitors	10,909	7,414	21.0%	22.3%	18,323
Inhaler	4,208	3,388	8.1%	10.2%	7,596
Anticoagulants	1,892	1,477	3.6%	4.5%	3,369
Antifungals	2,064	722	4.0%	2.2%	2,786
Diabetes medications	1,035	918	2.0%	2.8%	1,953
Antivirals	414	247	0.8%	0.7%	661
Dementia medications	275	143	0.5%	0.4%	418
Statins (HMG CoA reductase inhibitors)	193	171	0.4%	0.5%	364
Vitamins & supplements	3	-	0.0%	0.0%	3
Appetite stimulant	1	2	0.0%	0.0%	3
Total column	51,984	33,189	100.0%	100.0%	85,173
Total patients	32,530	21,158			
Prescription per patient	1.60	1.57			

Table 6. 6 Number and Percentage of Patients with Potentially Ineffective Drugs (2016)

Drug classes	Cancer	Heart	Lung	Dementia	Liver	Gastro-intestinal	Kidney
Antibiotics	4,861	1,718	1,936	2,089	165	181	87
Antihypertensives	2,900	2,991	1,183	1,128	129	94	162
Proton pump inhibitors	6,165	1,277	1,386	875	253	123	92
Inhaler	2,473	687	1,802	225	73	25	25
Anticoagulants	834	769	241	115	3	22	13
Antifungals	747	191	191	191	20	17	13
Diabetes medications	437	145	93	77	20	6	8
Antivirals	168	32	32	49	3	1	2
Statins (HMG CoA reductase inhibitors)	24	42	13	10	2	-	-
Dementia medications	4	2	1	48	-	-	-
Appetite stimulant	5	1	1	1	-	-	-
Vitamins & supplements	1	1	-	1	-	-	-
Column total	18,619	7,856	6,879	4,809	668	469	402
Total patients	12,612	4,326	3,714	3,384	437	340	262
Prescription per class	1.48	1.82	1.85	1.42	1.53	1.38	1.53

Table 6. 7 Relationship between Primary Condition and Potentially Ineffective Drugs (2015)

Drug classes	Cancer	Heart	Dementia	Lung	Gastro-intestinal	Kidney	Liver
Antibiotics	6,613	3,527	4,833	3,260	431	273	184
Antihypertensives	4,063	5,737	2,482	2,032	264	432	128
Proton pump inhibitors	7,294	2,366	1,712	2,108	271	210	245
Inhaler	2,546	994	299	2,611	43	66	42
Anticoagulants	883	1,111	178	283	33	37	3
Antifungals	902	293	408	336	43	28	22
Diabetes medications	550	285	230	195	14	33	14
Antivirals	226	72	98	70	11	2	5
Dementia medications	23	16	205	13	6	-	-
Statins (HMG CoA reductase inhibitors)	44	96	30	28	1	3	-
Vitamins & supplements	-	-	-	1	-	-	1
Appetite stimulant	-	-	1	-	1	-	-
Column total	23,144	14,497	10,476	10,937	1,118	1,084	644
Total patients	15,945	8,143	7,417	5,926	786	688	448
Prescription per class	1.45	1.78	1.41	1.85	1.42	1.58	1.44

Table 6. 8 Relationship between Primary Condition and Potentially Ineffective Drugs (2016)

Drug classes	Cancer	Heart	Lung	Dementia	Liver	Gastro-intestinal	Kidney
Antibiotics	38.5%	39.7%	52.1%	61.7%	37.8%	53.2%	33.2%
Antihypertensives	23.0%	69.1%	31.9%	33.3%	29.5%	27.6%	61.8%
Proton pump inhibitors	48.9%	29.5%	37.3%	25.9%	57.9%	36.2%	35.1%
Inhaler	19.6%	15.9%	48.5%	6.6%	16.7%	7.4%	9.5%
Anticoagulants	6.6%	17.8%	6.5%	3.4%	0.7%	6.5%	5.0%
Antifungals	5.9%	4.4%	5.1%	5.6%	4.6%	5.0%	5.0%
Diabetes medications	3.5%	3.4%	2.5%	2.3%	4.6%	1.8%	3.1%
Antivirals	1.3%	0.7%	0.9%	1.4%	0.7%	0.3%	0.8%
Statins (HMG CoA reductase inhibitors)	0.2%	1.0%	0.4%	0.3%	0.5%	0.0%	0.0%
Dementia medications	0.0%	0.0%	0.0%	1.4%	0.0%	0.0%	0.0%
Appetite stimulant	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Vitamins & supplements	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Column total	18,619	7,856	6,879	4,809	668	469	402
Total patients	12,612	4,326	3,714	3,384	437	340	262
Prescription per class	1.48	1.82	1.85	1.42	1.53	1.38	1.53

Table 6. 9 Frequency of Potentially Ineffective Drugs by Patient and Primary Condition (2015)

Drug classes	Cancer	Heart	Dementia	Lung	Gastro-intestinal	Kidney	Liver
Antibiotics	41.5%	43.3%	65.2%	55.0%	54.8%	39.7%	41.1%
Antihypertensives	25.5%	70.5%	33.5%	34.3%	33.6%	62.8%	28.6%
Proton pump inhibitors	45.7%	29.1%	23.1%	35.6%	34.5%	30.5%	54.7%
Inhaler	16.0%	12.2%	4.0%	44.1%	5.5%	9.6%	9.4%
Anticoagulants	5.5%	13.6%	2.4%	4.8%	4.2%	5.4%	0.7%
Antifungals	5.7%	3.6%	5.5%	5.7%	5.5%	4.1%	4.9%
Diabetes medications	3.4%	3.5%	3.1%	3.3%	1.8%	4.8%	3.1%
Antivirals	1.4%	0.9%	1.3%	1.2%	1.4%	0.3%	1.1%
Dementia medications	0.1%	0.2%	2.8%	0.2%	0.8%	0.0%	0.0%
Statins (HMG CoA reductase inhibitors)	0.3%	1.2%	0.4%	0.5%	0.1%	0.4%	0.0%
Vitamins & supplements	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.2%
Appetite stimulant	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%
Column total	23,144	14,497	10,476	10,937	1,118	1,084	644
Total patients	15,945	8,143	7,417	5,926	786	688	448
Prescription per class	1.45	1.78	1.41	1.85	1.42	1.58	1.44

Table 6. 10 Frequency of Potentially Ineffective Drugs by Patient and Primary Condition (2016)

Drug classes	Cancer	Heart	Lung	Dementia	Liver	Gastro-intestinal	Kidney	Row total
Antibiotics	44.0%	15.6%	17.5%	18.9%	1.5%	1.6%	0.8%	100.0%
Antihypertensives	33.8%	34.8%	13.8%	13.1%	1.5%	1.1%	1.9%	100.0%
Proton pump inhibitors	60.6%	12.6%	13.6%	8.6%	2.5%	1.2%	0.9%	100.0%
Inhaler	46.6%	12.9%	33.9%	4.2%	1.4%	0.5%	0.5%	100.0%
Anticoagulants	41.8%	38.5%	12.1%	5.8%	0.2%	1.1%	0.7%	100.0%
Antifungals	54.5%	13.9%	13.9%	13.9%	1.5%	1.2%	0.9%	100.0%
Diabetes medications	55.6%	18.4%	11.8%	9.8%	2.5%	0.8%	1.0%	100.0%
Antivirals	58.5%	11.1%	11.1%	17.1%	1.0%	0.3%	0.7%	100.0%
Statins (HMG CoA reductase inhibitors)	26.4%	46.2%	14.3%	11.0%	2.2%	0.0%	0.0%	100.0%
Dementia medications	7.3%	3.6%	1.8%	87.3%	0.0%	0.0%	0.0%	100.0%
Appetite stimulant	62.5%	12.5%	12.5%	12.5%	0.0%	0.0%	0.0%	100.0%
Vitamins & supplements	33.3%	33.3%	0.0%	33.3%	0.0%	0.0%	0.0%	100.0%

Table 6. 11 Frequency of Potentially Ineffective Drugs Classes by Primary Condition (2015)

Drug classes	Cancer	Heart	Dementia	Lung	Gastro-intestinal	Kidney	Liver	Row total
Antibiotics	34.6%	18.4%	25.3%	17.0%	2.3%	1.4%	1.0%	100.0%
Antihypertensives	26.8%	37.9%	16.4%	13.4%	1.7%	2.9%	0.8%	100.0%
Proton pump inhibitors	51.3%	16.7%	12.1%	14.8%	1.9%	1.5%	1.7%	100.0%
Inhaler	38.6%	15.1%	4.5%	39.6%	0.7%	1.0%	0.6%	100.0%
Anticoagulants	34.9%	43.9%	7.0%	11.2%	1.3%	1.5%	0.1%	100.0%
Antifungals	44.4%	14.4%	20.1%	16.5%	2.1%	1.4%	1.1%	100.0%
Diabetes medications	41.6%	21.6%	17.4%	14.8%	1.1%	2.5%	1.1%	100.0%
Antivirals	46.7%	14.9%	20.2%	14.5%	2.3%	0.4%	1.0%	100.0%
Dementia medications	8.7%	6.1%	77.9%	4.9%	2.3%	0.0%	0.0%	100.0%
Statins (HMG CoA reductase inhibitors)	21.8%	47.5%	14.9%	13.9%	0.5%	1.5%	0.0%	100.0%
Vitamins & supplements	0.0%	0.0%	0.0%	50.0%	0.0%	0.0%	50.0%	100.0%
6Appetite stimulant	0.0%	0.0%	50.0%	0.0%	50.0%	0.0%	0.0%	100.0%

Table 6. 12 Frequency of Potentially Ineffective Drugs Classes by Primary Condition (2016)

6.5 Results

The analysis above shows information about drug prevalence but does not provide information about the duration of that possession or the rate at which drugs are withdrawn.

To understand the rate at which drugs are terminated or deprescribed we calculate the Cumulative Incidence Function (the complement of the survival function or crude incidence rate) often used in the analysis of competing risks. Applying regular survival analysis in the presence of competing risks will lead to an overestimate of the true rate of the event of interest.

6.5.1 Competing risks

In our study of the termination of prescriptions, death is the competing risk event to prescription termination: the occurrence of death prevents the prescription from running for a full term (or being renewed) and is therefore a competing event to the prescription termination event. "Competing risks are said to be present when a patient is at risk of more than one mutually exclusive event, such as death from different causes, and the occurrence of one of these will prevent any other event from ever happening" [63]. "When estimating the crude incidence of outcomes, analysts should use the cumulative incidence function, rather than the complement of the Kaplan-Meier survival function. The use of the Kaplan-Meier survival function results in estimates of incidence that are biased upward, regardless of whether the competing events are independent of one another" [64].

Let $F_{rx}(t)$ be the cumulative incidence function (CIF) for the event of interest; in our case, the termination of prescriptions within a drug class. The CIF gives the proportion of patients whose prescriptions at time t have terminated but who are still alive and at risk of death. The CIF for prescription termination is calculated as follows:

$$F_{rx}(t) = \Pr(T \le t, D = rx) = \int_0^t h_{rx}(u, X) S(u) du \qquad (6.1)$$

Where D is the random variable denoting cause of failure, $h_{rx}(t)$ is the cause-specific hazard function at time t (i.e. the instantaneous risk of prescriptions being terminated given that the patient still has prescriptions at time t, X is the vector of covariates and $S(t)$ is the overall survival function. In this study, D is either "death" (coded as "1") when death occurs prior to prescription termination, or "rx termination" (coded as "2") when death occurs after termination of prescription. Censored events are coded as "0" (i.e. patients are alive with prescription end-point after the evaluation date).

In equation 6.3 calculation of the CIF is a two-step process: the first step is the application of the regular Kaplan-Meier approach to estimate the overall survival probability (the proportion of patients who have not experienced an end-point (death or prescription termination)). The second step is to compute the conditional probabilities of the event of interest (cause-specific probability).

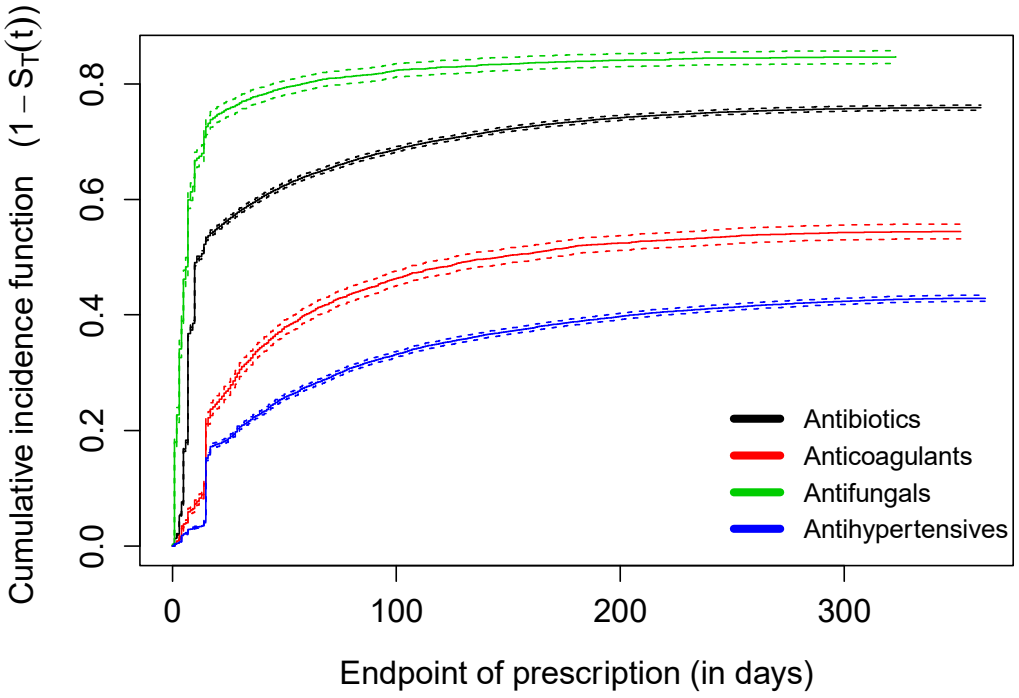
6.5.2 Cumulative Incidence Function analysis of termination rates

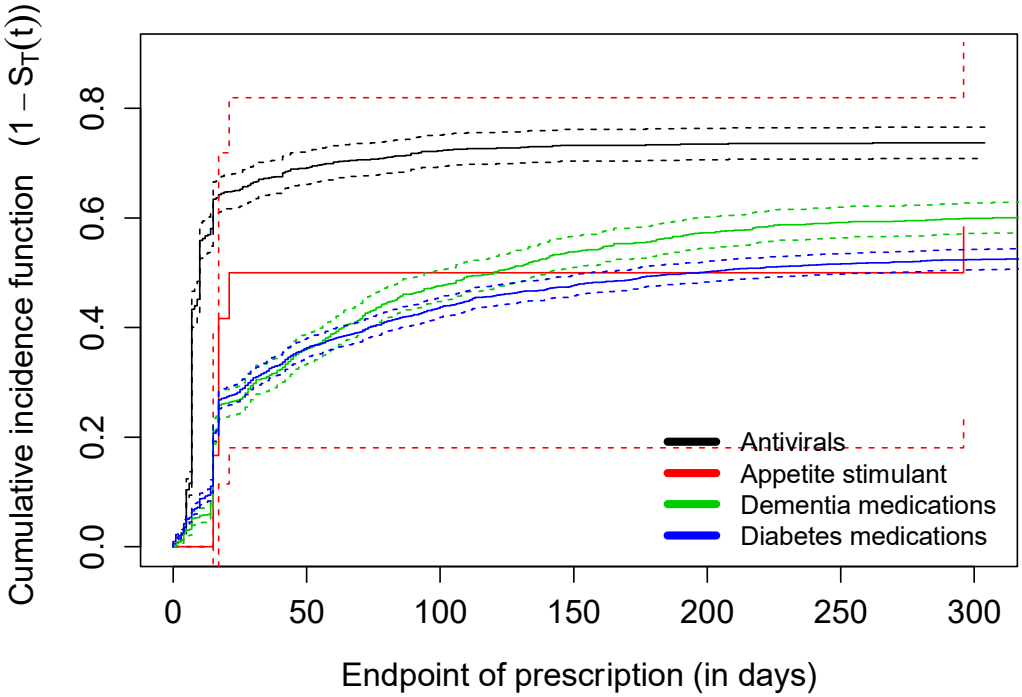
Initially, 100% of patients within a class have a prescription; over time, the CIF curve represents the patient drug discontinuation within the class. The CIF approach (figure 6.1) for competing risks estimates the duration of patients taking additional drugs while considering the patient's future lifetime during hospice admission. The y-axis shows the cumulative incidence rate; the x-axis shows the duration of drug prescription (days). Anti-fungal, anti-viral, and antibiotic medications are prescribed for the shortest period, with median prescription termination of seven, ten and twelve days, respectively. Twenty-five percent of patients have an anti-fungal prescription terminated at three days or less; seventy-five percent of patients have their anti-fungal medication withdrawn within twenty-two days. Conversely, proton pump inhibitors (PPI) and anti-hypertensives are withdrawn more slowly with twenty-fifth quantile prescription terminations of 43 and 47 days.Note that the median and the seventy-fifth quantile prescription for some of these classes are 'missing' ("NA" in Table 6.13) as the CIF curves never reach the levels of 0.5 and 0.75 on the y-axis. This suggests that there is limited deprescribing these prescriptions during patient's stay in hospice; the prescriptions persist during the patient's stay. In particular more than half of patients did not have their prescriptions terminated within a year.

Table 6.13 only reports duration quantiles; we also need to relate duration of the prescription to length of hospice stay, which we do using Medication Possession Ratios.

Drug classes	CIF (death is the competing risk event)		
	Q25	Q50	Q75
Antifungals	3	7	22
Antivirals	7	10	304
Antibiotics	7	12	240
Vitamins & supplements	15	21	27
Inhaler	5	23	183
Statins and other lipid-lowering agents	15	93	NA
Dementia medications	17	120	NA
Anticoagulants	21	146	352
Diabetes medications	17	197	NA
Appetite stimulant	17	296	296
Antihypertensives	47	NA	NA
Proton pump inhibitors	43	NA	NA

Table 6. 13 Quantile Survival Time of Drug Classes in Days





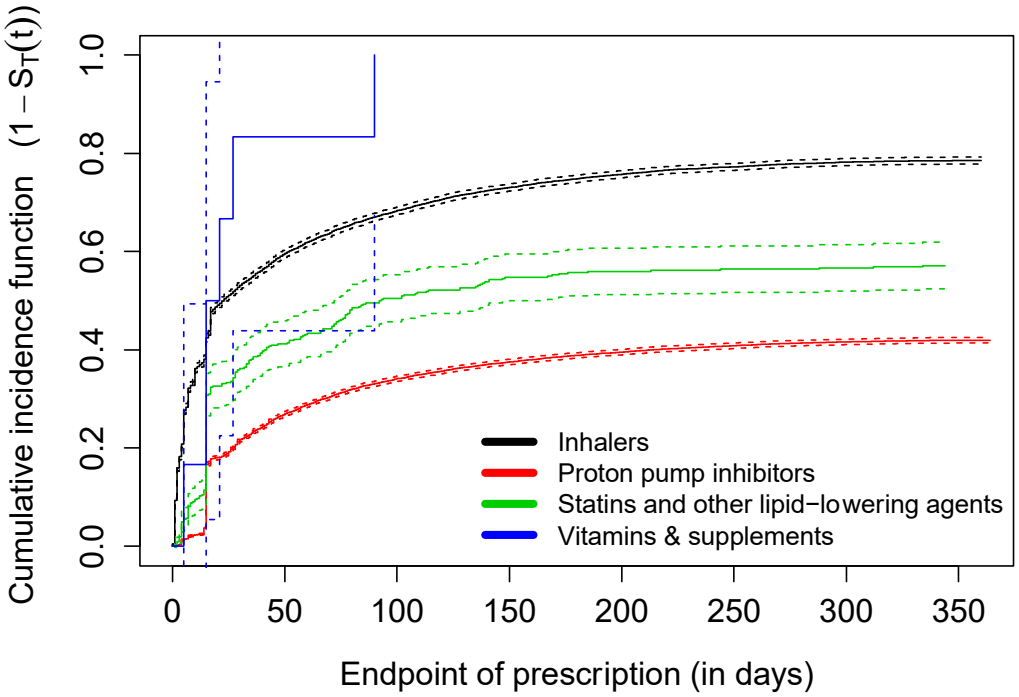


Figure 6. 1 Cumulative Incidence Function (CIF) Estimates of Termination of Preventive Drugs

6.5.3 Prescription Durations: Medication Possession Ratios

The CIF approach shows the rate at which drug classes are withdrawn; it does not show the relationship of prescription duration and hospice length of stay. Because patients have different durations on drugs, as well as different hospice length of stay, we need a way to relate the two. In addition to looking at the persistency of patient drug possession within each class we calculate a possession ratio at the individual patient level. Possession Ratio is defined as the percentage of time that a patient has access to a medication, relative to the time that the patient *could have had* the medication. On our context, the medication possession ratio for a patient is defined as: $\frac{\sum \text{Days supply during hospice stay}}{\sum \text{Duration of hospice stay in days}}$ for each medication.

Table 6.14 shows the distribution of Medication Possession Ratios for each drug.

Drug Class	Number of prescriptions	Min	Q25	Q50	Mean	Q75	Max
Antihypertensives	259,116	0.0000	0.7872	0.9299	0.8440	0.9834	1
Proton pump inhibitors	142,123	0.0000	0.7143	0.9009	0.8096	0.9756	1
Anticoagulants	33,675	0.0000	0.6410	0.8558	0.7659	0.9608	1
Diabetes medications	13,585	0.0000	0.6077	0.8421	0.7478	0.9565	1
Dementia medications	8,351	0.0061	0.6062	0.8377	0.7427	0.9400	1
Appetite stimulant	18	0.1339	0.5089	0.8000	0.7147	0.9565	0.9184
Statins and other lipid-lowering agents	2,020	0.0126	0.5120	0.7564	0.6881	0.9164	1
Inhalers	43,940	0.0000	0.4337	0.7551	0.6567	0.9241	1
Vitamins and supplements	16	0.0281	0.1042	0.7778	0.5732	0.9184	1
Antibiotics	91,691	0.0000	0.1911	0.5455	0.5223	0.8404	1
Antivirals	1,755	0.0014	0.0893	0.4233	0.4618	0.8182	1
Antifungals	6,578	0.0000	0.0411	0.1856	0.3237	0.5989	1

Table 6. 14 Distribution of Medication Possession Ratios for potentially-inappropriate drugs

In Table 6.14 the fractions indicate the proportion of their hospice stays that patients with the specific drug have a supply of the drug. In the case of hypertensive medications, for example the 25th Quantile is 0.7872, implying that 75% of all patients have the drug in their

possession for almost 80% of their stays. Proton pump inhibitors (PPIs) are another drug with high possession ratios: 50% of all patients have a PPI for more than 90% of their hospice stay. The conclusion from Table 6.14 is that, with the possible exception of antiviral and anti-fungal medications, patients have prescriptions for potentially-inappropriate medications for a considerable portion of their stays in hospice.

The variance in individual patients' medication possession ratios can be considerable in the case of some drugs. Figure 6.2 shows the mean and variance of each drug. PPIs, which have a high mean possession ratio also have a narrow confidence interval, implying that patients with these drugs take them for a considerable portion of their hospice stays, and that there is relatively little variation by patient in terms of the proportion of hospice stay during which the patient has one of these drugs. Antibiotics, anti-fungals and anti-viral medications have relatively low mean possession ratios, but also have relatively wide confidence intervals, implying that there is considerable variation in the length of the prescription by patient.

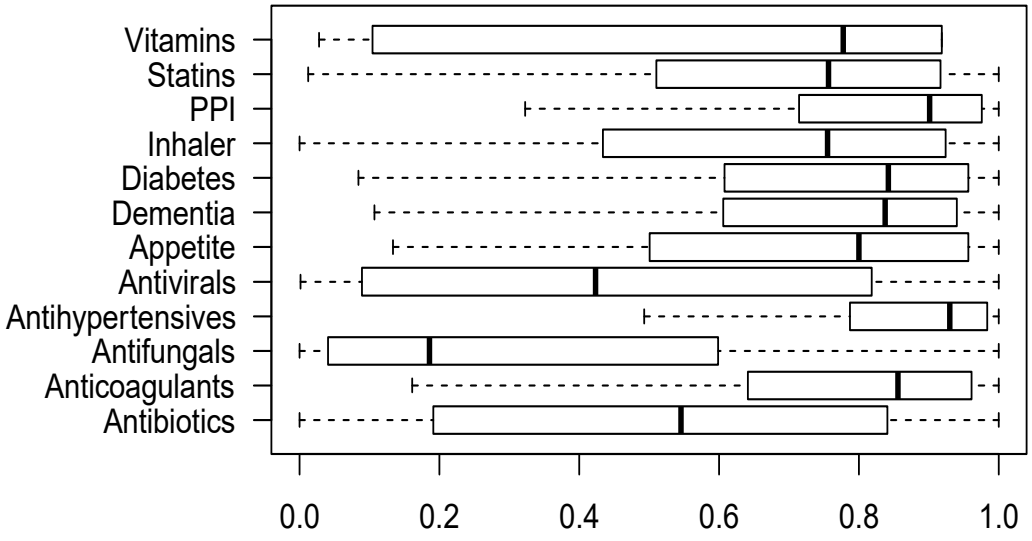


Figure 6. 2 Mean and variance of Medication Possession Ratios by drug class.

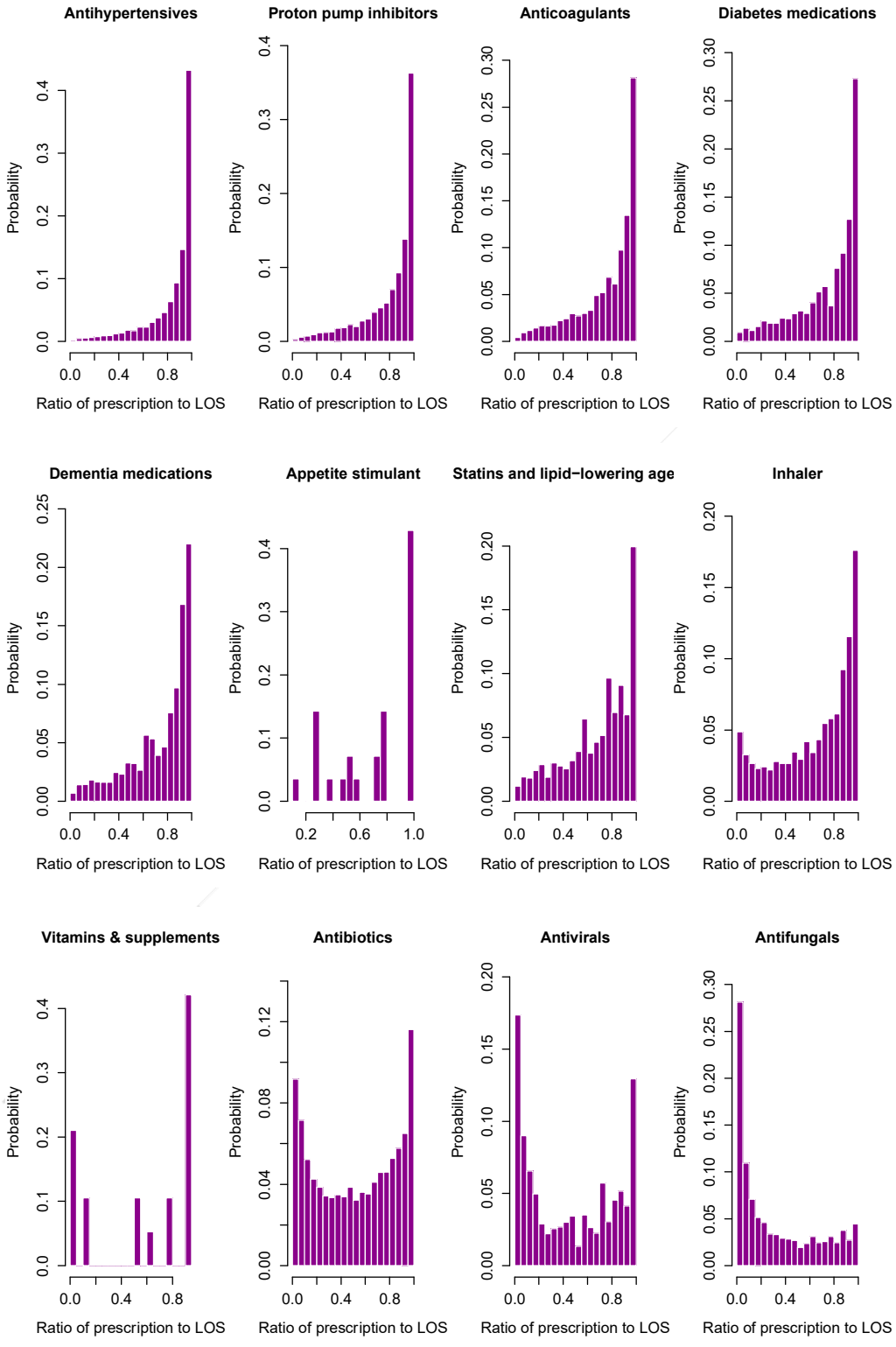


Figure 6.3 Distribution of Medication Possession Ratios for Potentially-ineffective drugs

Figure 6.3 shows graphically the distribution of medication possession by drug class. Anti-hypertensives, PPIs, anti-coagulants, diabetes medications and dementia medications are all heavily skewed toward possession for a high proportion of the hospice stay. Appetite stimulants, inhalers, antibiotics, anti-viral medications and statins are more uniformly distributed, although in all cases some proportion of patients have prescriptions for their entire stay. Anti-fungal medications are the exception with most patients having brief possession. Antibiotics and anti-viral medications are more uniformly distributed with relatively low frequencies of patients having these drugs for a high percentage of their stays. Other potentially-ineffective drugs, such as statins, continue to be prescribed: one patient in five has a statin for the entire hospice stay.

6.6 Discussion

Numerous studies point to the persistency of potentially ineffective drugs, leading to the possibility of polypharmacy in the hospice population. Using a large database of hospice drug claims, we found, among hospice patients, there is a high prevalence of drugs that are frequently over-prescribed and potentially inappropriate. The average patient has 16.9 prescriptions during the hospice stay, representing 3.5 classes of medications.

The median persistency of a drug class is shown in Table 6.13. Our CIF analysis shows that for several drug classes the median persistency is brief (7 days for anti-fungal medications and 10 days for antivirals). Even drugs considered to be candidates for deprescribing, such as statins, have long persistency (a median persistency of 93 days in the case of statins, implying that these drugs are deprescribed very slowly (if at all). For some drugs we are unable to calculate a median or higher quantile because prescriptions persist for these drugs well into the patient's stay.

Our data allows us to estimate the persistency of different drug classes within patients' hospice stays, as measured by the Medication Possession Ratio. Palliative drugs are prescribed with high frequency in the hospice population (with the exception of anti-nauseants, the frequency ranges between 72% and 93% of all patients). The incidence of most therapeutic drugs is low; with the exception of antibiotics, anti-hypertensives, and proton pump inhibitors (PPIs), no drug class is prescribed in more than 8% of the

population. Antibiotics, anti-hypertensives, and PPIs are classes that are frequently mentioned in the literature as candidates for deprescribing; between 17% and 23% of the population has one or more of these drugs. The sole exception to the low frequency of other drugs is inhalers, whose incidence is 28% among patients with a lung diagnosis.

Analysis of Medication Possession Ratios is a relatively straightforward way to understand the deprescribing rate for different medications among hospice patients. Medication possession shows the proportion of the time when a patient has a prescription for a drug compared with the time that the patient *could* have the drug. In our case the time when the patient could have the drug is the entirety of the patient's hospice stay. For most drugs Medication Possession ratios are high. This is especially true of drugs such as Proton Pump Inhibitors for which the median possession ratio is 90%: more than half of all patients with a PPI prescription have the drug for more than 90% of their stay. The only class of drugs with low possession ratios is anti-fungal, which is appropriate.

6.7 Conclusion

While the literature addresses principles of prescribing and desprescribing among patients of limited life expectancy (LLE), this is the first study, of which we are aware, that examines actual prescribing and medication possession rates among a large population of hospice patients. Using a database of hospice drug claims, we found there is a relatively high prevalence, among hospice patients, of some classes of drugs that are considered by clinical consensus to be frequently over-prescribed and potentially inappropriate, although high prevalence of potentially inappropriate drugs is limited to PPIs, anti-hypertensives, and antibiotics. In addition to high prevalence within the hospice population, these drugs are also prescribed for a high percentage of the patients' average stay in hospice, suggesting that more should be done to examine patients' medication regimens and deprescribe these drugs where appropriate.

6.7.1 Limitations

The drug classes examined in this study are potentially ineffective for patients at end of life; we did not examine patient charts that could indicate circumstances in which the prescriptions were appropriate. Although this study is based on a large national database of hospice drug claims, it represents the experience of one PBM. Our dataset consisted of demographic, prescription, and diagnosis data only and, therefore, does not include other

information about patient or prescriber-related factors that could affect prescribing behaviour.

6.8 Appendix A: Condition Categorization

Cancer

HCC8 = Metastatic Cancer and Acute Leukemia

HCC9 = Lung and Other Severe Cancers

HCC10 = Lymphoma and Other Cancers

HCC11 = Colorectal, Bladder, and Other Cancers

HCC12 = Breast, Prostate, and Other Cancers and Tumors

Dementia

HCC51 = Dementia With Complications

HCC52 = Dementia Without Complication

HCC54 = Drug/Alcohol Psychosis

HCC55 = Drug/Alcohol Dependence

HCC57 = Schizophrenia

HCC58 = Major Depressive, Bipolar, and Paranoid Disorders

Heart

HCC85 = Congestive Heart Failure

HCC86 = Acute Myocardial Infarction

HCC87 = Unstable Angina and Other Acute Ischemic Heart Disease

HCC88 = Angina Pectoris

HCC96 = Specified Heart Arrhythmias

Lung

HCC82 = Respirator Dependence/Tracheostomy Status

HCC83 = Respiratory Arrest

HCC84 = Cardio-Respiratory Failure and Shock

HCC111 = Chronic Obstructive Pulmonary Disease

HCC112 = Fibrosis of Lung and Other Chronic Lung Disorders

HCC114 = Aspiration and Specified Bacteria Pneumonias

HCC115 = Pneumococcal Pneumonia, Empyema, Lung Abscess

Gastrointestinal

HCC21 = Protein-Calorie Malnutrition

HCC22 = Morbid Obesity

HCC33 = Intestinal Obstruction/Perforation

HCC34 = Chronic Pancreatitis

HCC35 = Inflammatory Bowel Disease

Liver

HCC27 = End-Stage Liver Disease

HCC28 = Cirrhosis of Liver

HCC29 = Chronic Hepatitis

Kidney

HCC134 = Dialysis Status

HCC135 = Acute Renal Failure

HCC136 = Chronic Kidney Disease, Stage 5

HCC137 = Chronic Kidney Disease, Severe (Stage 4)

HCC138 = Chronic Kidney Disease, Moderate (Stage 3)

HCC139 = Chronic Kidney Disease, Mild or Unspecified (Stages 1-2 or Unspec.)

HCC140 = Unspecified Renal Failure

HCC141 = Nephritis

Other

HCC2 = Septicemia, Sepsis, Systemic Inflammatory Response Syndrome/Shock

HCC6 = Opportunistic Infections

HCC17 = Diabetes with Acute Complications

HCC18 = Diabetes with Chronic Complications

HCC19 = Diabetes without Complication

HCC122 = Proliferative Diabetic Retinopathy and Vitreous Hemorrhage

HCC39 = Bone/Joint/Muscle Infections/Necrosis

HCC40 = Rheumatoid Arthritis and Inflammatory Connective Tissue Disease

HCC46 = Severe Hematological Disorders

HCC166 = Severe Head Injury

HCC167 = Major Head Injury

HCC169 = Vertebral Fractures without Spinal Cord Injury

HCC170 = Hip Fracture/Dislocation

HCC173 = Traumatic Amputations and Complications

HCC176 = Complications of Specified Implanted Device or Graft

CHAPTER 7 – WHAT IS KNOWN ABOUT SURVIVAL OF HOSPICE PATIENTS: REVIEW OF THE LITERATURE[19]

Much of the (considerable) literature on patient survival rates in hospice addresses the accuracy of physician prognosis. Under Medicare rules, a patient must have a concurring prognosis from their own, and the hospice's, physician that life expectancy is six months or less. In 1996, Christakis and Escarce [65] analyzed a sample of Medicare data from 1990-1993 and found that median survival in hospice was 36 days, with significant variance, depending on the admitting diagnosis. About 15% of patients died within seven days and another 15% survived six months or longer. In the 1990s, Christakis [66] recognized the advantages of hospice care, but also the barriers, which included referring physicians' prognoses. As a result, the stay of many patients in hospice was very short.

There are two approaches to predicting survival of terminally-ill patients: clinical and statistical (actuarial). Clinical estimation involves specifying the amount of time a patient will survive, based on a combination of subjective clinical experience and prognostic factors. Physician assessment of prognosis, drawing on clinical experience, has been investigated in multiple studies and found to be largely unreliable [67]. In a study of over 1,500 cancer patients, Glare et al found that estimates were correct to within one week 25% of the time; two weeks, 43% of the time and four weeks 61% of the time [68]. One study found that physicians over-estimated survival, by a factor of five [69]. Tools, such as the palliative performance scale (PPS), are used by physicians and hospices to aid in the estimation of life expectancy.

7.1 Palliative Performance Scale to Estimate Length of Stay

The palliative performance scale was introduced in 1996 as a tool to estimate life expectancy for patients being admitted to palliative care services. This scale consists of five functional domains: ambulation, activity level and evidence of disease, self-care, oral intake, and level of consciousness. Patients are scored in each domain on a scale of 0% to 100%, by intervals of 10% (not a continuous scale). Scores on this scale are subjective and researchers have questioned its reliability. Nevertheless, the scale is widely used. Some researchers argue that PPS should be split into three categories: the stable stage (scores

[19] This literature review relates to the survival of patients in hospice, for which we develop models in the next chapter.

100% to 80%), the transitional stage (scores 70% to 40%), and the end-of-life stage (scores 30% to 0%) [70].

While certain patients may live longer than the six months, required by Medicare's eligibility rules, and still be eligible for hospice, these patients are likely to undergo regulatory scrutiny and will require documentation from a physician to justify the need for hospice care. In 2011, CMS began requiring hospices to conduct face-to-face visits to assess eligibility for hospice services when a patient is on service for 180 days [71]. Because of these regulations, studies have assessed whether hospices are able to predict length of stay, and, in particular, the accuracy of the six months' prediction. Numerous studies have been performed to assess the reliability of the palliative performance scale, as a predictor of life expectancy.

Harris et al. [72] looked at demographic variables, such as age, gender, race, and primary and secondary diagnoses of 126,620 patients in ten different hospices. Patients diagnosed with debility, or dementia, were likely to live past six months (> 50% probability). This study also found that patients who scored 60% or higher on the palliative performance scale were likely to live past six months (>50% probability).

A similar study, by Rothenberg [73], looked at the common characteristics of patients who received face-to-face visits. The study also found that patients with a primary diagnosis of debility or dementia were more likely to live past six months and receive a face-to-face visit. When compared to patients with a cancer diagnosis, debility, or dementia, patients were three times more likely to receive a face-to-face visit. Singh [74] studied the PPS Score of 7,574 patients in a Pennsylvania hospice. This study, unfortunately, does not report the numbers of patients who survive 180 days or more; however, Singh does report length of stay categories, by PPS score [63]. The data presented in table 7.1 are taken from this study.

PPS Score	**Frequency**	**LOS ≤ 7 days**	**LOS > 7 days**
< 30	41%	82%	18%
30	21%	44%	56%
40	22%	27%	73%
50	13%	16%	84%
60+	3%	7%	93%

Table 7. 1 Relationship Between PPS and Survival

As these results show, the PPS score is reasonably successful at categorizing patients into two groups (those patients that survive for fewer than 7 days and those that survive more than 7 days) by survival percentages. The number of "actuarial" or statistical, papers addressing survival is far fewer than the number of clinical papers, and we found few articles using prescribing data as covariates.

7.2 Actuarial (Statistical) Studies Estimating Length of Stay

Christakis and Escarce [65] applied Kaplan-Meier survival analysis and found significant differences, in terms of median survival, by admitting diagnosis (from 17 days for renal failure to 76.5 days for COPD) ($p<0.001$ using the Kruskal-Wallis test of difference in medians among diagnoses). Of note is that the authors found that 15% of patients survived for 180 days or more. These authors also model the influence of co-variates on length of stay: the number of recent hospitalizations, the type of hospice, and the risk profile of the patient all being significant factors. Han et al [75] developed a multi-variate model based on a number of dimensions of self-reported data including: socio-demographics, co-morbidities, health-related quality of life, activities of daily living (ADLs), and the medical outcomes study short form (SF-36). This model out-performs the traditional PPS score, in terms of predicting six-month survival rates. Some authors have addressed mathematical models of survival, for example Miladinovic and colleagues [76, 77] and Chiang and colleagues [78]. Chiang and colleges [78] developed a model for predicting death within seven days for cancer patients. Their full model relies on demographic, laboratory, and clinical data and outperforms a model based on demographic and clinical (diagnostic) data only (ROC c-statistic of 82.3% vs. 77.8%). Interestingly, Chiang et al point to a shortcoming of the statistical models: "..none of these methods can give us the full picture of the changes in survival probability for a given patient, over time, until death with the best available statistical accuracy." [79]. Chiang and colleagues present a method for estimating individual Cox proportional hazards models for patients based on covariates, but the models are static (based on initial covariate values). A different Chiang model uses time-dependent covariates [80], discussed below.

Mladinovic et al [76] developed a predictive model, based on age, sex, diagnosis, and PPS score, but found that the addition of other variables, to PPS, while increasing the accuracy somewhat, did not result in a satisfactory accuracy. This study used the Cox

proportional hazards models to estimate survival. The same authors applied the Royston-Parmar survival model [77] and found that the Royston-Parmar model fits the data significantly better than the Cox PH model.

A considerable number of studies apply Kaplan-Meier or Cox proportional hazards models to survival data with different covariates [81-89]. Significant covariates that are correlated with length of stay include age, marital status, secretions, performance scale (either PPS or Karnofsky performance scale, a similar index), and diagnosis. However, these studies are static. The present study, using dynamic modelling of prescription drugs, provides the first possibility for addressing this shortcoming.

7.3 Prescription Drug Use and Survival

There is a body of (clinical) work researching the relationship between drug use, primarily opioids, but also sedatives, and survival. Perhaps the best-known example of the role of opioids in hastening death, reported by Joseph Lelyveld in the New York Times in 1986, is that of his late Majesty, George V, whose doctor admitted to administering a lethal dose, in order that the King's death could be announced in the The Times the following morning [90]. As stated by Sykes and Thorns [91] in 2003, "Opioids and sedative drugs are commonly used to control symptoms in patients with advanced cancer. However, it is often assumed that the use of these drugs inevitably results in shortening of life." A review of selected studies, however, does not confirm this observation. A survey of Dutch physicians in 2005, by Rurup et al [92] (following up on 1995 and 2001 surveys), found some evidence of physicians prescribing opioids in order to hasten death. However, the frequency had dropped with successive surveys, from 7% in 1995 to 3.1% in 2005. The frequency with which physicians reported belief in the link between opioid use and earlier death also fell in successive surveys.

In a 1999 study of hospice patients, Bercovitch et al [93] found that high-dosage morphine use did not affect survival. In a later, 2004, study the same authors found similar results in a home hospice population: "very high doses of morphine … did not appear to affect the patients' life expectancy adversely." [94]. In another study of high-dosage OxyContin, Bercovitch and Adunsky [95] again found no relationship between dosage and shorter survival times. Azoulay et al [96] studied whether opioids help or hinder survival of advanced cancer patients in hospice. The authors conclude that opioid usage, even at high dosages, has no effect on survival. Sykes and Thorns [91] reviewed 17 studies of the

use of opoids at the end of life. The mean dose at admission varied significantly in six reported studies; however, the unweighted average increase in dosage in these studies between admission and death was 67%. The authors report five studies that examined the relationship between opioid use and survival (including the study by Bercovitch et al in 1999 [93]) and found no studies that showed that opioid use shortened life. Portenoy et al [97] studied 1,306 hospice patients and compared patients who received maximum doses with those who received usual doses of opioids. The authors found that in a multivariate regression study, while there was association between opioid dosage and shorter survival times, the model explained less than 10% of the overall variance in survival times. With the exception of Portenoy's study [97], most studies stratified the population by opioid dose into normal, high, or very high categories and compared the outcomes. In some cases, further analysis was conducted, according to different covariates such as age, sex, or admitting diagnosis. An example of such studies is a Spanish study of 223 patients by Bengoechea et al [98]. The authors stratify doses into two categories: regular (maximum dose less than 120 mg morphine) and high (maximum dose greater than 120 mg morphine)[20]. The authors find that those administered higher doses survive longer; however, adjusting for covariates, most of this survival difference disappears except in patients with maximum dose greater than twice their initial dose at admission.

Sykes and Thorns' study [91] also surveyed 17 studies that address the use of sedatives at the end of life. While analysis of sedation is more difficult than analysis of opioids, they conclude that "patients who received sedatives for over a week before death had better survival than those who did not receive sedation; patients who only had two or three days of sedatives had the same survival as those who never received sedation." The same authors [99] studied 237 hospice patients administered sedation and concluded "Sedation was given to 48% of patients. Of these, 13% received sedatives for seven days or more, while 56% commenced sedative use only in the last 48 hours of life. The groups receiving no sedation or sedation for less than 48 hours had the shortest survival from admission (mean, 14.3 and 14.2 days), whereas the seven-day sedation group survived for a mean of 36.6 days ($P <$. 001). Sedative use and dose increased toward the end of life." A

[20] It should be noted that this opioid dosage is higher than that recommended in the U.S. by the CDC (90 mg. morphine-equivalent per day); although, as our data show, it is more representative of the average daily dose for hospice patients.

Dutch study by Rietjens et al [100], looked specifically at sedative use and found slightly longer, but not statistically-significant, survival after admission (eight days vs. seven days), among sedated patients compared with those that did not receive sedation. Boland and colleagues, in a 2015 study [101], found little supporting evidence, in 20 studies reviewed, of shorter lifespans associated with opioid use, although this conclusion was largely due to short, poorly-constructed studies.

7.4 Studies of the Effect of Varying Dosage on Survival

There are few studies of the effect of variation in dosage. Chiang and Kao [80] report a Taiwanese study employing time-dependent Cox models to predict death. The authors' model finds that a three-day negative trend in morphine dosage is associated with death within one day. Other independent variables are also predictive, but none are related to opioid dosage. The Chiang and Kao study appears to be the only one of its type (using time-dependent covariates). In summary, most studies appear to show no, or a limited, relationship between opioid or sedative dosage and survival. However, there are indications that a more rigorous multivariate analysis may show different results, as we shall examine in the next chapter.

CHAPTER 8 - RESULTS

Introduction

In this chapter we attempt to fit both semi-parametric and non-parametric survival models to the same data. Cox regression requires no distributional assumption prior to fitting the model but it does require additional tools to predict life expectancy in hospice for new patients. Parametric models are chosen after we examine the distributional assumptions for the survival random variables. The estimation of future life expectancy in hospice for new patients is straightforward via parametric models.

8.1 Exploratory Data Analysis: Kaplan-Meier

Kaplan-Meier estimation provides a visual way to determine the shape of the underlying distribution of the baseline hazard function and the survival function. Earlier, we defined.

$$h_i(t) = \exp(\beta_1 x_{1i} + \beta_2 x_{2i} \ldots + \beta_p x_{pi}) h_0(t) \quad = = \exp(\boldsymbol{\beta}' \mathrm{X}) h_0(t) \tag{8.1}$$

Integrating: $\int_0^t h_i(u)du = \exp(\beta' \mathrm{X}) \int_0^t h_0(u)du$ (8.2)

and defining $H_i(t) = \exp(\boldsymbol{\beta}' \mathrm{X}) H_0(t)$ (8.3)

$$\ln H_i(t) = (\boldsymbol{\beta}' X) + \ln H_0(t) \tag{8.4}$$

or the log-cumulative hazard function. The plot of the log-cumulative hazard function, after converting data to a categorical basis, against the log of *t,* is a diagnostic for assessing the validity of the proportional hazards assumption.

Number of observations	Deaths	Median survival time	0.95 lower bound	0.95 upper bound
499,264	478,397	27	27	28

Median Survival Time: 27 days.

* 21,002 patients with observed survival exceeding 365 days have been excluded.

Table 8. 1 Kaplan-Meier Estimation of Survival

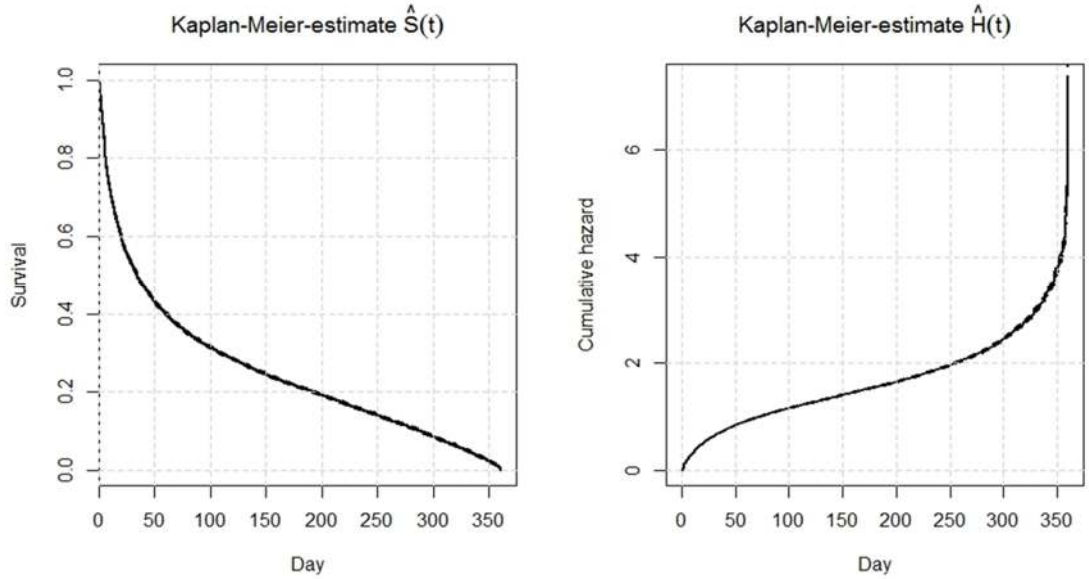


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Figure 8. 1 Kaplan-Meier estimate of Survival and Hazard Functions (Full Population)

8.1.1 Kaplan-Meier estimation of survival by sex

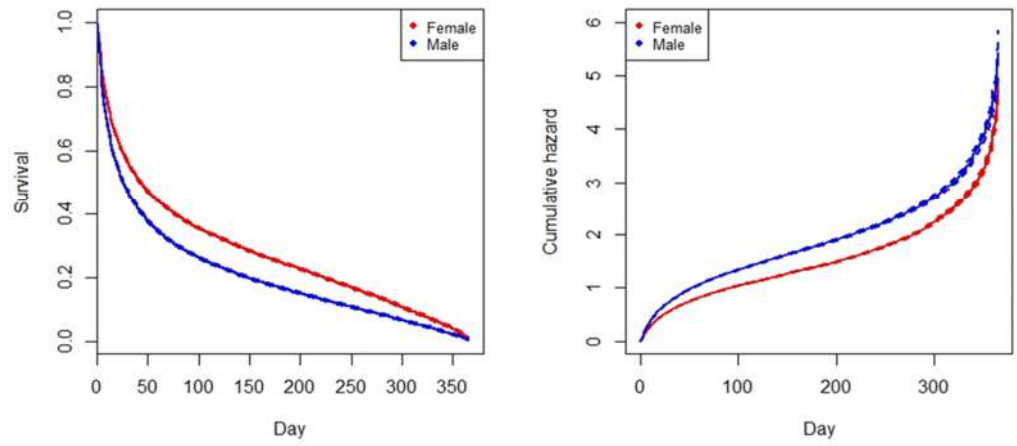


Figure 8. 2 Kaplan-Meier Estimate of Survival and Hazard Functions by Sex

Groups	Number of observations	Deaths	Median survival time	0.95 lower bound	0.95 upper bound
Females	289,376	274,621	43	31	32
Males	209,888	203,776	26	23	23
Total	499,264				

Table 8. 2 Kaplan-Meier Estimation of Survival by Sex

Female survival is longer than that of males; median female survival is 43 days, while for males it is 26 days.

8.1.2 Kaplan-Meier estimation of survival by site of care

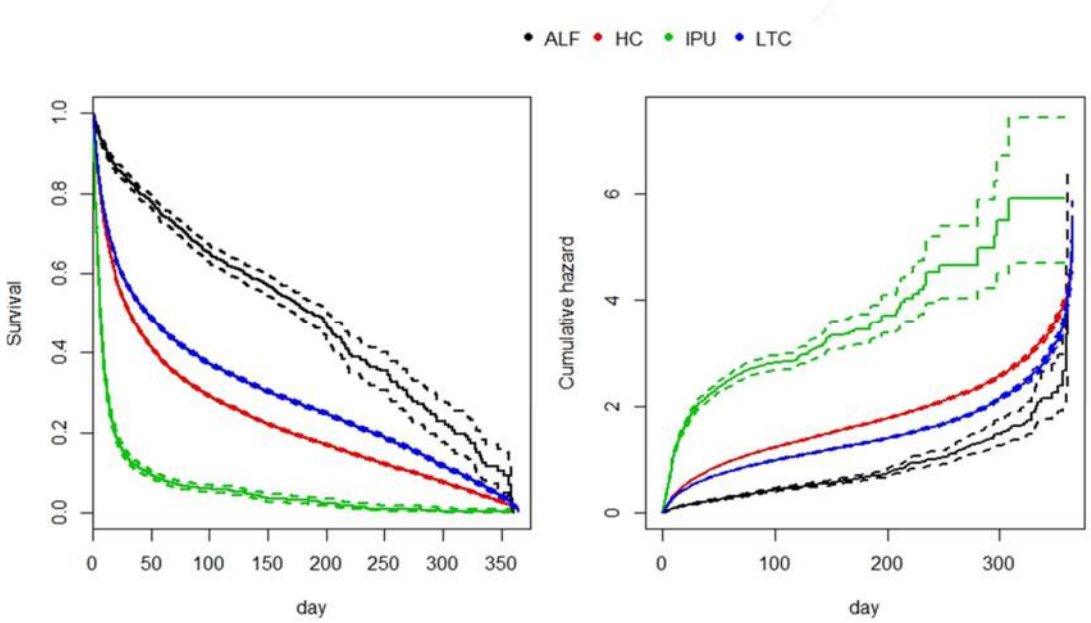


Figure 8. 3 Kaplan-Meier estimate of Survival and Cumulative Hazard Functions by Setting of Care (with confidence intervals)

Key to Figure 8.3

- **IPU: Inpatient Facility**
- **HC: Home Care**
- **LTC: Long-term Care Facility**
- **ALF: Assisted-living Facility**

Groups	Number of observations	Deaths	Median survival time	0.95 lower bound	0.95 upper bound
ALF	15,310	11,285	69	66	72
HC	327,812	316,294	27	27	27
IPU	143,483	135,541	7	7	7
LTC	12,608	11,285	33	33	34
Total	449,213				

Note: IPU = Inpatient Facility; HC = Home Care; LTC = Long-term Care Facility; ALF = Assisted-living Facility

Table 8. 3 K-M Estimation of Survival by Setting of Care

Survival varies significantly by setting of care, with inpatient facilities having the lowest median survival and assisted living facility the highest. However, both of these facilities have low numbers of patients. In the case of assisted-living facilities, there is high variability in observed survival time.

8.1.3 Survival and cumulative hazard functions for key primary diagnoses

Figure 8.4 shows the estimated survival time and hazard function for principal (admitting) diagnoses. In this figure, certain of the top 10 diagnoses, covered in Chapter 6 have been grouped, as follows:

- Cancer: sum of lung, breast, prostate, colorectal, bladder, lymphoma and other severe cancers, and tumours.
- Heart: congestive heart failure and heart disease
- CVA: ischaemic, or unspecified stroke, and cerebrovascular disease
- Lung: COPD
- Dementia: dementia without complications.

Cancer patients have the shortest survival time and dementia patients the longest.

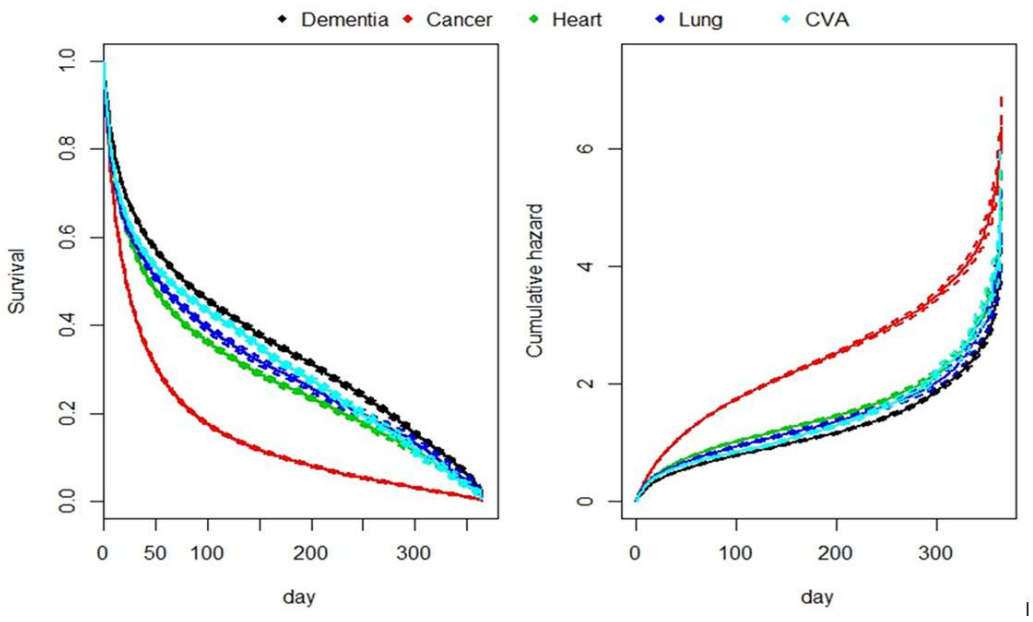


Figure 8. 4 Kaplan-Meier estimate of Survival and Cumulative Hazard Functions by Admitting Diagnosis

Key to Figure 8.4

- **Heart**
- **Cancer**
- **Lung**
- **Dementia**
- **CVA (cardio-vascular)**

Groups	Number of observations	Events	Median survival time	0.95 lower bound	0.95 upper bound
Cancer	172,185	170,004	21	21	22
Heart	64,544	61,479	31	31	32
Lung	33,062	31,336	38	37	39
CVA	41,849	38,436	40	39	41
Dementia	72,038	66,119	53	52	54
All	383,678	367,374			

Table 8. 4 Kaplan-Meier estimate of Survival and Hazard Functions by Admitting Diagnosis

8.2 Cox Regression Models

Recall the form of the Cox regression model is such that: $h_i(t \mid X) = h_0(t)e^{(\boldsymbol{\beta}^{'}X)}$ or $S_T(t \mid X) = [S_0(t)]^{\exp^{(\beta^{'}X)}}$. As the equation shows, the Cox model assumes that the covariates (X) have constant values over time. The hazard function, at time t, for a particular observation has a multiplicative effect, between the baseline hazard (where all values of covariates are equal to 0) and the functional form, which is a linear combination of the predictors. Cox regression is widely popular and used in many studies, due to few assumptions about the underlying distribution. We do not specify a form of distribution for the baseline hazard function $h_0(t)$ or the baseline survival function $S_0(t)$. However, because of the lack of a distribution assumption, Cox regression is less consistent with the theoretical survival function. The estimation of the parameter vector $\boldsymbol{\beta}$ can be performed using the partial likelihood method, which causes a challenge to re-construct and predict the survival function for future observations. At the same time, to apply the Cox model appropriately, one must carefully examine the PH assumption, as well as the functional form, as a linear combination of the covariates.

One of the crucial assumptions of the Cox model is the constant relative risk. However, in practice, we are interested in examining the effect of covariates, whose values change over time. In other words, if such covariates were added into a regular Cox model,

the proportional hazards assumption would no longer be true. An extension of the Cox model, to incorporate time-dependent covariates, is possible; however, assumptions, regarding the type of time-dependent covariates, must be met.

8.2.1 Cox regression models: results

The output of the final Cox regression model is presented in table 8.5. Variable selection procedures are performed using chi-squared tests. This model, without time-dependent covariates, is presented to demonstrate the insufficiency of the simple Cox model without time dependent covariates, indicating that the model violates the PH assumption (see Table 8.6). We further examine the PH assumption and assess the overall fit of the model.

To test the adequacy of the PH assumption, we perform the hypothesis test of Grambsch and Therneau [17] for each parameter in the model. Under this test, the null hypothesis is that the log hazard ratio function is constant over time. From table 8.6, the Grambsch-Therneau test indicates non-proportionality of hazards for several predictors *(p* < 0.05). This violation of the PH assumption can cause inaccurate interpretation for the estimated parameters. A potential solution is the addition of time-varying covariates into the model.

To study the overall fit of the Cox model, the standard approach for testing goodness-of-fit is the comparison of Cox-Snell residuals $r_i = \hat{H}_0(T_i)e^{(\boldsymbol{\beta}^{'}X)}$ with the cumulative hazard function. If the model is correct, the residual plot of the cumulative hazard rate $\hat{H}(r_i)$ vs. r_i should follow a straight line through the origin. Figure 8.5 indicates significant departure of the cumulative hazard rate from the straight line, indicating that the Cox model is a poor fit to the data. As we shall see later the log-normal model fits the data better than the Cox model.

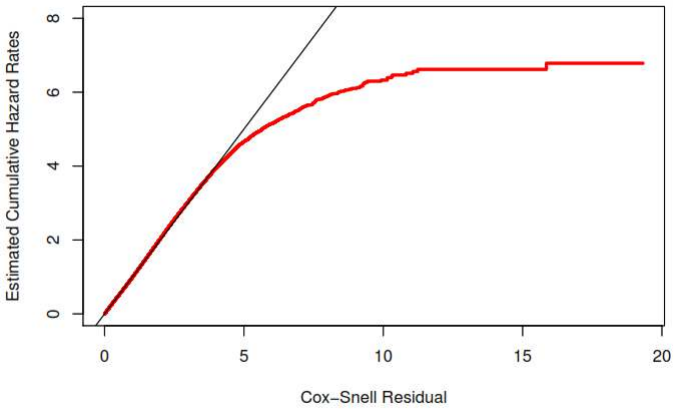


Figure 8. 5 Cox-Snell Residuals for the Cox model

Table 8.5 shows the coefficients calculated for the fitted Cox model, and table 8.6 shows the results of the hypothesis test for the PH assumption. As discussed in Chapter 2, the coefficients in the Cox model act on the hazard rate. Thus, a positive coefficient implies an exponentiated coefficient greater than 1.0 and, in turn, an increased hazard of death. For example, being male (compared with female) has an exponentiated coefficient of 1.125, implying that males have about a one-eighth shorter expected survival duration than females. All covariates in the Cox model are significant (*p* values equal to or close to zero), although we should be cautious about reading too much into this result because of the large sample size.

We note that cancer and kidney disease diagnoses have shorter expected survival duration, while dementia and other psychological disorders have longer expected durations. The impact of the risk factor is somewhat minor (about a 4.4% shorter expected duration for a 1% increase in risk score). However, because the diagnoses are covariates in the model, their effect enters the model directly.

Covariates	$\hat{\beta}$	$e^{\hat{\beta}}$ (HR)	P-value	Lower .95 % (of HR)	Upper .95% (of HR)
GenderMale	0.117	1.125	0	1.117	1.133
LevelOfCareHC (Home Care)	0.324	1.383	0	1.351	1.416
LevelOfCareIPU (In-Patient Unit)	1.401	4.060	0	3.939	4.184
LevelOfCareLTC (Long-Term Care)	0.349	1.418	0	1.385	1.452
Age	-0.004	0.996	0	0.996	0.997
hcc2 (Sepsis)	0.298	1.348	0	1.307	1.390
hcc8 (Metastatic Cancer and Acute Leukemia)	0.224	1.252	0	1.203	1.302
hcc9 (Lung Cancer)	0.242	1.273	0	1.250	1.297
hcc10 (Lymphoma Cancer)	0.190	1.209	0	1.185	1.233
hcc11 (Colorectal, Bladder Cancer)	0.138	1.149	0	1.129	1.168
hcc12 (Breast and Prostate Cancer)	0.132	1.141	0	1.122	1.160
hcc18 (Diabetes with Chronic Complications)	0.030	1.030	0.004	1.009	1.052
hcc21 (Protein-Calorie Malnutrition)	-0.086	0.918	0	0.898	0.939
hcc22 (Morbid Obesity)	-0.097	0.908	0.066	0.819	1.007
hcc23 (Metabolic Disorder)	-0.079	0.924	0.024	0.863	0.989
hcc27 (End-Stage Liver Disease)	0.252	1.287	0	1.215	1.363
hcc28 (Cirrhosis of Liver)	0.199	1.220	0	1.184	1.257
hcc33 (Intestinal Obstruction)	0.236	1.266	0	1.198	1.338
hcc46 (Severe Hematological Disorder)	0.217	1.242	0	1.181	1.306
hcc48 (Coagulation Defects and Other Specified Hematological Disorders)	0.036	1.036	0.024	1.005	1.069
hcc51 (Dementia with Complications)	-0.254	0.776	0	0.752	0.801
hcc52 (Dementia without Complications)	-0.229	0.795	0	0.787	0.804
hcc54 (Drug/Alcohol Psychosis)	-0.259	0.772	0.00001	0.689	0.864
hcc55 (Drug/Alcohol dependence)	-0.133	0.875	0.074	0.756	1.013
hcc57 (Schizophrenia)	-0.296	0.744	0	0.693	0.799
hcc58 (Major Depressive, Bipolar, and Paranoid Disorders)	-0.162	0.850	0	0.831	0.870
hcc70 (Quadriplegia)	-0.224	0.799	0.016	0.666	0.959
hcc71 (Paraplegia)	-0.161	0.851	0.079	0.711	1.019
hcc72 (Spinal Cord Disorders)	-0.208	0.813	0.00000	0.746	0.885
hcc73 (Amyotrophic Lateral Sclerosis)	-0.321	0.726	0	0.690	0.763
hcc74 (Cerebral Palsy)	-0.328	0.720	0	0.643	0.806
hcc75 (Polyneuropathy)	-0.140	0.869	0	0.829	0.911
hcc76 (Muscular Dystrophy)	-0.434	0.648	0.00000	0.551	0.763
hcc77 (Multiple Sclerosis)	-0.366	0.694	0	0.652	0.738
hcc78 (Parkinson's and Huntington's Diseases)	-0.254	0.776	0	0.760	0.792
hcc79 (Seizure Disorders and Convulsions)	-0.129	0.879	0	0.854	0.905
hcc84 (Cardio-Respiratory Failure and Shock)	0.098	1.103	0	1.076	1.131
hcc86 (Acute Myocardial Infarction)	0.080	1.083	0.013	1.017	1.154
hcc87 (Unstable Angina)	-0.058	0.944	0.043	0.892	0.998
hcc88 (Angina Pectoris)	-0.119	0.888	0.001	0.825	0.955
hcc96 (Specified Heart Arrhythmias)	0.047	1.048	0	1.032	1.065
hcc99 (Cerebral Hemorrhage)	0.337	1.400	0	1.327	1.478
hcc100 (Ischemic or Unspecified Stroke)	0.039	1.040	0.00000	1.024	1.057
hcc103 (Hemiplegia/Hemiparesis)	-0.119	0.887	0.00003	0.839	0.939
hcc106 (Gangrene)	0.271	1.312	0.00000	1.180	1.458
hcc111 (COPD)	-0.113	0.893	0	0.881	0.905
hcc112 (Chronic Lung Disorders)	-0.125	0.882	0	0.849	0.917
hcc114 (Bacterial Pneumonias)	0.203	1.225	0	1.171	1.282
hcc115 (Pneumococcal Pneumonia)	0.126	1.134	0.048	1.001	1.285
hcc134 (Dialysis Status)	0.322	1.380	0.002	1.130	1.686
hcc135 (Acute Renal Failure)	0.297	1.346	0	1.285	1.410
hcc136 (CKD-Stage 5)	0.410	1.506	0	1.460	1.554
hcc137 (CKD-Severe)	0.090	1.095	0.001	1.039	1.153

hcc138 (CKD-Moderate)	0.070	1.072	0.0003	1.033	1.113
hcc139 (CKD-Mild)	0.082	1.085	0	1.056	1.116
hcc141 (Nephritis)	0.109	1.115	0.00000	1.073	1.159
hcc157 (Pressure Ulcer of Skin)	0.318	1.375	0.105	0.935	2.021
hcc166 (Severe Head Injury)	0.505	1.658	0.050	0.999	2.751
hcc167 (Major Head Injury)	0.222	1.249	0.0002	1.112	1.403
hcc170 (Hip Fracture)	0.142	1.153	0.001	1.063	1.249
Neoplasm (Non-Chronic)	0.073	1.076	0.00001	1.042	1.111
Heart (Non-Chronic)	-0.069	0.933	0	0.921	0.945
Digestive (Non-Chronic)	0.030	1.030	0.008	1.008	1.053
Other	-0.012	0.988	0.003	0.980	0.996
Cerebrovascular (Non-Chronic)	-0.292	0.746	0	0.735	0.758
Gastrointestinal (Non-Chronic)	0.081	1.084	0.0003	1.038	1.133
Lung (Non-Chronic)	0.129	1.138	0	1.105	1.171
Pneumonia (Non-Chronic)	0.164	1.179	0	1.151	1.207
Unknown.Causes (Non-Chronic)	-0.056	0.945	0.00001	0.922	0.969
Risk Score	0.044	1.044	0.00000	1.028	1.061

Table 8. 5 Coefficients of the Cox PH Model

Variable	Rho	Chi-squared	*p*
GenderMale	-0.017	91.848	0
LevelOfCare HC (Home Care)	-0.008	19.426	0
LevelOfCare IPU (In-Patient Unit)	-0.023	171.033	0
LevelOfCare LTC (Long-Term care)	-0.010	35.287	0
Age	0.002	1.079	0.299
hcc2	-0.023	184.760	0
hcc8	0.009	24.621	0
hcc9	0.027	246.741	0
hcc10	0.029	280.675	0
hcc11	0.037	445.239	0
hcc12	0.034	380.750	0
hcc18	-0.008	20.948	0
hcc21	0.002	2.022	0.155
hcc22	0.001	0.088	0.766
hcc23	0.003	2.180	0.140
hcc27	-0.004	6.153	0.013
hcc28	0.000	0.002	0.961
hcc33	-0.007	15.339	0
hcc46	-0.002	1.736	0.188
hcc48	0.003	2.340	0.126
hcc51	0.005	9.243	0.002
hcc52	0.028	266.672	0
hcc54	0.001	0.272	0.602
hcc55	-0.003	2.815	0.093
hcc57	0.005	9.216	0.002
hcc58	0.005	8.317	0.004
hcc70	0.002	0.749	0.387
hcc71	0.004	5.485	0.019
hcc72	0.002	1.075	0.300
hcc73	0.015	75.677	0
hcc74	0.002	1.806	0.179
hcc75	0.004	6.603	0.010
hcc76	-0.002	1.971	0.160
hcc77	0.006	10.206	0.001
hcc78	0.018	103.109	0
hcc79	0.007	14.971	0
hcc84	-0.030	311.470	0
hcc86	-0.007	16.234	0
hcc87	0.003	2.198	0.138
hcc88	0.003	3.379	0.066
hcc96	-0.002	1.670	0.196
hcc99	-0.022	160.251	0
hcc100	-0.019	122.066	0
hcc103	0.002	0.822	0.365
hcc106	0.003	2.097	0.148
hcc111	0.004	5.231	0.022
hcc112	0.013	53.559	0
hcc114	-0.014	62.602	0
hcc115	-0.001	0.126	0.722
hcc134	-0.003	2.930	0.087
hcc135	-0.015	72.446	0
hcc136	-0.023	174.505	0
hcc137	-0.001	0.206	0.650
hcc138	-0.004	4.269	0.039
hcc139	-0.004	4.664	0.031
hcc141	0.006	13.190	0
hcc157	0.000	0.055	0.814

hcc166	0.000	0.064	0.800
hcc167	-0.002	1.220	0.269
hcc170	-0.004	4.412	0.036
Neoplasm	0.016	82.096	0
Heart	0.012	50.217	0
Digestive	-0.003	4.050	0.044
Other	0.012	46.218	0
Cerebrovascular	0.008	20.261	0
Gastrointestinal	-0.004	5.710	0.017
Lung	-0.007	15.560	0
Pneumonia	-0.014	70.052	0
Unknown.Causes	0.005	7.012	0.008
Risk Score	0.015	73.215	0

Table 8. 6 Hypothesis Test for PH Assumption

8.3 Accelerated Failure Time Models

8.3.1 Checking the applicability of the log-normal AFT model

A probability plot is applied to assess whether or not the data follow a log-normal distribution. Figure 8.6 shows some departure from the log-normal distribution, but in the tail, starting at the 99th percentile. Outliers of the extent of this quantile are rare in hospice, given that patients are not admitted with a life expectancy greater than six months (180 days).

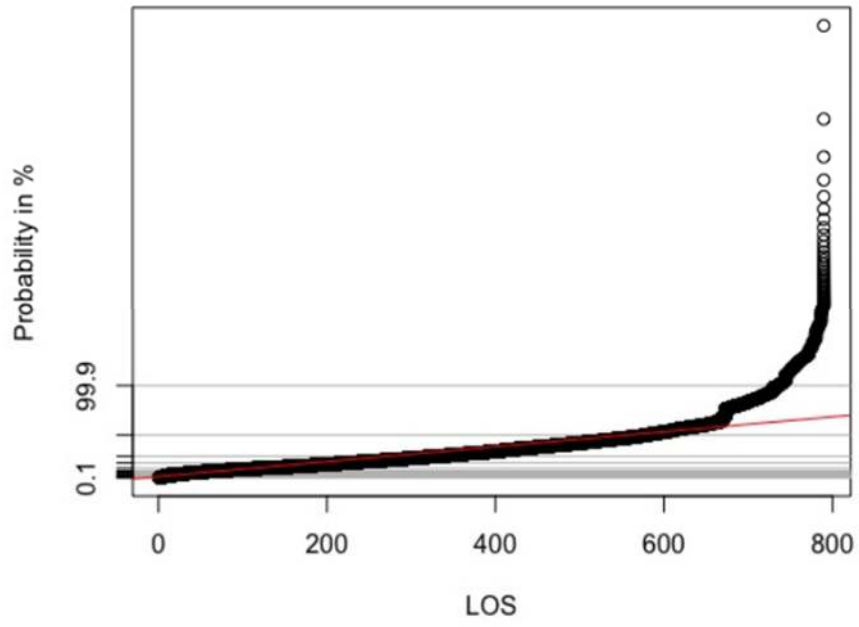
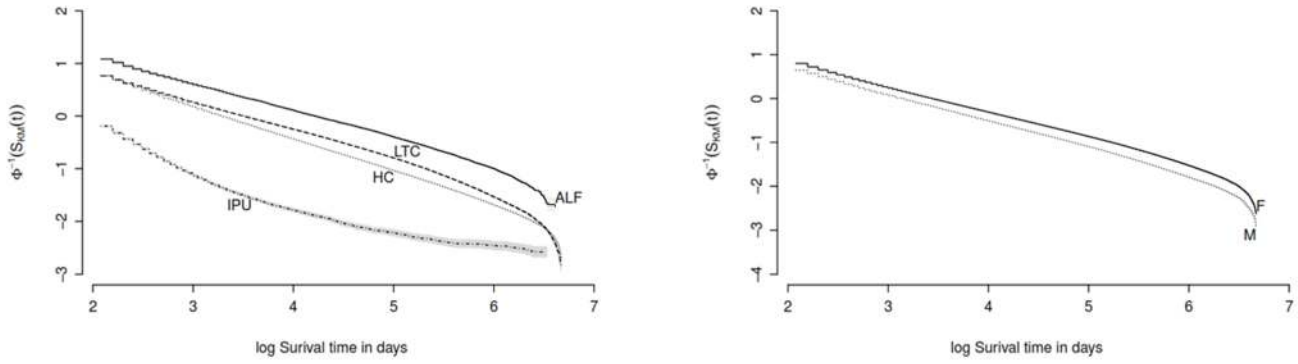


Figure 8. 6 Log-Normal Probability Plot

The log-normal distribution does appear to be a good fit for the majority of the data, and out-performs the Cox model.

Another tool to assess whether the log-normal AFT model fits our data is the Kaplan-Meier survival curve, stratified by different levels, within key predictors. For selected predictors, we plot the inverse normal transformation of K-M survival estimates against $\log(t)$. Parallel and linear patterns indicate an appropriate fit. Figure 8.8 shows two different examples, for two predictors (care setting and sex). There are signs of non-linearity in the tails, but, overall, the figures show adequate linearity.



(a) $\Phi^{-1}(S_{KM}(t))$ stratified by care settings

(b) $\Phi^{-1}(S_{KM}(t))$ stratified sex

Figure 8. 7 Assessment of Log-Normal Assumption for Care Setting and Sex

8.3.2 AFT model residuals

The standardized residual for the $i-th$ observation, in the log-normal AFT model, is defined as $\hat{s}_t = \dfrac{\log(t_i) - \hat{\mu}}{\hat{\sigma}}$ where t_i is the observed survival time for the $i-th$ observation, σ is the estimated scale parameter, and $\hat{\mu}$ is the estimated location parameter, which can be expressed as a linear combination of predictors. If the model is correctly specified, then the set $(s_i, \delta_i), i = 1, 2..n$ should behave like a censored sample from a log-normal distribution. δ_i is the censored status of the $i-th$ observation. In figure 8.8, we compute the Kaplan-Meier survival curve for the standardized residuals (computed from the model, in table 8.5). The Kaplan-Meier curve of residuals is compared with the survival curve,

using the log-normal function. Good concurrence indicates that the log-normal is an appropriate function to fit the data.

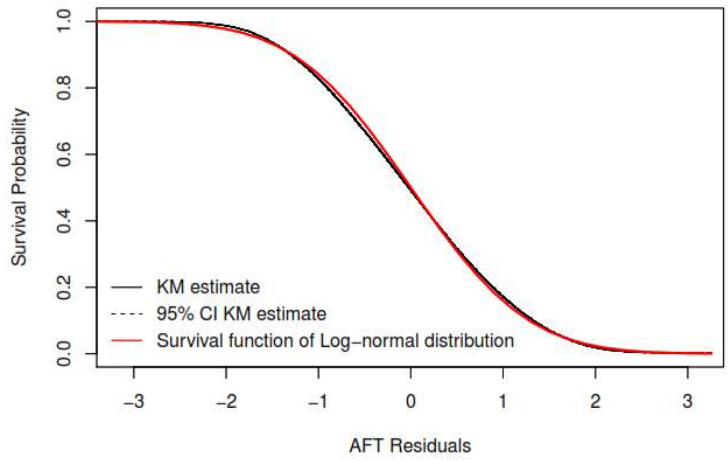


Figure 8. 8 Comparison Between K-M Survival and Log-Normal Residuals

8.3.3 Results of the log-normal AFT model

The estimated parameter coefficients and acceleration factors for the log-normal AFT model show the direct impact of predictors on the rate of survival in hospice. The final log-normal AFT model includes 63 significant predictors (out of 101 predictors, in total) and is chosen using model selection criteria AIC and chi-squared tests. For the AFT model, the Cox-Snell residual for the $i-th$ observation is defined as

$$\hat{r}_i = -\log\left(1-\Phi\left(\frac{\log(t_i)-\hat{\mu}}{\sigma}\right)\right), \tag{8.8}$$

where Φ is the cumulative distribution of the standard normal distribution. If the model is correctly specified, the set $(\hat{r}_i,\delta_i), i=1,2...n$ behaves similarly to a censored sample of unit exponentially-distributed variables. In figure 8.9, we show Cox-Snell residuals for the log-normal AFT model (the residuals of the Cox model were shown previously, in figure 8.5) and plot them against the cumulative hazard rates. The plots indicate that the Cox model does not fit the data as well as the log-normal AFT model.

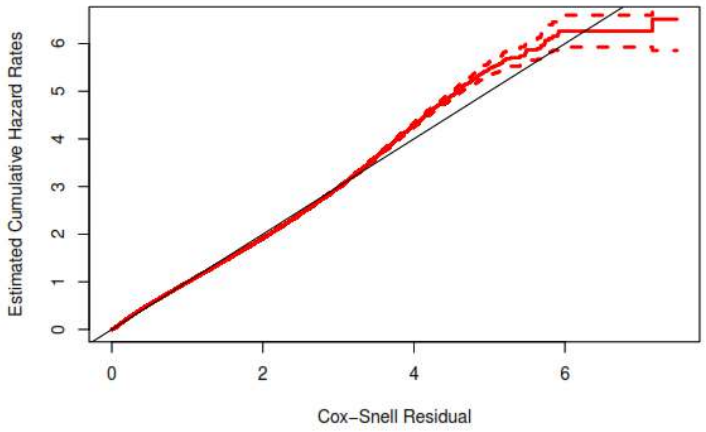


Figure 8. 9 Cox-Snell Residuals, Log-normal AFT Model

As discussed in Chapter 2, the coefficients of the AFT model act on survival, directly. Hence, a negative coefficient, when exponentiated, becomes a value less than 1.0, implying a shorter expected survival duration.

Sex and care setting play an important role in speeding, or slowing, the rate of survival in hospice. The coefficients are shown in table 8.7. As an example, the acceleration factor for males is 0.834, compared to female patients, implying that male survival is only 83.4% of that of females. Males will die, on average, 16.6% faster in hospice. Survival also depends on the facility in which the hospice patient is confined. The baseline facility is the assisted living facility (ALF). Assisted living setting patients have the longest life expectancy. Compared with ALF patients, patients in home care, inpatient, and long-term care settings die on average 39.0%, 82.6%, and 42.1% faster than those in assisted living. The effect of different care facilities on the survival rate of patients in hospice, estimated by the log-normal AFT model, is consistent with the observed survival in the Kaplan-Meier curves (figure 8.10 and table 8.8).

Covariates	**β̂**	**γ̂= eβ̂ (AF)**	**p-value**	**Lower .95% (of AF)**	**Upper .95% (of AF)**
(Intercept)	3.607	36.846	0.000	35.060	38.723
Gender (M)	-0.182	0.834	0.000	0.825	0.842
Level of care (Home Care)	-0.494	0.610	0.000	0.591	0.630
Level of care (In-Patient Unit)	-1.750	0.174	0.000	0.166	0.181

Level of care (Long-Term Care)	-0.547	0.579	0.000	0.560	0.598
Age	0.005	1.005	0.000	1.004	1.005
HCC2 (Sepsis)	-0.481	0.618	0.000	0.591	0.646
HCC8 (Metastatic Cancer and Acute Leukemia)	-0.172	0.842	0.000	0.795	0.892
HCC9 (Lung Cancer)	-0.219	0.803	0.000	0.782	0.825
HCC10 (Lymphoma Cancer)	-0.155	0.856	0.000	0.832	0.882
HCC11 (Colorectal, Bladder Cancer)	-0.089	0.915	0.000	0.893	0.938
HCC12 (Breast and Prostate Cancer)	-0.094	0.911	0.000	0.889	0.933
HCC18 (Diabetes with Chronic Complications)	-0.051	0.950	0.001	0.922	0.979
HCC19 (Diabetes without Complication)	0.037	1.037	0.009	1.009	1.066
HCC21 (Protein-Calorie Malnutrition)	0.144	1.154	0.000	1.117	1.192
HCC23 (Metabolic Disorders)	0.109	1.115	0.031	1.010	1.231
HCC27 (End-Stage Liver Disease)	-0.325	0.723	0.000	0.665	0.786
HCC28 (Cirrhosis of Liver)	-0.252	0.777	0.000	0.744	0.812
HCC33 (Intestinal Obstruction)	-0.367	0.693	0.000	0.639	0.751
HCC46 (Severe Hematological Disorder)	-0.272	0.762	0.000	0.708	0.820
HCC51 (Dementia with Complications)	0.385	1.469	0.000	1.405	1.537
HCC52 (Dementia without Complications)	0.365	1.441	0.000	1.419	1.463
HCC54 (Drug/Alcohol Psychosis)	0.342	1.408	0.000	1.198	1.655
HCC57 (Schizophrenia)	0.451	1.569	0.000	1.416	1.739
HCC58 (Bipolar and Paranoid Disorders)	0.254	1.289	0.000	1.248	1.332
HCC70 (Quadriplegia)	.0351	1.421	0.008	1.097	1.840
HCC71 (Paraplegia)	0.370	1.447	0.006	1.113	1.882
HCC72 (Spinal Cord Disorders)	0.302	1.352	0.000	1.196	1.529
HCC73 (Amyotrophic Lateral Sclerosis)	0.574	1.775	0.000	1.652	1.907
HCC74 (Cerebral Palsy)	0.453	1.574	0.000	1.340	1.848
HCC75 (Polyneuropathy)	0.230	1.259	0.000	1.177	1.347
HCC76 (Muscular Dystrophy)	0.464	1.590	0.000	1.262	2.003
HCC 77 (Multiple Sclerosis)	0.559	1.749	0.000	1.603	1.909
HCC78 (Parkinson's and Huntington's Disease)	0.416	1.516	0.000	1.473	1.561
HCC79 (Seisure Disorders)	0.204	1.226	0.000	1.176	1.279
HCC84 (Cardio-Respiratory Failure)	-0.244	0.783	0.000	0.756	0.811
HCC86 (AMI)	-0.164	0.849	0.000	0.776	0.929
HCC87 (Unstable Angina)	0.099	1.104	0.017	1.018	1.197
HCC88 (Angina Pectoris)	0.190	1.210	0.000	1.088	1.344
HCC96 (Specified Heart Arrhythmias)	-0.006	0.936	0.000	0.915	0.958
HCC99 (Cerebral Hemorrhage)	-0.608	0.544	0.000	0.503	0.589
HCC100 (Stroke)	-0.107	0.899	0.000	0.878	0.920
HCC103 (Hemiplegia)	0.166	1.181	0.000	1.090	1.279
HCC106 (Gangrene)	-0.292	0.747	0.000	0.640	0.872
HCC111 (COPD)	0.158	1.171	0.000	1.149	1.194
HCC112 (Chronic Lung Disorders)	0.229	1.257	0.000	1.190	1.328
HCC114 (Bacterial Pneumonias)	-0.372	0.689	0.000	0.646	0.736
HCC134 (Dialysis Status)	-0.457	0.633	0.000	0.473	0.847
HCC135 (Acute Renal Failure)	-0.463	0.629	0.002	0.588	0.673
HCC136 (CKD – Stage 5)	-0.593	0.552	0.000	0.528	0.578
HCC137 (CKD – Severe)	-0.121	0.886	0.002	0.822	0.955

HCC138 (CKD – Moderate)	-0.102	0.903	0.000	0.856	0.953
HCC139 (CKD – Mild)	-0.114	0.892	0.000	0.857	0.929
HCC141 (Nephritis)	-0.120	0.887	0.000	0.838	0.938
HCC167 (Major Head Injury)	-0.351	0.704	0.000	0.594	0.834
HCC170 (Hip Fracture)	-0.252	0.777	0.000	0.692	0.874
Heart (Non-Chronic)	-0.118	1.125	0.000	1.104	1.147
Digestive (Non-Chronic)	-0.063	0.939	0.000	0.910	0.969
Other (Non-Chronic)	0.033	1.034	0.000	1.021	1.046
Cerebrovascular (Non-Chronic)	0.413	1.512	0.000	1.479	1.545
Gastrointestinal (Non-Chronic)	-0.136	0.873	0.000	0.819	0.930
Lung (Non-Chronic)	-0.208	0.812	0.000	0.779	0.848
Pneumonia (Non-Chronic)	-0.283	0.753	0.000	0.728	0.780
Unknown Causes (Non-Chronic)	0.085	1.089	0.000	1.051	1.129
Weight Loss (Non-Chronic)	0.034	1.034	0.016	1.006	1.063
Risk Score	-0.055	0.947	0.000	0.925	0.969

Table 8. 7 Coefficients of the Log-normal AFT Model with $\hat{\sigma}=1.4768$

The effect of care facilities on the survival rates, as estimated by the log-normal AFT model, is consistent with the observed Kaplan-Meier survival curves, stratified by care setting (figure 8.10 and table 8.8).

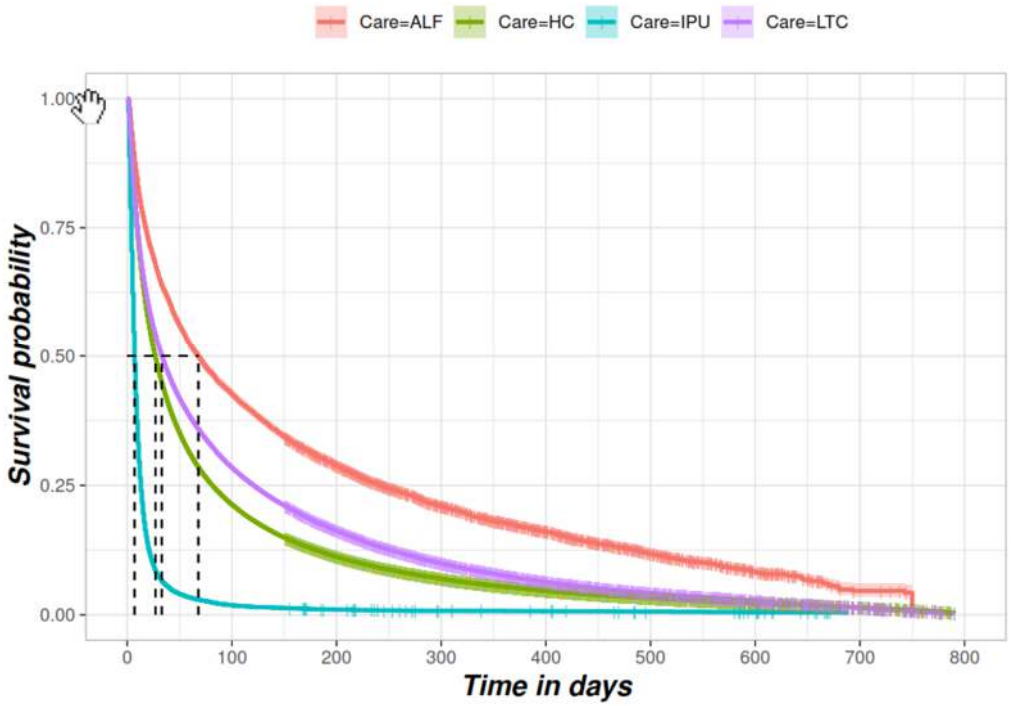


Figure 8. 10 Stratified Kaplan-Meier Curves for Different Care Settings

Care	Median Survival	Lower .95	Upper .95
ALF	68	64	72
HC	27	27	27
IPU	7	7	7
LTC	33	33	34

Table 8. 8 Summary Statistics for K-M Curves for Different Care Settings

From table 8.7, significant covariates are setting of care and sex; age is also statistically significant. While a one-year change in ageless significant impact on the survival rate, life expectancy of an individual significantly older would be much lower than that of a younger individual. Different diagnoses also have an effect on the survival rate. For example, patients with sepsis (0.618) and lung cancer (0.803) die approximately 40% and 20% faster than patients without these conditions. Patients with some diagnoses can be expected to survive for a much longer time. Patients with dementia and schizophrenia survive, respectively, 57% and 44% longer than other patients. The Kaplan-Meier curves for dementia are illustrated in figure 8.11 and table 8.9. Risk score (HCC) is a measure of relative risk of each patient and measures the severity of the patient's illness. With an acceleration factor of 0.947, the model indicates the correlation between risk score and survival: for a 1-unit increase in risk score, survival time is reduced by 5.3%[21] (This value is consistent with that of the coefficient of risk score for the Kaplan-Meier estimator in section 8.1.2, above).

[21] In the Appendix to Chapter 5 we noted that the average risk score is 0.87; risk score ranges from 0.0 to about 4.0.

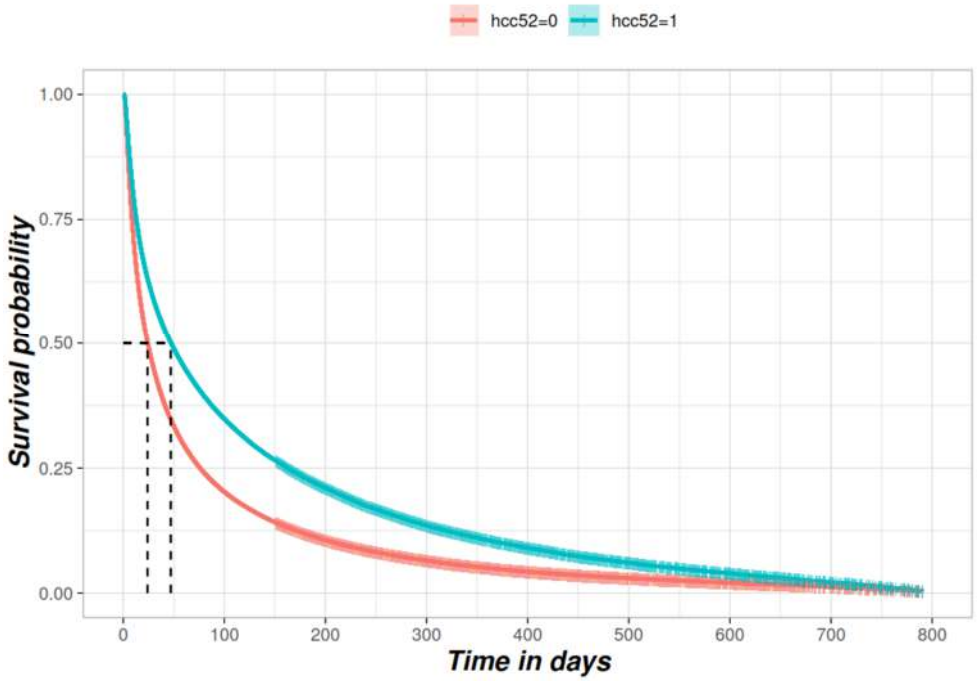


Figure 8. 11 Kaplan-Meier Curves for Patients with Dementia (HCC 52)

	Median Survival	Lower .95	Upper .95
Non-Dementia (hcc52 = 0)	24	24	24
Dementia (hcc52 = 1)	47	46	48

Table 8. 9 Summary Statistics for K-M Curves for Dementia (HCC 52)

8.4 Prediction using the Log-normal Accelerated Failure Time Model

8.4.1 Prediction and external validation using test set

Our objective in developing survival models, and in particular the log-normal AFT model, is to be able to predict survival (remaining life expectancy) of patients admitted to hospice. The survival curve is a representation of the death hazard rate (force of mortality, μ in actuarial terms). Future life expectancy is estimated as the integral of the survival function or the area under the survival curve:

$$E(T) = \int_0^\infty S(t)dt = \int_0^\infty \Pr(T > t)dt\,. \tag{8.9}$$

From the model in table 8.10, we can derive predictions of life expectancy using the time-quantiles function:

$$\log(t) = \hat{\mu} + \hat{\sigma}\,\boldsymbol{\Phi}^{-1}(1 - S(t)) = (\hat{\beta}_0 + \sum \hat{\beta}_i X_i) + \hat{\sigma}\,\boldsymbol{\Phi}^{-1}(1 - S(t))\,, \tag{8.10}$$

where $\log(t)$ is the estimated survival duration; Φ^{-1} is the inverse cumulative function of the normal standard distribution, and we fix the survival rate $S(t) = q$.

Figure 8.12 and table 8.10 show an example of a predicted survival curve for a new patient. The area under the survival curve is 67.50, compared to the actual length of stay of 65 days.

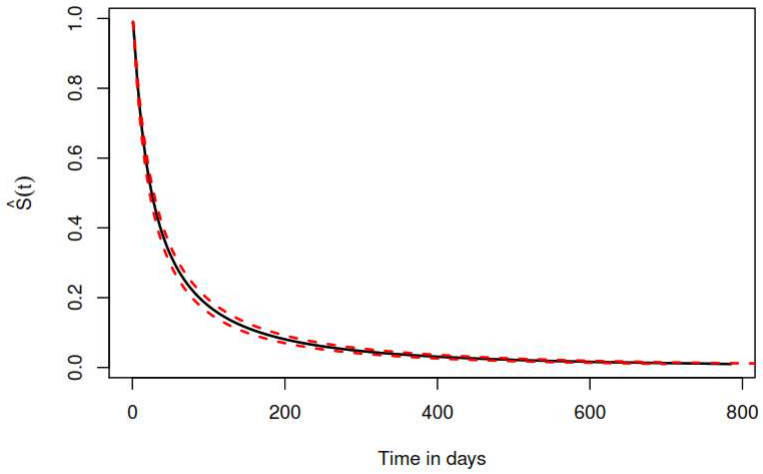


Figure 8. 12 Survival Curve for a Newly Admitted Patient

Gender	Level of Care	Age	Diagnoses	Score
Male	Home care	76	HCC11 – Colorectal and bladder cancer HCC48 – Coagulation defects HCC85 – Congestive heart failure HCC96 – Specified heart arrhythmias Non-chronic heart disease Other disease	1.225

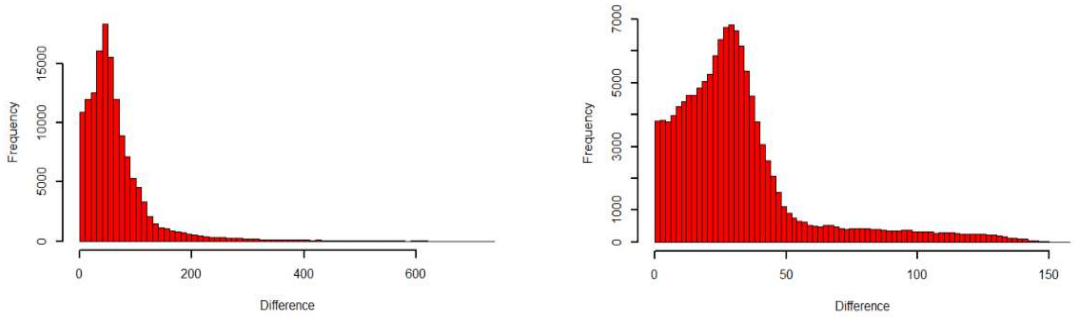
Table 8. 10 Sample Patient Characteristics for Newly Admitted Patient

Estimates of future life expectancy, obtained as the integral of the survival curve $E(T) = \int_0^\infty S(t)dt = \int_0^\infty \Pr(T > t)dt$ are not particularly accurate. This is due, in part, to the number of outliers in the data; a small number of patients survive for durations that significantly exceed the six months duration that is expected of terminally ill hospice patients. We, instead, modify the life expectancy function to be conditioned on $T \leq 180$ to be consistent with the CMS definition of expected maximum duration of patients admitted to hospice.

$$E(T \mid T \le 180) = \frac{1}{\Pr(T \le 180)} \int_0^{180} t\, f_T(t) dt \tag{8.11}$$

$$E(T \mid T \le 180) = \frac{1}{\Pr(T \le 180)} \int_0^{180} \frac{1}{\sqrt{2\pi\sigma}}\, e^{-\frac{(\log(t)-\mu)^2}{2\sigma^2}} dt \tag{8.12}$$

We define the error from the prediction as the absolute difference between the actual and the predicted lengths of stay. In the test (hold-out) set, we first exclude the censored patients and apply the long-normal AFT model to estimate the expectation of future lifetime and the conditional expected future lifetime, and then compare to the actual lengths of stay. Figure 8.13 shows histograms of the errors for the basic model $E(T)$ and the errors of the conditional model $E(T)$. The median error is 50.5 days (s.d. 68.3 days) when estimating the expectation using the basic model (figure 8.13 a) and 27 days (s.d. 25.6) when estimating the conditional model (figure 8.13 b).



(a) Difference= $|los - \widehat{E(T)}|$ **(b)** Difference =$|los - \widehat{E'(T)}|$

Figure 8. 13 Frequency Distribution of Differences between Actual and Predicted Lengths of Stay

In table 8.11, we aggregate the errors into five groupings to assess the distribution of the errors. Quintile 1 contains all observations where the difference between the predicted and actual values of life expectancy is between 0 and 15 days. Quintile five contains all observations where the difference between predicted and actual duration to death is in excess of 90 days.

Quintile	Range
1	[0,15)
2	[15,30)
3	[30,60)
4	[60,90)
5	[90,∞)

Table 8. 11 Error Groups

We compare aggregated errors between the actual and predicted lengths of stay in the test set. Table 8.12 compares error groups for the basic model and the conditional model.

Actual – Expected LOS	Group 1	Group 2	Group 3	Group 4	Group 5
Basic Model	0.12	0.13	0.35	0.20	0.20
Conditional Model	0.24	0.34	0.32	0.05	0.05

Table 8. 12 Distribution of Errors by Group

Predictions, using the conditional model, are reasonably accurate, with most errors falling with groups 1-3 (less than 60 days). Only 10% of all errors, using the conditional model, exceed 60 days.

8.5 Time Dependent Models

8.5.1 Time-dependent Cox model

The main focus of this study is the examination of the effect of demographic information at the beginning of hospice admission (e.g. care setting, gender, age, risk score from CMS HCC model, and diagnosis), together with drug information during hospice admission for the terminal event. We measure drug strength[22] in dosage of analgesic and other medications throughout the medication prescription history for all patients. In this case, strength is obviously a time-dependent covariate, whose values vary with time.

Above, we observed that the proportional hazards assumption, necessary for fitting the Cox model, is violated. We incorporated several variables, whose values vary with time, to relax the PH assumption. Several time-dependent variables added to the model are the daily analgesic dose, number of anxiolytic prescriptions, number of laxative prescriptions, and number of anti-nausea prescriptions. All of these time-dependent variables were obtained from the historical drug records available in our database. Earlier, we found that a parametric model, assuming the log-normal distribution for the survival time, is better at representing the data. Therefore, we fit both a time-dependent Cox model and a time-dependent parametric model and compare the goodness of fit of these models using AIC values.

For this model, we fit both fixed and time-dependent covariates. Fixed covariates in this model are care setting, sex, age at admission, risk score (from the CMS HCC 2013 model), and the presence of non-palliative drugs. In the case of non-palliative drugs, which enter the model as factors, the presence of the drug, at any time in the patient record, is counted as a positive value. Our time-dependent variables are number of analgesic drug prescriptions and drug strength, both of which vary with time.

[22] As a reminder (see Chapter 5), analgesic drug strength is measured relative to the strength of oral morphine, using an opioid converter.

8.5.2 Time-dependent log-normal AFT model

Let $D_i(t),\ N_i^{Lax}(t),\ N_i^{Antinau}(t),\ N_i^{Anxio}(t)$ be the daily dose of analgesic, number of laxative prescriptions, number of anti-nausea prescriptions, and number of anxiolytic prescriptions, respectively, for patient *i* at time *t*. The hazard function for the time-dependent Cox model is:

$$\lambda(t;\{D_i(v_1),\ v_1\in[o,t], N_i^{Lax}(v_2),\ v_2\in[o,t], N_i^{Antinau}(v_3),\ v_3\in[o,t], N_i^{Anxio}(v_4),\ v_4\in[o,t]\})$$

$$=\lambda_0(t)e^{\beta X+\alpha D_i(t)+\delta N_i^{Lax}(t)+\varphi N_i^{Antinau}(t)+\rho N_i^{Anxio}(t)}, \tag{8.13}$$

where $D_i(v_1),\ v_1\in[o,t], N_i^{Lax}(v_2),\ v_2\in[o,t], N_i^{Antinau}(v_3),\ v_3\in[o,t], N_i^{Anxio}(v_4),\ v_4\in[o,t]$ are the $\log T_i \sim N(\mu_i,\sigma^2)$ covariate paths for the daily analgesic dose, number of laxative prescriptions, number of anti-nausea prescriptions, and number of anxiolytic prescriptions for patient *i*, from time of admission to time *t*. α,δ,φ and ρ are the overall mean effects of the daily analgesic dose, number of laxative prescriptions, number of anti-nausea prescriptions, and number of anxiolytic prescriptions, respectively, on the hazard function, across all time points at which the covariates are measured. $\boldsymbol{X}$ is the fixed covariate matrix.

Similarly, the log-normal AFT model allows us to estimate the overall effect of the number of prescriptions and daily dose on the survival function.

Let T_i be the future lifetime random variable for the $i-th$ observation. We assume that $T_i \sim N(\mu_i,\sigma^2)$, or that the future lifetime of patient i is from the log-normal distribution. The mean parameters vary by observation while the variance is kept constant across all observations. μ_i is modelled as a linear combination of the fixed and time-dependent covariates. Once again, let $D_i(t),\ N_i^{Lax}(t),\ N_i^{Antinau}(t),\ N_i^{Anxio}(t)$ be the daily dose of analgesic, number of laxative prescriptions, number of anti-nausea prescriptions, and number of anxiolytic prescriptions, respectively, for patient *i* at time *t*. We have a historical path for for these time-dependent covariates up to time t:

$D_i(\upsilon_1),\ \upsilon_1\in[0,t],\ N_i^{Lax}(\upsilon_2),\ \upsilon_2\in[0,t],\ N_i^{Antinau}(\upsilon_3),\ \upsilon_3\in[0,t],\ N_i^{Anxio}(\upsilon_4),\ \upsilon_4\in[0,t]$.

Thus: $\mu_i(t)=BX+\alpha D_i(t)+\delta N_i^{Lax}(t)+\phi N_i^{Antinaus}(t)+\rho N_i^{Anxio}(t)$

where α,δ,ϕ and ρ are the overall mean effects of the daily analgesic dose and numbers of laxative, antinausea and anxiolytic prescriptions. We are interested in predicting the survival time beyond t for the $i-th$ observation.

$$\Pr(T_i > t) = 1 - \Pr(T_i \le t) = 1 - \Pr(\ln T_i \le \ln t)$$

$$= 1 - \Pr\left(\frac{\ln T_i - \mu_i(t)}{\sigma} \le \frac{\ln t - \mu_i(t)}{\sigma}\right) = 1 - \Phi\left(\frac{\ln t - \mu_i(t)}{\sigma}\right) \qquad (8.14)$$

Where Φ is the cumulative function of the standard normal distribution.

We make one change in the modelling at this point: instead of incorporating all 89 HCCs individually, we aggregate the HCCs into diagnosis groups (e.g. cancer, kidney, diabetes, etc.) to reduce the dimensionality of the data. In total, we have 18 fixed covariates and two time-dependent variables (number and daily dose of analgesic prescriptions, respectively). Tables 8.13 and 8.14 show the results of the Cox regression and log-normal AFT models, respectively.

Covariates	**Coefficient**	**Exp(coeff) (Hazard ratio)**	**P-value**	**Lower 95 % (of HR)**	**Upper 95% (of HR)**
Gender Male	0.117	1.124	0	1.117	1.132
Level Of Care HC (Home Care)	0.265	1.303	0	1.273	1.334
Level Of Care IPU (In-Patient Unit)	1.454	4.28	0	4.152	4.411
Level Of Care LTC (Long-Term care)	0.397	1.488	0	1.453	1.524
Age	0.002	1.002	0	1.002	1.002
Infection	0.323	1.381	0	1.342	1.421
Cancer	0.23	1.259	0	1.246	1.272
Diabetes	-0.003	0.997	0.7	0.984	1.011
Gastrointestinal	-0.031	0.97	0.001	0.952	0.988
Liver	0.249	1.283	0	1.251	1.316
Musculoskeletal	0.07	1.073	0	1.045	1.101
Psych	-0.224	0.799	0	0.791	0.806
Lung	-0.073	0.93	0	0.921	0.939
Heart	0.043	1.044	0	1.035	1.054
Kidney	0.213	1.238	0	1.219	1.257
Injury	0.199	1.221	0	1.096	1.359
HCCs Risk Score	0.028	1.028	0	1.022	1.034
Analgesic Dose (Time-Dependent)	0.068	1.07	0	1.07	1.071

Number of Laxative Prescriptions (Time-Dependent)	0.002	1.002	0.008	1.001	1.004
Number of Anti-Nausea Prescriptions (Time-Dependent)	0.005	1.005	0.004	1.002	1.009
Number of Anxiolytic (Time-Dependent)	0.116	1.123	0	1.122	1.125

Table 8. 13 Time-Dependent Cox Model Coefficients

Covariates	**Coefficient**	**S.E**	**Exp (coeff) (Aceeleration Factor)**	**Lower 95% (of AF)**	**Upper 95% (of AF)**
Meanlog (Intercept)	4.375	0.026			
Sdlog ()	1.466	0.002			
Gender Male	-0.166	0.005	0.847	0.838	0.856
Level Of Care HC (Home Care)	-0.411	0.017	0.663	0.641	0.685
Level Of Care IPU (In-Patient Unit)	-1.854	0.022	0.157	0.150	0.164
Level Of Care LTC (Long-Term care)	-0.607	0.017	0.545	0.527	0.563
Age	0.001	0.000	1.001	1.000	1.001
Infection	-0.517	0.021	0.596	0.572	0.622
Cancer	-0.238	0.008	0.788	0.776	0.800
Diabetes	0.026	0.010	1.026	1.006	1.046
Gastrointestinal	0.048	0.014	1.049	1.021	1.078
Liver	-0.332	0.019	0.718	0.691	0.745
Musculoskeletal	-0.086	0.020	0.918	0.883	0.954
Psych	0.358	0.007	1.430	1.411	1.450
Lung	0.071	0.007	1.074	1.058	1.090
Heart	-0.049	0.007	0.952	0.939	0.965
Kidney	-0.314	0.011	0.731	0.715	0.747
Injury	-0.297	0.081	0.743	0.634	0.871
HCCs Risk Score	-0.020	0.005	0.980	0.972	0.989
Analgesic Dose (Time-Dependent)	-0.098	0.001	0.907	0.906	0.908
Number of Laxative Prescriptions (Time-Dependent)	-0.004	0.001	0.996	0.993	0.999
Number of Anti-Nausea Prescriptions (Time-Dependent)	0.002	0.003	1.002	0.996	1.008
Number of Anxiolytic (Time-Dependent)	-0.215	0.002	0.807	0.804	0.810

Table 8. 14 Time-Dependent Log-Normal AFT Model Coefficients

Both models agree on the significant impact of both the number of prescriptions in laxatives and anxiolytics and the daily analgesic dose on the hazard rate and survival time in hospice. For the log-normal model, both the number of prescriptions and the daily analgesic dose reduce survival time: for each percentage increase, daily dose survival is reduced by 9.3%, on average, across all time points. Similarly, the survival time is reduced by 0.4% and 19.3%, on average, across all time points (at which the number of prescriptions is recorded), for each additional laxative prescription and anxiolytic prescription respectively.

In building Accelerated Failure Time models, a number of different AFT models were examined prior to selection of the log-normal model: Weibull, gamma, log-normal, log-logistic and generalized gamma models. Among these models, the log-normal distribution performed best, passed the diagnostic tests for distribution assumptions and had the smallest AIC. At the same time the log-normal AFT model is relatively straightforward to implement and interpret.

8.6 Prediction Using the Time-Dependent Log-Normal AFT Model

Using the output of the time-dependent log-normal AFT model, we are able to predict the expected remaining lifetime of a patient at any time point t, given that the patient is still alive at time t. Given that the criterion for admission to hospice is a life expectancy of less than six months, we exclude censored patients and all patients whose length of stay exceeds 180 days in the test (hold-out) set. For each individual in the test set, at any point in time t, we predict the conditional remaining expected lifetime, given that the patient is alive at time t and will die in the remaining $(180 - t)$ days, $E(T \mid T \geq t, T \leq (180 - t))$ and further compare with the actual remaining lifetime. Estimated mean errors at each interval and their confidence intervals are shown in figure 8.14.

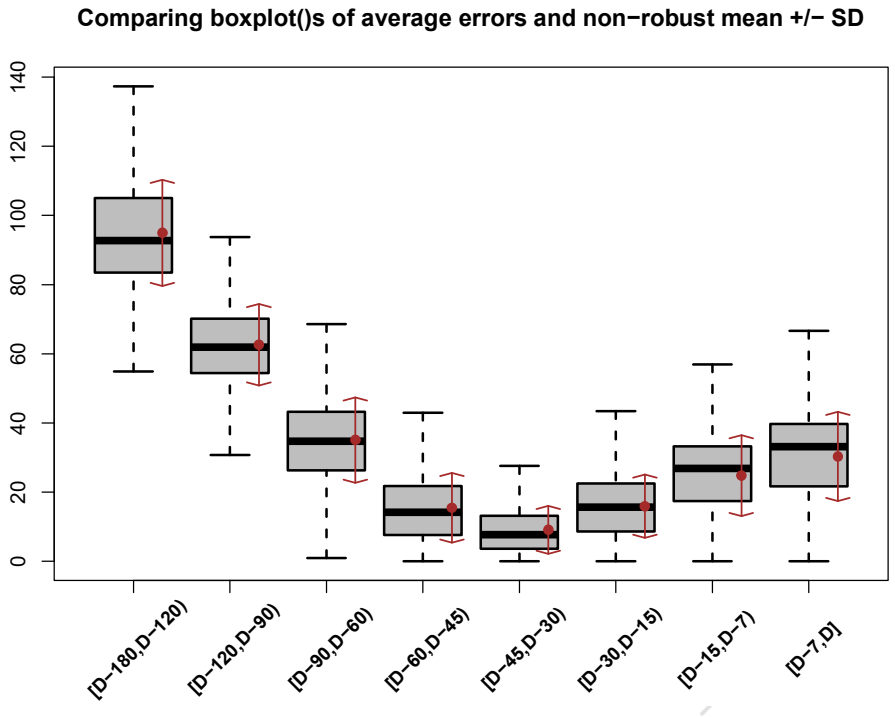


Figure 8. 14 Distribution of Mean Errors at Different Times

In Figure 8.14 the errors in each time period before death diminish as death approaches, reaching a minimum 30-45 days before death. The errors increase again closer to death, possibly because of the shape of the drug utilization distribution (see Figures 5.4 to 5.7 above).

8.7 Conclusion

We set out to model the survival of patients in hospice, and in particular, to find ways to incorporate covariates into the model to improve accuracy of estimated future life expectancy. The Cox regression model is widely used to study the effect of multiple predictors on time-to-event outcomes, due to its flexible assumptions regarding the survival distribution. However, one assumption in the Cox model is that the effect of covariates on the hazard function is constant over time (Cox PH assumption). In our analysis, we found that the Cox PH assumption is violated. In addition to violating the Cox PH assumption, we found that the Cox-Snell residuals indicate that the Cox model is not a good choice of model.

Possible remedies for the PH assumption violation include stratifying the failing categorical variables, incorporating time-dependent covariates, and fitting separate Cox models for different time intervals. Ultimately, however, the Cox model is rejected, based on the difficulty of calculating life expectancy.

Our analysis shows that parametric survival models should be considered in place of the Cox model. In particular, the log-normal AFT model outperforms the Cox model in fitting the dataset. We test the goodness-of-fit of the log-normal AFT model to the training data (residuals vs. cumulative hazard function). For out-of-sample testing we show the cross-validation errors on a test set (see Figure 8.14).

A further test of the log-normal AFT model fit is to compare the Average Expected LOS to Average Actual (remaining) LOS. Because of the dynamic nature of the model, we perform this test for different levels of t (actual survival time). A perfect model would have a ratio of 1.0 (average expected remaining lifetime = average actual remaining lifetime).

Figure 8.15 shows the ratio of $\frac{\text{Average Expected Future Lifetime}}{\text{Average Actual Future Lifetime}} \mid \text{Survival to } t$. In this figure, Length of Stay (LOS) is measured from time t. We test this ratio for 4 different survival groups: $t \in [0,5), t \in [5,10), t \in [10,30)$ and $t \geq 30$. (Thus for example for group $t \in [10,30)$ we assume that the patient has survived for 10 days and we are estimating survival beyond day 10.)

The ratio for the first survival group ($t \in [0,5)$ is low, indicating that the model initially underestimates actual survival significantly. Once the patient has survived for 10 days, however, the predictions become more accurate, with the initial prediction ratio for survival groups $t \in [10,30)$ and $t \geq 30$ close to 1.0.

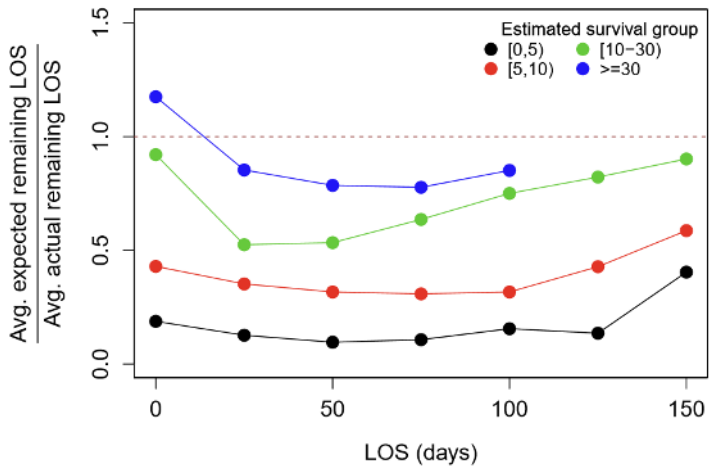


Figure 8. 15 Comparison of Expected and Actual Survival times for patients surviving different durations

In contrast to Cox regression, the log-normal AFT model provides the direct impact of many factors on survival outcomes, together with smooth estimates of survival and hazard functions. Ultimately, the time-dependent log-normal AFT model provides satisfactory predictions of life expectancy for patients, conditioning on life expectancy of less than six months. Implementing the model in an operational setting is another issue entirely.

8.8 Appendix A: Concurrence of Training and Test Datasets

The fit of the K-M model is demonstrated by comparing the distribution of survival of the training and test (holdout) data.

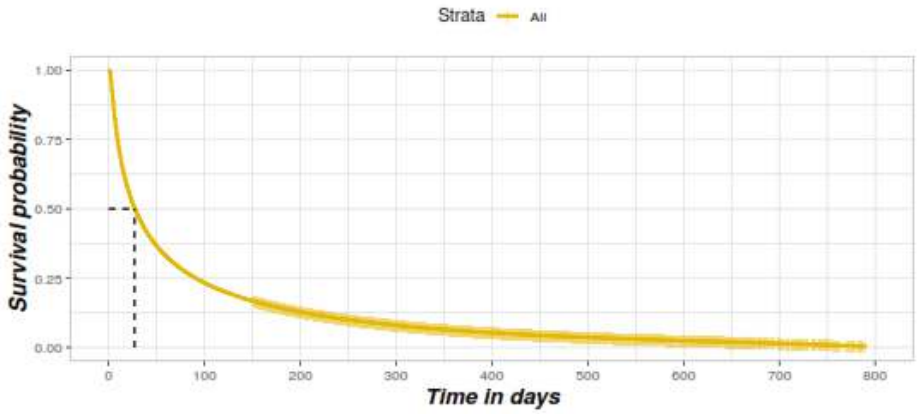


Figure A8.1a Kaplan-Meier distribution of Training Set (70%; Median Survival Time 27 days)

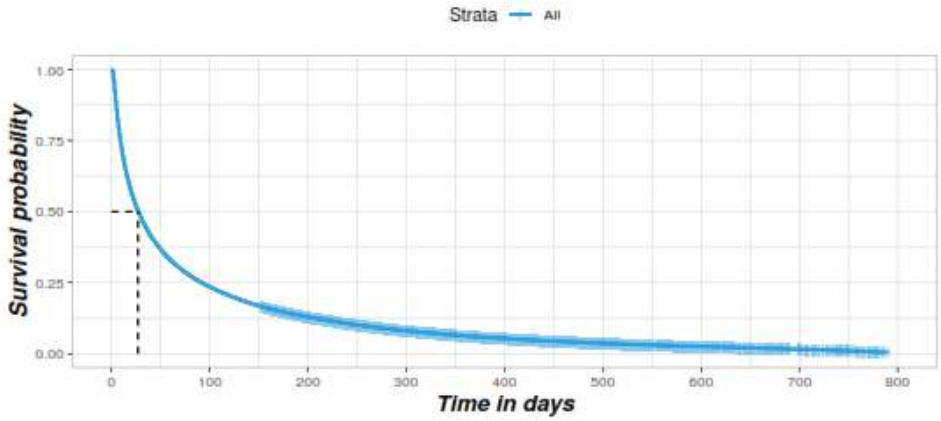


Figure A8.1b Kaplan-Meier distribution of Test Set (30%)

	Number at risk								
Days	0	100	200	300	400	500	600	700	800
Training Set (70%)	348,785	81,557	41,528	21,426	11,329	5,959	2,939	663	0
	100%	23%	12%	6%	3%	2%	1%	0%	0%
Test Set (30%)	149,479	35,328	17,953	9,244	4,828	2,530	1,278	318	0
	100%	24%	12%	6%	3%	2%	1%	0%	0%

Table A8.1 Kaplan-Meier Survival: Training vs. Test Sets

8.9 Appendix B: Sample predictions using the log-normal AFT model

In this section, we show the relationship between analgesic dose and life expectancy for four sample patients. Figures A8.2 – A8.5 show clearly the inverse relationship between changes in dosage and life expectancy. Patient 2's life expectancy increases at about 13 days prior to death, but this is because an anxiolytic drug is temporarily discontinued (not shown in the figure, but clearly seen in table A8.1). Patient 3's life expectancy decreases significantly at day 4, prior to death, although the patient's analgesic dose does not increase until day 3. This is because an anxiolytic prescription was added one day prior to the increase in analgesic dosage.

Cph PatientID Patient 1:	***t***	**Analgesic Dose**	**Lax-ative**	**Anti-nausea**	**Anxio-lytic**	**Actual LOS**	**Remaining expected life time**	**Remaining LOS**	**Absolute difference**
xxxx278	0	0.600	2	1	2	10	17.603	9.0	8.603
xxxx278	1	0.683	2	1	2	10	17.473	8.0	9.473
xxxx278	2	0.683	2	1	2	10	17.447	7.0	10.447
xxxx278	3	21.240	1	0	2	10	3.036	6.0	2.964
xxxx278	4	3.983	1	0	1	10	16.087	5.0	11.087
xxxx278	5	4.223	1	0	0	10	18.487	4.0	14.487
xxxx278	6	21.240	1	0	1	10	3.727	3.0	0.727
xxxx278	7	21.240	1	0	1	10	3.726	2.0	1.726
xxxx278	8	21.240	1	0	0	10	4.561	1.0	3.561
xxxx278	9	21.240	1	0	0	10	4.559	0.0	4.559

Table A8.2 Predicted and Actual Future Lifetime (Sample Patient 1)

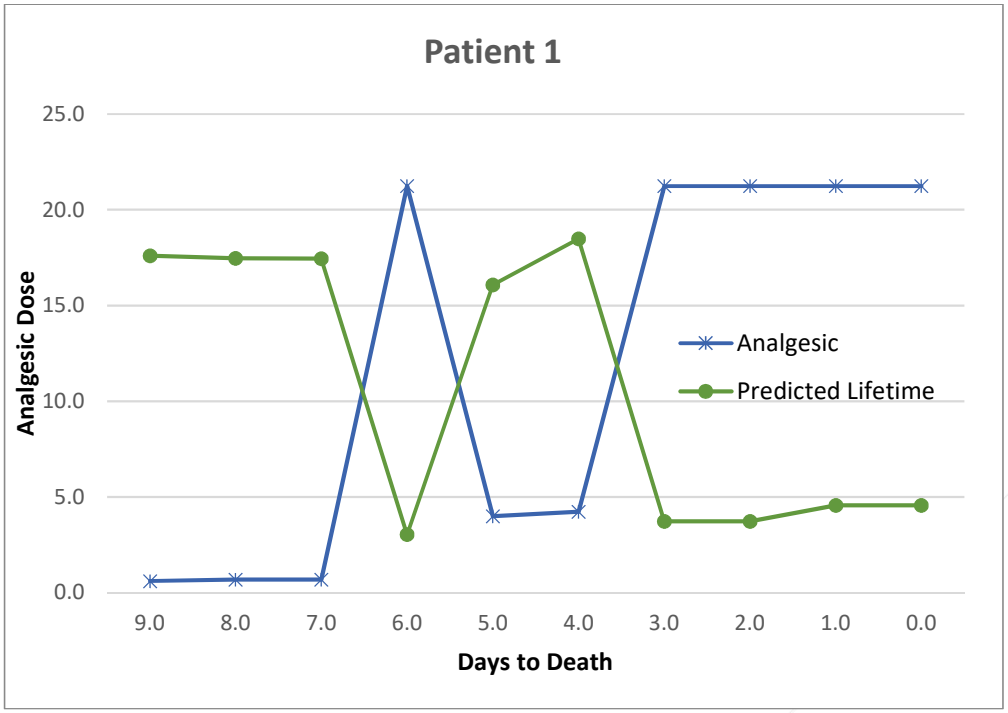


Figure A8.2 Analgesic Drug Dosage vs. Predicted Days to Death (Sample Patient 1)

Cph PatientID Patient 2:	*t*	Analgesic Dose	Lax-ative	Anti-nausea	Anxio-lytic	Actual LOS	Remaining expected life time	Remaining LOS	Absolute difference
xxxx225	0	0.001	0	0	0	59	45.101	58.0	12.899
xxxx225	1	0.001	0	0	0	59	44.962	57.0	12.038
xxxx225	2	0.003	0	4	0	59	44.974	56.0	11.026
xxxx225	3	0.003	0	4	0	59	44.833	55.0	10.167
xxxx225	4	0.003	0	4	0	59	44.691	54.0	9.309
xxxx225	5	0.003	0	4	0	59	44.549	53.0	8.451
xxxx225	6	0.003	0	4	0	59	44.406	52.0	7.594
xxxx225	7	0.003	0	4	0	59	44.262	51.0	6.738
xxxx225	8	0.003	0	4	0	59	44.118	50.0	5.882
xxxx225	9	0.003	0	4	0	59	43.973	49.0	5.027
xxxx225	10	0.003	0	4	0	59	43.828	48.0	4.172
xxxx225	11	0.003	0	4	0	59	43.682	47.0	3.318
xxxx225	12	0.003	0	4	0	59	43.535	46.0	2.465
xxxx225	13	0.003	0	4	0	59	43.388	45.0	1.612
xxxx225	14	0.003	0	4	0	59	43.240	44.0	0.760
xxxx225	15	0.003	0	4	0	59	43.091	43.0	0.091
xxxx225	16	0.003	0	4	0	59	42.942	42.0	0.942
xxxx225	17	0.003	0	4	0	59	42.792	41.0	1.792
xxxx225	18	0.003	0	4	0	59	42.641	40.0	2.641
xxxx225	19	0.450	0	4	2	59	34.093	39.0	4.907
xxxx225	20	0.450	0	4	2	59	33.989	38.0	4.011
xxxx225	21	0.450	0	4	2	59	33.883	37.0	3.117
xxxx225	22	0.450	0	4	2	59	33.778	36.0	2.222
xxxx225	23	0.450	0	4	2	59	33.672	35.0	1.328
xxxx225	24	0.450	0	4	2	59	33.565	34.0	0.435
xxxx225	25	0.450	0	4	2	59	33.457	33.0	0.457
xxxx225	26	0.450	0	4	2	59	33.349	32.0	1.349
xxxx225	27	0.450	0	4	2	59	33.240	31.0	2.240
xxxx225	28	0.450	0	4	2	59	33.131	30.0	3.131
xxxx225	29	0.450	0	4	2	59	33.021	29.0	4.021
xxxx225	30	0.450	0	4	2	59	32.910	28.0	4.910
xxxx225	31	0.450	0	4	2	59	32.799	27.0	5.799
xxxx225	32	0.450	0	4	2	59	32.687	26.0	6.687
xxxx225	33	0.453	0	4	2	59	32.570	25.0	7.570
xxxx225	34	0.453	0	4	2	59	32.457	24.0	8.457

xxxx225	35	0.453	0	4	2	59	32.343	23.0	9.343
xxxx225	36	0.453	0	4	2	59	32.228	22.0	10.228
xxxx225	37	0.453	0	4	2	59	32.113	21.0	11.113
xxxx225	38	0.453	0	4	2	59	31.998	20.0	11.998
xxxx225	39	0.453	0	4	2	59	31.881	19.0	12.881
xxxx225	40	0.453	0	4	2	59	31.764	18.0	13.764
xxxx225	41	0.453	0	4	2	59	31.646	17.0	14.646
xxxx225	42	0.453	0	4	2	59	31.528	16.0	15.528
xxxx225	43	0.453	0	4	2	59	31.408	15.0	16.408
xxxx225	44	0.453	0	4	2	59	31.288	14.0	17.288
xxxx225	45	0.453	0	4	2	59	31.168	13.0	18.168
xxxx225	46	0.453	0	4	2	59	31.046	12.0	19.046
xxxx225	47	0.453	0	4	0	59	37.304	11.0	26.304
xxxx225	48	0.453	0	4	0	59	37.136	10.0	27.136
xxxx225	49	0.453	0	4	0	59	36.967	9.0	27.967
xxxx225	50	0.453	0	4	0	59	36.798	8.0	28.798
xxxx225	51	0.453	0	4	0	59	36.627	7.0	29.627
xxxx225	52	0.453	0	4	0	59	36.455	6.0	30.455
xxxx225	53	0.453	0	4	0	59	36.283	5.0	31.283
xxxx225	54	0.453	0	4	2	59	30.048	4.0	26.048
xxxx225	55	0.453	0	4	2	59	29.920	3.0	26.920
xxxx225	56	0.453	0	4	2	59	29.791	2.0	27.791
xxxx225	57	0.453	0	4	2	59	29.661	1.0	28.661
xxxx225	58	0.453	0	4	2	59	29.531	0.0	29.531

Table A8.3 Predicted and Actual Future Lifetime (Sample Patient 2)

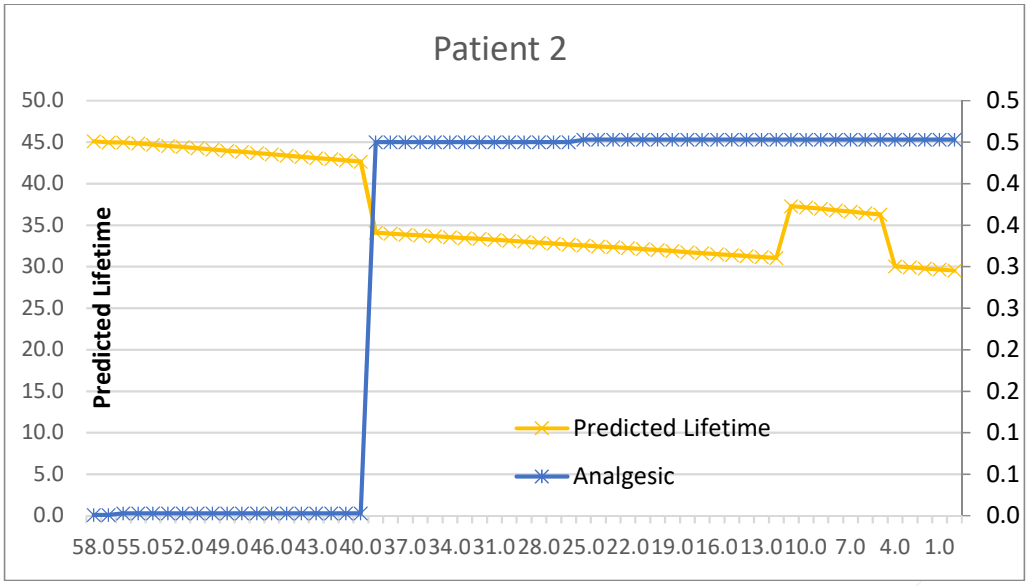


Figure A8.3 Analgesic Drug Dosage vs. Predicted Days to Death (Sample Patient 2)

Cph Patient ID Patient 3:	***t***	**Analgesic Dose**	**Laxative**	**Anti-nausea**	**Anxiolytic**	**Actual LOS**	**Remaining expected life time**	**Remaining LOS**	**Absolute difference**
xxxx545	0	0.000	0	0	0	7	21.682	6.0	15.682
xxxx545	1	0.000	0	0	0	7	21.643	5.0	16.643
xxxx545	2	0.000	0	0	0	7	21.605	4.0	17.605
xxxx545	3	0.000	0	0	8	7	5.296	3.0	2.296
xxxx545	4	2.571	0	0	8	7	4.187	2.0	2.187
xxxx545	5	2.571	0	0	8	7	4.186	1.0	3.186
xxxx545	6	2.571	0	0	8	7	4.184	0.0	4.184

Table A8.4 Predicted and Actual Future Lifetime (Sample Patient 3)

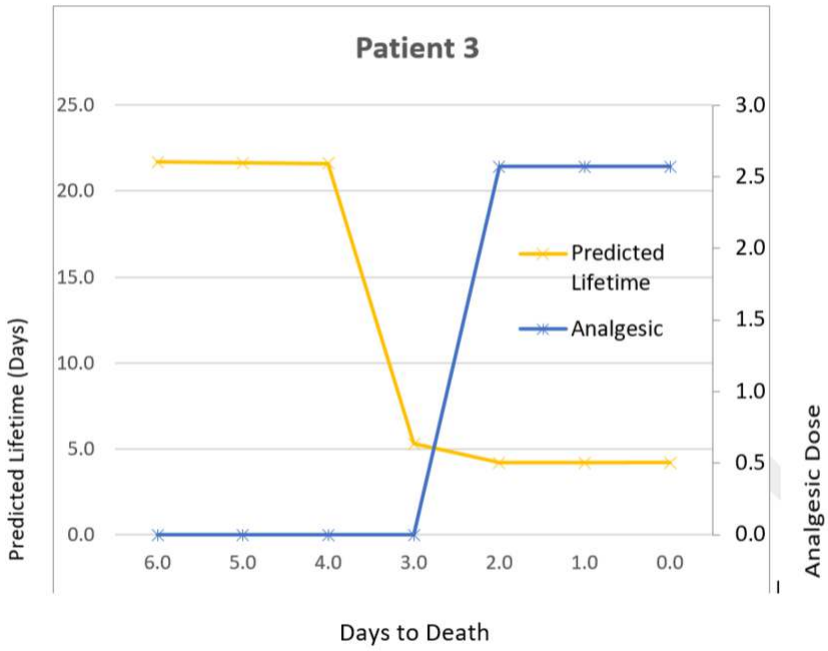


Figure A8.4 Analgesic Drug Dosage vs. Predicted Days to Death (Sample Patient 3)

Cph PatientID Patient 4:	*t*	Analgesic Dose	Laxative	Anti-nausea	Anxiolytic	Actual LOS	Remaining expected life time	Remaining LOS	Absolute difference
xxxx133	0	0.000	0	0	0	22	46.819	21.0	25.819
xxxx133	1	0.000	0	0	0	22	46.671	20.0	26.671
xxxx133	2	1.080	0	0	2	22	36.090	19.0	17.090
xxxx133	3	1.080	0	0	2	22	35.993	18.0	17.993
xxxx133	4	1.080	0	0	2	22	35.895	17.0	18.895
xxxx133	5	1.080	0	0	2	22	35.797	16.0	19.797
xxxx133	6	1.080	0	0	2	22	35.698	15.0	20.698
xxxx133	7	1.080	0	0	2	22	35.599	14.0	21.599
xxxx133	8	1.080	0	0	2	22	35.500	13.0	22.500
xxxx133	9	1.080	0	0	2	22	35.400	12.0	23.400
xxxx133	10	1.080	0	0	2	22	35.299	11.0	24.299
xxxx133	11	2.160	2	0	8	22	14.300	10.0	4.300
xxxx133	12	2.160	2	0	8	22	14.280	9.0	5.280
xxxx133	13	2.160	2	0	8	22	14.260	8.0	6.260
xxxx133	14	2.160	2	0	8	22	14.241	7.0	7.241
xxxx133	15	2.160	2	0	8	22	14.220	6.0	8.220
xxxx133	16	2.220	2	0	8	22	14.137	5.0	9.137
xxxx133	17	2.220	2	0	8	22	14.116	4.0	10.116
xxxx133	18	2.220	2	0	8	22	14.096	3.0	11.096
xxxx133	19	2.220	2	0	8	22	14.075	2.0	12.075
xxxx133	20	2.220	2	0	8	22	14.054	1.0	13.054
xxxx133	21	2.220	2	0	8	22	14.033	0.0	14.033

Table A8.5 Predicted and Actual Future Lifetime (Sample Patient 4)

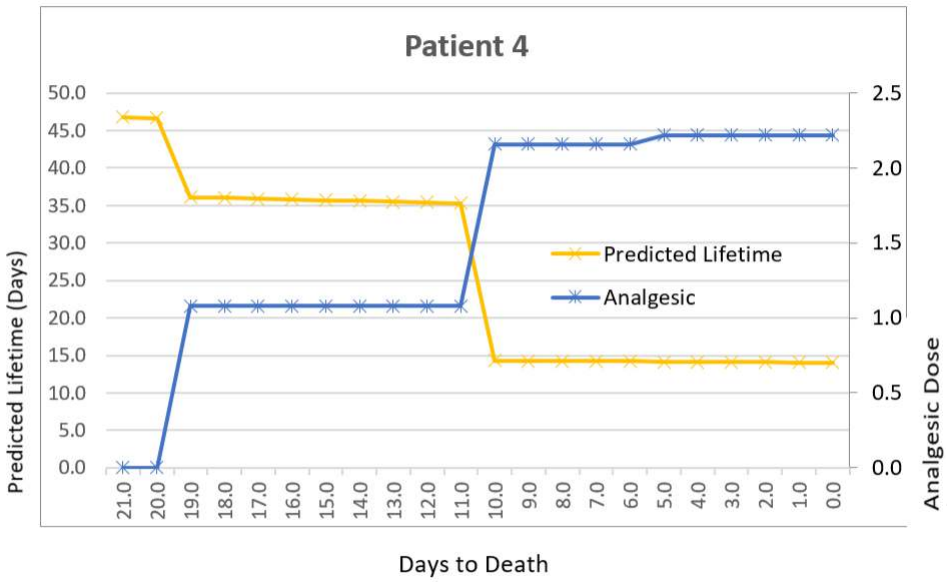


Figure A8.5 Analgesic Drug Dosage vs. Predicted Days to Death (Sample Patient 4)

These sample patients show the potential usefulness of this model in an operational setting. Hospice operators need to know, for planning and staffing purposes, the expected length of service of their patients. The examples show that incorporation of the drug dosage and prescription data into the planning process can provide valuable information about life expectancy of hospice patients.

CHAPTER 9 – CONCLUSION AND FUTURE WORK

The purpose of this study was to demonstrate the applicability and value of survival models in real-world health and health insurance situations of the type that a health actuary might encounter. In our first example, we evaluated survival of permanently disabled workers with lifetime medical benefits under the workers' compensation laws of California. We fitted standard actuarial parametric models (Gompertz), as well as different polynomial functions. Neither the actuarial functions nor the prescribed U.S. Life table fitted the empirical data well. Among polynomial functions, a quadratic function fitted reasonably well to the underlying data, while higher-order functions appeared to over-fit the data. From a purely reserving perspective, a table of mortality rates, based on the quadratic function, would appear to provide more accurate reserve estimates. However, we also fitted both stratified Kaplan-Meier and Cox Proportional Hazards models. The Kaplan-Meier estimator generates a survival model, while the Cox model allows us to estimate the effect of covariates on the hazard of claim termination. The advantage of these models, for the management of the business, lies in their inclusion of covariates, which are not available in typical actuarial mortality models. Estimates of coefficients, of different covariates, allow management to concentrate claims adjuster attention on claimants who are at highest-risk of persistency. Typically, a reserve would provide management information about relative risk, and the claims adjuster could concentrate on managing, or negotiating, a settlement of high reserve claims. In the case of California permanently disabled claimants, the reserve is potentially mis-leading in two respects. Our analysis shows that survival is over-estimated, while, at the same time, failure to include a provision for medical claims inflation (in a medical environment where 5% to 6% annual increases are common) implies that the reserve is probably under-stated, particularly for those claimants with expected longer survival.

Our other two examples pertain to hospice patients at the end of life. Our hospice dataset contains observations of patients from admission to hospice until end of life (or censor date), including their prescription drug history. To facilitate analysis of the dataset, we constructed a number of derived variables, including (for drugs in the four commonly-prescribed classes at end of life) an index of relative drug strength, the cumulative strength over the course of hospice stay, and the number of prescriptions filled for each drug class.

We also mapped patient diagnoses to the Medicare Hierarchical Condition Categories (HCCs) for ease of analysis at the diagnostic level.

Access to prescription drug data allows us to develop two different survival models: the rate at which drugs from potentially ineffective classes are withdrawn, and the life expectancy of patients following admission to hospice. Patients with limited life expectancy are at risk of polypharmacy and attendant adverse drug events. In addition, cost, wastage, and diversion[23] of drugs are problems that pharmacists can manage with models that predict which drugs and patient profiles are most subject to ineffective prescribing. The first application requires the implementation of a competing risks model because patients are subject to two risks simultaneously: termination of the prescription and death. We applied the Cumulative Incidence Function (CIF) approach to estimate the rate at which drugs are withdrawn from terminally-ill patients. Because the termination rate takes no account of the patient's length of hospice stay, we also calculated Medication Possession Ratios, relating the duration of the prescription to the patient's length of hospice stay. While a few drugs are withdrawn quickly most classes of drugs are prescribed for most of the patient's hospice stay, risking polypharmacy and adverse drug reactions. A version of this model is being implemented in a hospice pharmacy to identify combinations of drugs and patient variables that are likely to result in persistency of prescriptions that are potentially ineffective, so that these drugs may be withdrawn earlier.

Our second application is a more typical actuarial application, estimating life expectancy of hospice patients. Accurate estimates of expectancy are important for the management of hospice clinical resources, as well as drug prescriptions, because of the potential for wastage and cost of drugs in terminal patients. Access to detailed prescription data, including dosage, allows us to apply time-dependent and accelerated failure time models to account, dynamically, for the effect on life expectancy of changes in prescriptions and dosage.

Access to detailed prescription data allows us to analyse prescribing patterns over the duration of a patient's hospice stay. Generally, the dosage of analgesic and anxiolytic drugs increases during the stay, with anti-nausea and laxative drugs showing a more

[23] A problem with drugs (particularly opioids which are addictive and for which there is "street" demand) is potential theft and re-sale by care-givers.

uniform pattern. As may be expected, cancer patients experience the highest dosages of drugs, although the four palliative drug classes are found in all diagnostic groups. The dosage patterns, over time and by diagnosis, provide us with the ability to incorporate these time-dependent covariates into models of survival. We tested a number of different semi-parametric and parametric models, with the time-dependent Cox model and accelerated failure time log-normal models providing the best fit to the data. Finally, we illustrated the application of the models, within an operational environment, with four examples, drawn from the database. Discussions are currently in progress with EP to implement the predictive model into their patient management system to give nurses and pharmacists real-time warning of changes in patient life expectancy. In conclusion, we set out to illustrate the potential usefulness of survival models for health actuarial practice. Our examples have illustrated use of both typical (static covariate) models, as well as a type of model with which actuaries will be less familiar: time-dependent models. Our workers' compensation example shows the usefulness of covariate models as a management tool for managing a book of claimants. However, as our hospice example shows, more useful information about patient status may be derived from covariates that change over time, leading to improved patient management.

These are new tools for most health actuaries, but they provide both powerful insights, as well as opportunities for health actuaries to expand their practice into non-traditional areas of medical management.

Future work: the patient's drug pathway unfolds as a stochastic process. The incorporation of stochastic processes into the modelling opens a large subject, beyond our current scope. Incorporation of stochastic and point processes is a potentially useful direction for future work.

One last point, which is important to make about this thesis and health actuaries generally, is that health actuaries are, first and foremost, risk managers, serving business clients, and secondly statisticians. This thesis is somewhat representative of the work of a health actuary, in that it required in-depth knowledge of a number of business topics specific to the application of the survival models. From a statistical perspective, the models may be relatively straightforward; as the hospice examples show, the business context in which they are applied is not. We could not have applied survival modelling to hospice patients without understanding the regulatory model within which hospices operate, as well

as the diagnostic and prescription drug information available. Over time, actuarial modelling will, no doubt, become more sophisticated, but the health actuary of the future will be required to be part risk modeller, part epidemiologist, and part statistician.

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