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Analysis

Estimate hazard ratios in small clinical trials without reported hazard ratios

Shuyuan Wang[1] · Ziwei Song[2] · Mingjie Wu[3] · Yuanjian Huang[4]

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Abstract

Background For survival studies, pooling hazard ratios (HRs) across multiple clinical trials through meta-analysis is commonly performed to achieve widely accepted and robust conclusions. However, clinical trials sometimes do not report HRs.

Methods We developed a new, simple approach to estimate HRs by reconstructing life tables from Kaplan–Meier (KM) curves, particularly for small clinical trials. First, we extracted the time points and survival rates from the published KM curves. Then, we reconstructed the life table by reverse derivation of its parameters, using time points and survival rates extracted from the KM curves. Finally, we replotted the KM curves using the Kaplan–Meier method and estimated the HRs via the Cox regression method by SPSS software, using the survival data from the reconstructed life table.

Results The estimated HRs of 3 examples were 0.510 (95% CI 0.272–0.958, P = 0.036), 2.472 (95% CI 1.548–3.949, P < 0.001), and 0.591 (95% CI 0.291–1.199, P = 0.145), compared with the original HRs of 0.51 (95% CI 0.27–0.96, P = 0.04), 2.33 (95% CI 1.45–3.73, P < 0.001), and 0.62 (95% CI 0.31–1.26, P = 0.18), respectively.

Conclusions This simple approach allows for the estimate of HRs from published KM curves in small survival studies without reported HRs, facilitating their inclusion in meta-analyses. This increases the overall sample size and enhances the reliability of synthesized clinical evidence.

Keywords Hazard ratio · Kaplan–Meier curve · Life table · Survival analysis · Clinical trial

1 Introduction

To compare the efficacies of treatments for cancer, clinical trials usually require long-term follow-up [1]. In such scenarios, traditional efficacy indicators, such as odds ratios and relative risks, become less applicable because evaluating treatments involves not only determining whether a specific event, such as disease progression or death, has occurred but

Shuyuan Wang and Ziwei Song have contributed equally to this work.

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✉ Mingjie Wu, 498102205@qq.com; ✉ Yuanjian Huang, huangyuanjian@njmu.edu.cn; Shuyuan Wang, wangsy@njmu.edu.cn; Ziwei Song, 765767195@qq.com | [1]Department of Cardiology, The First Affiliated Hospital with Nanjing Medical University, Nanjing 210029, Jiangsu, China. [2]College of Acupuncture and Moxibustion, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu, China. [3]College of Traditional Chinese Medicine, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu, China. [4]Department of General Surgery, The First Affiliated Hospital with Nanjing Medical University, Nanjing 210029, Jiangsu, China.

also considering the time until these events occur. Therefore, survival analysis, which combines the observation of events with the time experienced, is considered the most appropriate statistical method for these clinical trials [2].

Survival analysis involves the collection of survival data, including endpoint events (e.g., disease progression, death, or other events of interest), survival time, and censoring (e.g., loss to follow-up, withdrawal from the trial, or failure to complete the endpoint event) [2]. These survival data can be summarized into a life table and then presented more intuitively in the form of Kaplan–Meier (KM) curves, often accompanied by a hazard ratio (HR) [3, 4]. The HR is defined as the ratio of the hazards, representing the instantaneous risk conditional on no prior events, averaged over the observed event times [4].

Often, multiple similar clinical trials are conducted simultaneously or sequentially to compare the same treatments for the same caner. However, due to limitations such as small sample sizes, the influence of various confounding factors, and differences in study designs, the HRs for the same treatment reported by different clinical trials may be inconsistent or even contradictory [4]. To obtain a widely accepted and robust conclusion, meta-analyses are commonly performed to pool HRs across multiple trials [5]. This process collects existing or unpublished studies with comparable characteristics and integrates the results into a quantified combined effect estimate [5]. However, some studies do not report HRs, leading to incomplete synthesis of clinical evidence for meta-analysis. Several investigators have developed their own approaches to estimate HRs from KM curves to facilitate meta-analysis, but these methods can be complex [6–9].

To estimate HRs from studies that reported the KM curves but do not provide HRs, we developed a new, simple approach to estimate HRs by reconstructing life tables from KM curves, particularly for small clinical trials. This approach increases the number of studies included in the meta-analysis, thereby enhancing the reliability of the pooled HR and providing a more accurate reflection of the efficacies of treatments for cancer.

2 Methods

2.1 Workflow of constructing life table, plotting KM curve, and calculating HR

In this section, we briefly describe the standard workflow for constructing a life table, plotting a KM curve, and calculating the HR in a clinical trial. This will enhance the understanding of the methodology we developed to estimate HRs.

Suppose that a clinical trial evaluating the efficacies of certain treatments for cancer has been completed. During the follow-up, death or censoring occurred i times in total, with corresponding time points denoted as T_i. Note that each time death or censoring occurs, the number of deaths (D_i) or censored patients (C_i) should be ≥ 1. The values of T_i, D_i, and C_i can be easily obtained during the follow-up.

Then, the number of risk patients (N_i) is calculated by

$$N_i = N_{i-1} - D_{i-1} - C_{i-1} (i \geq 2). \tag{1}$$

Note that N_1 is the number of patients included at the start of the clinical trial and can be easily determined according to the study design.

The survival probability (P_i) is the probability of living for N_i risk patients at time point T_i and is calculated by

$$P_i = \frac{N_i - D_i}{N_i} (i \geq 1) \tag{2}$$

The survival rate (S_i) is the probability of living until time point T_i and is calculated as the cumulative product of P_i:

$$S_i = P_1 P_2 P_3 \ldots P_{i-1} P_i (i \geq 2). \tag{3}$$

Note that $S_1 = P_1$ at time point T_1. Finally, based on the above parameters, the life table for this clinical trial can be constructed (Table 1).

For better visualization of survival, the KM curve, a series of declining horizontal steps, can be plotted based on the T_i and S_i values from the life table (Fig. 1A) [3, 10]. The parameters in the life table can be understood from the perspective of the KM curve as follows: The follow-up time is divided into a series of steps corresponding to i time intervals $[0, T_1]$, $(T_1, T_2]$, $(T_2, T_3]$, …, $(T_{i-1}, T_i]$ for i ≥ 1 [11]. These time intervals are defined such that at least one patient either died or was

Table 1 Parameters of the life table

Number (i)	Time (T_i)	Death (D_i)	Censored (C_i)	Risk patients (N_i)	Survival probability (P_i)	Survival rate (S_i)
1	T_1	D_1	C_1	N_1	$P_1 = \frac{N_1 - D_1}{N_1}$	$S_1 = P_1$
2	T_2	D_2	C_2	$N_2 = N_1 - D_1 - C_1$	$P_2 = \frac{N_2 - D_2}{N_2}$	$S_2 = P_1 P_2$
3	T_3	D_3	C_3	$N_3 = N_2 - D_2 - C_2$	$P_3 = \frac{N_3 - D_3}{N_3}$	$S_3 = P_1 P_2 P_3$
…	…	…	…	…	…	…
i-1	T_{i-1}	D_{i-1}	C_{i-1}	$N_{i-1} = N_{i-2} - D_{i-2} - C_{i-2}$	$P_{i-1} = \frac{N_{i-1} - D_{i-1}}{N_{i-1}}$	$S_{i-1} = P_1 P_2 P_3 \ldots P_{i-2} P_{i-1}$
i	T_i	D_i	C_i	$N_i = N_{i-1} - D_{i-1} - C_{i-1}$	$P_i = \frac{N_i - D_i}{N_i}$	$S_i = P_1 P_2 P_3 \ldots P_{i-1} P_i$

The values of T_i, D_i, and C_i can be easily obtained during the follow-up. Based on T_i, D_i, and C_i, the values of N_i, P_i, and S_i can be calculated. This table demonstrates how to construct the life table for a clinical trial

censored at the end of the interval (i.e., at time point T_i of each interval (T_{i-1}, T_i]). D_i and C_i represent the numbers at the end of the interval. N_i represents the number at the start of the interval (i.e., at time point T_{i-1} of each interval (T_{i-1}, T_i]).

The survival data of patients, i.e., the values of T_i, D_i, and C_i in the life table, can be input into SPSS (IBM, v25) (Fig. 1B). Then, the KM curve is plotted using the Kaplan–Meier method (Fig. 1C). The HR is calculated using the Cox regression method (Fig. 1D).

2.2 Extraction of T_i and S_i from the KM curve

For the clinical trials that only reported the KM curves without presenting HRs, if the values of T_i and S_i can be extracted from the KM curve and combined with Eqs. (1–3), the values of T_i, D_i, and C_i in the life table could be reversely derived, and the HR can be estimated accordingly. In the subsequent sections, we will elaborate on the procedures of our methodology.

The KM curve is plotted with T_i values as x-axis coordinates and S_i values as y-axis coordinates, where vertical tick-marks indicate censored patients (Fig. 1A) [3]. The coordinates of the endpoints at the end of each time interval and the coordinates of all the tick-marks on the KM curve are extracted using Engauge Digitizer (github.com/markummitchell/engauge-digitizer/releases, v12.1). Briefly, the x-axis and y-axis are defined by mouse-clicking the start and end points of each axis in the KM plot. Then, all endpoints and tick-marks are selected by clicking to be read off from the curve. The resulting T_i and S_i coordinates are then exported for the reverse derivations of parameters in the life table.

2.3 Reverse derivation of parameters in the life table

An empty life table is created in the Excel (Microsoft, v2406) sheet, and the T_i and S_i coordinates are input into it (Fig. 2A).

The values of censored patients C_x ($1 \le x \le i$) will be set as 0 if no censoring and will be set as 1 a priori if corresponding to the tick-marks on the KM curve (see next section for more information) (Fig. 2B). The survival rate, S_{i-1}, can be written in the following equations:

$$S_{i-1} = P_1 P_2 P_3 \ldots P_{i-1} (i \ge 2), \tag{4}$$

so that

$$P_i = \frac{S_i}{S_{i-1}} (i \ge 2) \tag{5}$$

if Eq. (3) is divided by Eq. (4). Note that $P_1 = S_1$ at time point T_1. All other values of P_i can be calculated using Eq. (5) (Fig. 2B).

The number of patients included at the start of clinical trial, N_1, can be determined by the study design (Fig. 2C). According to Eq. (2), the number of deaths, D_i, can be written in the following equation:

$$D_i = N_i \left(1 - P_i\right) (i \ge 1), \tag{6}$$

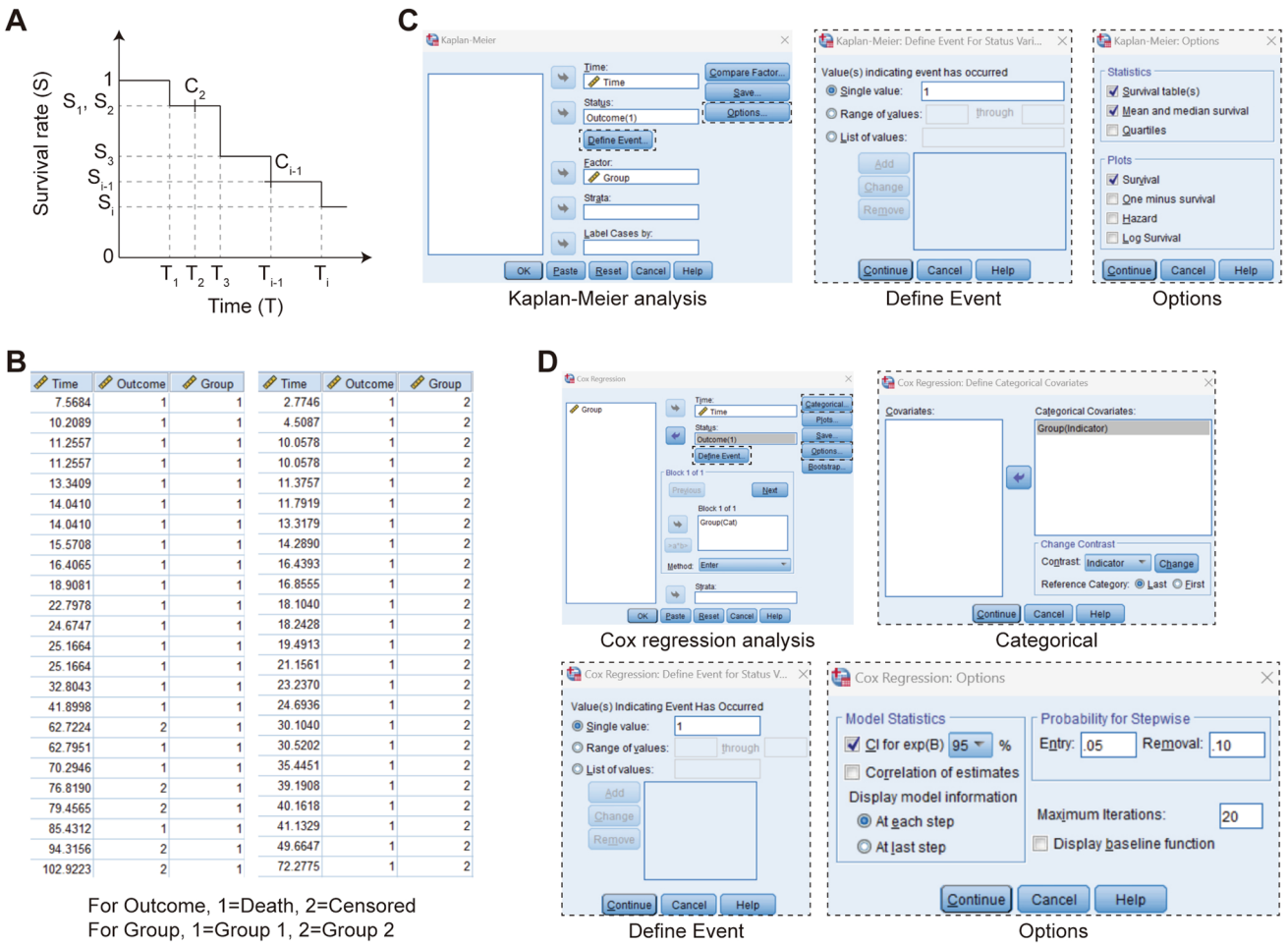

Fig. 1 Workflow of constructing life table, plotting KM curve, and calculating HR. **A** Example of a standard KM curve. The endpoint of each declining horizontal step (i.e., the end of each time interval) represents dead patients. Vertical tick-marks represent censored patients. T, Time; S, Survival rate; C, Censored patients; i, Number. **B** Example of survival data input into SPSS. For the outcome variable, 1 represents death, and 2 represents censoring. For the group variable, 1 and 2 represent different groups according to the design of the clinical trial. **C** Kaplan–Meier analysis in SPSS. In the 'Kaplan–Meier' dialog box, the variables 'Time', 'Status', and 'Factor' were set as the data for 'Time', 'Outcome', and 'Group', respectively. In the 'Define Event' dialog box, 'Single value' was set to 1, representing death. In the 'Options' dialog box, 'Survival' was additionally selected. **D** Cox regression analysis in SPSS. In the 'Cox regression' dialog box, the variables 'Time', 'Status', and 'Covariates' were set as the data for 'Time', 'Outcome', and 'Group', respectively. In the 'Categorical' dialog box, 'Categorical covariates' was set to 'Group (Indicator)'. In the 'Define Event' dialog box, 'Single value' was set to 1, representing death. In the 'Options' dialog box, 'CI for exp(B) 95%' was selected

so that $D_1 = N_1(1 - P_1)$ (Fig. 2C). The number of risk patients, N_i, can be calculated using Eq. (1), so that $N_2 = N_1 - D_1 - C_1$ (Fig. 2C).

Then, the other values of D_i and N_i can be auto filled by double-clicking the fill handles of the sheet cells of D_1 and N_1, respectively (Fig. 2D). The values of D_i will be auto corrected once the values of N_i are auto filled. Finally, the life table is reconstructed (Table 2).

2.4 Rules to reconstruct the life table

During the above process to reconstruct the life table, 3 rules should be followed.

First, although one tick-mark on the KM curve may indicate several patients censored at the same time point T_x (where $1 \le x \le i$), the number of censored patients C_x corresponding to the tick-mark will be set as 1 a priori. This assumption is reasonable for small clinical trials because the number of censored patients is usually very small. This setting ensures that the values of D_{x+m} (where $m = 1, 2, 3, \ldots$) representing the number of deaths at the following m time intervals after

A

Number (i)	Time (T_i)	Death (D_i)	Censored (C_i)	Risk Patients (N_i)	Survival Probability (P_i)	Survival rate (S_i)
1	① T_1					② S_1
2	T_2					S_2
3	T_3					S_3
…	…					…
i-1	T_{i-1}					S_{i-1}
i	T_i					S_i

B

Number (i)	Time (T_i)	Death (D_i)	Censored (C_i)	Risk Patients (N_i)	Survival Probability (P_i)	Survival rate (S_i)
1	T_1	③	C_1=0, 1, or …		④ $P_1=S_1$	S_1
2	T_2		C_2=0, 1, or …		$P_2=S_2/S_1$	S_2
3	T_3		C_3=0, 1, or …		$P_3=S_3/S_2$	S_3
…	…					…
i-1	T_{i-1}		C_{i-1}=0, 1, or …		$P_{i-1}=S_{i-1}/S_{i-2}$	S_{i-1}
i	T_i		C_i=0, 1, or …		$P_i=S_i/S_{i-1}$	S_i

C

Number (i)	Time (T_i)	Death (D_i)	Censored (C_i)	Risk Patients (N_i)	Survival Probability (P_i)	Survival rate (S_i)
1	T_1 ⑥	$D_1=N_1(1-P_1)$	C_1=0, 1, or …	N_1 ⑤	$P_1=S_1$	S_1
2	T_2		C_2=0, 1, or …	$N_2=N_1-D_1-C_1$ ⑦	$P_2=S_2/S_1$	S_2
3	T_3		C_3=0, 1, or …		$P_3=S_3/S_2$	S_3
…	…					…
i-1	T_{i-1}		C_{i-1}=0, 1, or …		$P_{i-1}=S_{i-1}/S_{i-2}$	S_{i-1}
i	T_i		C_i=0, 1, or …		$P_i=S_i/S_{i-1}$	S_i

D

Number (i)	Time (T_i)	Death (D_i)	Censored (C_i)	Risk Patients (N_i)	Survival Probability (P_i)	Survival rate (S_i)
1	T_1	$D_1=N_1(1-P_1)$	C_1=0, 1, or …	N_1	$P_1=S_1$	S_1
2	T_2		C_2=0, 1, or …	$N_2=N_1-D_1-C_1$	$P_2=S_2/S_1$	S_2
3	T_3	⑧ Atuofill	C_3=0, 1, or …	⑨ Atuofill	$P_3=S_3/S_2$	S_3
…	…					…
i-1	T_{i-1}		C_{i-1}=0, 1, or …		$P_{i-1}=S_{i-1}/S_{i-2}$	S_{i-1}
i	T_i		C_i=0, 1, or …		$P_i=S_i/S_{i-1}$	S_i

Fig. 2 Workflow for the reverse derivation of parameters in the life table. **A** Input the T_i and S_i coordinates into the Excel spreadsheet. **B** Input the pre-assumed values of C_i and calculation of the values of S_i. **C** Calculation of the values of N_1, D_1, and N_2. **D** Auto fill of the remaining values of D_i and N_i. The values of D_i will be auto corrected once the values of N_i are auto filled. ① to ⑧ represents the sequence of operations

$(T_{x-1}, T_x]$ are close to integers. If they are not, C_x will be increased to 2 or more, termed a sensitivity test, until the values of D_{x+m} are close to integers.

Table 2 Reverse derivations of parameters in the life table

Number (i)	Time (T_i)	Death (D_i)	Censored (C_i)	Risk patients (N_i)	Survival probability (P_i)	Survival rate (S_i)
1	T_1	$D_1 = N_1(1-P_1)$	C_1	N_1	$P_1 = S_1$	S_1
2	T_2	$D_2 = N_2(1-P_2)$	C_2	$N_2 = N_1 - D_1 - C_1$	$P_2 = \frac{S_2}{S_1}$	S_2
3	T_3	$D_3 = N_3(1-P_3)$	C_3	$N_3 = N_2 - D_2 - C_2$	$P_3 = \frac{S_3}{S_2}$	S_3
…	…	…	…	…	…	…
i-1	T_{i-1}	$D_{i-1} = N_{i-1}(1-P_{i-1})$	C_{i-1}	$N_{i-1} = N_{i-2} - D_{i-2} - C_{i-2}$	$P_{i-1} = \frac{S_{i-1}}{S_{i-2}}$	S_{i-1}
i	T_i	$D_i = N_i(1-P_i)$	C_i	$N_i = N_{i-1} - D_{i-1} - C_{i-1}$	$P_i = \frac{S_i}{S_{i-1}}$	S_i

The values of T_i and S_i can be extracted from the KM curve. Based on T_i and S_i, the values of P_i, N_i, and D_i can be calculated. This table demonstrates how to reconstruct the life table through reverse derivation of parameters within the life table

Second, in cases where the steps of the KM curve decline too rapidly over a very short period, the values of D_i are still not close to integers after the sensitivity test. This is typically due to too many steps clustering within relatively short time intervals, which makes the manually extracted coordinates inevitably deviate from the actual numbers. Therefore, if the consistent sum of D_x, D_{x+1}, …, D_{x+m} across m + 1 time intervals, $\sum_{k=x}^{x+m} D_k$, is near an integer, it will be acceptable to combine these short steps as a whole step, meaning that $\sum_{k=x}^{x+m} D_k$ patients died at time point T_{x+m}. In other words, the pairs (T_x, D_x), (T_{x+1}, D_{x+1}), …, (T_{x+m}, D_{x+m}) will be changed to (T_x, 0), (T_{x+1}, 0), …, (T_{x+m}, $\sum_{k=x}^{x+m} D_k$) in the life table, respectively.

Third, if any parameter values, such as deaths, censored patients, and risk patients, have been reported in the original trial, the data modification following the above rules will conform to the original data.

2.5 Reconstruction of KM curve and estimate of HR

Similarly, based on the reconstructed life table, the survival data were input into SPSS for the replotting of the KM curve and the estimate of HR (Fig. 1B-D).

3 Results

3.1 Estimate HRs from clinical trials reporting no number of censored or risk patients

Example 1 (Fig. 3A, i.e., Fig. 2 of Cashin [12]) includes KM curves depicting the overall survival of patients with colorectal peritoneal metastases, comparing those who underwent cytoreductive surgery combined with intraperitoneal chemotherapy (surgery group) to those who received systemic chemotherapy (chemotherapy group) [12]. The study reported that 24 patients were included at the start of the trial in both groups. At the end of the trial, 19 deaths were observed in the surgery group and 24 deaths in the chemotherapy group. However, no numbers of censored patients or risk patients were reported.

From Fig. 3A, the x-axis coordinates (T_i) and y-axis coordinates (S_i) of the endpoints at the end of each time interval and all tick-marks on the KM curves were extracted (Table S1, left panel). Then, the values of T_i and S_i were filled into the 'Time' and 'Survival Rate' columns of the reconstructed life tables (Table S1, middle panel), respectively. According to the 1st rule for reconstructing the life tables outlined in the Methods, C_i values corresponding to each tick-mark were set as 1 a priori, and the values of other parameters were calculated based on Eqs. (1), (5), and (6) (Table S1, middle panel). A sensitivity test was performed by increasing C_i to 2 or more due to non-integer values for D_3, D_4, D_6, D_7, D_{13}, and D_{14} in the surgery group, which remained non-integer afterward. This indicated that adjusting the values of C_i could not resolve the issue. Subsequently, according to the 2nd rule, D_3 and D_4, which were initially 0.6327 and 1.3470, were changed to 0 and 2, respectively, indicating that no patients died at 10.6282 months and 2 patients died at 11.2557 months (Table S1, middle panel). Similar adjustments were made for D_6, D_7, D_{13}, and D_{14}. Then, the reconstructed life tables were modified by changing all D_i values to integers (Table S1, middle panel). According to the 3rd rule, the recalculated total numbers of deaths (19 in the surgery group and 24 in the chemotherapy group) were verified to be consistent with the original

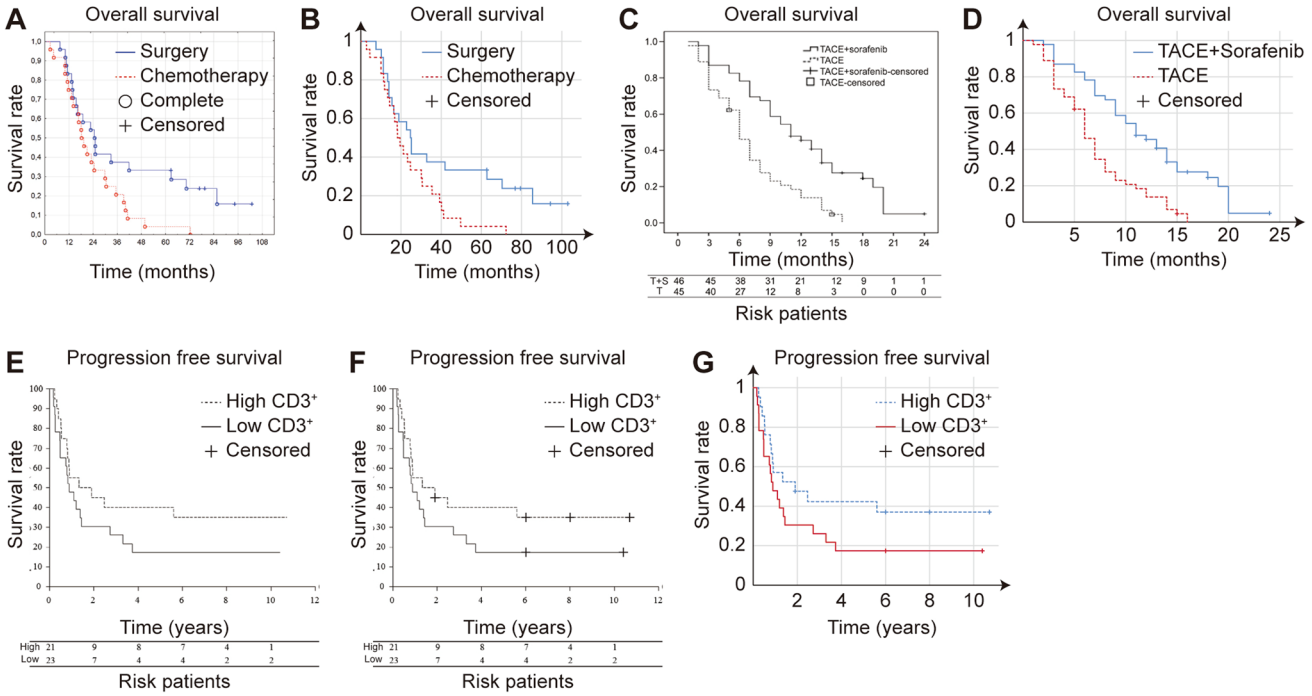

Fig. 3 Original and reconstructed KM curves. **A**, **B**, Original (**A**) and reconstructed (**B**) KM curves of Example 1. **C**, **D**, Original (**C**) and reconstructed (**D**) KM curves of Example 2. The orginial study reported risk patients (**C**). **E**–**G**, Original (**E**), censoring tick-marks rebuilt (**F**), and reconstructed (**G**) KM curves of Example 3. The orginial study reported the number of risk patients but did not mark censored patients with tick-marks on the KM curves (**E**). We rebuilt the tick-marks based on the table of risk patients (**F**). All the reconstructed KM curves (**B**, **D**, **G**) match the original ones (**A**, **C**, **E**) in size

numbers reported in the study [12]. Finally, the survival data from the modified life tables were input into SPSS (Table S1, right panel).

The reconstructed KM curves of Example 1 are shown in Fig. 3B. The estimated HR was 0.510 (95% CI 0.272–0.958, P = 0.036), whereas the original HR was 0.51 (95% CI 0.27–0.96, P = 0.04) [12]. The deviation of the estimated HR from the original HR was 0.

3.2 Estimate HRs from clinical trials reporting risk patients

Example 2 (Fig. 3C, i.e., Fig. 2a of Zhu [13]) includes KM curves depicting the overall survival of patients with hepatocellular carcinoma, comparing those who underwent transarterial chemoembolization combined with sorafenib (TACE + sorafenib group) to those who underwent TACE alone (TACE group) [13]. The study reported that 46 patients were included in the TACE + sorafenib group and 45 patients in the TACE group at the start of the trial. At the end of the trial, 37 deaths were observed in the TACE + sorafenib group and 43 deaths in the TACE group. The numbers of risk patients were reported (Risk patients in Fig. 3C), but the numbers of censored patients were not.

From Fig. 3C, the values of T_i and S_i were extracted and filled into the reconstructed life tables (Table S2, left panel). C_i values were set as 1 a priori, and then the values of other parameters within the life tables were calculated (Table S2, middle panel). However, the calculated values of D_{16}-D_{18} were not close to integers when C_{15} was 1 in the TACE + sorafenib group. A sensitivity test was performed by increasing C_{15} up to 3, resulting in D_{16} being close to 1, D_{17} close to 3, and D_{18} close to 0 (Table S2, middle panel). Then, the reconstructed life tables were modified by changing all D_i values to integers (Table S2, middle panel). The recalculated total numbers of deaths (37 in the TACE + sorafenib group, 43 in the TACE group) and the numbers of risk patients at different timepoints (Table S2, middle panel) were verified to be consistent with the original numbers reported in the study [13]. Finally, the survival data from the modified life tables were input into SPSS (Table S2, right panel).

The reconstructed KM curves of Example 2 are shown in Fig. 3D. The estimated HR was 2.472 (95% CI 1.548–3.949, P < 0.001), whereas the original HR was 2.33 (95% CI 1.45–3.73, P < 0.001) [13]. The deviation of the estimated HR from the original HR was 6.09%.

3.3 Estimate HRs from clinical trials reporting risk patients but losing censoring information

Example 3 (Fig. 3E, i.e., Fig. 3b of Tanis [14]) includes KM curves depicting progression free survival of patients with liver metastases after colorectal surgery, comparing those with high $CD3^+$ lymphocyte density at the tumour-normal interface (high $CD3^+$ group) to those with low $CD3^+$ lymphocyte density (low $CD3^+$ group) [14]. The study reported that 21 patients were included in the high $CD3^+$ group and 23 in the low $CD3^+$ group at the start of the trial. The numbers of risk patients were reported (Risk patients in Fig. 3E), but the numbers of deaths or censored patients were not.

From Fig. 3E, the life tables were reconstructed (Table S3) as usual. However, the numbers of risk patients generated from these life tables (Table S3, right panel) were inconsistent with the table of risk patients reported in the study (Fig. 3E) [14]. We then realized that the authors did not mark censored patients with tick-marks on the KM curves. We rebuilt the tick-marks based on the table of risk patients (Fig. 3F). From Fig. 3F, the values of T_i and S_i were extracted and filled into the reconstructed life tables (Table S4, left panel). Guided by the table of risk patients, C_{11}, C_{14}, C_{15}, and C_{16} in the high $CD3^+$ group were easily set as 3, 3, and 1, respectively, and C_{18} and C_{19} in the low $CD3^+$ group were both set as 2. Then, the values of other parameters within the life tables were calculated (Table S4, middle panel). A sensitivity test was unnecessary since all the calculated D_i values were close to integers in both groups. Then, the reconstructed life tables were modified by changing all D_i values to integers (Table S4, middle panel). The numbers of risk patients at different timepoints (Table S4, middle panel) were verified to be consistent with the original numbers reported in the study [14]. Finally, the survival data of the modified life tables were input into SPSS (Table S4, right panel).

The reconstructed KM curves of Example 3 are shown in Fig. 3G. The estimated HR was 0.591 (95% CI 0.291–1.199, $P = 0.145$), whereas the original HR was 0.62 (95% CI 0.31–1.26, $P = 0.180$) [14]. The deviation of the estimated HR from the original HR was 4.68%.

3.4 More examples

To eliminate selection bias, we estimated additional HRs from several small clinical trials [15–18] using this approach. The deviations of the estimated HRs from the original ones ranged from 0.21 to 2.29% (Table S5), suggesting good repeatability and accuracy.

4 Discussion

This study develops a new, simple approach to estimate HR by reconstructing life tables from KM curves, particularly for small survival studies. Utilizing this approach, the reliability of meta-analysis can be enhanced by pooling more clinical trials, even those that do not report HRs, thereby generating more accurate synthesized clinical outcomes.

Several studies have proposed methods to estimate HRs from KM curves [6–9]. Parmar et al. assumed that censoring was uniform across the entire follow-up period, patient information was collected at regular time intervals, and there was minimal missing information on the endpoint [6]. However, this assumption ignored the true follow-up status of clinical trials. Williamson et al. relied on the proportional hazards regression assumption [7], which may not be accessible to beginners unfamiliar with Cox regression equations. Tierney et al. estimated censoring using the minimum and maximum follow-up periods [8], but this approach discarded some survival information. Previous investigators [6–8] extracted limited time points from the KM curves, whereas we, along with Guyot et al. [9], utilized all available time points to preserve complete survival information. In contrast, while Guyot et al. [9] employed R programming for their method, our approach is notably simpler, relying on user-friendly software with a graphical interface, such as Excel and SPSS.

Additionally, our approach reconstructs life tables and simulates the process of constructing the KM curves, making it easy to understand. Moreover, unlike the complex equations used by previous investigators [6–9] to estimate log(HR) and its variance, our approach calculates parameters within the life table based on the time points (T_i) and survival rates (S_i) of the KM curves using simple Eqs. (1), (5), and (6) in Excel, making the process highly convenient. While studies that do not report HRs may be considered less rigorously conducted, when only a few clinical trials address a specific clinical issue, using our approach to estimate HRs for meta-analysis can still provide scientific significance.

Our study has limitations. First, our approach is based on the low-censoring assumption (the 1st rule for reconstructing life tables in the Methods). In clinical trials with high censoring rates, or when KM curves lack markings for censored patients or do not provide a risk patient table, the number of censored patients is difficult to estimate, and our approach may produce suboptimal results. Second, although our approach can theoretically estimate HRs from KM curves of any sample size, in practice, the coordinates of adjacent declining horizontal steps in KM curves with large sample sizes are often too close to be accurately extracted. These two limitations restrict the applicability of our approach primarily to small clinical trials. Based on our experience, parameter optimization for life table reconstruction becomes challenging when the sample size per group exceeds 50. Thus, in this context, we consider a 'small' clinical trial as one with fewer than 50 patients per group. Third, high-resolution publication of KM curves is required so that the declining steps remain clearly identifiable even when the curve is enlarged. Errors in extracting T_i and S_i coordinates may occur due to poor publication quality of the curve or carelessness during point extraction. Therefore, each coordinate should be manually verified, which is time-consuming. Nevertheless, since coordinates are manually extracted, deviations from their true values remain unavoidable, regardless of the resolution of the KM curve or the level of care taken during extraction. These limitations are also common challenges faced by other similar studies [6–9].

In conclusion, our study proposed a new, simple approach to estimate HRs from published KM curves for small survival studies without reported HRs. This approach will help researchers to include small trials in meta-analysis and increase the sample size and reliability of synthesized clinical evidence.

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Generative AI Language, grammar, and terminology edits were performed by ChatGPT to meet the language requirements for publication. ChatGPT did not generate or alter any data or content in this study. Authors are responsible for all data and content of this study.

Author contributions Y.H. conceived and designed this study. S.W. and Z.S. searched for clinical trials, extracted data, reconstructed life tables and KM curves, reproduced HRs, and wrote the manuscript. S.W., Z.S., M.W. and Y.H. examined the statistical methodology and verified the results. S.W., Z.S., M.W. and Y.H. critically revised the manuscript. All authors approved the final version that was submitted.

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Data availability All original KM plots can be found in the cited clinical trials. All extracted coordinates can be found in the supplementary tables.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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