IMPACT OF LUMBAR PUNCTURE ON SURVIVAL OF COMATOSE MALAWIAN CHILDREN: A PROPENSITY-SCORE-BASED ANALYSIS

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ABSTRACT

IMPACT OF LUMBAR PUNCTURE ON SURVIVAL OF COMATOSE MALAWIAN CHILDREN: A PROPENSITY-SCORE-BASED ANALYSIS

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Coma is a frequent clinical presentation of severely ill children in sub-Saharan Africa. It may have a number of infectious and non-infectious etiologies including cerebral malaria, viral encephalitis, and bacterial and tuberculous meningitis [7]. Due to its high rates of mortality and morbidity, rapid diagnosis and targeted interventions to optimize outcomes are critical. However, clinical assessment alone cannot distinguish between these etiologies, identifying coma etiologies by lumbar puncture (LP) is important.

LP is a clinical procedure that is used to collect and examine the cerebrospinal fluid surrounding the brain and spinal cord. It has been widely utilized to diagnose symptoms and signs caused by infection, inflammation, cancer, or bleeding in the central nervous system. LP is an essential, simple, and widely available, procedure that is generally the only way to definitively identify underlying infectious coma etiologies. Despite the clear efficacy of LP, clinicians may be reluctant to perform the procedure in a comatose child, due to concerns that the procedure may bring out cerebral herniation and death [4].

In this thesis, we aim to assess the impact of LP on the survival of comatose children. We performed a retrospective cohort study on survival of comatose Malawian pediatric inpatients recruited over consecutive rainy seasons from 1997-2013. Due to the lack of randomness in being treated (LP) and untreated (Non-LP) groups, baseline characteristics are not balanced. We applied propensity score methods to compensate the imbalance. Our analysis results showed no impact in death rate associated with LP.

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Chapter 1

Introduction

1.1 Cerebral Malaria and Lumbar Puncture

In low and middle-income countries, coma is a frequent clinical presentation of severely ill children. The most common cause of these comatose patients is cerebral malaria (CM). The global annual incidence of severe malaria can be estimated at approximately two million cases and about 90% of the world's severe and fatal malaria occurs to young children in sub-Saharan Africa [15].

The World Health Organization (WHO) defines cerebral malaria as a clinical syndrome characterized of coma (inability to localize a painful stimulus) at least one hour after termination of a seizure or correction of hypoglycemia, asexual forms of *Plasmodium falciparum* parasites on peripheral blood smears, and exclusion of other causes of encephalopathy (e.g. viral encephalitis, poisoning, and metabolic disease) [10]. However, this definition is not well observed in practice. Patients whose coma is caused by other encephalopathies or previously unrecognized neurological abnormalities but have incidental parasitemia may be included. Due to the lack of specificity, using clinical evaluation by itself cannot differentiate between these etiologies [18]. By reasons of the amount of risk and the low feasibility of experimentally treating all cases of infectious coma etiologies in suspected children with CM, utilizing lumbar puncture (LP) increases the chance for correct treatment and accurate diagnoses.

Lumbar puncture (LP) is a clinical procedure that is used to collect and examine the

cerebrospinal fluid (CSF) surrounding the brain and spinal cord. It has been widely utilized to diagnose symptoms and signs caused by infection, inflammation, cancer, or bleeding in the central nervous system. LP is also used to measure the CSF pressure within the epidural space [9]. In particular, LP has been a valuable and generally the only available tool for identifying the etiology of CM. Despite its efficacy, clinicians who lack access to such resources like pre-procedural neuro-imaging may be hesitant to perform it. This is because performing LP on comatose patients may incur cerebral herniation and death if the absence of brain shift or increased intracranial pressure (ICP) is not verified through neuroimaging or molecular testing [19, 1].

Moxon et al. examined safety of LP in comatose African children with clinical features of CM [2]. They found no evidence that undergoing LP increases mortality in comatose children with suspected CM. This was also true in children with magnetic resonance imaging (MRI) evidence of severe brain swelling. In addition, the study provided evidence that LP does not play a causal role in fatal herniation in the context of diffusely increased ICP. They conjecture that LP does not exacerbate herniation in CM because, during LP, the CSF pressure is able to rapidly equilibrate.

In this study, we extend the Moxon's work to survival analysis. We conduct statistical analysis to assess the impact of LP on the death rate of comatose children. In particular, we examine whether i) the temporal association between LP and death implies causation; ii) LP contributes to mortality in children with CM who have increased ICP by comparing the hospital death rates between the treatment and control groups; and iii) effect of LP on death in CM children with and without Papilledema.

1.2 Survival Data and Survival Analysis

Survival data are in the form of time from a well-defined origin until the occurrence of some particular event or end-point such as death, disease onset, machine failure, automobile accidents, promotions, or end of marriage [3]. Survival data are not amenable to conventional statistical procedures because of their special feature, *censoring*. Censoring is a typical characteristic in survival analysis, representing a particular type of coarsened data. It occurs when the end-point of interest has not been observed for a subject due to end of investigation, drop-out of subjects, or the experiment design with threshold for the time window. The information of such censored observations is therefore incomplete. In addition, survival data are also generally not symmetrically distributed but positively skewed [3]. The survival times usually have specialized non-normal distributions, such as the exponential, Weibull, and log-normal. Hence, conventional statistical analysis methods are limited for dealing with survival data.

Unlike conventional statistical methods, survival analysis correctly incorporates information from both censored and uncensored observations in estimating important model parameters. Two key elements of survival data are i) a time to event/censoring indicating how long until the subject either experienced the event or was censored, and ii) a censoring indicator denoting whether an observational event was experienced or censored. Based on the two elements, the survival and hazard functions are estimated for describing the distribution of event times. The survival function represents the probability that an individual survives (or does not experience the event) beyond any given time. The hazard function gives the potential risk or hazard of an event at the specified time. It is generally of interest in survival analysis to describe the relationship of a factor of interest (e.g. treatment) to the

time to event, in the presence of several covariates (e.g. age, gender, race, etc.) A number of models from parametric, nonparametric and semi-parametric approaches are available to analyze the relationship of a set of predictor variables with the survival time.

In our survival analysis, we examine the death hazard rate between patients with LP, (i.e. the treatment group) and without LP (i.e. the control group.) Discharge from the medical institution is regarded as a competing endpoint, which is actually dependent on time to death. All the survival analyses in this study are therefore for competing risks, i.e. estimating cause-specific hazard of death.

1.2.1 Lumbar Puncture Data

We conduct a retrospective cohort study of pediatric inpatients recruited from 1997 to 2015 at the Pediatric Research Ward at Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi. The study population contains $1,772$ comatose children aged two months to fourteen years, including $1,442$ patients in the treatment group and 350 patients in the control group. Patients in the treatment group received LPs in one of two ways. If the patients were directly admitted to QECH, the procedure was done as part of the admission process. On the other hand, if patients were referred to QECH from other accident and emergency departments, the LPs were done at those institutions. LPs were not done in the control group because clinicians determined that the children were not stable enough to tolerate the procedure. The dataset at hand is comprised of characteristic variables on the admission to the medical institution that influenced a clinician's decision to perform a LP or were independently associated with death. Several time variables such as time of admission, death, hospital discharge, and LP operation are also included in the dataset.

1.2.1.1 Treatments and Outcomes

The treatment group contains 81.4% and the control group contains 18.6% of comatose children. The total number of subject is $1,772$. The patients in the control group have not received LP because of one or more of five reasons below:

1. The clinician was concerned that the child was not stable enough to tolerate an LP based on shock, severe respiratory distress or intractable seizures.
2. The clinician identified Papilledema on retinal examination.
3. LP was attempted but failed for technical reason(s).
4. The parent did not consent to LP.
5. The child regained consciousness before LP was performed.

For outcome, 3, 6, 12-hour mortality rates and overall mortality rate during hospitalization were used to evaluate the treatment effects.

1.2.1.2 Characteristic Variables

The statistical analysis includes factors which affect a physician's decision to perform LP and others obtained from previous studies associated with a fatal outcome.

- Depth of coma (Blantyre Coma Score)
- Systolic blood pressure for age
- Weight-for-height z-score (nutritional status)
- Respiratory distress or acidotic breathing

- Pulse rate
- Cardiovascular system examination (signs of heart failure)
- Gender
- Admission blood glucose concentration
- Peripheral parasite density
- Hematocrit
- Malaria retinopathy status
- Papilledema

Weight-for-height z-score was created by weight and height according to the WHO Child Growth Standards [8]. Respiratory distress or acidotic breathing was determined from sign of grunting, deep breath and normal chest exam: if any of the three is abnormal, then it suggests that respiratory disease is present. In the data, 256 patients did not have malaria retinopathy status on admission. As a result we imputed the value of this status utilizing logistic regression based on: platelet count, hematocrit, and glucose. Where the probability of retinopathy is greater than 50%, we set this value as positive, if not negative. The threshold for the probability was set to be consistent with Moxon's [2]. Papilledema was considered an important factor for the statistical analysis. However, a significant portion of children (i.e. 43%) have missing information of Papilledema determination. We therefore performed sub-analysis without Papilledema for confirming significant role of Papilledema in statistical analysis. Any subjects with missing data, other than retinopathy or Papilledema,

were excluded from the statistical analysis. Tables 1.1 and 1.2 shows explanatory variables from the original data set and their descriptions.

Table 1.1: Descriptions of Categorical Variables from the Original Data. The Total Number of subjects in the original data set is 2,399.

Variable	Description	Units	Count
COMASC	Depth of comma (Blantyre coma score: ≤ 2 = unrousable coma)	0=Most severe 1=Severe 2=Less Severe No. of Missing	383 949 1,067 0
BPSTAT	Systolic blood pressure for age	0=Low 1=Normal 2=High No. of Missing	28 2,071 89 211
WH	Weight-for-Height Z-score (Nutritional status)	0=Normal 1=Low No. of Missing	2,067 211 121
RESPDIS	Respiratory distress	0=Not Present 1=Present No. of Missing	1,228 821 350
PULSESTAT	Pulse rate	0=Low 1=Normal 2=High No. of Missing	43 925 1,299 132
NHEART	Cardiovascular system examination (Normal heart test)	0=Normal 1=Abnormal No. of Missing	135 2,236 28
SEX	Gender	0=Male 1=Femal No. of Missing	1,143 1,252 4
ADMRETIN	Malaria retinopathy status	0=Not Present 1=Present No. of Missing	822 1,321 256
PAP	Papilledema	0=Not Present 1=Present No. of Missing	1,033 241 1,125

Table 1.2: Descriptions of Continuous Variables from the Original Data. The Total Number of subjects in the original data set is 2,399.

Variable	No. of Missing	Description	LP	Mean	SD	Min	Max
ADMHCT	122	Hematocrit	Non-LP	21.34	8.38	6.00	59.00
			LP	23.75	8.07	2.00	46.90
ADMGLUC	10	Admission blood glucose	Non-LP	6.29	3.98	0.5	29.60
			LP	6.78	4.05	0.3	33.00
LOGADMPTA	189	Peripheral parasite Density	Non-LP	10.22	3.32	0	14.29
			LP	9.22	4.27	0	15.02

1.2.1.3 Time Variables

Several time variables such as times of admission, death and hospital discharge as well as LP operation are included in the dataset. The time origin is the time of LP performed for the treatment group or the time of admission for the control group. Time of death is regarded as the endpoint while discharge from the medical institution is regarded as a competing endpoint. Table 1.3 compares the distributions of time to event (i.e. death or discharge) between LP and Non-LP groups. Figures 1.1 and 1.2 show distributions of time to event in LP and Non-LP groups.

Table 1.3: Distributions of Time to Event.

LP	Outcome	No. of Subjects	Mean	SD	Min	Max
Non-LP	Discharge	259	3.555	2.34	0.500	26.79
	Death	91	0.798	1.38	0.014	11.17
LP	Discharge	1206	3.791	2.98	0.208	33.77
	Death	216	1.411	3.27	0.021	31.11

1.2.1.4 Selection Bias

As we mentioned above, decisions about whether LPs were medically contraindicated were made by different admitting clinicians, resulting in non-random variation in severity of illness among children who did and did not received LPs. Due to the lack of randomness in treated

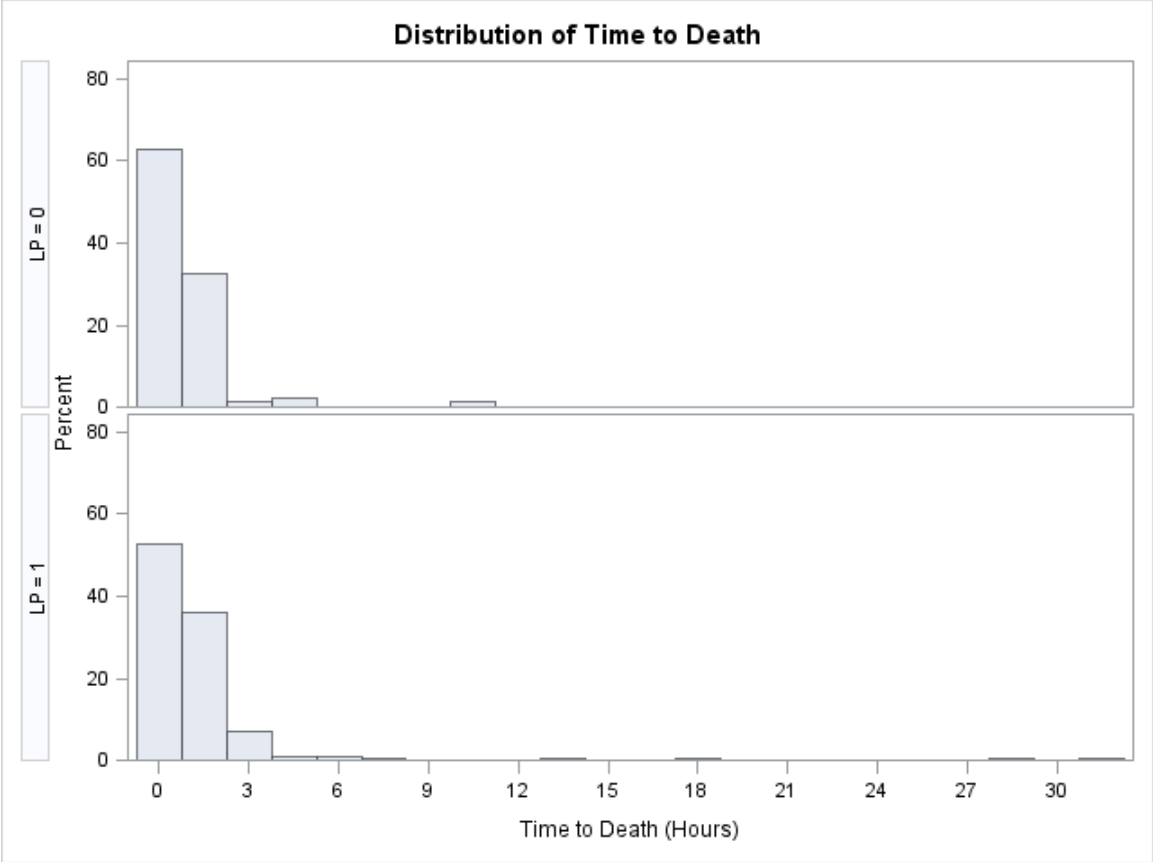

Figure 1.1: Distributions of Time to Death for LP (LP=1) and Non-LP (LP=0) Groups.

(LP) and untreated (non-LP) groups, a number of baseline characteristics of the two groups are not balanced. As a result, a simple comparison of mortality rates between the treated and untreated groups would be biased [12]. Because less ill children would be more likely to undergo an LP, resulting in a survival bias accruing to that group. To address this bias, we apply propensity score (PS) methods to alleviate the imbalance between the two groups in the survival analysis. PS methods allow us to reduce the confounding effect that can occur due to differences in the distributions of baseline characteristics between the groups. Similar to randomization, PS methods compare outcomes in the treated and untreated subjects who have a similar distribution of measured baseline covariates. We discuss propensity score methods in Section 2.2 in detail.

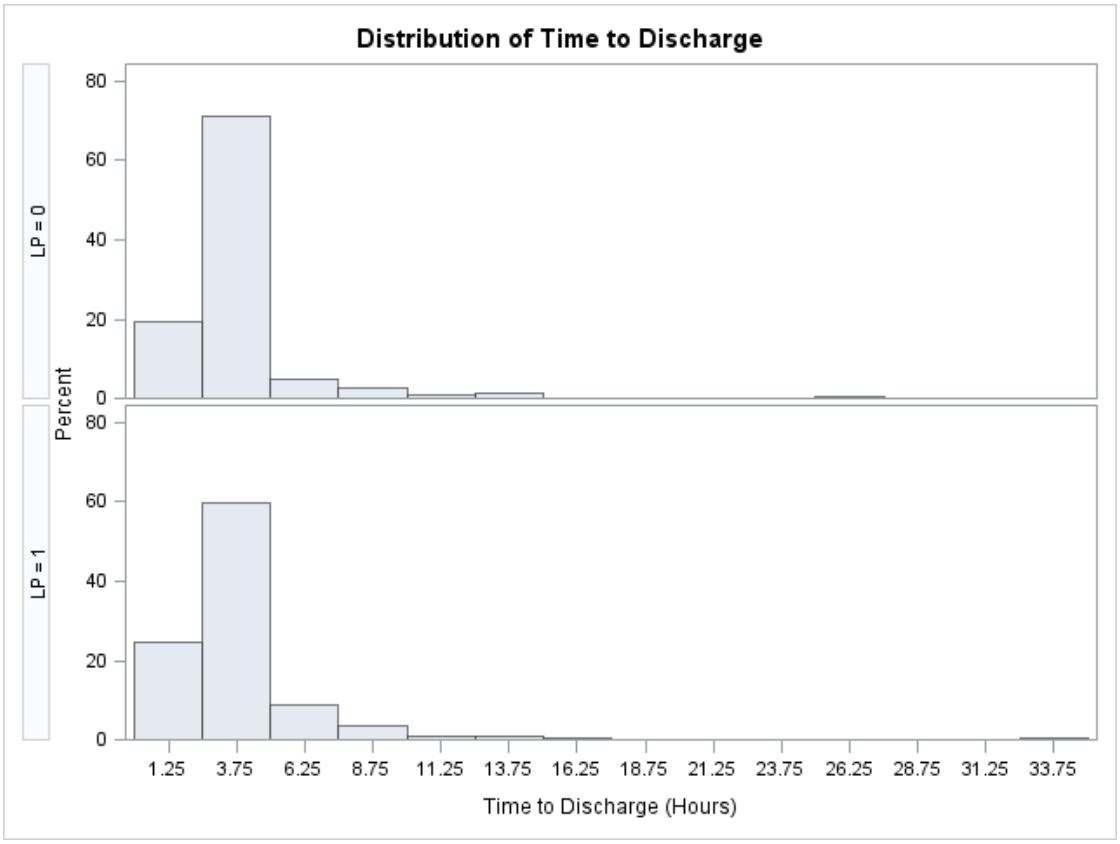

Figure 1.2: Distributions of Time to Discharge for LP (LP=1) and Non-LP (LP=0) Groups.

Chapter 2

Methods

We first compute two non-parametric estimators of the hospital death rates for the LP and non-LP groups respectively: i) inverse probability of treatment weighted (IPTW) kernel-smoothed hazard, and ii) PS-stratified kernel-smoothed hazard. We then perform a PS-adjusted log-rank test [7] and a PS-stratified log-rank test to compare the cause-specific hazard of death between LP and non-LP subjects. We found that the proportional hazards assumption holds according to the estimated death hazard function, so that our methods are appropriate. In addition to the primary analysis, we also perform sub-analyses restricted to patients i) with Papilledema and ii) with high cerebral volume scores (edema). By fitting two IPTW Cox models to the subgroups, we will examine whether the presence of Papilledema or severe edema modifies the causal effect of LP on time to death and infer the causal effect of LP in the subgroups of Papilledema (severe edema) and no Papilledema (no severe edema). We discuss fundamental concepts of the hazard function, competing risk, Cox proportional hazard model and log-rank test that are relevant to this study. Finally, we introduce SAS procedures that were utilized for the data analysis.

2.1 Survival Analysis

Survival data are generally summarized by the survivor function, the hazard function, and the cumulative hazard function. Let T be a non-negative random variable representing the

time until the occurrence of an event. We assume that T is a continuous random variable with probability density function $f(t)$ and cumulative distribution function $F(t) = P(T < t) = \int_0^t f(u)du$ representing the probability that the event has occurred by duration t. Survival function $S(t)$ is then defined to be the probability that the event of interest has not occurred by duration t.

$$S(t) = P\{T \geq t\} = 1 - F(t) = \int_t^{\infty} f(u)du \tag{2.1}$$

2.1.1 The Hazard Function

The hazard function is a widely used function to determine the risk or probability of an event such as the loss of life at a certain time t. This function is conditioned on the subject having survived until time t, and it is obtained from the probability of the patient's death at time t. The T lies somewhere between t and $t + \delta t$, conditional on T being equal or greater than t, $P(t \leq T < t + \delta t \mid T \geq t)$. The rate is given by the conditional probability being expressed when the probability per unit time is divided by the time interval representing by δt. The resulting function is now the limiting value, as δt goes to zero, i.e., the hazard function below:

$$h(t) = \lim_{\delta t \to 0} \left\{ \frac{P(t \leq T < t + \delta t \mid T \geq t)}{\delta t} \right\} \tag{2.2}$$

Equation (2.2) defines the rate of the event at time t, as long as the event has not occurred before the selected time t. If the survival time is measured in days, $h(t)$ is the approximate probability that an individual, who is at risk of the event occurring at the beginning of day t, experiences that event during that day. Therefore, the hazard function at day t can be regarded as the expected number of events experienced by an individual in the day, given that the event has not occurred before the day t.

The conditional probability in the numerator in Equation (2.2) can be represented as the ratio of the joint probability that T is in the interval $[t, t+dt)$ and $T \geq t$ to the probability of the condition $T \geq t$. The probability $P([t, t+dt))$ can be written as $f(t)dt$ for small dt, while the probability $P(T \geq t)$ is $S(t)$ by definition. Dividing by dt and passing the limit gives the result,

$$h(t) = \frac{f(t)}{S(t)} \tag{2.3}$$

From Equation (2.3), it follows that

$$h(t) = -\frac{d}{dt}\{logS(t)\}, \tag{2.4}$$

and so

$$S(t) = exp\{-H(t)\}, \tag{2.5}$$

where

$$H(t) = \int_0^t h(u)du. \tag{2.6}$$

The function $H(t)$ is the cumulative hazard function. From Equation (2.5), the cumulative hazard function can also be obtained from the survivor function,

$$H(t) = -logS(t). \tag{2.7}$$

An instinctive way to estimate the hazard function is to compare the number of deaths and the number of individual at risk at that time. If the assumption is made that the hazard function is constant over time period, then the hazard per unit time can be found by further dividing by the time interval. In other words, if the number of deaths by the jth death time,

$t_{(j)}$, $j = 1, 2, ..., r$, is d_j and n_j at risk at time $t_{(j)}$, the hazard function in the interval from $t_{(j)}$ to $t_{(j+1)}$ can be estimated by

$$\hat{h}(t) = \frac{d_j}{n_j \tau_j}, \tag{2.8}$$

for $t_{(j)} \leq t < t_{(j+1)}$, where $\tau_j = t_{(j+1)} - t_{(j)}$.

In practice, the hazard function estimate in (2.8) is not consistent and tend to be irregular. As a result the plots of the hazard function are made more clear by '*smoothing*'. The hazard function can be smoothed through various methods, which bring about a weighted average of the values at time of death close to t estimated by hazard $\hat{h}(t)$. An example is the *kernel smoothed* approximation (using the Epanechnikov kernel) of the hazard function, established by the r ordered death times, $t_{(1)}, t_{(2)}, ..., t_{(r)}$, with d_j deaths and n_j at risk at time $t_{(j)}$, as shown in Equation (2.9).

$$h^{\dagger}(t) = \frac{1}{b} \sum_{j=1}^{r} \frac{3}{4} \left\{ 1 - \left(\frac{t - t_j}{b} \right)^2 \right\} \frac{d_j}{n_j}, \tag{2.9}$$

where the value of bandwidth b needs to be chosen.

The interval from b to $t_{(r)} - b$ defines every value of t in $h^{\dagger}(t)$ and $t_{(r)}$ is the largest time of death. For any value of t in this interval, the death time in the interval $(t - b, t + b)$ will contribute to the weighted average. The bandwidth b is the controlling factor for the shape of the plot. The larger b gets the more 'smooth', or clear the smoothed curve becomes.

2.1.2 Competing Risks

A competing risks situation occurs when both the event time T and its cause J are taken into consideration where the causes of event are mutually exclusive. In our study, there are two types of causes for the terminal stage, i.e. death and discharge from the hospital. The

probability of event by time t from cause j is defined by the *cumulative incidence function* (CIF) for cause j is $F_j(t) = P[T \leq t, J = j]$. The *cause-specific hazard function* is then

$$h_j(t) = \lim_{dt \to 0} \{ \frac{P(t \leq T \leq t + dt, J = j \mid T \geq t)}{dt} \} \tag{2.10}$$

and the *cumulative cause-specific hazard function* is

$$H_j(t) = \int_0^t h_j(u) du \tag{2.11}$$

Therefore, the CIF can be expressed in terms of the hazards by $F_j(t) = \int_0^t h_j(u) S(u) du$, $j = 1, 2, ..., m$ where m is size of J.

2.1.3 Cox Proportional Hazards Model

The Cox model is a semi-parametric model in which the hazard function of the survival time is given by

$$h(t; X) = h_0(t) e^{\beta' \mathbf{X}(t)}, t > 0 \tag{2.12}$$

where $h_0(t)$ is an arbitrary and unspecified baseline hazard function, $X(t)$ is a vector of time-dependent covariates, and β is a vector of unknown regression parameters for the explanatory variables [6]. When using a covariate of the form

$$\theta = exp\{\beta_0 + \beta_1 x\} \tag{2.13}$$

β_0 is incorporated into the baseline hazard function $h_0(t)$. When x is changed, the hazard functions proportionally change with one another. Hazard functions for any pair of different

covariate values x_i and X_j can be compared using hazard ratio:

$$HazardRatio = \frac{h_0(t)exp\{\beta x_i\}}{h_0(t)exp\{\beta x_j\}} = exp\{\beta(x_i - x_j)\}, i \neq j \tag{2.14}$$

Therefore, the hazard ratio is a constant proportion and this model is a proportional hazards model.

The reason that the model is referred to as a semi-parametric model is because part of the model involves the unspecified baseline function over time (which is infinite dimensional) and the other part involves a finite number of regression parameters. To estimated β, Cox [6] introduced the partial likelihood function, which eliminates the unknown baseline hazard function $h_0(t)$ and accounts for censored survival times. The partial likelihood of the Cox model also allows time-dependent covariates. An explanatory variable is time-dependent if its value for any given individual can change over time. The validity of the proportional hazards model can be tested by testing for interaction between time-dependent covariates and the response time.

2.1.4 Log-Rank Test

Log-rank test is one of the most popular methods of comparing the survival of groups. Intuitively, one may compare the proportions of surviving at any specific time, but this approach does not provide a comparison of the total survival information. It only provides a comparison at some arbitrary time points. On the other hand, the log-rank test takes the whole follow-up period into consideration while it does not require information of the shape of the survival curve nor the distribution of survival times [5].

The log-rank test is used to test the null hypothesis that there is no difference between

the groups in the probability of an event at any time point, i.e. the two groups having identical survival or hazard functions. For each event time in each group, the test calculates the observed number of events and the number of expected events under the null of no difference between groups. In case of censored subjects, the individuals are considered to be at risk of the event at the time of censoring, but not in the subsequent time point.

Let $j = 1, ..., J$ be the distinct times of observed events in either group. For each time j, let N_{1j} and N_{2j} be the number of subjects at risk at the start of period j in the two groups, respectively. Let $N_j = N_{1j} + N_{2j}$. Let O_{1j} and O_{2j} be the observed number of events in the groups at time j, and define $O_j = O_{1j} + O_{2j}$. Given that O_j events happened across both groups at time j, under the null hypothesis, O_{1j} has the hypergeometric distribution with parameters N_j, N_{1j}, and O_j. This distribution has expected value

$$E_{1j} = \frac{O_j}{N_j} N_{1j} \tag{2.15}$$

and variance

$$V_j = \frac{O_j (N_{1j}/N_j)(1 - N_{1j}/N_j)(N_j - O_j)}{N_j - 1}. \tag{2.16}$$

The log-rank statistic compares each O_{1j} to its expectation E_{1j} under the null hypothesis and is defined as

$$Z = \frac{\sum_{j=1}^{J} (O_{1j} - E_{1j})}{\sqrt{\sum_{j=1}^{J} V_j}}. \tag{2.17}$$

The log-rank test is most likely to detect a difference between groups when the hazard of an event is consistently greater for one group than another over time, but it is unlikely to detect a difference when survival curves cross [5]. In addition, the log-rank test is a test of significance so that it does not provide the size of the difference between the groups.

In the statistical analysis, we apply inverse probability of treatment weighted log-rank test to compare the cause-specific hazard of death for the LP and Non-LP groups by treating the failure times from causes other than the cause of interest as censored observations.

2.2 Propensity Score

Allocation to LP was non-random and was associated with severity of illness. We conduct propensity score-based analysis to reduce for this bias and assess the impact on LP on the survival of the patients.

Propensity score (PS) is the probability of treatment assignment conditional on the given vector of observed covariates [14]. PS can be viewed as a balancing score because the distribution of observed characteristic covariates will be similar between control and treatment groups based on the propensity score. Hence, propensity score allows one to analyze a non-randomized observational study so that it mimics some of the characteristics of a randomized controlled trial. PS estimation method is especially useful if a data set contains a number of variables, possibly continuous, because it will be hard to adjust for such high-dimensional confounders with common techniques.

The propensity score was defined by Rosenbaum & Rubin [14]. Let Z_i be an indicator variable denoting the treatment received ($Z_i = 0$ for control group vs. $Z_i = 1$ for treatment group) and $\mathbf{X}_i$ be the covariates of subject i. Then, the propensity score for subject i, e_i, can be defined as

$$e_i = Pr(Z_i = 1 \mid \mathbf{X}_i) \tag{2.18}$$

such that Z_i and $\mathbf{X}_i$ are independent given e_i. Consequently, a large number of covariates can be reduced to a number between 0 and 1.

Propensity scores are commonly estimated by regression methods such as logistic regression and probit regression of Z on $\mathbf{X}$. We apply logistic regression model to estimate the propensity scores of the LP data given a linear combination of all the covariates, as shown in (2.19)

$$\ln \frac{e_i}{1-e_i} = \ln \frac{P(Z_i = 1 \mid \mathbf{X}_i)}{1 - P(Z_i = 1 \mid \mathbf{X}_i)} = \beta_0 + \beta \mathbf{X}_i \tag{2.19}$$

There are three common ways of utilizing the estimated PS: i) PS is used as a covariate in addition to the treatment indicator in a multivariable regression for the outcome of interest, ii) subjects are stratified into bins of the estimated PS, and iii) a treated subject is matched to one or more comparison subject(s) based on the estimated PS [11]. In this study, we utilized the two PS methods, i.e. inverse probability of treatment weighting and stratification.

2.2.1 Inverse Probability of Treatment Weighting

Inverse probability of treatment weighting (IPTW) uses the propensity score to construct a pseudo-population for estimating the causal parameters of interest. Then, the distribution of measured baseline covariates is independent of treatment assignment in the pseudo-population [16]. As we defined earlier, let Z_i be an indicator denoting treatment assignment and e_i be the propensity score for ith subject. Weight for subject i, i.e. w_i, can be defined as

$$w_i = \frac{Z_i}{e_i} + \frac{(1 - Z_i)}{1 - e_i}. \tag{2.20}$$

The pseudo-population created by IPTW consists of w_i copies of each subject i and the individual's weight is equal to the inverse of the probability of receiving the treatment that the subject actually received. Because the distribution of $\mathbf{e}$ between $Z = 0$ and $Z = 1$ are the same in the weighted pseudo-population, the connection between Z and $\mathbf{e}$ is then removed.

2.2.2 Stratification

Stratification involves partitioning subjects into mutually exclusive subsets based on the estimated propensity score. Subjects are ranked according to their estimated propensity score and then stratified into subsets based on pre-defined thresholds. A common approach is to stratify subjects into five equal-size strata of the propensity scores. Rosenbaum and Rubin [17] claimed that stratifying on the quintiles of the propensity score eliminates approximately 90% of the bias due to measured confounders when estimating a linear treatment effect. An improvement in bias reduction should appear with increasing number of total strata. Within each propensity score stratum, treated and untreated subjects have nearly similar values of the propensity score. Therefore, the distribution of covariates will be approximately similar between treated and untreated groups in the same stratum if the propensity score has been correctly specified. Then, the treatment effects are estimated in each stratum with a weighted average of the effects will give an overall estimate of the treatment effects.

2.3 SAS Procedures

SAS Ver. 9.4 software[1] was used for the current data analysis. We applied two SAS procedures: i) PROC LIFETEST, a non-parametric procedure for estimating the survivor function, and ii) PROC PHREG, a semi-parametric procedure that fits the Cox proportional hazards model, in the statistical analysis of the LP data set.

The LIFETEST procedure can be used to compute nonparametric estimates of the survivor function either by the product-limit method (also called the Kaplan-Meier method) or by the life table method. The procedure produces the survival distribution function (SDF),

[1]

the cumulative distribution function (CDF), the probability density function (PDF), and the hazard function. We compute IPTW kernel-smoothed hazard function, PS-stratified kernel-smoothed hazard function, and the Aalen-Johansen estimator of PS-stratified cumulative incidences function (CIF) of death. Note that we only compute CIF for PS-stratified hazard since IPTW CIF is currently not available in SAS software. PROC LIFETEST provides several rank tests to evaluate significance of difference between treated and untreated groups. We adopt the log-rank test to compare the hospital death rate for the treated and untreated groups. The LIFETEST procedure is also applied for making plots to compare hazard curves among groups.

The PHREG procedure performs subgroup analyses of the LP data based on the Cox proportional hazards model. The procedure is also applied to test proportional hazard assumption.

Chapter 3

Results

3.1 Data Exploration

The LP data have information of comatose children (Blantyre coma score ≤ 2) aged two months to 14 years. It originally contains $2,399$ observations. We discarded about 26% of the individuals (i.e. 629 subjects) after retinopathy imputation due to missing explanatory variables because they caused missing values in propensity score estimation. There are nine discrete variables (such as depth of coma, gender, and blood pressure), and three continuous variables (such as admission, blood glucose concentration, and hematocrit). When Papilledema is considered as a covariate, the LP data contains $1,010$ total number of subjects in the LP data including 810 treated and 200 untreated individuals. In the case of where Papilledema is excluded in propensity score estimation, there are $1,772$ total number of subjects in the data including $1,442$ treated and 350 untreated individuals. The study population in the LP data set is shown in Figure 3.1, Table 3.1, and Table 3.2.

3.2 Propensity Score Estimation

Propensity scores are used to reduce confounding and thus include variables thought to be related to both treatment and outcome. To estimate a propensity score, a common first step is to use a logit or probit regression with treatment (i.e. indication of LP performed in our

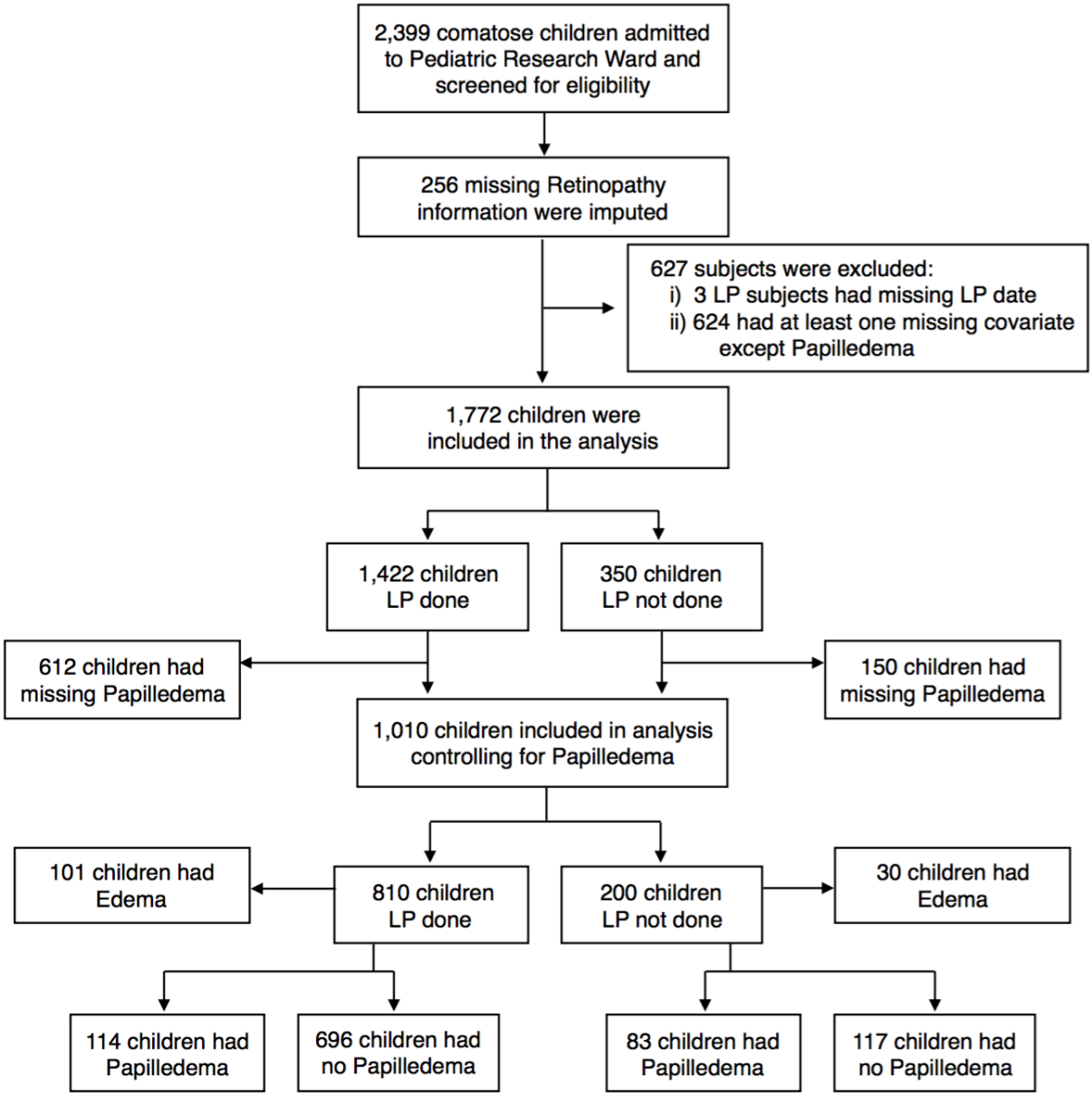

Figure 3.1: Study Populations in the LP data set.

Table 3.1: Baseline Characteristics of the Children before Propensity Score Adjustment (Analysis including Papilledema).

Variable	LP (N=810)		Non-LP (N=200)	
	Mean	SD	Mean	SD
COMASC	1.31	0.71	1.29	0.74
BPSTAT	1.01	0.19	1.03	0.27
WH	0.09	0.29	0.12	0.33
RESPDIS	0.34	0.47	0.42	0.49
PULSESTAT	1.57	0.53	1.56	0.54
NHEART	0.97	0.18	0.93	0.26
SEX	0.54	0.50	0.52	0.50
ADMRETIN	0.59	0.49	0.74	0.44
PAP	0.14	0.35	0.42	0.49
ADMHCT	23.86	8.17	21.27	8.58
ADMGLUC	6.86	4.08	6.28	3.31
LOGADMPTA	8.96	4.46	10.17	3.59

Table 3.2: Baseline Characteristics of the Children before Propensity Score Adjustment (Analysis excluding Papilledema).

Variable	LP (N=1,422)		Non-LP (N=350)	
	Mean	SD	Mean	SD
COMASC	1.30	0.71	1.21	0.76
BPSTAT	1.03	0.22	1.01	0.26
WH	0.08	0.28	0.10	0.30
RESPDIS	0.37	0.48	0.48	0.50
PULSESTAT	1.57	0.53	1.55	0.54
NHEART	0.96	0.19	0.93	0.26
SEX	0.53	0.50	0.54	0.50
ADMRETIN	0.58	0.49	0.75	0.44
ADMHCT	23.95	8.07	21.34	8.38
ADMGLUC	6.76	4.06	6.26	3.99
LOGADMPTA	9.22	4.26	10.22	3.23

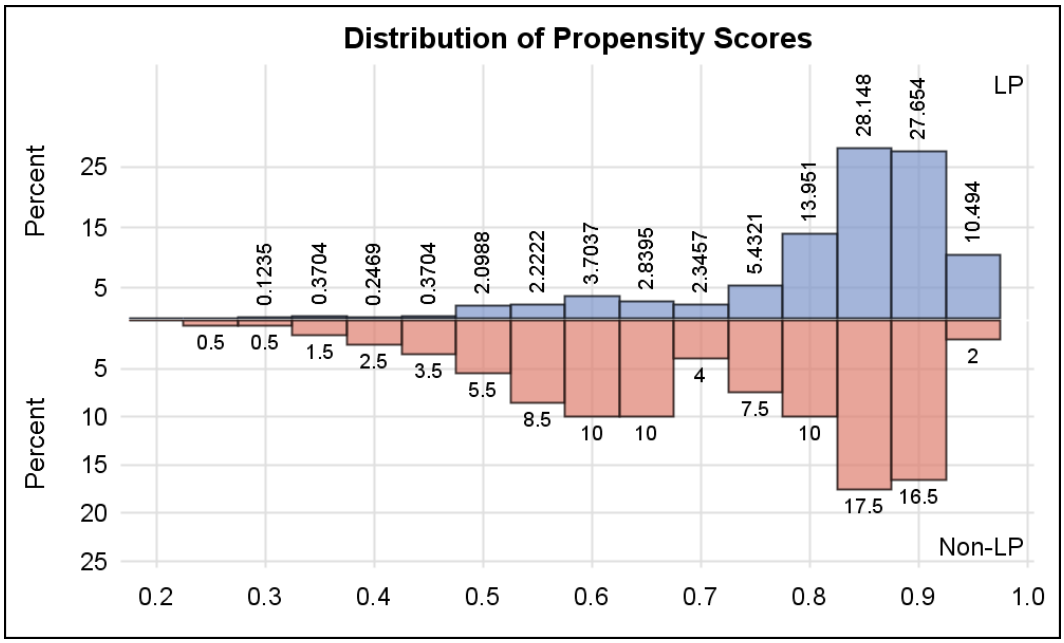

Figure 3.2: Distribution of Propensity Score across LP and Non-LP groups. Papilledema information was included in propensity score estimation.

Table 3.3: Summary Statistics of Propensity Score in LP and Non-LP groups. Papilledema was included in PS estimation. The number of subjects is 1,010.

Treatment	No. of Subjects	Mean	SD	Minimum	Maximum
LP	810	0.824	0.112	0.318	0.967
Non-LP	200	0.713	0.163	0.268	0.968

data) as the outcome variable and the explanatory variables. Since our dependent variable is binary, we applied logistic regression with the 12 explanatory variables. We estimated two sets of PS with and without Papilledema information.

Once a propensity score has been estimated for each observation, we must ensure that there is overlap in the range of propensity scores across LP and Non-LP groups. No inferences about treatment effects can be made for a treated individual for whom there is not a comparison individual with a similar propensity score. Common support is subjectively assessed by examining a graph of propensity scores across treatment and control groups. The overlap of the distribution of the propensity scores across LP and Non-LP groups is displayed in Figures 3.2 and 3.3. The propensity scores of children in LP and Non-LP groups

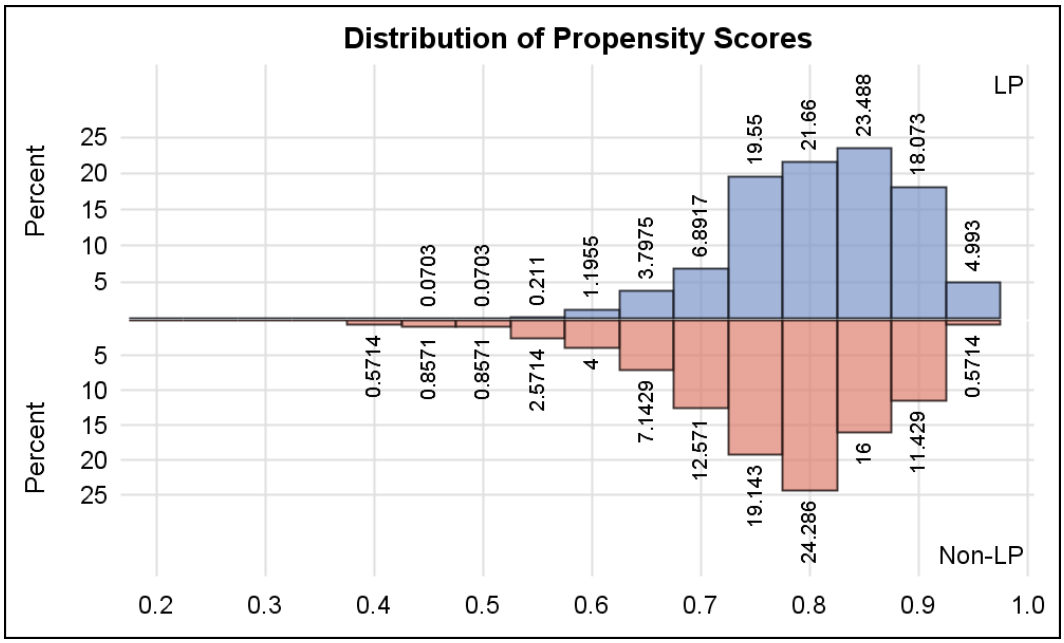

Figure 3.3: Distribution of Propensity Score across LP and Non-LP groups. Propensity scores were estimated without Papilledema information.

Table 3.4: Summary Statistics of Propensity Score in LP and Non-LP groups. Papilledema was excluded in PS estimation. The number of subjects is 1,772.

Treatment	No. of Subjects	Mean	SD	Minimum	Maximum
LP	1,422	0.812	0.077	0.431	0.958
Non-LP	350	0.766	0.098	0.393	0.928

overlapped significantly indicating that propensity score matching analysis was feasible.

In addition to overlapping, the propensity score should have a similar distribution (i.e. balanced distribution) in the treated and comparison groups. A rough estimate of the propensity score's distribution can be obtained by descriptive statistics such as mean and standard deviation (see Tables 3.3 and 3.4). The mean propensity score with Papilledema in treated is 0.824 with a standard deviation (SD) of 0.122 and in untreated 0.713, with SD 0.168. When excluding Papilledema in PS estimation, the mean propensity score in treated is 0.81 with SD, 0.077 and in untreated 0.766 with SD 0.09. Balance on 12 covariates was checked based on standardized difference as a test measurement. It has been suggested that if the standardized difference is greater than 10%, there is a meaningful imbalance in covariates in

two groups [13]. We found that only four variables, (i.e. coma score, blood pressure, pulse rate, and gender), and three variables, (i.e. weight/height score, pulse rate, and gender) were balanced in the dataset with and without Papilledema, respectively. After PS adjustment, balances in all 12 covariates (11 covariates excluding Papailledema) were achieved across LP and Non-LP groups.

3.3 Impact of LP on In-Hospital Death Rate

Based on the propensity score adjusted analysis, we assessed impact of lumbar puncture on survival of comatose children. We found that there was no significant difference in hospital death rates between treated and untreated groups with Papilledema information. However, when Papilledema information was excluded in the PS estimation, we found a significant difference between the two groups. These results were the case regardless of the propensity score adjustment methods.

3.3.1 Results from Inverse Probability of Treatment Weighting

According to the IPTW method, the hospital death rate was not significantly different in children who underwent LP compared to those who did not if the Papilledema information was included in the propensity score estimation (p-value from a log-rank test = 0.775). Hazard functions with different bandwidth values, (i.e. default value optimized by SAS, 8, 10 and 12) are shown in Figures 3.4, 3.5, 3.6, and 3.7, respectively.

On the other hand, we found a significant difference between the groups where Papilledema information was excluded in the PS estimation. The p-value from a log-rank is 0.009. Hazard functions based on excluding Papilledema are shown in Figures 3.4, 3.9, 3.10,

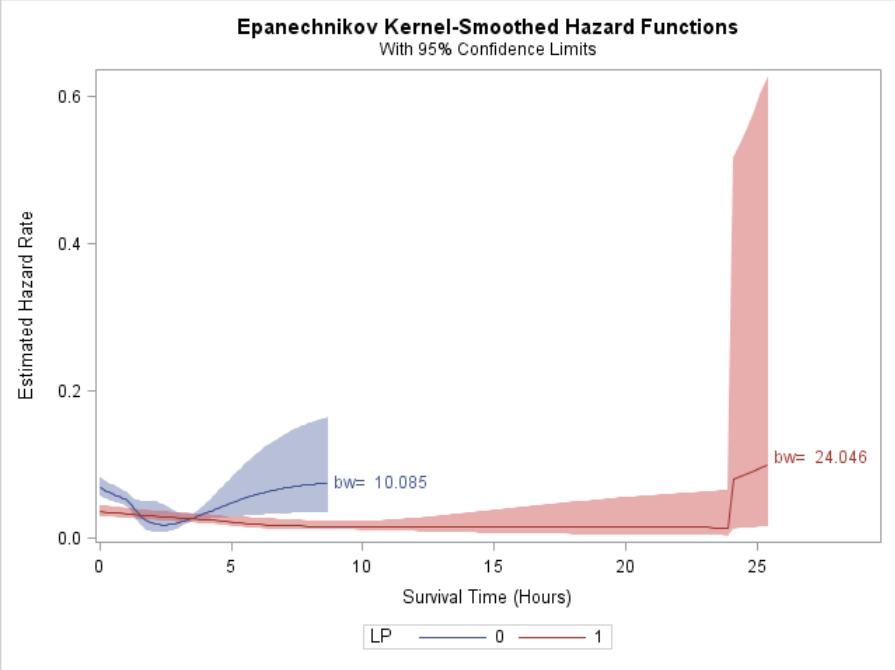

Figure 3.4: Comparison of Hazard functions between LP (LP=1) and Non-LP (LP=0) groups. The PS was estimated with Papilledema. The value of the bandwidth was set with default value.

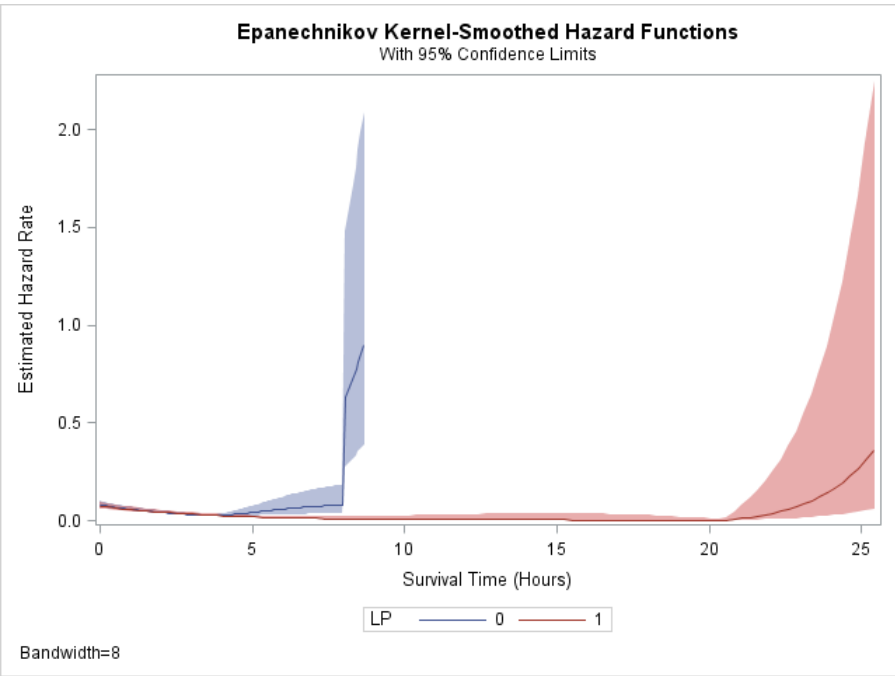

Figure 3.5: Comparison of Hazard functions between LP (LP=1) and Non-LP (LP=0) groups. The PS was estimated with Papilledema. The value of the bandwidth was set as 8.

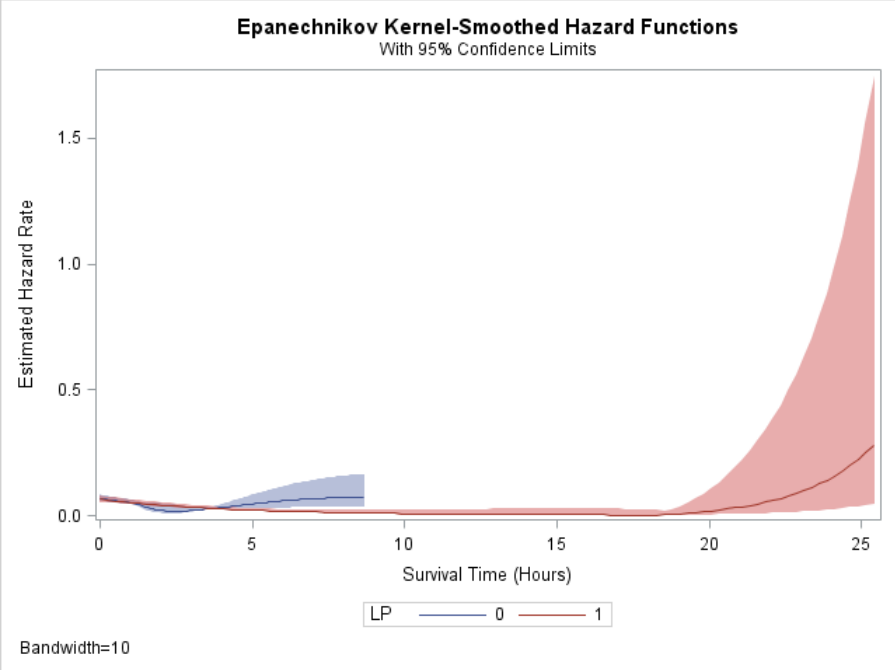

Figure 3.6: Comparison of Hazard functions between LP (LP=1) and Non-LP (LP=0) groups. The PS was estimated with Papilledema. The value of the bandwidth was set as 10.

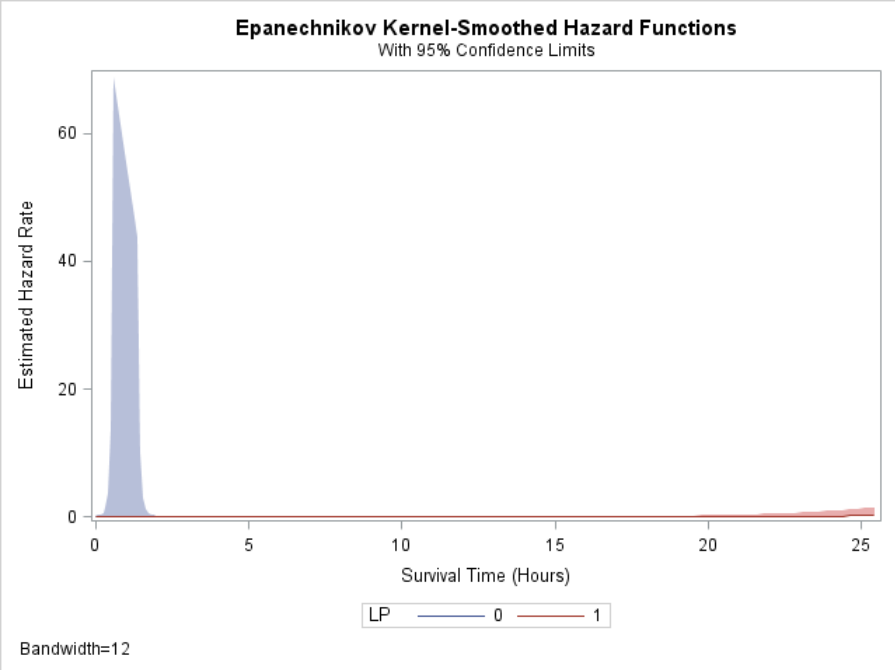

Figure 3.7: Comparison of Hazard functions between LP (LP=1) and Non-LP (LP=0) groups. The PS was estimated with Papilledema. The value of the bandwidth was set as 12.

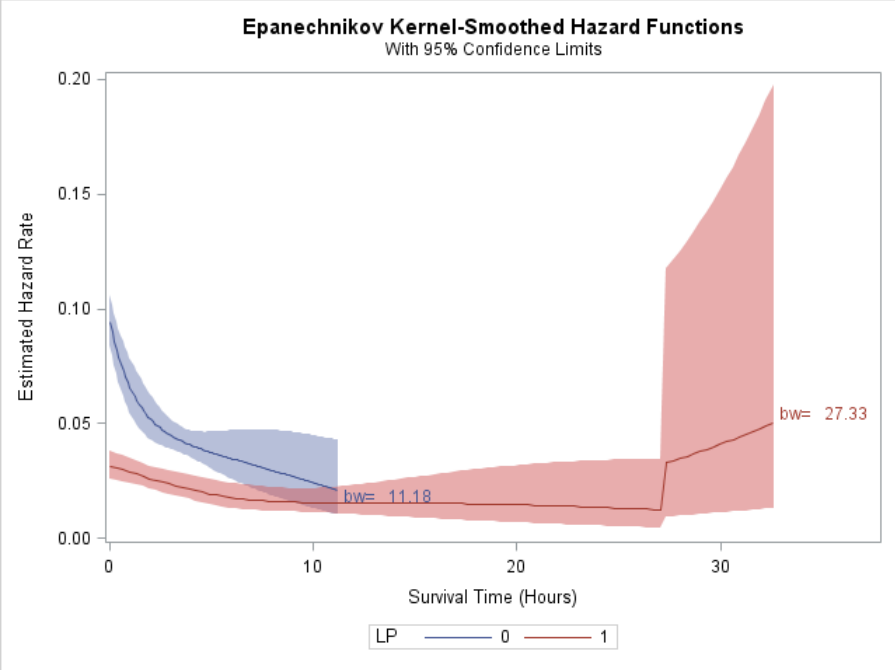

Figure 3.8: Comparison of Hazard functions between LP (LP=1) and Non-LP (LP=0) groups. The PS was estimated without Papilledema. The value of the bandwidth was set with default value.

and 3.11, with different bandwidth values (i.e. default value optimized by SAS, 8, 10 and 12), respectively.

3.3.2 Results from Stratification

For stratification based analysis, we stratified the PS into five strata containing both patients in the treatment group and the control group. Each stratum has similar distributions of PS for treated and untreated subjects and the sample sizes in five strata are similar with each other (Table 3.5). We found consistent results with that from the IPTW method. With the PS adjustment including Papilledema, we found no significant difference in hospital death rate between treated and untreated groups. The p-value from a log-rank test is 0.309. The PS-adjusted cumulative incidence functions (CIFs) also found no difference between the groups. The p-value from Gray's test for equality of CIFs is 0.3118 (Figure 3.12). On the

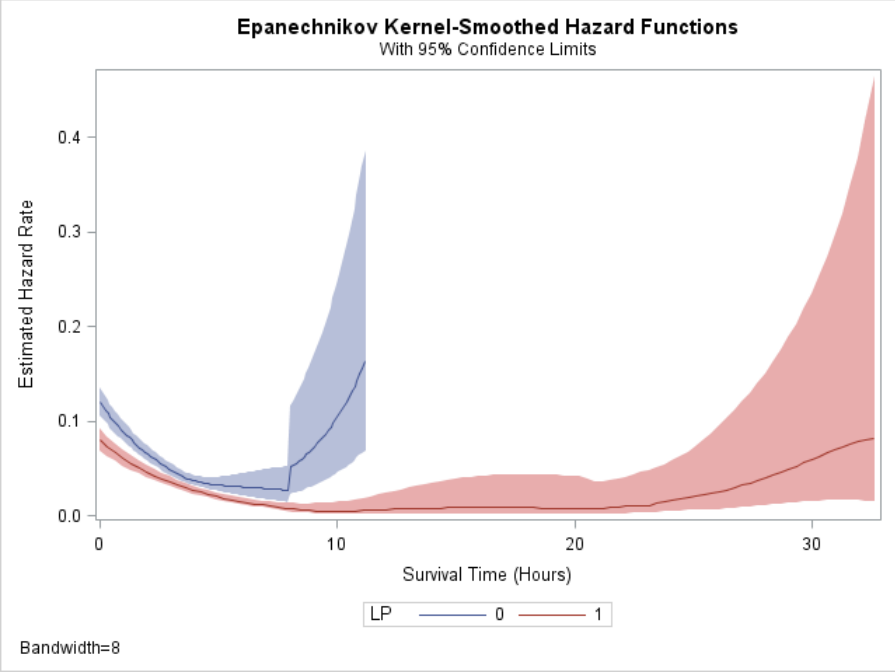

Figure 3.9: Comparison of Hazard functions between LP (LP=1) and Non-LP (LP=0) groups. The PS was estimated without Papilledema. The value of the bandwidth was set as 8.

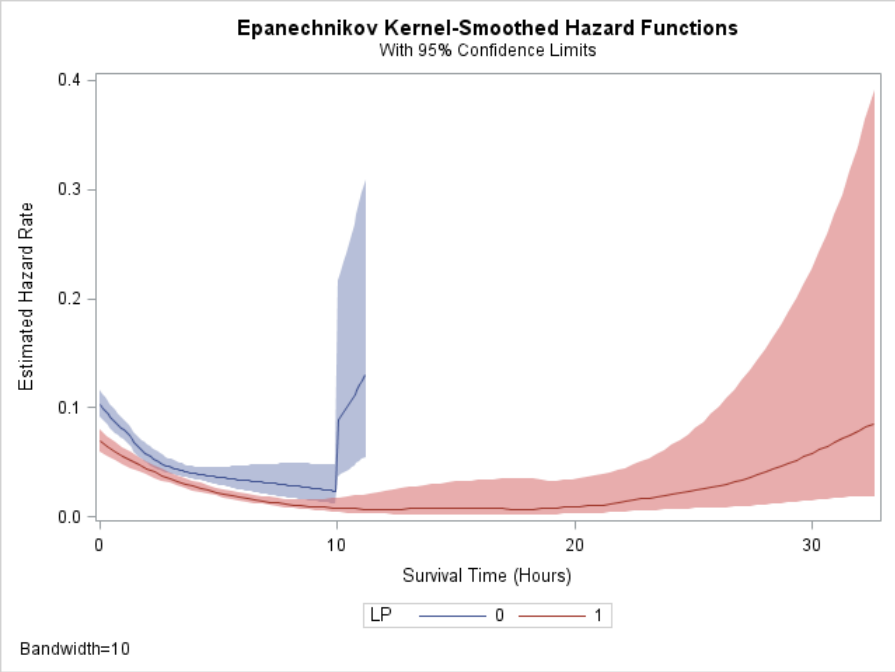

Figure 3.10: Comparison of Hazard functions between LP (LP=1) and Non-LP (LP=0) groups. The PS was estimated without Papilledema. The value of the bandwidth was set as 10.

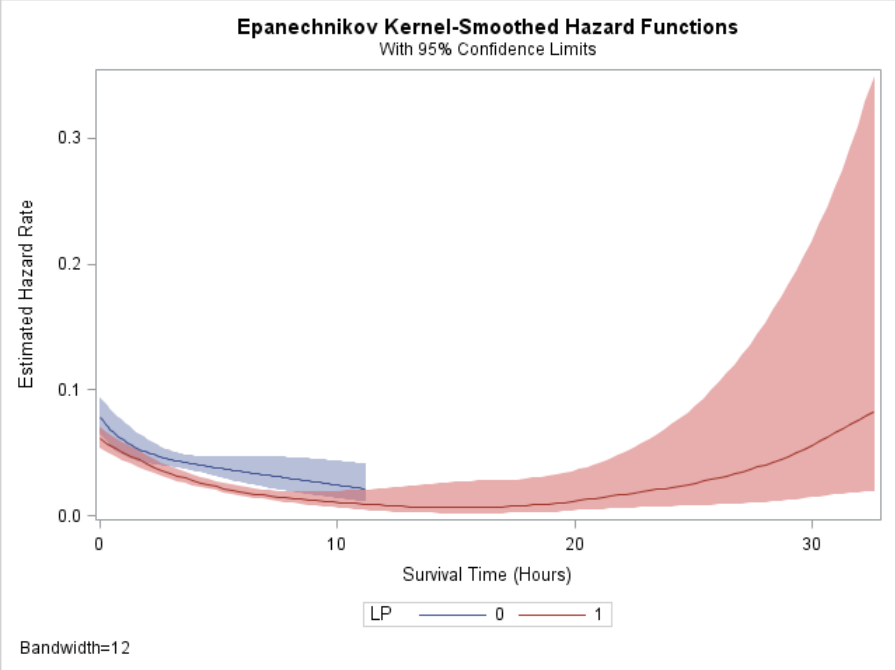

Figure 3.11: Comparison of Hazard functions between LP (LP=1) and Non-LP (LP=0) groups. The PS was estimated without Papilledema. The value of the bandwidth was set as 12.

Table 3.5: Number of Subjects in Each Stratum.

Stratum	**With Papilledema**		**Without Papilledema**	
	LP (%)	**Non-LP (%)**	**LP (%)**	**Non-LP (%)**
1	112 (55.45)	90 (44.55)	236 (66.67)	118 (33.33)
2	164 (81.19)	38 (18.81)	290 (81.69)	65 (18.31)
3	172 (85.15)	30 (14.85)	274 (77.40)	80 (22.60)
4	181 (89.60)	21 (10.40)	310 (87.32)	45 (12.68)
5	181 (89.60)	21 (10.40)	312 (88.14)	42 (11.86)

other hand, with the PS adjustment excluding Papilledema, there is significant difference between the treated and untreated groups, i.e. p-value from a log-rank test is 0.0001. The p-value from Gray's test for equality of CIFs is < 0.0001 (Figure 3.13).

3.3.3 Comparison of Death Rates over Different Time Windows

We compared the time specific death rates over three, six and 12 hours from the time origin (i.e. the time of LP performed for treated and the time of admission for untreated subjects).

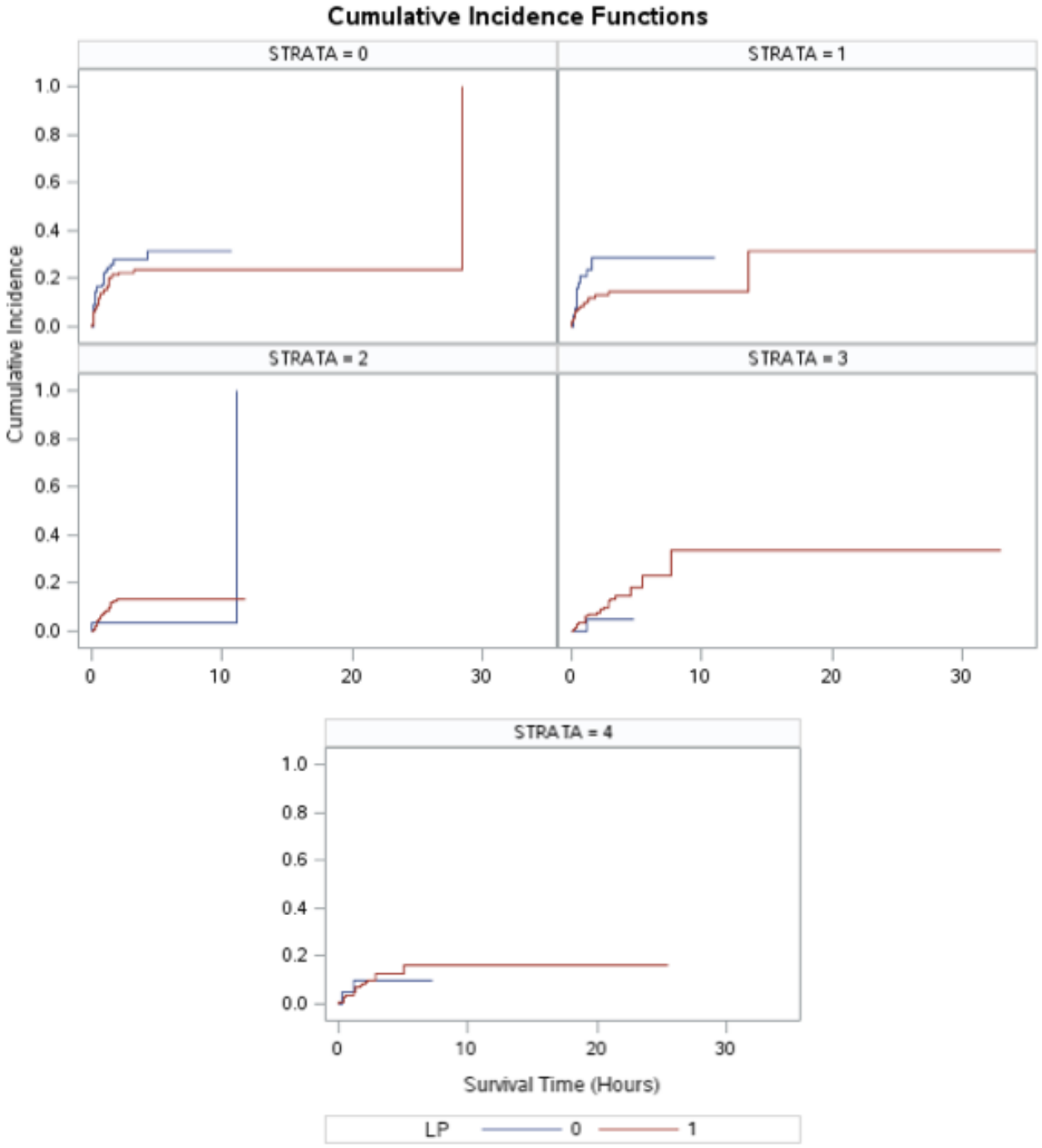

Figure 3.12: Comparison of Cumulative Incidence Functions between LP (LP=1) and Non-LP (LP=0) groups. The PS was estimated with Papilledema.

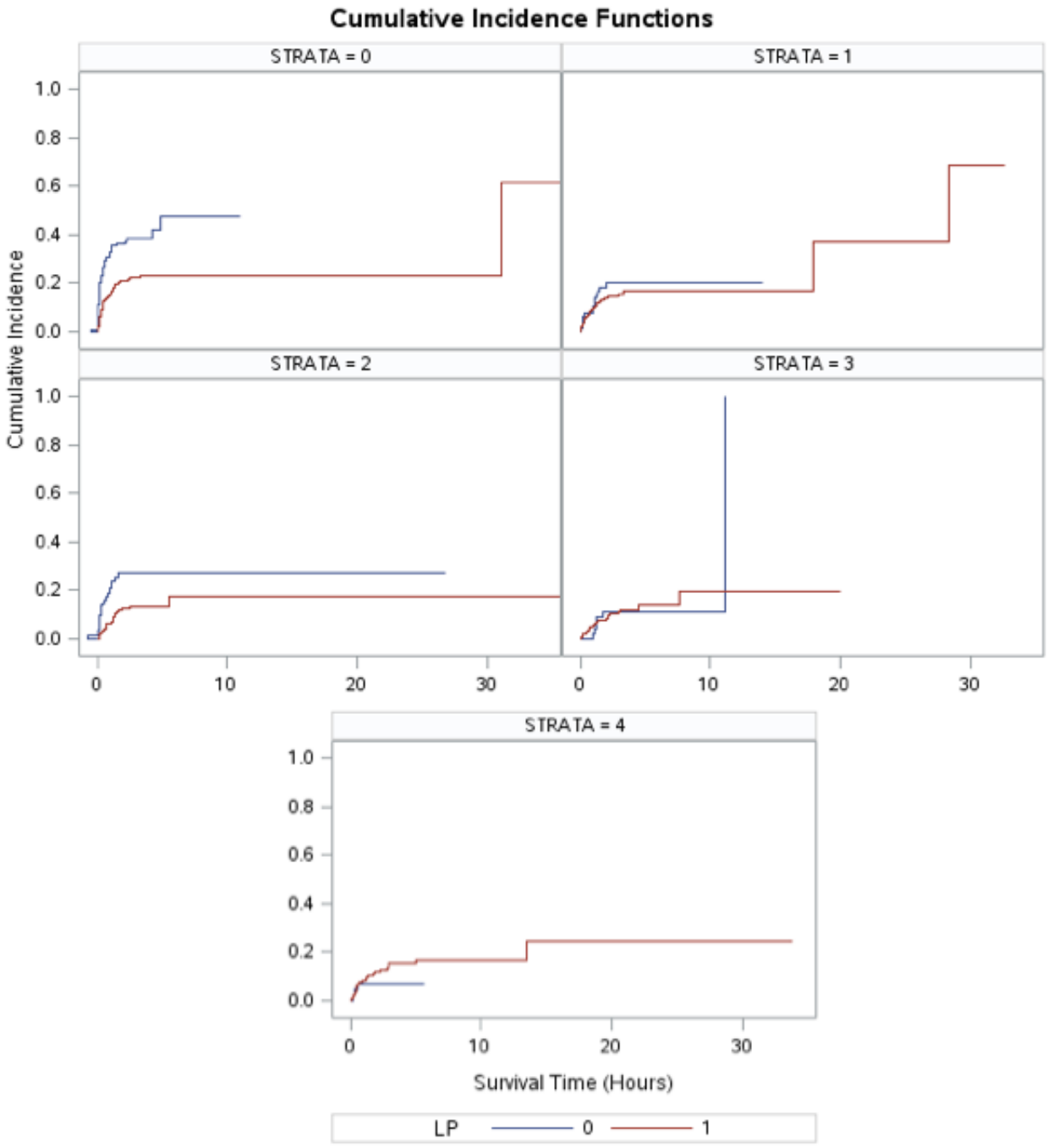

Figure 3.13: Comparison of Cumulative Incidence Functions between LP (LP=1) and Non-LP (LP=0) groups. The PS was estimated without Papilledema.

Table 3.6: Results of Log-Rank Tests for Effect of Treatment over Specific Time Windows.

Time	Chi-Square	Pr >ChiSq
3 Hour	1.029	0.310
6 Hour	0.925	0.336
12 Hour	2.871	0.090

IPTW log-rank tests based on the estimated PS with Papilledema were used to compare the effect of LP on death rate over specific time windows. We found no significant effect of the treatment, i.e. p-value of 0.310 for three hour from the time origin, 0.336 for six hour, and 0.09 for 12 hour from log-rank tests, respectively (Table 3.6).

3.3.4 Subgroup Analyses

3.3.4.1 Influence of Papilledema

To examine whether the presence of Papilledema changes the impact of LP on the survival of the patients, we assessed the interaction between Papilledema and LP in the IPTW weighted Cox regression model. We found that the effect of LP on survival was not different (p-value = 0.279) between children with positive and negative Papilledema (Table 3.7). In addition, we found no significant effect of LP in each of the two groups, i.e. p-values are = 0.8963 with positive and 0.167 with negative Papilledema groups.

We found that Papilledema is a confounder. This is because Papilledema is a common cause to LP operation and the outcome (i.e. death or discharge). If a child was suspected to have Papilledema by a funduscopic examination, LP was not performed. In the LP data set, we found only 58% of subjects with positive Papilledema had LP while 85% of patients with negative Papilledema had LP (Table 3.8). In addition, children with negative Papilledema tend to have longer time to death/discharge (Figures 3.14 and 3.15). Therefore, Papilledema should be accounted for a confounder in the analysis to correctly estimate the relationship

Table 3.7: Results of Analysis of Maximum Likelihood Estimates for the IPTW Cox Model Considering the Effect Modification by Papilledema.

Parameter	Estimate	Error	Chi-Square	p-value
LP	0.039	0.302	0.017	0.896
PAP	1.124	0.347	10.487	0.001
LP*PAP	-0.445	0.412	1.168	0.279

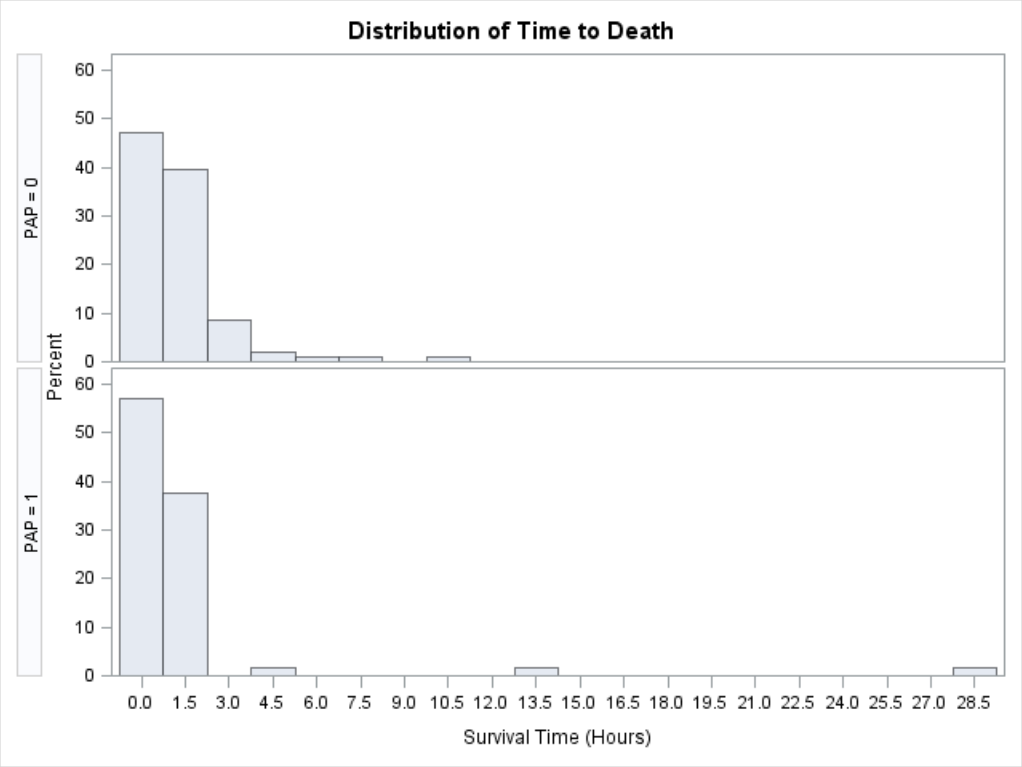

Figure 3.14: Comparison of Distributions of Time to Death between Positive (PAP=1) and Negative (PAP=0) Papilledema Groups.

between dependent and independent variables.

3.3.4.2 Impact of LP on survival of children with increased brain volume

In the LP data, the variable *Edema* contains information of increased brain volume examined by the brain MRI scan. It is a categorical variable with 9 different values from 0 to 8 where higher number means worse condition. 131 children underwent MRI scans with 101 treated and 30 untreated subjects (Table 3.9) where the PS were estimated with Papilledema

Table 3.8: Distributions of LP and Non-LP groups within Positive and Negative Papilledema Groups.

Papilledema	**No. of Subjects**		**Total**
	LP	**Non-LP**	
Positive	114	83	197
Negative	696	117	818
Total	810	200	1,010

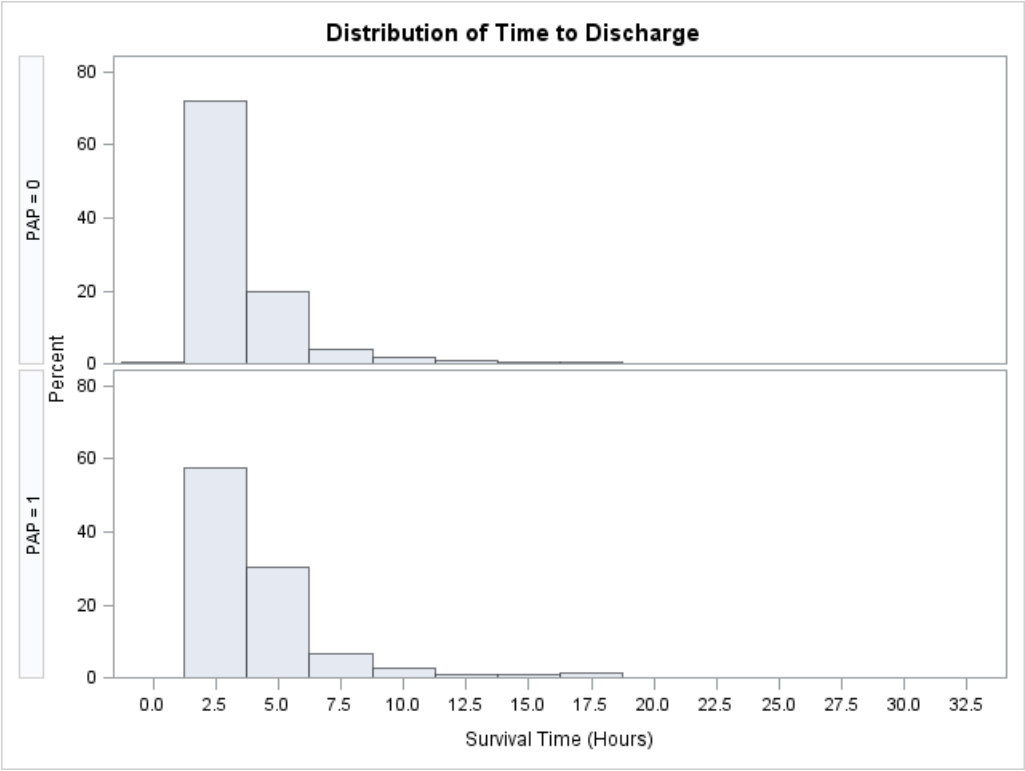

Figure 3.15: Comparison of Distributions of Time to Discharge between Positive (PAP=1) and Negative (PAP=0) Papilledema Groups.

Table 3.9: Distribution of Subjects who have Edema score.

LP	Severity									Total
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Performed	2	0	6	8	12	17	25	26	5	101
Not-Performed	0	1	2	3	1	2	11	4	5	30
Total	2	1	8	12	13	19	36	30	10	131

Table 3.10: Results of Analysis of Maximum Likelihood Estimates for the IPTW Cox Model Considering the Effect Modification of Edema.

Parameter	Estimate	Error	Chi-Square	p-value
LP	1.435	1.221	0.078	0.780
EDEMA	2.793	1.094	6.519	0.011
LP*EDEMA	-0.686	1.365	0.245	0.620

information. We redefined the Edema variable as binary with non-severe (i.e. edema < 7) and severe (i.e. edema ≥ 7) based on physician's recommendation and fitted the IPTW Cox model. As a result, we found no significant effect modification by Edema on the survival (p-value = 0.620) (Table 3.10). In addition, we found no significant effect of LP in each of the two groups, i.e. p-values are 0.700 with non-severe Edema and 0.680 with severe Edema groups.

3.3.5 Validation of Assumption

When modeling a Cox proportional hazard model, a key assumption is proportional hazards. To validate the assumption, we included time dependent covariates in the Cox model by creating products of the covariates and a function of time. In this study we applied the log function of survival time. If any of the time dependent covariates are significant it indicates that the covariate is not proportional. In SAS, it is possible to create all the time dependent variable inside PROC PHREG. By using the TEST statement, we tested all the time dependent covariates all at once. We confirmed that the proportional assumption is valid for variables LP (p-value = 0.895) and Papilledema (p-value = 0.539), and also for the

interaction between LP and Papilledema (p-value = 0.981) from the subgroup analysis of Papilledema (Table 3.11). The assumption is also valid in the subgroup analysis of Edema. The p-values are 0.380 for LP, 0.359 for Edema, and 0.266 for the interaction between LP and Edema (Table 3.12).

Table 3.11: Results of Linear Hypotheses Testing Results for Proportionality: Papilledema Subgroup Analysis.

Variable	**Wald Chi-Square**	**p-value**
LP	0.017	0.895
PAP	0.377	0.539
LP*PAP	0.001	0.981

Table 3.12: Results of Linear Hypotheses Testing Results for Proportionality: Edema Subgroup Analysis.

Variable	**Wald Chi-Square**	**p-value**
LP	0.770	0.380
EDEMA	0.839	0.359
LP*EDEMA	1.236	0.266

Chapter 4

Conclusion and Discussion

In this study, we conducted a retrospective analysis to assess the impact of lumbar puncture (LP) on survival of comatose Malawian children. Overall, our analysis results showed no impact on survival of the patients associated with LP. We found that after balancing the treated (LP=1) and untreated (LP=0) groups using Papilledemia information, it did not result in a significant difference in the hospital death rates. Although exclusion of Papilledema information from the statistical analysis resulted in the opposite conclusion (i.e. there is a significant difference in the death rates), we considered Papilledema as an important covariate in the analysis because the information is the primary element in making the decision for performing LP. We also confirmed that different status in Papilledema and Edema does not have a significant difference in the hazard of death between both treated and untreated patients.

The LP data have a fundamental limitation, i.e. lack of randomness in the treated and control groups, by the nature of observational study. We compensated this limitation by utilizing propensity score (PS) methods. The propensity scores were estimated by using a linear combination of 12 characteristic covariates. Through the PS method, we could obtained balance in covariates between treatment and control groups. We utilized the propensity score, an average treatment effect for each subject, in two ways, i) inverse probability of treatment weighting (IPTW) and ii) stratification. We found the same results, i.e. no significant evidence of LP impact on survival of comatose patients with Papilledema information, through

both methods. Although PS method overcame the lack of randomness in the LP data, we were also confronted by its own limitation. Because the propensity score is based on observed data and clinicians' experience, it is possible to have unmeasured and unobserved confounders which cannot be controlled. Therefore, covariates in the LP data may cause bias on the outcome and there might be other unobserved factors that would affect the decision to undergo the LP operation. In addition, the PS method only uses observed covariates so that we needed to discard a large portion of the data set with missing covariate information. As a result, we excluded 57.9% and 26.1% of the original data in the analysis with Papilledema and without Papilledema, respectively. The exclusion may incur decrease in power as well as loss of useful information.

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