REPRESENTING THE RESULTS OF SUBGROUP ANALYSIS IN COMPARATIVE CLINICAL STUDIES BY A GRAPH

by

Nanami Taketomi, **Takashi Yanagawa** and **Kenta Murotani**

Reprinted from the Bulletin of Informatics and Cybernetics
Research Association of Statistical Sciences, Vol.55, No. 3

FUKUOKA, JAPAN
2023

Bulletin of Informatics and Cybernetics, Vol. 55, No. 3, 2023

REPRESENTING THE RESULTS OF SUBGROUP ANALYSIS IN COMPARATIVE CLINICAL STUDIES BY A GRAPH

By

Nanami Taketomi[*], **Takashi Yanagawa**[†] and **Kenta Murotani**[‡]

Abstract

Subgroup analysis is an exploratory analysis often conducted with the expectation of providing useful information to establish new research hypotheses in medicine. However, use of subgroup analysis is currently limited, as the number of subgroups is often small, and thus subgroups are selected arbitrarily and typically deviate from subgroups in which the readers of a paper are interested in. In this study, we propose a method for representing the results of subgroup analysis in graphical form by focusing on a comparative clinical study of treatment versus control groups, with survival time as the primary endpoint, and in which subgroups are created by dividing the range of continuous biomarkers. This method unifies and strengthens fragmented data, enabling findings obtained in each subgroup by assuming the Cox proportional hazard model. Moreover, this method renders it possible to obtain information about any subgroup that an outside researcher is interested in.

Key Words and Phrases: comparative clinical study, confidence interval, Cox proportional hazards model, hazard ratio, subgroup.

1. Introduction

Subgroup analysis is often conducted in a comparative clinical study of the treatment group versus the control group in phases 2 or 3, and with a typically small sample size. The subgroup analysis is conducted by dividing the total sample size for the main study into subgroups; thus, the number of subgroups is limited, and the size of each subgroup is not sufficient to statistically appreciate the results obtained in each subgroup. Subgroup analyses have been criticized in the field of statistics [Assmann et al. (2000), Guillemin (2007), Harrington et al. (2019), Moyé and Deswal (2001), Priebe (2020)].

Subgroup analyses are commonly used in medicine. It is an exploratory analysis and is anticipated to provide medical researchers with valuable information in establishing research hypotheses for their new clinical studies. It is often conducted to check whether the treatment group is favored for each subgroup, when the treatment group favors the

[*] Department of Biostatistics, Graduate School of Medicine, Kurume University, 67 Asahi-machi, Kurume-city, Fukuoka, 830-0003, Japan. TEL +81–942–31–7835 nnmamikrn@gmail.com

[†] Biostatistics Center, Kurume University, 67 Asahi-machi, Kurume-city, Fukuoka, 830-0003, Japan. TEL +81–942–31–7835

[‡] Biostatistics Center, Kurume University, 67 Asahi-machi, Kurume-city, Fukuoka, 830-0003, Japan. TEL +81–942–31–7835

entire population [Sun et al. (2012), Thompson and Higgins (2002), White and Elbourne (2005)]. In addition, it is used to search for populations with more (or less) favorable effects. Guidelines for conducting appropriate subgroup analyses have been previously published [Harrington et al. (2019), European Medicines Agency (Accessed: 2021–07–27)].

The results of subgroup analysis are usually available from the published papers, clinical study reports and so on. If the original data is available, it is possible to assess the result not only in the subgroups that are published but also in any subgroup that researchers are interested in. However, in general, not anyone is accessible to the original data which was used for subgroup analysis. Therefore, researchers can only guess the result in any subgroup by the published results. The methods for assessing the result in such subgroups have not been established and discussed.

In this paper, we focus on a comparative clinical study of the treatment group versus the control group with survival time as the primary endpoint, in which subgroups are created by dividing the range of continuous biomarker. In particular, we focused on the subgroup analysis conducted for the purpose of screening certain cancer patients who could benefit from anti-PD-L1 immunotherapy, where programmed death-ligand 1 (PD-L1) expression level is used as a biomarker. We suppose that the number of subgroups was ≥ 2, and the sample size, value of the hazard ratio (HR), and 95% confidence interval (CI) are summarized for each subgroup; the HRs and CIs were computed under the assumption of the Cox proportional hazard model.

We developed a method to unify and strengthen the fragmented and weak findings in each subgroup, to represent them in a simple graph (see Fig 1, 2, and 3 below), and to make it possible to obtain information about the HR and its CI for any subgroup in which an outside researcher is interested in.

2. Materials and methods

2.1. Patients and ethical considerations

The data used for the application of the methods proposed in this paper are summarized in tables in published papers; thus, no ethical considerations are provided.

2.2. Mathematical development

Suppose that in a published paper, there are k ($k \geqslant 2$) subgroups and the i-th subgroup is created by collecting individuals in the treatment and control groups whose value of the biomarker is between b_i and b_{i+1}, which we call the subgroup B_i, $i = 1, \cdots, k$, throughout this paper. We assume that subgroups are not overlapped; that is, individuals that simultaneously belong to several subgroups do not exist.

We assume that sample size, the value of HR and its CI have been given in subgroup B_i and we denote them by n_i, hr_i, and $[l_i, u_i]$, respectively.

We assume the following Cox proportional hazard model.

$$\ln \frac{\lambda(t|z,x)}{\lambda_0(t)} = \alpha_1 z + \alpha_2 x + \alpha_3 zx,$$

where t is the time to event, $z = 1(0)$ if the treatment group (the control group), x is a value of the biomarker, $\lambda_0(t)$ is the baseline hazard function, α_1, α_2 and α_3 are

unknown parameters. Then, the log HR of treatment group relative to control group at x, say $\beta(x)$, may be represented by

$$\beta(x) = \ln \frac{\lambda(t|z=1,x)}{\lambda(t|z=0,x)} = \alpha_1 + \alpha_3 x. \tag{1}$$

In the following sections, we try to assess the value and the CI of HR at any value of x based on n_i, hr_i, $[l_i, u_i]$, and Eq.(1).

2.2.1. Assessing the value of HR at any value of the biomarker

Let HR_i be a random variable that corresponds to the given value of HR in subgroup B_i and approximate the mean of $\ln HR_i$ by $\beta(x_i)$, where x_i is the midpoint of the interval (b_i, b_{i+1}), i.e., $x_i = (b_i + b_{i+1})/2$. Then, since $\ln HR_i$ follows approximately the asymptotic normal distribution with mean $\beta(x_i)$ and variance σ_i^2/n_i [Fleming and Harrington (2005)], we may reasonably represent $\ln HR_i$ by

$$\ln HR_i = \beta(x_i) + \varepsilon_i = \alpha_1 + \alpha_3 x_i + \varepsilon_i,$$

where ε_i is the error that satisfies $E[\varepsilon_i] = 0$, $V[\varepsilon_i] = \sigma_i^2/n_i$, and σ_i is the unknown positive parameter. Assuming $\sigma_1 = \cdots = \sigma_k$, the estimates of α_1 and α_3 are obtained by minimizing the weighted squared errors $\sum_{i=1}^k n_i \{\ln HR_i - \beta(x_i)\}^2$ as follows:

$$\hat{\alpha}_1 = \overline{\ln HR} - \tilde{x}\hat{\alpha}_3, \quad \hat{\alpha}_3 = \frac{\sum_{i=1}^k n_i (x_i - \tilde{x}) \left(\ln HR_i - \overline{\ln HR}\right)}{\sum_{i=1}^k n_i (x_i - \tilde{x})^2} \tag{2}$$

when $k \geqslant 2$, where n_i is the sum of sample sizes of treatment group and control group in B_i, $\tilde{x} = \sum_{i=1}^k n_i x_i / \sum_{i=1}^k n_i$, and $\overline{\ln HR} = \sum_{i=1}^k n_i \ln HR_i / \sum_{i=1}^k n_i$.

Let $HR(x)$ be the true value of HR at any x. Using these $\hat{\alpha}_1$ and $\hat{\alpha}_3$ we propose to assess the value of $\ln HR$ at any x, say $\ln HR(x)$, by

$$\ln \widehat{HR}(x) = \hat{\alpha}_1 + \hat{\alpha}_3 x.$$

The mean of $\ln \widehat{HR}(x)$ is given by

$$E\left[\ln \widehat{HR}(x)\right] = \ln HR(x).$$

Finally, we propose to assess the value of $HR(x)$ by

$$\widehat{HR}(x) = \exp\left(\hat{\alpha}_1 + \hat{\alpha}_3 x\right). \tag{3}$$

The simulation below ensures the accuracy of assessing the true $HR(x)$ by $\widehat{HR}(x)$, even when $k = 2$, provided that the Cox proportional hazard model fits to the data, although its variance tends to be large when k is small, as will be shown in the next section.

2.2.2. Assessing CI

In this section, we first derive the variance of $\ln \widehat{HR}(x)$. Then, we propose a method for assessing the CI of HR at any value of the biomarker.

Assuming $\sigma^2 = \sigma_1^2 = \cdots = \sigma_k^2$, the variance of $\ln \widehat{HR}(x)$ may be approximated by

$$V\left[\ln \widehat{HR}(x)\right] \approx \left\{ \frac{1}{\sum_{i=1}^k n_i} + \frac{(x-\tilde{x})^2}{\sum_{i=1}^k n_i (x_i - \tilde{x})^2} \right\} \sigma^2. \tag{4}$$

Then, the $100\,(1-\alpha)\%$ CI of $\ln HR(x)$ is approximately given by

$$\left[\ln \widehat{HR}(x) - z_{\alpha/2} \sqrt{V(\ln \widehat{HR}(x))}, \qquad \ln \widehat{HR}(x) + z_{\alpha/2} \sqrt{V(\ln \widehat{HR}(x))} \right],$$

where z_α is the upper $100\,(1-\alpha)\%$ percentile of the standardized normal distribution. From this interval, the $100\,(1-\alpha)\%$ approximate CI of $HR(x)$ is obtained by

$$\left[\widehat{HR}(x) \Big/ \exp\left(z_{\alpha/2} \sqrt{V(\ln \widehat{HR}(x))} \right), \quad \widehat{HR}(x) \exp\left(z_{\alpha/2} \sqrt{V(\ln \widehat{HR}(x))} \right] . \right.$$

Unknown σ is involved in this CI, which may be assessed as follows. Since the $100(1-\alpha)\%$ CI of $\beta(x_i)$ is given by $\left[\ln HR_i - z_{\alpha/2}\sigma_i \Big/ \sqrt{n_i}\,, \ln HR_i + z_{\alpha/2}\sigma_i \Big/ \sqrt{n_i} \right]$ and furthermore the CI of HR_i, $[\ell_i, u_i]$, is supposed to have been given in subgroup B_i. Thus, we may identify

$$\ln \ell_i = \ln HR_i - z_{\alpha/2} \frac{\sigma_i}{\sqrt{n_i}}, \qquad \ln u_i = \ln HR_i + z_{\alpha/2} \frac{\sigma_i}{\sqrt{n_i}}.$$

From this we may get

$$\sigma_i = \sqrt{n_i} \left(\frac{\ln u_i - \ln \ell_i}{2 z_{\alpha/2}} \right).$$

Since $\sigma = \sigma_i$ is assumed for $i = 1, \cdots, k$, we propose to assess σ by

$$\hat{\sigma} = \frac{1}{k} \sum_{i=1}^k \sigma_i = \frac{1}{k} \sum_{i=1}^k \sqrt{n_i} \left(\frac{\ln u_i - \ln \ell_i}{2 z_{\alpha/2}} \right). \tag{5}$$

Therefore, we propose to assess the $100\,(1-\alpha)\,\%$ confidence interval of $\ln HR\,(x)$ by

$$\left[\widehat{HR}\,(x) \Big/ \exp\left(z_{\alpha/2} \sqrt{\widehat{V}\left(\ln \widehat{HR}\,(x) \right)} \right), \quad \widehat{HR}\,(x) \exp\left(z_{\alpha/2} \sqrt{\widehat{V}\left(\ln \widehat{HR}\,(x) \right)} \right) \right],$$

where $\widehat{V}\left[\ln HR\,(x)\right]$ is the estimates of $V\left[\ln HR\,(x)\right]$ that $\hat{\sigma}$ was pluged into σ.

2.2.3. HR and CI in a new subgroup

It is often the case that the subgroups analyzed in published papers are not those in which researchers planning new studies are interested in. Suppose that the marker levels of the subgroup in which the researcher is interested in are from a to b, we may assess the value of HR in the subgroup by

$$\widehat{HR}\,(a,b) = \exp\left(\int_a^b \log \widehat{HR}(x) f(x) dx\right),$$

where $\widehat{HR}(x)$ is given in Eq.(3) and $f(x)$ is a probability density function of X. Setting $f(x)$ a uniform distribution over (a,b), it follows that

$$\widehat{HR}\,(a,b) = \widehat{HR}\left(\frac{a+b}{2}\right). \tag{6}$$

Let n be the sample size to be taken in the new subgroup (a,b). We propose to assess the value of HR in the new subgroup by Eq.(6), then the upper and the lower CI of the HR in the subgroup (a,b) are given by

$$\left[\widehat{HR}(x^*)\,/\exp\left(z_{\alpha/2}\hat{\sigma}/\sqrt{n}\right),\quad \widehat{HR}(x^*)\exp\left(z_{\alpha/2}\hat{\sigma}/\sqrt{n}\right)\right],$$

where $\hat{\sigma}$ is given in Eq.(5) and $x^* = (a+b)/2$.

3. Results

We analyzed two datasets to illustrate the proposed method in real results of subgroup analysis.

3.1. Application of the proposed method when $k = 2$

We applied the proposed method to the results of subgroup analysis from Hellmann et al. (2019). They compared the overall survival between Nivolumab plus ipilimumab and a chemotherapy in a phase 3 randomized controlled trial. One of the goals is to explore the effect of the treatment in the subgroups of the PD-L1 expression level. Table 1 shows a part of the results of the exploratory subgroup analysis. In Table 1, the number of subgroups is two; the first subgroup is composed of PD-L1 expression levels 1-49% whose upper CI of HR exceeds 1 and the second subgroup is composed of PD-L1 expression levels $\geqslant 50\%$ whose upper CI is less than 1.

Table 1: Result of the exploratory subgroup analysis with respect to PD-L1 expression levels in nivolumab plus ipilimumab vs. chemotherapy. The result was copied from Hellmann et al. (2019).

Additional exploratory subgroup analysis	n	HR for death (CI)
PD-L1 expression level 1-49%	396	0.94 [0.75, 1.18]
PD-L1 expression level $\geqslant$50%	397	0.70 [0.55, 0.90]

After applying the proposed method, we obtained $\hat{\alpha}_1 = 0.086$, $\hat{\alpha}_3 = -0.590$, $\hat{\sigma} = 2.032$ and Fig 1 that shows the $HR(x)$ and its CI over the entire range of PD-L1 expression.

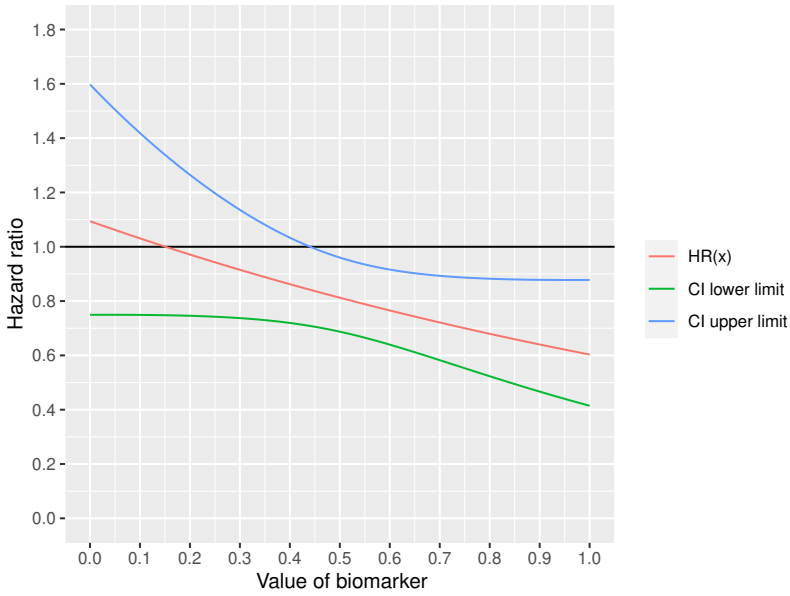

Figure 1: $HR(x)$ and its 95% CI assessed from Table 1.

The subgroups in Table 1 are crude and could fail to respond to questions from researchers, such as the value of the PD-L1 expression level whose 95% upper CI of $HR(x)$ crosses $HR\,(x) = 1$ (Q_1), or what would be the values of HR and its CI in the new subgroup made by the PD-L1 expression level from a to b (Q_2). We may answer to Q_1 and Q_2 as follows;

Q_1: The answer to Q_1 is immediately obtained as about 44% by the inspection of Fig 1.

Q_2: Suppose that a new subgroup is given by the PD-L1 expression level from 40% to 80% and $n = 350$, then we have $\hat{\sigma} = 2.402$, and HR and CI in the subgroup are assessed to be $\widehat{HR} = 0.765$, and 95%CI= $[0.595, 0.984]$ by the proposed methods.

3.1.1. Application of the proposed method when $k > 2$

We applied the proposed method to the results of subgroup analysis from Borghaei et al. (2015). They compared the overall survival between Nivolumab and Docetaxel in the phase 3 trial. One of the goals is to explore the treatment effect in the subgroups of PD-L1 expression level.

Table 2 summarizes the results of the subgroup analysis of the clinical trial that compared Nivolumab vs. Docetaxel for lung cancer, in which PD-L1 expression levels were used to establish the subgroups. This table is a copy of the table published on the European Medicines Agency website (European Medicines Agency, 2015) [12]. Five subgroups are given in the table; however, one subgroup, subgroup SG_2, is overlapped with subgroups SG_i, $i = 3, 4, 5$. Since no overlap is assumed among subgroups in the proposed methods, we apply first the methods to subgroups, SG_1, SG_3, SG_4 and SG_5,

excluding SG_2, then to subgroups SG_1 and SG_2. Note that, although the value of HR in SG_3 is outstandingly large from the values of HR in the other subgroups, we include it in the analysis since it is the value obtained from 81 patients.

Table 2: Overall survival hazard ratio in subgroups of PD-L1 expression levels.*

Subgroup	PD-L1 expression level	events (sample size) Nivolumab	Docetaxel	HR	95%CI
SG_1	$< 1\%$	77 (108)	75 (101)	0.90	$[0.66, 1.24]$
SG_2	$\geqslant 1\%$	68 (123)	93 (123)	0.59	$[0.43, 0.82]$
SG_3	$\geqslant 1\%$ and $<10\%$	27 (37)	30 (44)	1.33	$[0.79, 2.24]$
SG_4	$\geqslant 10\%$ and $<50\%$	11 (20)	26 (33)	0.61	$[0.30, 1.23]$
SG_5	$\geqslant 50\%$	30 (66)	37 (46)	0.32	$[0.20, 0.53]$

* Copy of the table from Hellmann et al. [11].

When we apply the proposed method to subgroups SG_1, SG_3, SG_4 and SG_5, we obtain $\hat{\alpha}_1 = 0.020$, $\hat{\alpha}_3 = -1.537$, $\hat{\sigma} = 2.493$, and Fig 2; and when we apply the method to $SG1$ and SG_2, we obtain $\hat{\alpha}_1 = -0.101$, $\hat{\alpha}_3 = -0.845$, $\hat{\sigma} = 2.454$, and Fig 3.

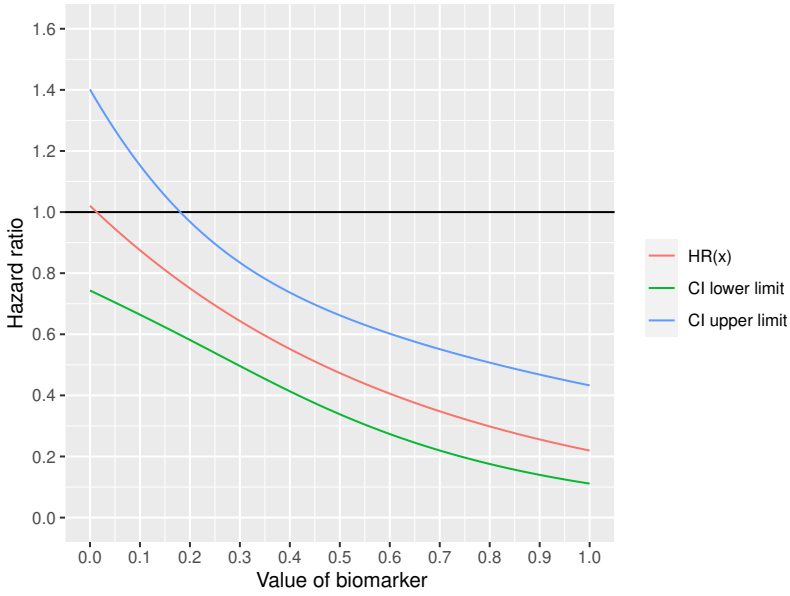

Figure 2: $HR(x)$ and its 95% CI: obtained from SG_1, SG_3, SG_4 and SG_5

Inspection of the figures shows shapes of $HR(x)$ over the whole range of x in Fig 2 and 3 are fairly close, but the 95% CI in Fig 3 is wider than that in Fig 2, in particular, when x is away $\tilde{x}$. Nevertheless, the values of the PD-L1 expression levels whose value of the upper CI crosses 1 is not far from each other, namely 0.18 in Fig 2 and 0.03 in Fig 3. These findings would indicate that the proposed method works fairly well in practice, even when the number of subgroups is only two.

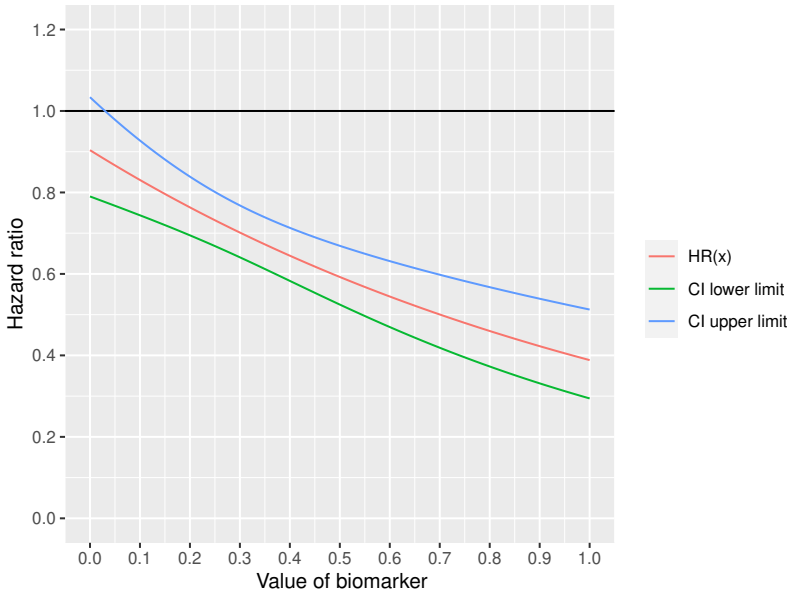

Figure 3: $HR(x)$ and its 95% CI: obtained from SG_1 and SG_2

Comparing between Fig 1, Fig 2, and Fig 3, in which the numbers of subgroups is two, the CI in Fig 3 is much wider than that in Fig 1. This is because the sample sizes of the subgroups in Fig 3 are approximately 1/5 of those sizes in Fig 1.

4. Simulation

The Monte Carlo simulation was conducted to verify the validity of the proposed method by assigning subgroups, sample sizes, and underlying distributions. The four simulation scenarios are presented in Table 3; the number of subgroups in all scenarios is two, and the ranges, the midpoint x_i^*, and the sample sizes n_i of the subgroup are identical in scenario A, B, C, and D except for σ_i $(i = 1, 2)$. The ranges of the subgroups of the scenarios are at one end, i.e., (0, 0.1) and (0.1, 0.3).

We set $\beta(x) = 0.1 - 1.5x$. We generated $\ln HR_i \sim N\left(\beta\left(x_i^*\right), \sigma_i^2/n_i\right)$ $(i = 1, 2)$ in each scenario given in Table 3. The parameters α_1 and α_3 were assessed based on Eq. (2). We calculated $\widehat{HR}(x_0)$ for $x_0 = 0.1, 0.2, \cdots, 0.9$.

Let $\widehat{HR}(x_0)_j$ be the assessed value of $\widehat{HR}(x_0)$ in the j-th repetition $(j = 1, \cdots, 500)$. We computed the Monte Carlo average of $\widehat{HR}(x_0)_1, \cdots, \widehat{HR}(x_0)_{500}$ for each x_0.

Figure 4 presents the Monte Carlo average values in the four scenarios and the true value of $HR(x_0)$. The inspection of the figure shows that

(i) the curves of scenarios A, B, and C are close to the true curve, meaning that the proposed method assesses well the values of the true HR even if the given number of subgroups are two, lean to the smallest side of the PD-L1 expression levels, and the assumption of equal standard deviations (s.d.) is violated a little, i.e., less than $\sigma_1 = 1$ vs. $\sigma_2 = 4$,

Table 3: The four scenarios in the simulation.

Scenarios	Subgroup i	Subgroup ranges	n_i	x_i^*	σ_i
A	1	$(0, 0.1)$	160	0.05	1
	2	$(0.1, 0.3)$	40	0.2	1
B	1	$(0, 0.1)$	160	0.05	1
	2	$(0.1, 0.3)$	40	0.2	2
C	1	$(0, 0.1)$	160	0.05	1
	2	$(0.1, 0.3)$	40	0.2	4
D	1	$(0, 0.1)$	160	0.05	1
	2	$(0.1, 0.3)$	40	0.2	10

(ii) and furthermore, the curve of scenario D shows that if the assumption of equal s.d. is violated large, i.e., $\sigma_1 = 1$ vs. $\sigma_2 = 10$, the proposed method is valid even if the ranges of subgroups are at the one end of the PD-L1 expression level, indicating that the proposed method is robust against the violation of equal s.d. assumption if the number of subgroups is increased ($k > 2$).

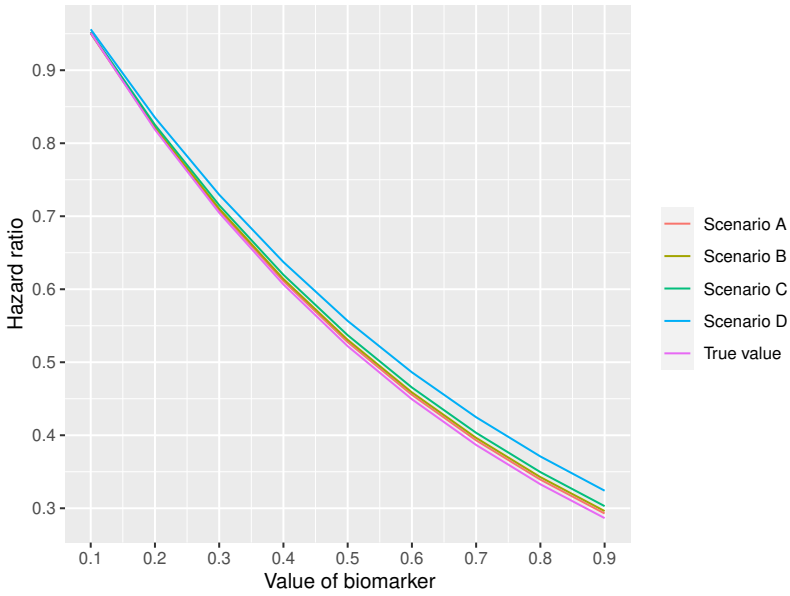

Figure 4: The Monte Carlo average of the assessed hazard ratios in the four scenarios and the true value of hazard ratio

5. Discussion

A wide variety of subgroup analyses were performed for various subqroups. Among them, the focus of this paper is subgroups that are made by dividing the range of

continuous biomarkers, such as PD-L1 expression, which is often used in cancer clinical trials to examine the effect of immunotherapy. The purpose of subgroup analyses in these studies is to explore the level of PD-L1 expression that could benefit patients from anti-PD-L1 immunotherapy. Examining Fig 1 to Fig 3, it is clear that the proposed method enables this purpose better than reporting the findings in fragmented tables in each subgroup. Furthermore, the subgroups in published papers are often made arbitrarily, but the proposed methods can liberate this arbitrariness.

One may fear over-interpretation of graphs, but the simulation shows that this would not be the case as long as the Cox proportional hazard model fits well with the data. The majority of papers on comparative cancer clinical studies of treatment vs. control groups, and with survival time as the primary endpoint, tend to apply the log rank tests or the stratified log rank test for statistical analysis using this assumption of the Cox proportional hazard model.

6. Conclusion

Using graphs is a modern research approach that offers holistic and visual perspectives of results, compared to the use of tables. In particular, it is effective in the case of subgroup analysis in which the number of subgroups is limited and the size of the subgroup is small. From the graph, We can also assess the values of HR and its CI for any subgroup that researchers are interested in. We hope that the proposed method can become a standard tool for representing the results of subgroup analyses in the future.

Acknowledgement

We thank the editors and the reviewers for their insightful comments on our paper. Nanami Taketomi was partly supported by grant from Kurume University for the Promotion of female researcher. Comments from the audience helped improve the article.

References

Assmann SF, Pocock SJ, Enos LE and Kasten LE (2000). Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet*. 355(9209): 1064–1069.

Guillemin F (2007). Primer: the fallacy of subgroup analysis. *Nature Clinical Practice Rheumatology*. 3: 407–413.

Harrington D, D'Agostino Sr RB, Gatsonis C, Hogan JW, Hunter DJ et al. (2019). New guidelines for statistical reporting in the journal. *New England Journal of Medicine*. 381(3): 285–286.

Moyé LA and Deswal A (2001). Trials within trials: Confirmatory subgroup analyses in controlled clinical experiments. *Controlled Clinical Trials*. 22(6): 605–619.

Priebe HJ (2020). Problems of subgroup analysis in randomized controlled trial. *BMC Anesthesiology*. 20: 186.

Sun X, Briel M, Busse JW, You JJ, Akl EA, Mejza F, Bala MM et al. (2012). Credibility of claims of subgroup effects in randomised controlled trials: systematic review. *BMJ*. 344: e1553.

Thompson SG and Higgins JPT (2002). How should meta-regression analyses be undertaken and interpreted?. *Statistics in Medicine*. 21(11): 1559–1573.

White, IR and Elbourne, D. (2005). Assessing subgroup effects with binary data: can the use of different effect measures lead to different conclusions?. *BMC Medical Research Methodology*. 5: 15.

European Medicines Agency (Accessed: 2021–07–27). *Guideline on the investigation of subgroups in confirmatory clinical trials*. https://www.ema.europa.eu/en/investigation-subgroups-confirmatory-clinical-trials.

Fleming TR and Harrington DP. (2005). *Counting Processes and Survival Analysis*. John Wiley & Sons.

Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW et al. (2019). Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. *New England Journal of Medicine*. 38: 2021–2031.

European Medicines Agency (Accessed: 2019–11–13). Opdivo : Epar - product information. https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo.

Received: November 13, 2023
Revised: December 11, 2023
Accept: December 11, 2023

REPRESENTING THE RESULTS OF SUBGROUP ANALYSIS IN COMPARATIVE CLINICAL STUDIES BY A GRAPH

Taketomi, Nanami
Department of Biostatistics, Graduate School of Medicine, Kurume University

Yanagawa, Takashi
Biostatistics Center, Kurume University

Murotani, Kenta
Biostatistics Center, Kurume University

出版情報：Bulletin of informatics and cybernetics. 55(3), pp.1-11, 2023. 統計科学研究会
https://doi.org/10.5109/7160659