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Cutoff Value for Wilcoxon-Mann-Whitney Test by Minimum *P*-value: Application to COVID-19 Data

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Abstract

Dependent and independent variables may appear uncorrelated when analyzed in full range in medical data. However, when an independent variable is divided by the cutoff value, the dependent and independent variables may become correlated in each group. Furthermore, researchers often convert independent variables of quantitative data into binary data by cutoff value and perform statistical analysis with the data. Therefore, it is important to select the optimum cutoff value since performing statistical analysis depends on the cutoff value. Our study determines the optimal cutoff value when the data of dependent and independent variables are quantitative. The piecewise linear regression analysis divides an independent variable into two by the cutoff value, and linear regression analysis is performed in each group. However, the piecewise linear regression analysis may not obtain the optimal cutoff value when data follow a non-normal distribution. Unfortunately, medical data often follows a non-normal distribution. We, therefore, performed the Wilcoxon-Mann-Whitney (WMW) test with two-sided for all potential cutoff values and adopted the cutoff value that minimizes the *P*-value (called minimum *P*-value approach). Calculating the cutoff value using the minimum *P*-value approach is often used in the log-rank and chi-squared test but not the WMW test. First, using Monte Carlo simulations at various settings, we verified the performance of the cutoff value for the WMW test by the minimum *P*-value approach. Then, COVID-19 data were analyzed to demonstrate the practical applicability of the cutoff value.

Keywords: COVID-19 data, cutoff value, minimum *P*-value approach, non-normal distribution, quantitative data, Wilcoxon-Mann-Whitney test

1. Introduction

The clarified relationship between dependent and independent variables in the medical field can result in optimal patient treatment. These variables may appear uncorrelated when analyzed in the full range. However, when an independent variable is divided by the cutoff value, dependent and independent variables may become correlated in each group. Since the performance of the statistical analysis depends on the cutoff value, selecting the optimum cutoff value is important. The receiver operating characteristic curve is a recognized method for predicting the dependent variable of binary data from the independent variable of quantitative data (Greiner, Pfeiffer, & Smith, 2000; Zou, O'Malley, & Mauri, 2007). The linear regression analysis often predicts the outcome when both dependent and independent variables are quantitative data and show a linear relationship (Shiraishi, Matsuda, Ogura, & Iwamoto, 2021). Although medical data may not be a linear relationship when analyzed in a full range of independent variables, it may possess a linear relationship in each group when an independent variable is divided and grouped into two. The piecewise linear regression analysis is recognized method for predicting the outcome from such data (Nakamura, 1986; Vieth, 1989). However, when the data follow a non-normal distribution, the piecewise linear regression analysis may not obtain the optimal cutoff value.

First reported in Wuhan, China, COVID-19 patients have spread worldwide (World Health Organization, 2020, 2021). Many clinical trials are conducted to discover an effective treatment for COVID-19 patients (Capra et al, 2020; Hogan II et al., 2020; Aiswarya et al., 2021). Using Supplementary data of Hogan II et al. (2020), we investigated the relationship between the age and days to discharge in COVID-19 data. The data of the days to discharge were considered to follow a non-normal distribution. We then searched for the optimum cutoff value in this situation. We perform the Wilcoxon-Mann-Whitney (WMW) test with two-sided for all potential cutoff values and adopted the cutoff value that minimizes the *P*-value (called minimum *P*-value approach). Calculating the cutoff value using the minimum *P*-value approach showed excellent results in the log-rank and chi-squared tests (Altman, Lausen, Sauerbrei, & Schumacher, 1994; Mazumdar & Glassman, 2000; Liu et al., 2020) but not the WMW test. First, using Monte Carlo simulations (MCSs) at various settings, we verified the performance of the cutoff value for the WMW test by the minimum *P*-value approach. Then, COVID-19 data were analyzed to demonstrate the practical applicability of the cutoff value.

In Section 2, we described the cutoff value for the WMW test by the minimum P-value approach, while Section 3 verified the performance of the cutoff value using MCSs. Additionally, in Section 4, we presented an attempt to calculate the cutoff value using COVID-19 data and finally concluded conclude the research in Section 5.

2. Cutoff Value by Minimum P-Value Approach

Let $(\boldsymbol{x}, \boldsymbol{y}) = \{(x_1, y_1), \ldots, (x_n, y_n)\}$ be two-dimensional random vectors of sample size $n \geq 2$, where $\boldsymbol{x}$ and $\boldsymbol{y}$ are independent and dependent variables, respectively. Let $x_{(i)}$ denote the i-th order statistics, $x_{(1)} \leq \cdots \leq x_{(n)}$. The potential cutoff value is written as $c_{(j)} = (x_{(j)} + x_{(j+1)})/2$, $j = 1, \ldots, n-1$. The data are divided into two groups: $\{(x_{(1)}, y_{(1)}), \ldots, (x_{(j)}, y_{(j)})\}$ and $\{(x_{(j+1)}, y_{(j+1)}), \ldots, (x_{(n)}, y_{(n)})\}$, depending on whether $x_{(i)} < c_{(j)}$ or $x_{(i)} \geq c_{(j)}$, where $y_{(i)}$ is the data paired with $x_{(i)}$ ($y_{(i)}$ is not the order statistic of y_i). We performed the WMW test between $\{y_{(1)}, \ldots, y_{(j)}\}$ and $\{y_{(j+1)}, \ldots, y_{(n)}\}$ in sequence from $j = 1$ to $n - 1$, and the P-value was written as $\{P_{(1)}, \ldots, P_{(n-1)}\}$. The optimal cutoff value was $c = c^{\min}_{(j)}$ corresponding to $P^{\min}_{(j)} = \min(P_{(1)}, \ldots, P_{(n-1)})$. Since there is almost no advantage of dividing by the cutoff value when the sample size of one group is small, we used the cutoff value where each group has five or more patients in this manuscript.

3. MCSs

We verified the effectiveness of the cutoff value using MCSs. The population cutoff value was set to 50. In Patterns 1–9, $\{x_1, \ldots, x_n\}$ were generated from a normal distribution $\mathrm{N}(\mu, \sigma^2)$ and $\{y_1, \ldots, y_n\}$ were generated from a three-parameter gamma distribution $\mathrm{Ga}(\alpha, \beta, \gamma)$, where μ, σ^2, α, β, and γ are the mean, variance, shape, scale, and location parameters, respectively. In Patterns 10–18, both $\{x_1, \ldots, x_n\}$ and $\{y_1, \ldots, y_n\}$ were generated from $\mathrm{Ga}(\alpha, \beta, \gamma)$. Also, the parameters of $\mathrm{Ga}(\alpha, \beta, \gamma)$ where y_i were generated and differed depending on whether $x_i < 50$ or $x_i \geq 50$. Our simulation settings are summarized in Table 1. Although data are expected to be heavily biased in the cases of x_i generated from $\mathrm{N}(40, 10^2)$ and $\mathrm{N}(60, 10^2)$, it is necessary to have high estimation accuracy of the cutoff value even in such settings. The sample size is set to $n = 50, 100, 150$. We used the cutoff value where the sample size of one group is at least 5. The replication size used in this study is 1 000 000. We used the software R version 4.1.1 (R core team, 2021) for the MCSs. The MCS was conducted using the following procedure:

1. Generate random samples $\{x_1, \ldots, x_n\}$ from distribution in Table 1.
2. Generate random samples $\{y_1, \ldots, y_n\}$ from distribution in Table 1 (The distribution used depends on whether $x_i < 50$ or $x_i \geq 50$).
3. Combine $\{x_1, \ldots, x_n\}$ and $\{y_1, \ldots, y_n\}$ into two-dimensional random vectors $(\boldsymbol{x}, \boldsymbol{y}) = \{(x_1, y_1), \ldots, (x_n, y_n)\}$.
4. Sort $\{x_1, \ldots, x_n\}$ in ascending order, $x_{(1)} \leq \cdots \leq x_{(n)}$.
5. Set potential cutoff value $c_{(j)} = (x_{(j)} + x_{(j+1)})/2$, $j = 5, \ldots, (n-5)$.
6. Divide into two groups, $\{(x_{(1)}, y_{(1)}), \ldots, (x_{(j)}, y_{(j)})\}$ and $\{(x_{(j+1)}, y_{(j+1)}), \ldots, (x_{(n)}, y_{(n)})\}$, depending on whether $x_{(i)} < c_{(j)}$ or $x_{(i)} \geq c_{(j)}$.
7. Perform the WMW test between two groups for each $c_{(j)}$ and express the P-value as $P_{(j)}$.
8. Repeat steps 5–7 from $j = 5$ to $n - 5$.
9. Decide optimal cutoff value $c = c^{\min}_{(j)}$ that satisfies $P^{\min}_{(j)} = \min(P_{(5)}, \ldots, P_{(n-5)})$.
10. Independently, repeat steps 1–9 1 000 000 times.
11. Calculate summary statistics and proportion of cutoff value in range.

Table 1. Distributions of generating random samples of x and y in MCSs

Pattern	x	y ($x_i < 50$)	y ($x_i \geq 50$)	Pattern	x	y ($x_i < 50$)	y ($x_i \geq 50$)
1	$\mathrm{N}(40, 10^2)$	Ga(1.5,10,10)	Ga(2.5,10,10)	10	Ga(1.5,10,30)	Ga(1.5,10,10)	Ga(2.5,10,10)
2	$\mathrm{N}(50, 10^2)$	Ga(1.5,10,10)	Ga(2.5,10,10)	11	Ga(1.5,10,35)	Ga(1.5,10,10)	Ga(2.5,10,10)
3	$\mathrm{N}(60, 10^2)$	Ga(1.5,10,10)	Ga(2.5,10,10)	12	Ga(1.5,10,40)	Ga(1.5,10,10)	Ga(2.5,10,10)
4	$\mathrm{N}(40, 10^2)$	Ga(1.5,10,10)	Ga(1.5,15,15)	13	Ga(1.5,10,30)	Ga(1.5,10,10)	Ga(1.5,15,15)
5	$\mathrm{N}(50, 10^2)$	Ga(1.5,10,10)	Ga(1.5,15,15)	14	Ga(1.5,10,35)	Ga(1.5,10,10)	Ga(1.5,15,15)
6	$\mathrm{N}(60, 10^2)$	Ga(1.5,10,10)	Ga(1.5,15,15)	15	Ga(1.5,10,40)	Ga(1.5,10,10)	Ga(1.5,15,15)
7	$\mathrm{N}(40, 10^2)$	Ga(1.5,10,10)	Ga(1.5,10,20)	16	Ga(1.5,10,30)	Ga(1.5,10,10)	Ga(1.5,10,20)
8	$\mathrm{N}(50, 10^2)$	Ga(1.5,10,10)	Ga(1.5,10,20)	17	Ga(1.5,10,35)	Ga(1.5,10,10)	Ga(1.5,10,20)
9	$\mathrm{N}(60, 10^2)$	Ga(1.5,10,10)	Ga(1.5,10,20)	18	Ga(1.5,10,40)	Ga(1.5,10,10)	Ga(1.5,10,20)

We use the cutoff values calculated by the Student's t-test and Welch's t-test for comparison in this manuscript. They were obtained by changing the WMW test in step 7 of the MCS procedure to the Student's t-test and Welch's t-test. Tables 2–4 show the summary statistics (mean, standard deviation (SD), first quartile (Q1), median, and third quartile (Q3)) for the cutoff value and the proportion of the cutoff value that fall into five ranges ($49 \leq c \leq 51$, $48 \leq c \leq 52$, $47 \leq c \leq 53$, $46 \leq c \leq 54$, and $45 \leq c \leq 55$). Within the five ranges set, the proportion of cutoff value calculated by the WMW test was the highest of the three tests, except for Patterns 1, 3, 4, and 6 at $n = 50$.

Table 2. Summary of cutoff values in MCSs ($n = 50$)

		Summary statistics					Proportion of cutoff value in range				
Pattern		Mean	SD	Q1	Median	Q3	49-51	48-52	47-53	46-54	45-55
1	WMW	44.845	7.432	40.675	47.912	50.083	27.2%	41.6%	51.2%	57.9%	62.8%
	Student's	45.442	7.581	41.392	48.658	50.567	27.1%	42.3%	52.6%	59.7%	64.8%
	Welch's	41.310	8.553	33.518	43.026	49.221	17.7%	27.4%	34.3%	39.5%	43.6%
2	WMW	49.794	4.620	48.121	49.941	51.489	37.4%	54.5%	65.2%	72.6%	78.2%
	Student's	50.899	4.999	48.920	50.368	52.953	33.7%	50.0%	60.7%	68.4%	74.2%
	Welch's	47.817	5.682	44.235	49.085	50.658	29.2%	43.2%	52.5%	59.3%	64.9%
3	WMW	54.925	7.451	49.792	51.817	58.974	27.5%	42.3%	52.2%	59.0%	63.9%
	Student's	56.305	7.714	50.246	53.455	61.661	22.8%	35.5%	44.4%	50.9%	55.9%
	Welch's	54.461	7.446	49.684	51.540	57.377	27.0%	42.7%	53.8%	61.6%	67.1%
4	WMW	45.660	6.938	42.961	48.545	50.150	31.6%	47.2%	57.1%	63.8%	68.6%
	Student's	46.635	6.967	44.581	49.441	50.829	32.1%	48.9%	59.7%	67.0%	72.0%
	Welch's	41.484	8.477	33.773	43.533	49.255	19.1%	29.1%	35.9%	41.1%	45.1%
5	WMW	49.715	3.998	48.443	49.925	51.067	43.3%	61.2%	71.7%	78.5%	83.4%
	Student's	51.253	4.443	49.450	50.489	52.851	38.2%	55.4%	66.0%	73.3%	78.7%
	Welch's	47.502	5.224	44.367	48.983	50.347	32.9%	47.4%	56.5%	63.1%	68.3%
6	WMW	54.033	6.959	49.664	51.148	56.551	31.9%	48.0%	58.2%	65.0%	69.7%
	Student's	55.983	7.475	50.262	53.073	60.693	24.9%	38.1%	47.0%	53.5%	58.4%
	Welch's	53.586	6.926	49.587	51.057	54.989	30.9%	48.1%	59.7%	67.7%	73.2%
7	WMW	46.042	6.394	44.301	48.674	50.032	35.9%	51.9%	61.5%	67.9%	72.4%
	Student's	45.274	7.360	41.553	48.355	50.256	28.5%	43.4%	53.3%	60.1%	65.0%
	Welch's	42.919	8.309	35.783	46.550	49.758	26.3%	38.4%	45.8%	51.0%	54.7%
8	WMW	49.226	3.515	48.270	49.778	50.519	48.5%	66.4%	76.3%	82.5%	86.7%
	Student's	49.855	4.436	48.325	49.965	51.352	40.0%	57.3%	67.9%	75.0%	80.2%
	Welch's	48.061	5.026	45.638	49.431	50.513	36.3%	51.6%	60.8%	67.3%	72.3%
9	WMW	53.151	6.558	49.409	50.582	54.515	35.9%	53.1%	63.6%	70.4%	74.9%
	Student's	54.292	7.107	49.730	51.311	57.145	31.2%	46.9%	56.8%	63.6%	68.3%
	Welch's	54.455	7.371	49.718	51.621	57.176	26.9%	42.5%	53.4%	61.3%	67.0%
10	WMW	47.853	6.651	44.559	49.241	51.266	25.3%	39.6%	49.7%	57.4%	63.5%
	Student's	48.995	7.177	45.593	49.940	52.801	23.0%	36.4%	46.3%	54.1%	60.4%
	Welch's	44.571	7.750	37.131	45.950	50.137	17.8%	28.0%	35.4%	41.3%	46.2%
11	WMW	49.692	5.446	47.249	49.797	51.572	32.0%	48.1%	58.7%	66.5%	72.4%
	Student's	50.980	6.173	48.154	50.278	53.303	28.7%	43.7%	54.1%	61.9%	68.0%
	Welch's	47.355	6.241	42.257	48.248	50.495	24.0%	36.3%	44.9%	51.5%	57.0%
12	WMW	50.916	5.173	48.490	49.999	51.740	38.3%	55.7%	66.7%	74.4%	80.3%
	Student's	52.269	6.132	49.179	50.464	53.563	34.3%	50.7%	61.3%	68.9%	74.7%
	Welch's	49.663	5.502	46.228	49.423	50.894	30.8%	46.0%	56.5%	65.1%	73.0%
13	WMW	48.274	5.947	45.960	49.461	51.076	30.0%	45.7%	56.3%	64.0%	70.0%
	Student's	50.011	6.487	47.691	50.271	53.153	26.8%	41.6%	51.9%	60.0%	66.3%
	Welch's	44.450	7.393	37.374	46.098	49.995	19.9%	30.6%	38.1%	44.0%	48.8%
14	WMW	49.670	4.717	47.835	49.827	51.178	37.6%	54.9%	65.7%	73.2%	78.7%
	Student's	51.510	5.650	49.084	50.492	53.369	32.9%	49.0%	59.6%	67.2%	72.9%
	Welch's	47.018	5.666	42.426	48.171	50.235	26.9%	39.9%	48.6%	55.1%	60.4%
15	WMW	50.537	4.367	48.704	49.969	51.204	44.3%	62.4%	73.1%	80.2%	85.3%
	Student's	52.384	5.733	49.584	50.572	53.357	38.7%	55.7%	66.0%	73.0%	78.0%
	Welch's	49.154	4.682	46.290	49.345	50.519	34.9%	50.7%	61.3%	69.6%	77.1%
16	WMW	48.006	5.122	46.289	49.296	50.489	35.3%	52.1%	62.8%	70.3%	75.7%
	Student's	48.197	6.582	45.136	49.474	51.464	26.2%	40.7%	50.8%	58.5%	64.6%
	Welch's	45.615	7.008	39.802	48.082	50.201	26.5%	39.4%	47.8%	53.9%	58.5%
17	WMW	49.113	3.889	47.769	49.658	50.544	43.3%	61.2%	71.8%	78.7%	83.6%
	Student's	49.826	5.331	47.546	49.875	51.545	33.9%	50.2%	60.9%	68.5%	74.3%
	Welch's	47.683	5.365	44.148	49.042	50.381	32.6%	46.9%	55.9%	62.2%	67.1%
18	WMW	49.875	3.541	48.490	49.823	50.598	48.8%	67.2%	77.6%	84.3%	89.1%
	Student's	50.833	4.963	48.647	50.007	51.497	41.3%	59.1%	69.9%	77.3%	82.7%
	Welch's	49.556	4.752	46.901	49.617	50.753	36.4%	52.6%	63.1%	71.3%	78.3%

In Patterns 1, 3, 4, and 6 at $n = 50$, the data were biased due to the generation of $\boldsymbol{x}$ from $N(40, 10^2)$ or $N(60, 10^2)$. When the sample size increased to $n = 100$ and 150, the cutoff value calculated by the WMW test was the best even when the data were biased.

Table 3. Summary of cutoff values in MCSs ($n = 100$)

		Summary statistics					Proportion of cutoff value in range				
Pattern		Mean	SD	Q1	Median	Q3	49-51	48-52	47-53	46-54	45-55
1	WMW	47.507	6.239	47.012	49.582	50.486	41.3%	58.4%	68.5%	75.0%	79.5%
	Student's	48.237	6.634	47.747	49.996	51.415	37.0%	53.8%	64.5%	71.9%	77.5%
	Welch's	42.970	9.499	35.445	47.563	50.019	28.0%	40.1%	47.5%	52.8%	56.7%
2	WMW	49.865	3.067	49.112	49.972	50.705	56.0%	74.0%	82.9%	88.1%	91.4%
	Student's	50.781	3.912	49.493	50.203	51.566	49.8%	67.6%	77.0%	82.8%	86.7%
	Welch's	47.633	5.383	45.968	49.518	50.318	42.9%	57.8%	66.0%	71.3%	75.2%
3	WMW	52.248	6.276	49.293	50.284	52.705	40.5%	57.8%	68.1%	74.9%	79.5%
	Student's	53.763	7.331	49.724	50.884	55.153	35.4%	51.4%	61.1%	67.7%	72.3%
	Welch's	51.711	6.917	48.356	50.153	52.283	33.7%	50.7%	62.0%	70.4%	76.7%
4	WMW	48.194	5.121	47.946	49.695	50.381	48.5%	66.3%	75.9%	81.6%	85.4%
	Student's	49.365	5.327	49.012	50.165	51.577	43.0%	60.9%	71.6%	78.8%	83.9%
	Welch's	43.138	9.232	36.428	47.710	49.961	30.7%	42.9%	50.1%	55.0%	58.8%
5	WMW	49.839	2.327	49.287	49.965	50.501	63.6%	80.9%	88.7%	92.7%	95.1%
	Student's	50.969	3.289	49.755	50.258	51.451	56.0%	73.6%	82.3%	87.2%	90.3%
	Welch's	47.544	4.959	46.347	49.499	50.180	47.6%	62.3%	69.8%	74.6%	78.0%
6	WMW	51.528	5.259	49.339	50.163	51.784	46.8%	64.8%	74.8%	81.0%	85.1%
	Student's	53.455	6.787	49.858	50.830	54.197	39.9%	56.4%	65.8%	72.0%	76.2%
	Welch's	51.010	6.025	48.448	50.084	51.567	38.8%	56.8%	68.3%	76.4%	82.2%
7	WMW	48.398	4.071	48.209	49.627	50.137	56.4%	73.5%	81.8%	86.6%	89.5%
	Student's	47.957	6.112	47.522	49.783	50.722	41.9%	59.0%	69.1%	75.7%	80.4%
	Welch's	45.160	8.432	43.617	49.253	50.095	43.7%	57.5%	64.5%	68.7%	71.6%
8	WMW	49.592	1.901	49.221	49.901	50.251	69.2%	85.2%	91.7%	94.9%	96.7%
	Student's	49.932	3.067	49.202	49.990	50.658	58.5%	76.1%	84.4%	89.1%	92.0%
	Welch's	48.277	4.545	47.869	49.784	50.320	52.6%	68.0%	75.4%	79.8%	82.9%
9	WMW	50.832	4.590	49.109	50.016	51.100	50.3%	68.6%	78.5%	84.5%	88.4%
	Student's	51.711	5.879	49.219	50.134	51.831	45.1%	62.7%	72.6%	78.9%	83.1%
	Welch's	51.904	6.892	48.585	50.232	52.640	33.3%	50.2%	61.7%	70.2%	76.7%
10	WMW	49.205	5.021	47.863	49.794	50.932	40.0%	57.5%	68.1%	75.1%	80.1%
	Student's	50.613	6.198	48.633	50.215	52.472	34.7%	51.0%	61.3%	68.5%	73.9%
	Welch's	45.789	7.541	40.340	48.487	50.248	29.2%	42.3%	50.4%	56.1%	60.4%
11	WMW	49.892	3.755	48.764	49.928	50.815	49.4%	67.7%	77.6%	83.7%	87.8%
	Student's	51.181	5.255	49.276	50.227	51.982	43.3%	60.7%	70.9%	77.3%	81.9%
	Welch's	47.599	5.562	44.662	49.232	50.295	37.4%	51.9%	60.3%	66.1%	70.4%
12	WMW	50.318	3.394	49.215	49.990	50.757	56.8%	74.9%	83.7%	88.9%	92.1%
	Student's	51.494	5.155	49.551	50.213	51.648	50.6%	68.2%	77.4%	83.0%	86.6%
	Welch's	49.030	4.523	46.938	49.618	50.389	43.6%	59.4%	68.4%	74.8%	79.9%
13	WMW	49.326	3.941	48.362	49.820	50.650	47.1%	65.6%	75.9%	82.3%	86.6%
	Student's	51.235	5.303	49.379	50.376	52.479	40.1%	57.4%	67.8%	74.7%	79.5%
	Welch's	45.614	7.013	40.942	48.448	50.093	32.4%	45.8%	53.9%	59.3%	63.4%
14	WMW	49.807	2.830	49.011	49.926	50.564	56.9%	75.4%	84.4%	89.5%	92.7%
	Student's	51.413	4.646	49.651	50.311	51.889	49.1%	66.9%	76.5%	82.3%	86.1%
	Welch's	47.386	4.970	45.020	49.187	50.143	41.4%	56.0%	64.1%	69.4%	73.3%
15	WMW	50.112	2.458	49.364	49.983	50.537	64.4%	81.7%	89.3%	93.3%	95.6%
	Student's	51.490	4.632	49.781	50.263	51.506	56.7%	73.9%	82.1%	86.7%	89.7%
	Welch's	48.776	3.763	47.213	49.611	50.235	48.9%	64.4%	72.9%	78.7%	83.3%
16	WMW	49.035	2.990	48.405	49.708	50.260	54.8%	73.1%	82.4%	87.8%	91.2%
	Student's	49.589	5.104	48.205	49.919	51.114	41.2%	58.7%	69.1%	75.9%	80.7%
	Welch's	47.101	6.163	46.135	49.441	50.227	43.9%	59.2%	67.3%	72.2%	75.5%
17	WMW	49.491	2.113	48.975	49.844	50.261	63.7%	81.1%	89.0%	93.1%	95.5%
	Student's	50.076	3.929	48.927	49.978	50.844	51.2%	69.4%	79.0%	84.7%	88.5%
	Welch's	48.276	4.432	47.515	49.681	50.275	50.1%	65.6%	73.4%	78.0%	81.1%
18	WMW	49.790	1.821	49.291	49.920	50.286	69.5%	85.7%	92.3%	95.6%	97.4%
	Student's	50.332	3.541	49.284	49.997	50.665	59.7%	77.3%	85.6%	90.2%	93.0%
	Welch's	49.242	3.743	48.063	49.825	50.418	51.1%	67.2%	75.6%	81.2%	85.4%

As n increases, the proportion of the cutoff value calculated by the WMW test in each range increases. In the range of $45 \leq c \leq 55$, the proportion of cutoff value calculated by the WMW test was greater than 90% in many patterns at $n = 150$.

Table 4. Summary of cutoff values in MCSs ($n = 150$)

		Summary statistics					Proportion of cutoff value in range				
Pattern		Mean	SD	Q1	Median	Q3	49-51	48-52	47-53	46-54	45-55
1	WMW	48.692	4.732	48.514	49.828	50.458	52.6%	70.2%	79.2%	84.5%	88.0%
	Student's	49.394	5.291	49.032	50.093	51.310	46.4%	63.9%	73.7%	79.9%	84.4%
	Welch's	44.404	9.233	41.138	48.949	50.101	38.1%	51.4%	58.7%	63.4%	66.8%
2	WMW	49.909	2.056	49.432	49.983	50.455	68.0%	84.3%	91.1%	94.5%	96.4%
	Student's	50.557	2.899	49.671	50.128	50.975	61.8%	78.7%	86.5%	90.7%	93.2%
	Welch's	48.095	4.710	47.819	49.762	50.243	54.6%	69.3%	76.4%	80.6%	83.5%
3	WMW	51.106	4.829	49.352	50.095	51.321	51.3%	69.1%	78.3%	83.9%	87.6%
	Student's	52.407	6.238	49.681	50.402	52.517	45.9%	62.9%	72.2%	78.0%	81.8%
	Welch's	50.530	5.972	48.164	50.009	51.238	40.3%	57.5%	67.9%	75.2%	80.6%
4	WMW	49.116	3.501	48.897	49.854	50.318	60.8%	78.1%	86.0%	90.2%	92.7%
	Student's	50.170	3.892	49.573	50.195	51.338	53.1%	70.9%	80.1%	85.7%	89.4%
	Welch's	44.596	8.835	42.322	48.959	50.031	41.4%	54.6%	61.4%	65.8%	69.0%
5	WMW	49.893	1.477	49.540	49.978	50.323	75.4%	89.8%	95.0%	97.2%	98.4%
	Student's	50.631	2.361	49.833	50.158	50.891	68.3%	84.2%	90.6%	93.8%	95.6%
	Welch's	48.133	4.310	48.085	49.749	50.143	59.7%	73.5%	79.7%	83.3%	85.8%
6	WMW	50.621	3.667	49.441	50.053	50.915	58.4%	76.1%	84.6%	89.3%	92.1%
	Student's	52.147	5.542	49.829	50.402	52.089	51.7%	68.8%	77.5%	82.5%	85.8%
	Welch's	50.064	4.991	48.434	50.002	50.906	46.3%	64.2%	74.3%	80.9%	85.6%
7	WMW	49.167	2.486	48.984	49.795	50.112	69.2%	84.5%	90.7%	93.8%	95.6%
	Student's	49.039	4.587	48.792	49.934	50.614	53.6%	71.0%	79.8%	85.0%	88.4%
	Welch's	46.692	7.506	47.913	49.683	50.114	57.7%	71.2%	76.8%	80.0%	81.9%
8	WMW	49.739	1.203	49.502	49.937	50.168	80.3%	92.6%	96.6%	98.2%	99.0%
	Student's	49.933	2.040	49.489	49.993	50.417	70.7%	86.2%	92.3%	95.2%	96.8%
	Welch's	48.822	3.743	48.974	49.909	50.260	65.3%	79.3%	85.1%	88.2%	90.1%
9	WMW	50.176	3.117	49.279	49.977	50.580	61.4%	78.8%	86.9%	91.2%	93.9%
	Student's	50.777	4.533	49.318	50.035	50.919	55.9%	73.5%	82.0%	86.9%	90.0%
	Welch's	50.827	5.999	48.507	50.073	51.547	39.7%	57.1%	67.9%	75.4%	81.0%
10	WMW	49.608	3.629	48.743	49.896	50.670	51.2%	69.7%	79.5%	85.3%	89.0%
	Student's	50.846	5.064	49.260	50.194	51.765	44.7%	62.5%	72.5%	78.8%	83.2%
	Welch's	46.765	6.628	44.903	49.281	50.235	39.8%	54.7%	63.0%	68.3%	72.0%
11	WMW	49.918	2.565	49.223	49.960	50.541	61.2%	78.9%	87.2%	91.7%	94.3%
	Student's	50.901	4.138	49.556	50.159	51.283	54.6%	72.3%	81.3%	86.4%	89.7%
	Welch's	48.103	4.620	47.138	49.624	50.241	49.0%	64.3%	72.1%	76.9%	80.3%
12	WMW	50.113	2.184	49.488	49.992	50.476	68.9%	85.0%	91.6%	94.9%	96.7%
	Student's	50.925	3.921	49.700	50.129	50.991	62.6%	79.2%	86.7%	90.6%	93.0%
	Welch's	49.050	3.543	48.107	49.805	50.284	54.9%	70.2%	78.0%	82.9%	86.6%
13	WMW	49.626	2.654	49.004	49.899	50.448	59.2%	77.4%	86.1%	90.9%	93.7%
	Student's	51.139	4.265	49.650	50.274	51.670	51.0%	69.0%	78.5%	84.1%	87.8%
	Welch's	46.667	6.101	45.258	49.239	50.105	43.8%	58.4%	66.1%	71.0%	74.5%
14	WMW	49.865	1.830	49.374	49.955	50.373	69.1%	85.6%	92.3%	95.5%	97.2%
	Student's	50.961	3.541	49.776	50.202	51.174	61.0%	78.3%	86.2%	90.4%	92.9%
	Welch's	48.038	4.135	47.407	49.599	50.127	53.7%	68.4%	75.5%	79.9%	82.8%
15	WMW	50.013	1.501	49.585	49.988	50.343	76.1%	90.3%	95.3%	97.5%	98.6%
	Student's	50.878	3.370	49.847	50.159	50.898	68.9%	84.3%	90.4%	93.4%	95.1%
	Welch's	48.974	3.005	48.368	49.805	50.183	60.7%	75.1%	81.9%	86.1%	89.2%
16	WMW	49.401	1.932	49.003	49.821	50.180	66.9%	83.7%	90.8%	94.4%	96.4%
	Student's	49.857	3.760	48.947	49.970	50.763	52.8%	71.0%	80.5%	86.0%	89.6%
	Welch's	48.158	4.906	48.360	49.748	50.200	57.8%	73.2%	80.1%	83.8%	86.1%
17	WMW	49.660	1.368	49.341	49.901	50.175	75.3%	89.8%	95.0%	97.4%	98.5%
	Student's	50.010	2.716	49.323	49.988	50.541	63.5%	80.8%	88.5%	92.5%	94.9%
	Welch's	48.882	3.425	48.852	49.859	50.227	63.7%	78.4%	84.5%	87.7%	89.7%
18	WMW	49.827	1.131	49.536	49.948	50.186	80.4%	93.0%	97.0%	98.6%	99.3%
	Student's	50.104	2.357	49.527	49.996	50.413	71.8%	87.0%	93.0%	95.8%	97.3%
	Welch's	49.380	2.890	48.952	49.925	50.324	62.8%	77.9%	84.6%	88.6%	91.3%

4. COVID-19 Data

We demonstrated the cutoff value calculated by the WMW test using COVID-19 data. We utilized the clinical outcomes data in 110 hospitalized COVID-19 patients treated with famotidine and cetirizine for a minimum of 48 h (Hogan II et al., 2020), as shown in Table 5. The data are presented by Supplementary data of their paper. The dosage and administration route were famotidine 20 mg intravenously (IV) and cetirizine 10 mg IV (or oral) at 12 h intervals. The duration of the clinical trials was from April 3, 2020, to June 13, 2020. Recently, it was revealed that cetirizine (Histamine-1 blocker) (Freedberg, et al., 2020; Janowitz et al., 2020) and famotidine (Histamine-2 blockers) (Blanco et al., 2021) showed a significant effect as an anti-SARS-CoV-2 which is the name of the pathogen that causes COVID-19.

Table 5. Clinical outcomes in 110 hospitalized COVID-19 patients (x: age (years old), y: days to discharge (day))

x	79	53	34	64	78	50	83	71	85	91	73	65	81	57	93	79	71	59	50	43
y	5	6	2	32	18	5	11	4	5	33	35	14	18	8	12	8	9	4	5	7
x	80	58	39	46	41	60	68	89	83	39	72	45	63	87	43	92	22	92	64	72
y	20	29	7	8	6	7	11	-	-	18	16	15	11	-	7	12	10	11	10	21
x	92	72	51	81	56	74	64	58	57	70	17	38	81	69	51	51	80	61	80	25
y	6	5	11	20	5	6	8	6	13	7	7	-	6	42	9	11	4	25	11	10
x	63	89	76	24	71	69	97	27	71	76	66	60	79	84	63	49	94	79	68	63
y	-	-	-	7	10	19	-	6	9	5	9	-	7	7	-	6	17	5	30	13
x	69	91	79	61	48	33	76	50	37	21	53	73	56	67	45	73	75	73	43	55
y	-	-	-	-	7	15	19	4	3	4	-	13	8	5	11	8	8	5	12	-
x	68	63	48	38	70	60	73	57	75	72										
y	16	8	-	6	5	13	14	7	4	8										

-: Died without recovery.

The independent variable x is the age (years old), and the dependent variable y is the days to discharge (day). Patients whose dependent variable was listed as hyphens in Table 5 died without recovery. In this manuscript, we used 93 patients that have recovered and were discharged. We also used the software R to calculate the cutoff value by the WMW test, and the sample code was presented in Appendix. Figure 1 is a scatter plot of the age and days to discharge, and the dashed line shows the cutoff value calculated by the WMW test. The days to discharge of all young patients were short. On the other hand, the days to discharge of many elderly patients were short, but the days to discharge of some elderly patients were long. Therefore, the scatter plot looked like a lower right triangle. There was no linear relationship between x and y, and y that followed a non-normal distribution. The cutoff value calculated by the WMW test was 59.5 years old, and the P-value using that cutoff value was 0.011. Since we set the potential cutoff value as $c_{(j)} = (x_{(j)} + x_{(j+1)})/2$ to accommodate a variety of quantitative data, the cutoff value was output as 59.5 years old. Because the age data were in 1-year increments, the two groups of less than 59.5 years old and greater than or equal to 59.5 years old were the same as the two groups of less than 60 years old and greater than or equal to 60 years old. Considering the scatter plot, the patient of $(x, y) = (58, 29)$ may seem better in the right-hand group. However, if the cutoff value was 57.5 years old, the patients of $(x, y) = (58, 6)$ and (59,4) would also move to the right-hand group. Additionally, since even a large value for only one patient has a little effect on the WMW test, it is believed that 59.5 years old was selected as the cutoff value.

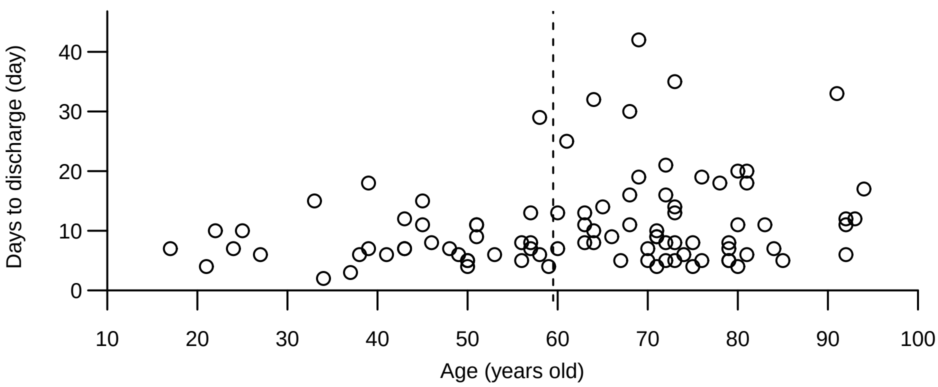

Figure 1. Scatter plot of the age and days to discharge in COVID-19 data of 93 recovered patients. The dashed line shows the cutoff value

Reznikov et al. (2021) identified antihistamine candidates for repurposing by mining electronic health records of usage in a population of more than 219 000 subjects tested for SARS-CoV-2. They concluded that prior usage of loratadine, diphenhydramine, cetirizine, hydroxyzine, and azelastine was associated with a reduced incidence of positive SARS-CoV-2 test results in the group of greater than or equal to 61 years old. It is believed that the cutoff value calculated by the WMW test obtained a good result, because there was a report that the cutoff value set at age 61 years old provided beneficial effects.

5. Conclusions

This study divides the COVID-19 data, which followed a non-normal distribution, into two cutoff values. In the log-rank and chi-squared tests, the method of calculating the cutoff value by the minimum *P*-value approach was well established. However, because there was no application of cutoff value for the WMW test by the minimum *P*-value approach, we verified the performance when the method was applied to the WMW test using MCSs at various settings. The MCS results at various settings showed high performance of the cutoff value calculated by the WMW test. Furthermore, in COVID-19 data, when the data were divided into two groups with the cutoff value calculated by the WMW test, it was confirmed that they were split into two groups with different characteristics. Therefore, we concluded that the cutoff value for the WMW test by the minimum *P*-value approach is valid.

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Appendix

Sample code of the software R

We presented a sample code of the software R for calculating the cutoff value using COVID-19 data. Another practical example can be calculated by replacing two vectors of x and y with suitable ones.

```
library(exactRankTests)
x<-c(79,53,34,64,78,50,83,71,85,91,73,65,81,57,93,79,71,59,50,43,80,58,39,46,41,60,68,
     39,72,45,63,43,92,22,92,64,72,92,72,51,81,56,74,64,58,57,70,17,81,69,51,51,80,61,
     80,25,24,71,69,27,71,76,66,79,84,49,94,79,68,63,48,33,76,50,37,21,73,56,67,45,73,
     75,73,43,68,63,38,70,60,73,57,75,72)
y<-c(5,6,2,32,18,5,11,4,5,33,35,14,18,8,12,8,9,4,5,7,20,29,7,8,6,7,11,18,16,15,11,7,
     12,10,11,10,21,6,5,11,20,5,6,8,6,13,7,7,6,42,9,11,4,25,11,10,7,10,19,6,9,5,9,7,
     7,6,17,5,30,13,7,15,19,4,3,4,13,8,5,11,8,8,5,12,16,8,6,5,13,14,7,4,8)
n<-length(x); dat0<-data.frame(x,y); dat1<-dat0[order(dat0[,1]),]; res<-NULL
for(j in 5:(n-5)){cj<-(dat1$x[j]+dat1$x[j+1])/2; y1<-y[x<cj]; y2<-y[x>=cj]
res<-rbind(res,c(Cutoff=cj,Pvalue=wilcox.exact(y1,y2)$p))}; res[order(res[,2]),][1,]
```

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