Determining the optimal time to report mortality after lobectomy for lung cancer: An analysis of the time-varying risk of death

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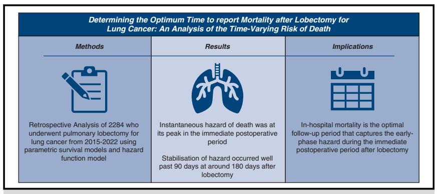
ABSTRACT

Objective: Surgical mortality has traditionally been assessed at arbitrary intervals out to 1 year, without an agreed optimum time point. The aim of our study was to investigate the time-varying risk of death after lobectomy to determine the optimum period to evaluate surgical mortality rate after lobectomy for lung cancer.

Methods: We performed a retrospective study of patients undergoing lobectomy for lung cancer at our institution from 2015 to 2022. Parametric survival models were assessed and compared with a nonparametric kernel estimate. The hazard function was plotted over time according to the best-fit statistical distribution. The time points at which instantaneous hazard rate peaked and stabilized in the 1-year period after surgery were then determined.

Results: During the study period, 2284 patients underwent lobectomy for lung cancer. Cumulative mortality at 30, 90, and 180 days was 1.3%, 2.9%, and 4.9%, respectively. Log-logistic distribution showed the best fit compared with other statistical distribution, indicated by the lowest Akaike information criteria value. The instantaneous hazard rate was greatest during the immediate postoperative period (0.129; 95% confidence interval, 0.087-0.183) and diminishes rapidly within the first 30 days after surgery. Instantaneous hazard rate continued to decrease past 90 days and stabilized only at approximately 180 days.

Conclusions: In-hospital mortality is the optimal follow-up period that captures the early-phase hazard during the immediate postoperative period after lobectomy. Thirty-day mortality is not synonymous to "early mortality," as instantaneous hazard rate remains elevated well past the 90-day time point and only stabilizes at approximately 180 days after lobectomy. (JTCVS Open 2023;16:931-7)



In-hospital mortality best captures the early hazard of death after lobectomy.

CENTRAL MESSAGE

The time point for measuring surgical mortality remains arbitrary. Measuring mortality at the earliest instance after lobectomy may best represent the time-varying risk of death for lung cancer.

PERSPECTIVE

The time point at which surgical mortality is measured differs across various institutions and national databases. Our findings suggest in-hospital mortality is the optimal time point in measuring mortality for patients undergoing lobectomy for lung cancer as it is the time point which best captures the early phase hazard in the immediate postoperative period.

Postoperative mortality is the most commonly used outcome metric to evaluate surgical quality and is routinely measured and reported by surgeons, institutions, and health care bodies.[1] Despite a number of shortcomings, it is still considered as the objective measure to assess surgical performance, evaluate hospital quality, and is often cited as a benchmark for quality improvement initiatives.[2]

The magnitude of postoperative mortality is dependent on the follow-up time. In the context of thoracic surgical procedures, the 2 most commonly used time points are

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Abbreviations and Acronyms
CABG = coronary artery bypass grafting
NSCLC = non–small cell lung cancer

30-day and 90-day mortality.[3,4] Numerous studies have established the importance of tracking beyond the 30-day period and suggested 90-day mortality as a more accurate picture of the postoperative outcomes after pulmonary resection,[5] as mortality was nearly double that of 30 days.[6] Although many different time points for mortality have been reported, each remains as an arbitrary determination for predicting mortality after surgery. There is no current consensus on the optimum time point(s) to evaluate this outcome, as little is known on the relationship between risk of death and time. We therefore sought to quantify the instantaneous hazard rate after surgery to help understand and inform on the optimal follow-up period for assessing mortality after lobectomy for lung cancer.

METHODS

All patients who underwent pulmonary lobectomy for lung cancer were retrospectively reviewed from a prospectively collected database from January 2015 to February 2022 at the Royal Brompton and Harefield Hospitals. Clinical variables, patient demographics, and mortality data were obtained from an electronic database and patient medical records. This study was approved by the Quality and Safety Department at the Royal Brompton Hospital as a service evaluation and was registered via CIRIS (Continuous Improvement in Regulated Industries and Services) with project identification number 4761.

Continuous data are presented as mean with standard deviation or median with interquartile range as appropriate to the data distribution. Categorical and count data are presented as frequency and percentage (%). Parametric survival models were created using the following statistical distributions: Exponential, Weibull, Gompertz, Gamma, Lognormal, Log-Logistic, and Generalized Gamma. Model selection was conducted using the Akaike information criterion to assess which distribution has the best fit as compared with the nonparametric kernel estimate model. The most appropriate parametric model was then superimposed against nonparametric Kaplan–Meier survival estimates for visual inspection of model fit. We calculated and plotted the hazard function over time, with time zero defined as the day of the procedure according to the best-fit statistical distribution. To address the concern of heterogeneity in our cohort, we performed a subanalysis focusing specifically on the hazard function of death in the 1-year postoperative period after lobectomy for patients with early-stage (stage IA and IB) non–small cell lung cancer (NSCLC). In this analysis, the nonparametric kernel estimate model was used, as it provides a more flexible modeling approach without making assumptions about the shape of the distribution in a smaller cohort focusing solely on the 1-year postoperative period. The time points at which instantaneous hazard rate peaked and stabilized in the 1-year period after surgery were then determined in this specific cohort of patients. Statistical analysis was undertaken using R 4.2.0 (R Foundation for Statistical Computing).

RESULTS

A total of 2284 patients who underwent pulmonary lobectomy for lung cancer between 2015 and 2022 were included in our analysis. The mean age (standard deviation) of the cohort was 68 (10) years, and 1066 (47%) were men. The majority of patients had a history of tobacco use. Comorbid cardiopulmonary diseases were common, with 296 (13.0%) having ischemic heart disease and 569 (24.9%) having chronic obstructive pulmonary disease among the study cohort. The median (interquartile range) time to follow-up was 32 (15-55) months, and the 1- and 5-year overall survival rates were 90% and 67%, respectively. Baseline characteristics, demographic profile, pathologic stage, and comorbidities are presented in Table 1.

On parametric survival modeling, log-logistic distribution demonstrated the best goodness of fit when compared with other statistical distribution, with the lowest Akaike information criterion value of 3992.238. The hazard functions derived from the parametric survival models were then plotted against nonparametric kernel estimation, as presented in Figure 1. Parametric survival estimates using the log-logistic distribution were then superimposed against the Kaplan–Meier survival estimate, which demonstrated a good visual fit. An analysis of the overall hazard function for the total follow-up period as presented in Figure 2 indicates that the instantaneous hazard rate is greatest in the immediate postoperative period and diminishes rapidly during the first year after lobectomy and continues to decrease at a

TABLE 1. Overall patient characteristics

Demographic	No. (%) or median (IQR)
No.	2284
Mean age, y (SD)	68 (10)
Male, n (%)	1066 (47%)
Smoking (current and ex-smoker), n (%)	1776 (78%)
Approach, n (%)	
Video-assisted thoracoscopic surgery	1257 (55%)
Thoracotomy	1023 (45%)
FEV1, %	89.0 (76.0-103.1)
Histology, n (%)	
Adenocarcinoma	1426 (62.4%)
Squamous cell carcinoma	415 (18.2%)
Large cell carcinoma	33 (1.4%)
Others	410 (18.0%)
Pathologic stage, n (%)	
IA	1024 (44.8%)
IB	377 (16.5%)
IIA	164 (7.2%)
IIB	278 (12.2%)
IIIA	266 (11.6%)
IIIB	38 (1.7%)
IVA	41 (1.8%)
COPD, n (%)	569 (24.9%)
Ischemic heart disease, n (%)	296 (13.0%)

IQR, Interquartile range; *SD*, standard deviation; *FEV1*, forced expiratory volume in 1 second; *COPD*, chronic obstructive pulmonary disease.

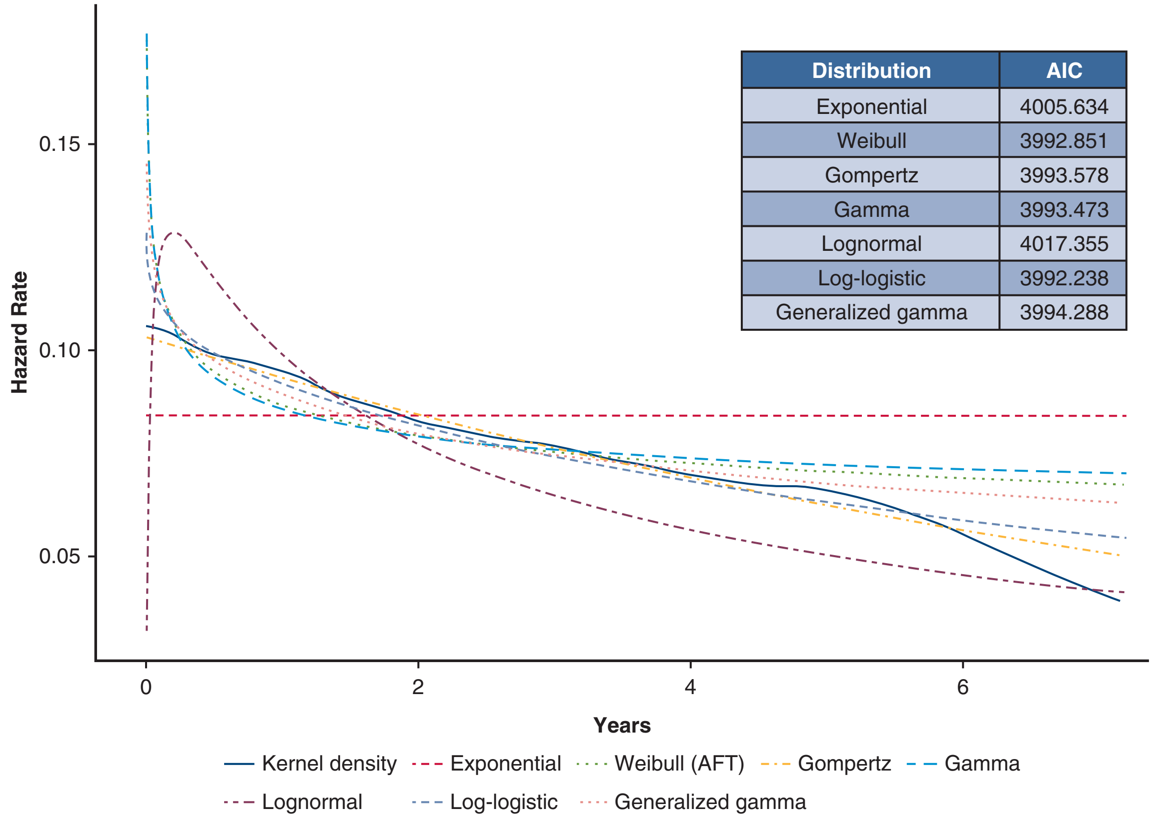

FIGURE 1. Parametric hazard functions applied with different statistical distributions. There were 7 statistical distributions applied and parametric survival models were created using the following 7 statistical distributions: Exponential, Weibull, Gompertz, Gamma, Lognormal, Log-Logistic, and Generalized Gamma. The lowest AIC represented the best-fit model as compared with a nonparametric kernel estimate model, as represented by the kernel density line. The kernel density line is a nonparametric estimate of the varying risk of an event occurring over time. It uses smooth, symmetric functions (kernels) to estimate the hazard at different time points, providing insights into the temporal patterns of risk. Log-logistic distribution demonstrated the best fit with the lowest AIC value of 3992.238. *AIC*, Akaike information criterion; *AFT*, Accelerated Failure Time.

slower rate during the course of the remaining follow-up period of over 7 years.

As a majority of the instantaneous hazard rate diminishes within the first year after lobectomy, further analysis was done to investigate the hazard function within 1 year after surgery, as demonstrated in Figure 3. The instantaneous hazard rate was at its peak immediately after surgery (0.129; 95% confidence interval, 0.087-0.183) and decreased rapidly during the first 30-day period after lobectomy. It continued to remain elevated through the 90-day time point and then stabilized at approximately 180 days (0.100; 95% confidence interval, 0.090-0.110). Moreover, at the 180-day time point, mortality rate was 4.9%, an additional 3.6% as compared with the 1.3% that was captured by 30-day mortality.

Furthermore, a detailed subanalysis was conducted with a homogenous subset of 1179 patients with stage IA and IB NSCLC undergoing lobectomy. An analysis of the nonparametric kernel density estimates as demonstrated in Figure 4 showed that the instantaneous hazard rate was similarly at its peak immediately after surgery and decreased rapidly through the 30-day and 90-day time points. However, instead of stabilization, the hazard function of death reaches a nadir at 182 days and then gradually increased for the remainder of the 1-year period. Therefore, capturing 180-day mortality is likely to be the longest extent to which surgical factors are likely to have any residual influence.

DISCUSSION

The results of our study suggests that the instantaneous hazard rate decreases rapidly from its peak immediately after surgery until the 90-day time point, stabilizing around 180 days, and reducing gradually thereafter. In the subanalysis of patients with stage I NSCLC undergoing lobectomy, the hazard function was similarly composed of an early decrease phase, reaching a nadir at 182 days, before a late increasing phase. In thoracic surgery, commonly reported time points when reporting and comparing mortality include in-hospital and 30 and 90 days. If the aim for quality metrics is to measure and compare the greatest impact of surgery on risk of death, our results suggest the time point

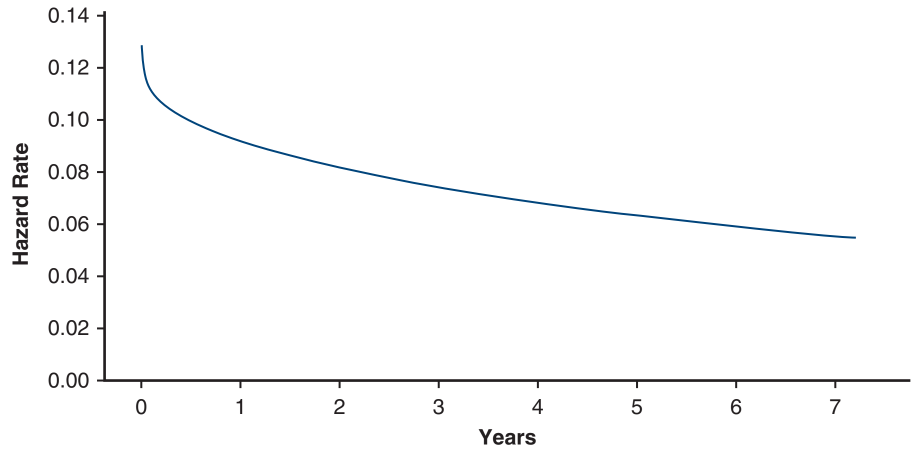

FIGURE 2. Overall log-logistic hazard function of total follow-up period. In this evaluation of the overall hazard function of the total follow-up period as plotted with the best fit log-logistic distribution, the instantaneous hazard was at its maximum in the immediate postoperative period and rapidly decreases during the first year after lobectomy, constituting approximately one half of the decrease in instantaneous hazard in the total follow-up period. The decrease is continuous after 1 year but at a much slower rate, and this continues for the remaining follow-up period.

should be closest to the time of operation as applied by risk models such as Thoracoscore and the European Society Objective Score (ESOS.01) that evaluate in-hospital mortality.[7] Although many institutions and risk models use different time points, few have explored the impact of the continuum of risk when determining the optimum time to assess mortality. From our estimates, the hazard function for lobectomy stabilizes around 180 days. A substantial number of deaths occurred in between the 31- and 180-day period, resulting in a more than 3-fold increase in

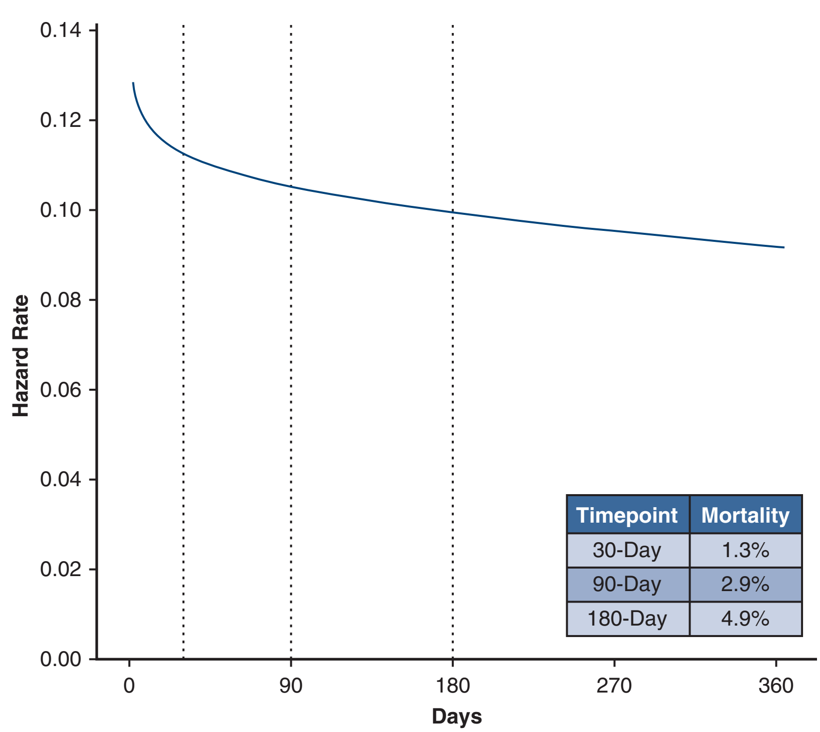

FIGURE 3. Close-up analysis of hazard function within the first year after lobectomy. A close-up analysis of the hazard function was conducted within the first year after lobectomy. The 30-day, 90-day, and 180-day mortality of our dataset of 2284 patients were plotted on the table and the respective time points were plotted onto the graph, as demonstrated from the *dotted lines*.

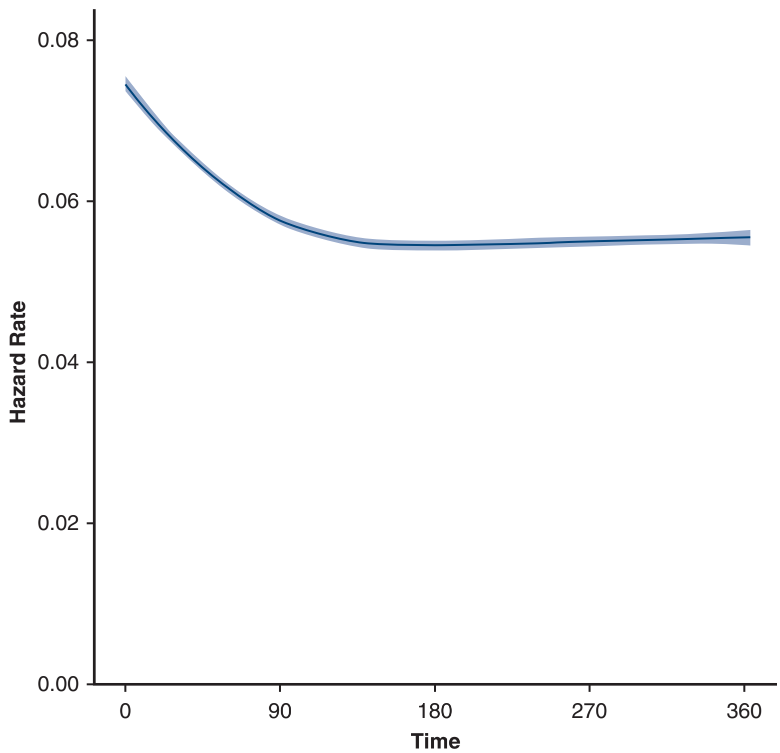

FIGURE 4. Subanalysis of the hazard function for stage I NSCLC within the first year of lobectomy. A subanalysis of the hazard function after lobectomy was conducted in a subset group of patients with stage I NSCLC. The *shaded region* corresponds to the 95% confidence interval. The hazard function decreased until it reached a nadir at 182 days. It gradually increased for the rest of the remaining period of time 1 year after lobectomy. *NSCLC*, Non–small cell lung cancer.

mortality at 180 days (4.9%) compared with mortality at 30 days (1.3%). Furthermore, with 41% of deaths during the first 180 days after surgery falling outside of the time point and definition of 90-day mortality, it is evident that the traditional measures of 30 and 90-day mortality underreport as the comparative time interval increases.

The 30-day time point is the most commonly period to evaluate surgical performance in large-scale national databases. A study of surgery for 8 different cancers including lung cancer recommended the use of 30-day mortality as an international reporting standard.[8] Currently, the Society of Thoracic Surgeons Lung Cancer Resection Risk Model is used to predict 30-day mortality in thoracic surgery.[9] Significant advances in surgical techniques, perioperative care has significantly reduced postoperative 30-day mortality across all spectrums of surgical procedures, prompting thoracic surgeons to extend the postoperative mortality timeframe beyond 30 to 90 days. Pezzi and colleagues[6] conducted a retrospective analysis of 124,418 patients undergoing pulmonary resection from the National Cancer Data Base and concluded that the overall 90-day conditional mortality rate was 2.6%, which was nearly as high as the overall 30-day mortality rate of 2.8%, whereas Powell and colleagues[10] compared 30- and 90-day mortality in 10,991 patients from the United Kingdom's National Lung Cancer Audit and reported that the 3% mortality rate at 30 days almost doubled to 5.9% at the 90-day time point. Powell and colleagues[10] also demonstrated no significant differences in demographics, comorbidities, and tumor characteristics between those who died within 30 days or 31 to 90 days after surgery. Moore and colleagues[11] examined the change in hospital rankings at various time points after lung resection surgery for NSCLC and reported rankings fluctuated most during the early mortality time point of 30 days and only demonstrated less variability when mortality was assessed after the 90-day period. Identifying the optimal time point to assess mortality after lobectomy is therefore critical, as it has direct implications on both patient care and also hospital benchmarking for quality improvement initiatives.

The use of the parametric hazard function modeling approach has enabled us to better understand the time-varying trends of mortality after lobectomy. Blackstone and colleagues[12] suggested that the hazard function can be subdivided into an early, constant, and a late phase and concluded that the early hazard for death after coronary artery bypass grafting (CABG) did not stabilize until approximately 6 months (approximately 180 days), arguing that in order to perform an optimal measurement of periprocedural mortality, in-hospital mortality and mortality after 180 days

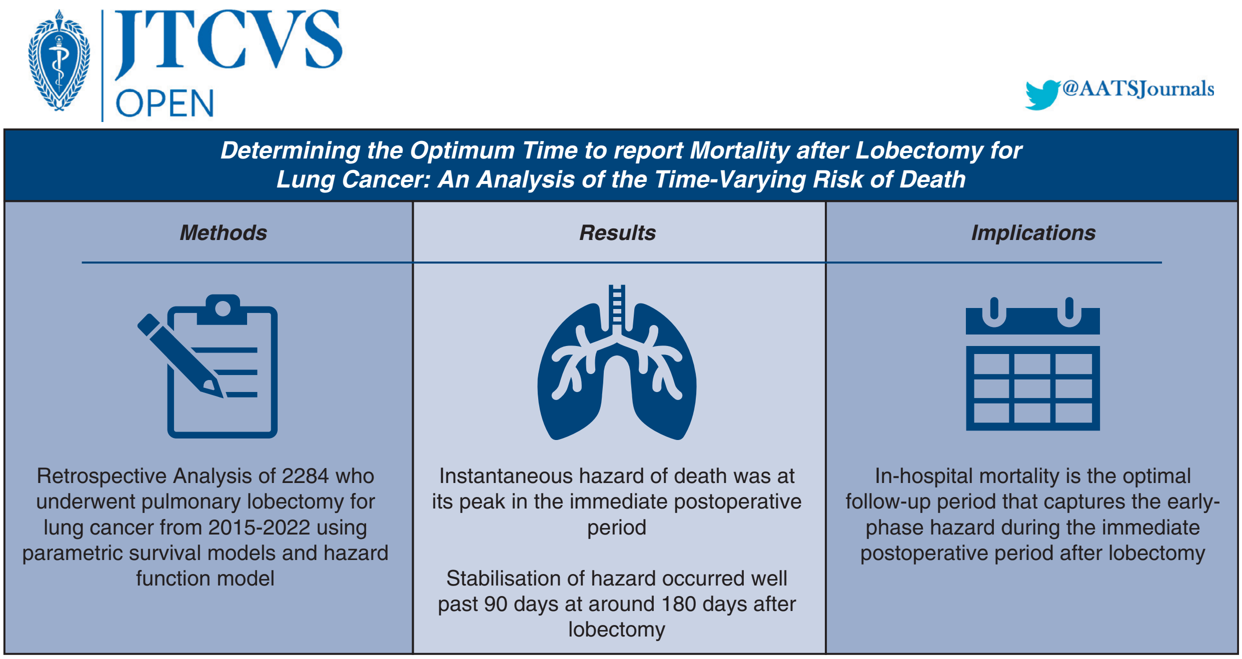

FIGURE 5. In this retrospective analysis of the time-varying risk of death for 2284 patients who underwent lobectomy for lung cancer, the instantaneous hazard of death was greatest in the immediate postoperative period and continued to decrease past 90 days and stabilized only at approximately 180 days.

should be used together to better capture the early phase of hazard associated with CABG.[13] To identify an optimal cutoff time point for assessing postoperative mortality after lobectomy for lung cancer, we specifically evaluated the early phase of the hazard function within the 1-year postoperative period. Central to the philosophy of "optimum" is to understand why we need to capture this information. If it is to assess surgical risk management, quality, and care, then in-hospital mortality is the optimum time point in measuring the greatest risk of death after lobectomy. However, it is also important that surgeons recognize the argument for arbitrarily defined 30-day mortality as a synonym to "early postoperative mortality" is flawed, as risk of death from surgery continues well beyond the 30-day time point until 180 days, as suggested from our study. Hence, 180-day mortality is likely to be the longest time frame to address any surgical factors associated with mortality after lobectomy for lung cancer.

It is noteworthy that the hazard function methodology, originally introduced by Blackstone and colleagues,[12] has been applied not only in the context of CABG but also extended to thoracic surgical procedures including pneumonectomy. In a notable study conducted by Jones and colleagues,[14] this novel approach was used to analyze the hazard function of death following pneumonectomy in a cohort of 355 patients. Their findings revealed a distinct temporal pattern, with the hazard function reaching a nadir at 90 days' postpneumonectomy, followed by a gradual increase throughout the remaining year. This contrasts with our study, where we observed a stabilizing trend and nadir approximately 180 days after lobectomy. This may be due to the difference in patient characteristics, with nearly one half (48%) of the patients being pathologic stage III as compared with our study of 13.3%. In addition, in a propensity-matched analysis comparing lobectomy and pneumonectomy by Jones and colleagues,[15] it was also revealed that patients undergoing pneumonectomy were at significantly greater risk of major complications and death at 90 days, further highlighting the differences in the pattern of mortality after these 2 procedures. These disparate temporal patterns in the hazard function suggests that different extent of lung resections exhibit unique dynamics in postoperative mortality. The variations observed between our study on lobectomy and the study by Jones and colleagues[14] on pneumonectomy ultimately underscore the significance of considering procedure-specific characteristics when evaluating mortality outcomes. Further studies using hazard function methodology in the context of other thoracic surgical procedures would provide valuable insights into the variation in the trends of mortality and morbidity after surgery so that surgical outcomes can be better assessed and compared across national databases.

Study Limitations

To our knowledge, this is the first study to define an optimal time point for assessing mortality after pulmonary lobectomy for lung cancer. However, there are several limitations to our study. First, this study represents a retrospective analysis of patients treated at a single high-volume institution, which may limit the generalizability of our observations. Second, although the use of a longer follow-up time point to assess postoperative mortality allows for a greater number of surgical-related deaths to be captured, it may simultaneously account for a larger number of disease-related death. As the cause of death is not reported in databases in our institution, we currently lack the granularity in discriminating between the competing hazards of disease related and surgery-related deaths. Therefore, the use of longer follow-up time points may possibly overestimate surgical-related mortality among patients with lung cancer. However, we believe that although patients with lung cancer are at risk of dying from oncologic causes, for the population of patients with early-stage lung cancer (who constitute a majority of our study cohort and patients undergoing pulmonary lobectomy in general), oncologic-related death within 180-day mortality is not commonly observed, with most deaths within the period more attributable towards surgical-related or nononcologic causes.[16] Moreover, in the time-varying analysis of mortality after pneumonectomy by Jones and colleagues, oncologic causes of death were negligible during the initial early phase decrease in hazard and was only observed after the nadir was reached.[14] Lastly, our study was limited to lobectomy only. The hazard function of death may differ in other lung resection procedures.

CONCLUSIONS

Our results suggest that the optimal time point to assess surgical risk management, quality, and care is in-hospital mortality (Figure 5). Among metrics that are commonly reported in thoracic surgery databases, 30-day mortality rate may underestimate the true risk of lobectomy, as we did not observe any specific point of a stabilization in the hazard function to warrant an arbitrary 30-day cut-off, since instantaneous hazard rates continues to be elevated well beyond hospital discharge to 180 days and reducing gradually thereafter. This study echoes concerns raised that 30-day mortality may not be the most optimum and appropriate metric for comparing surgical outcomes in nationwide databases and application in lung resection risk models.

Conflict of Interest Statement

E.L. reports personal fees from Covidien, Roche, Lilly Oncology, Boehringer Ingelheim, Medela, Ethicon, AstraZeneca, Beigene, Roche, and BMS; grants and personal fees from ScreenCell; and grants from Clearbridge Biomedics, Illumina, and Guardant Health, outside the submitted work. In addition, E.L. has patents P52435GB and P57988GB issued to Imperial Innovations. E.L. is Chief Investigator for VIOLET NIHR HTA (13/04/03), MARS 2 NIHR HTA (15/188/31), and RAMON NIHR HTA (131306); and founder of My Cancer Companion Healthcare Companion, Ltd. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: hazard function, lobectomy, lung cancer, mortality, outcomes analysis