Editorial

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Restricted Mean Survival Time for Survival Analysis: A Quick Guide for Clinical Researchers

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Take-home points

- Restricted mean survival time (RMST) is suggested as a novel alternative measure in survival analyses and may be useful when proportional hazards assumption cannot be made or when event rate is low.
- RMST is defined as the area under the survival curve up to a specific time point and is generally more reliably estimable than mean or median survival times.
- The time point should be explicitly chosen to obtain an RMST to reflect the clinically relevant time horizon.
- In the case of crossing survival curves, the efficacy of an intervention may be demonstrated by showing a difference in RMST between two curves although the log-rank test may fail to detect differences.
- The role of the RMST in radiology research deserves greater attention.

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In radiological research, survival analysis has been increasingly used to evaluate prognostic outcomes [1]. Researchers may be familiar with the use of Cox proportional hazards (PH) regression to quantify the effect of predictors, such as treatment, imaging, or radiological variables, using hazard ratios. Cox regression requires the proportional hazards assumption, which means that the ratio of hazards between groups is constant over the entire study period, to be valid; however, this scenario is rarely achieved with real-world data. In addition, the hazard ratio simply quantifies the relative difference in risk based on a model-based approach; therefore, it is difficult to interpret the absolute effect directly. To overcome these limitations, other types of Cox regression, such as stratified Cox regression or Cox regression with time-varying covariates, or parametric survival models, such as the accelerated failure time model, can be applied; however, these analytical methods still yield hazard ratios as the output. Other traditional options for the output in survival analysis include several model-free summary measures based on survival rate at a given time (e.g., 1-year survival) or percentiles of the survival function (e.g., median survival time). Interestingly, a more simplified and intuitive approach, namely RMST, has been recently proposed as an alternative output in survival analysis to hazard ratio [2].

What Is RMST?

RMST is defined as the area under the survival curve up to a specific time point (Fig. 1). It can be interpreted as the average survival time or life expectancy during a defined time period ranging from time 0 to a specific follow-up time point, which is a straightforward and clinically meaningful

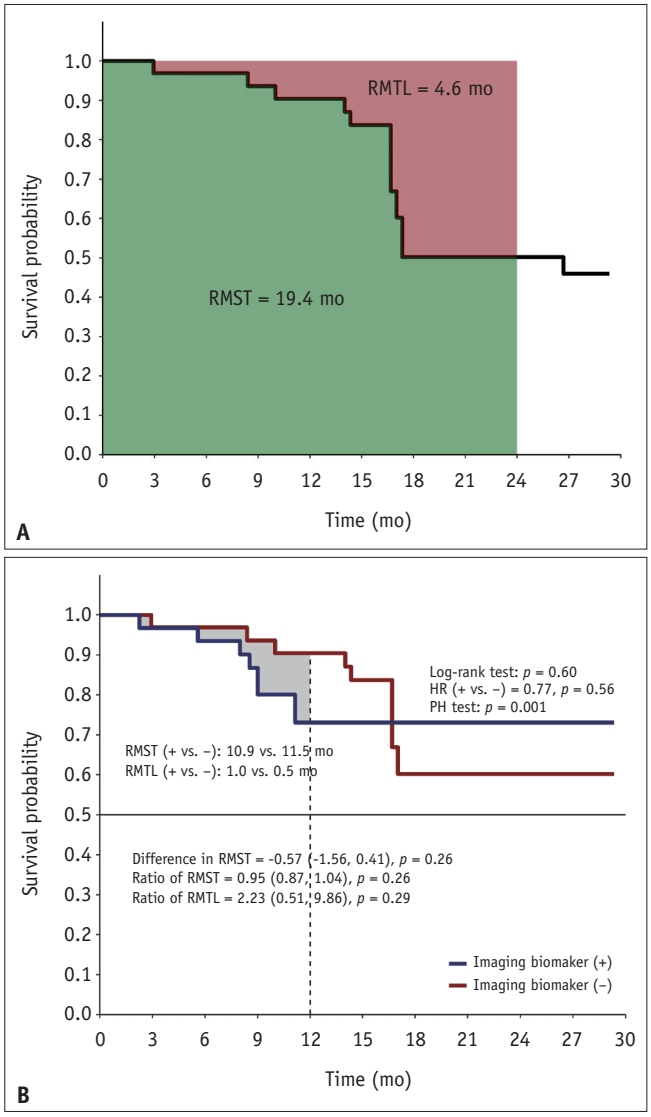

Fig. 1. Example Kaplan–Meier survival curves with related summary survival measures.
A. The estimated RMST up to 24 mo (green area) is 19.4 mo and the estimated RMTL up to 24 mo (red area) is 4.6 mo. **B.** Two Kaplan–Meier survival curves, one each for patients with (blue) and without (red) an imaging biomarker, are shown. The median survival time cannot be obtained for both groups. The entire survival curves are not significantly different (p = 0.6 by log-rank test). The HR (+ vs. –) estimated using the Cox PH regression model is 0.77 (p = 0.56); however, the proportionality of hazard assumption is not met (test based on the Schoenfeld residual, p = 0.009). The estimated RMST up to 12 mo is 10.9 vs. 11.5 mo for + and – groups, respectively. The estimated RMTL up to 12 mo is 1.0 vs. 0.5 for + and – groups, respectively. The gray area is the RMST difference between the two groups. The difference in RMST, the ratio of RMST, and the ratio of RMTL between the two groups are presented in the lower left portion of the figure. Numbers in parentheses indicate the 95% confidence interval. HR = hazard ratio, mo = months, PH = proportional hazards, RMST = restricted mean survival time, RMTL = restricted mean time lost

way to interpret the contrast in survival between groups. The RMST has been recommended as an alternative measure to overcome some of the limitations of proportional hazard modeling [3,4] in medical fields such as oncology [2,5,6], pulmonary medicine [7], and cardiology [8,9]. It was initially proposed by Irwin [10] and was recently implemented in a time-to-event trial by Uno et al. [2]. In a recent study, the hazard ratio was compared with differences in RMST using individual patient data from 54 randomized controlled trials [6]. The results indicated that the hazard ratio may seem large even when the absolute effect is small and suggested that RMST-based measures should be routinely reported in randomized trials with time-to-event outcomes.

The RMST may provide valuable information for comparing two survival curves when the proportional hazards assumption is not met, such as in cases of crossing or delayed separation of survival curves. It may be useful in some clinical settings that often present with a violation of the assumption of proportional hazards, for example, assessing durable responses in immuno-oncology or long-term survival.

Along with the difference in or the ratio of RMST, the ratio of the restricted mean time lost (RMTL), which is the area above the survival curve, may also be a useful summary measure (Fig. 1). It is currently unknown which is preferred between RMST and RMTL, although some studies of their application to individual patient data from published clinical trials [8,11] reported they had similar properties. The RMTL ratio may be approximate to the hazard ratio when the event rate is low; however, the difference in RMST can provide an absolute effect size unavailable with hazard ratios.

Most statistical programs provide survival analysis, including Kaplan-Meier estimates, with the log-rank test and Cox PH regression, which are commonly used in medical research. Software such as MedCalc, R, SAS, and STATA can implement the RMST method [12-15].

To obtain the RMST, a time point should be chosen explicitly to reflect a clinically relevant temporal horizon. However, it may be challenging to select a time point, a priori, before commencing the study. Clearly, the treatment effect can be explored over a range of alternative time points as part of the analysis. Researchers must formulate an appropriate rationale for selecting a particular time point before performing the analysis because the statistical significance of the results depends on the chosen time point.

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What Is the Difference between the Mean and Median Follow-Up Times, Mean and Median Survival Times, and RMST?

The length of the follow-up period is often summarized as the median with the minimum and maximum, 25th and 75th percentiles, or mean of the follow-up time. It is important to distinguish the median (or mean) of the length of the follow-up period from the median (or mean) survival time, because the former does not include information on survival status.

The mean survival time can be estimated by calculating the area under the survival curve (incorporating both survival status and time) of the survival function up to infinity. If there are no censored observations, the mean survival time can be used. However, if the last observation is censored, the mean cannot be estimated from the Kaplan-Meier curve without making assumptions about the distribution beyond the last event time. Moreover, survival data are often skewed to the right, and in some situations, the median is preferred over the mean for summarization.

The median survival time is defined as the length of time in which half of patients develop clinical events. Sufficient follow-up is required for survival to be estimated to be less than 50%. Otherwise, the median survival time cannot be determined.

RMST is similar to the mean survival time but is restricted by a specified time point. Its advantage is that it is more reliable than the mean or median survival times in certain situations, for example, when we have a censored case at a specified time point.

What Is the Difference between the Log-Rank Test and Comparison of RMST for Comparing Survival Curves?

The log-rank test can be used to compare survival curves; however, it does not provide an estimate of the treatment effect (i.e., magnitude of the difference in survival). Some studies present the median survival time or survival rate at a specific time as descriptive statistics that correspond to the log-rank test, which is not appropriate [16]. There are no corresponding summary statistics that present the entire survival distribution. The log-rank test calculates the test statistics using the survival rate at each time point, and then summarizes them to test the equality of the survival curves as a whole for the entire follow-up period.

RMST can be compared using the absolute difference or relative ratio scale [17]. A comparison of the RMST between two survival curves, one each with and without an exposure, provides an estimate of the duration of time gained or lost associated with the exposure. Royston and Parmar [4] demonstrated a method for estimating the 95% confidence interval and *p* value for RMST using a statistically asymptotic method. Alternatively, bootstrapping can be employed [18]. Although RMST has an advantage over the hazard ratio, a previous study showed that the difference in RMST often has operating characteristics similar to the log-rank test under the proportional hazards assumption [4]. However, in the case of crossing survival curves, the efficacy of an intervention may be demonstrated by showing a difference in RMST between the two curves, although the log-rank test may fail to detect a difference because of the occurrence of nonproportional hazards.

How Has the RMST been Applied in Radiologic Research?

The RMST is not yet popular in radiology; however, one multicenter study [19] compared 2-year survival between two different techniques, that is, CT angiography and CT perfusion versus invasive coronary angiography (ICA) and single-photon emission CT, using standard Kaplan-Meier curves and the RMST. The RMST was used to interpret the expected event-free survival within 2 years after ICA.

Another study [18] showed various approaches to utilize the RMST to compare the treatment effects of radiofrequency ablation (RFA) versus liver transplantation (LT) and surgical resection (SR) for hepatocellular carcinoma. The study employed RMST with and without inverse probability of treatment weighting adjustment to balance covariates and compared the treatment effect. Using RMST, a clinically interpretable result was obtained to quantify the survival benefit. The 3-, 5-, and 10-year adjusted difference in the RMST of overall survival was used to compare the treatment groups for LT over RFA and were +4.5, +12.4, and +36.3 months, respectively, while for the SR versus RFA group, the survival benefit was +2.3, +6.1, and +15.8 months, respectively. The incremental survival benefit of SR over RFA was only half that of LT over RFA.

Recent Updates to the RMST

RMST was primarily proposed based on the Kaplan-Meier estimate, which can limit its performance because

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extrapolation beyond the follow-up time is impossible and the Kaplan-Meier curve at time points with a small number of subjects at risk may have large variance. Currently, the RMST, which is based on other types of survival curves, such as survival curves derived from a parametric survival model or multivariable adjusted curves, is applicable. Dynamic RMST curves have been proposed to overcome the drawbacks of the Kaplan-Meier estimate, where the RMST difference or ratio over a range of values to the restriction time is computed [20]. The RMST in the non-inferiority trial [21] and competing risk [22,23] can be found elsewhere. A regression method using pseudo values [24] or prediction modeling with respect to the RMST with subject baseline covariates [25] are available.

Key words

Restricted mean survival time; Restricted mean time lost; Hazard ratio; Survival curve; Survival analysis

Availability of Data and Material

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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