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A spreadsheet tool for designing statistical quality control programs based on patient risk parameters

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ABSTRACT

Background: Quality control (QC) in the laboratory aims to reduce the risk of harm to a patient due to erroneous results, as highlighted by the Clinical Laboratory Standards Institute (CLSI) guidance for Statistical Quality Control (SQC) (C24-Ed4). To effectively reduce patient risk, a convenient spreadsheet tool was developed to assist laboratories in SQC design based on patient risk parameters.

Methods: In accordance with Parvin's patient risk model and the mathematical formula for calculating the expected number of unreliable final patient results [$E(N_{uf})$], the function is edited using Excel software, and the maximum $E(N_{uf})$ [$MaxE(N_{uf})$] value and other risk parameters based on the current QC strategy are calculated to assess the risk of the QC strategy.

Results: A convenient spreadsheet tool is proposed in this study. After the quality requirements, performance parameters, practical run size, QC rules and the number of QC results of test items are input, the laboratory is enabled to quickly obtain $MaxE(N_{uf})$ value, maximum run size and other data based on the strategy. The QC strategy conforming to the risk requirements can be developed by changing the QC rules or the quantity of run size. Moreover, the Power Function Graph of the QC strategy and two risk diagrams are presented simultaneously.

Conclusions: Convenient spreadsheet tools can be adopted by laboratories to assess the risks of QC strategies and design appropriate risk-based SQC strategies to reduce patient risk to acceptable levels.

1. Introduction

The Clinical Laboratory Standards Institute (CLSI) C24-Ed4 guidance [1] for quality control (QC) practices highlights that laboratories should rigorously evaluate QC rules and place stress on the frequency of QC events when designing internal quality control (IQC) strategies. The previous IQC design placed a focus on the ability of QC to detect critical systematic errors (ΔSE_{crit}) [2]. However, when the QC strategy fails to detect out-of-control conditions, or when the number of patient samples tested in the respective batch is significantly different, several questions are often overlooked [3,4], including whether the QC strategies used should be adjusted, and whether there is a risk of adverse patient care in the reports.

Parvin proposed a patient risk model based on the parameter the maximum expected number of unreliable final patient results [$MaxE(N_{uf})$] in combination with CLSI EP23 (a guideline for a risk management-based laboratory quality control) [5] after a considerable amount of research. However, the calculation of this parameter is extremely complicated, involving numerous concepts that are difficult to understand. Moreover, C24-Ed4 only provides the principle and definition of statistical quality control (SQC), whereas the document does not give examples and tool recommendations for calculating $MaxE(N_{uf})$ [6]. As a result, the application of this model in laboratories is limited. In this study, a convenient chart tool is developed using the commonly used Excel software based on the mathematical formula of the $E(N_{uf})$ value and simple programming. Besides calculating the risk parameter "$MaxE(N_{uf})$" value and maximum run size in the risk model, this tool can calculate other parameters in the risk model and provide a risk diagram, thus helping laboratories design a SQC scheme easily based on patient risk.

2. Materials and method

In Parvin's patient risk model, the "bracketed QC" mode is employed

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under the continuous detection mode. When the QC strategy does not detect an out-of-control condition, the number of unreliable (erroneous / incorrect) patient results that exceed the quality requirements will increase compared with the number of unreliable patient results that exceed the quality requirements during control, and the increased number is termed the total Expected Number of unreliable results [E(N_u)]. E(N_u) can be divided into the expected number of unreliable results produced between the inception of the out-of-control condition and the last accepted QC event [E(N_{uf})] and the expected number of unreliable results achieved between the last accepted QC event and the QC rule rejection [E(N_{uc})]. Moreover, E(N_{uf}) is called Expected Number of unreliable final patient results. E(N_{uc}) is also referred to as Expected Number of unreliable correctable patient results. QC strategies focusing on patient risk should be designed to control the number of E(N_{uf}) and consider controlling the maximum number of E(N_{uf}) [MaxE(N_{uf})] under a certain number.

The calculation of E(N_{uf}) requires parameters, e.g., the performance of the measurement procedure, the candidate QC rule, the analytical quality goal of the testing items, and the number of patient samples tested between QC events (run size). For the detailed derivation of E(N_{uf}), please refer to paper [7], and its calculation formula [8] is written as follows:

$$E(N_{uf}) = \Delta P_E\{(ARL_{ed}\text{-}1)E(N_B)\text{-}(1\text{-}P_1)[E(N_B)\text{-}E(N_0)]\}$$

The formula has a total of five parameters. ΔP_E denotes the increase of the probability that the test result exceeds the quality requirement [expressed as the allowable total error (TEa)]. It is equal to the probability of the QC result exceeding TEa under an out-of-control error condition minus the probability of exceeding TEa at a stable state. P_1 expresses the error detection probability of the QC rule after an out-of-control error condition occurs. ARL_{ed} represents the average number of QC required to detect an out-of-control error condition, equaling the inverse of P_1. E(N_B) expresses the expected number of patient specimens tested between QC events (practical run size). E(N_0) denotes the expected number of patient results produced between the time an out-of-control error condition occurs and the next QC event, and E(N_0) = E(N_B)/2. Thus, the formula can be simplified as $E(N_{uf}) = \Delta P_E[(1/P_1\text{-}1)E(N_B)\text{-}(1\text{-}P_1)E(N_B)/2]$.

P_1 denotes the key parameter in the entire calculation formula. The probability of error detection P_{ed}(SE) of QC rules should be obtained when different sizes of systematic errors (SE) occur, and draw the Power Function Graph of the QC rules based on it. The following are the methods for calculating P_{ed}(SE) of various QC rules using the Excel software.

2.1. P_{ed}(SE) of 1_{ks} rule

The 1ks rule refers to a type of single rule adopted to judge whether the QC data exceeds a fixed QC limit in each QC event. Common 1_{ks} rules comprise 1_{2s}, $1_{2.5s}$, 1_{3s}, $1_{3.5s}$, with different numbers of QC results N (N usually reaching 1 to 4). The calculation of the power of a single rule is relatively simple and has been presented in existing research [9]. The mathematical formula is: $P_{ed}(SE) = 1\text{-}(1\text{-}P)^N$, where $P = 1\text{-}[\Phi(k\text{-}SE)\text{-}\Phi(\text{-}k\text{-}SE)]$, Φ represents the cumulative distribution function of the standard normal distribution. After the formula is transformed, the Excel calculation formula is written as $P_{ed}(SE) = 1\text{-}((NORMSDIST(k\text{-}SE)\text{-}NORMSDIST(\text{-}k\text{-}SE))\hat{}N)$. "NORMSDIST" denotes a function used to obtain the standard normal cumulative distribution function in Excel, "^" is the function of power in Excel. SE here and in subsequent Excel formulas is the magnitude of the systematic error, which is expressed as the multiples of standard deviation (SD).

2.2. P_{ed}(SE) of Repeat 1:2s rule

The rule is that when the QC data exceeds the mean ± 2s control limit, the QC material will be repeatedly tested, and then whether it is acceptable or not will be judged according to the repeated results. According to a cohort study [10], quite a few large academic medical centers are using the above-described rule. Parvin classified these rules and evaluated the error detection probabilities of different types of rules [11].The Repeat 1:2s Rule in this study is defined as follows: when 2 or 3 levels of QC materials are used (N=2,3), if all initial QC results are within mean ± 2s control limits, the result is accepted. If > 1 QC results exceed control limits, the result is rejected. If there is only 1 QC result that exceeds control limits, repeat all levels of QC materials. If all repeated QC results are within mean ± 2s control limits, then accept. The mathematical formula is: $P_{ed}(SE) = 1-(1-P)^N[1+NP(1-P)^{N-1}]$, where the main parameter P denotes the probability of a single QC result exceeding the control limit of ± 2s. The Excel formula is expressed as P = NORMSDIST(-2-SE)+(1-NORMSDIST(2-SE)).

2.3. P_{ed}(SE) of multi rule

A multi-rule program combines two or more single QC rules, each with a different definition. Accordingly, for each QC event, it is necessary to judge the rejected or accepted status of the QC data under each rule. In this study, the power of several multi-rules is calculated, including $1_{3s}/2_{2s}$ (N=2), $1_{3s}/2of3_{2s}$ (N=3), $1_{3s}/2_{2s}/R_{4s}$ (N=2), $1_{3s}/2of3_{2s}/R_{4s}$ (N=3), $1_{3s}/2of3_{2s}/R_{4s}/3_{1s}$ (N=3), $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ (N=4), where the R_{4S} rule indicates that one QC result exceeds the +2s limit and one exceeds the −2s limit per QC event, and all rules are applied in a single run. In the following, $1_{3s}/2_{2s}$ (N=2) and $1_{3s}/2_{2s}/R_{4s}$ (N=2) are taken as the examples to introduce the calculation method of multi-rule power.

The power of QC rules or probability of error detection (P_{ed}) can refer to the probability change of the standard normal distribution under different error conditions [12]. The probability of error detection can be considered as the probability of being rejected by the QC rules. The probability of not violating the QC rules pertains to the acceptance probability. Subtracting the acceptance probability from 1 gives P_{ed} for the rule. First, all possible cases of rejection or acceptance of the QC data are analyzed in accordance with the definition of the QC rules. The QC data of $1_{3s}/2_{2s}$ and $1_{3s}/2_{2s}/R_{4s}$ (N=2) will fall into five intervals, i.e., < −3s, −3s ~ −2s, −2s ~ 2s, 2s ~ 3s, > 3s. To be specific the data in the < −3s and > 3s violates the 1_{3s} rule, so the above two intervals can be excluded. Thus, just consider the case where 2 QC data (A and B) will fall in the remaining three intervals. According to the permutation and combination, there will be nine situations (3^2). The possible cases of rejection or acceptance are listed in Table 1.

By observing the rejection or acceptance in Table 1, the probability of a single QC result falling in interval 1 is set to "a", and the Excel calculation formula is expressed as a = NORMSDIST(-2-SE)-NORMSDIST(-3-SE), the probability of interval 2 is "b", and the Excel calculation formula is written as b = NORMSDIST(2-SE)-NORMSDIST(-2-SE), the probability of interval 3 is "c", and the Excel calculation formula is denoted as c = NORMSDIST(3-SE)-NORMSDIST(2-SE). The acceptance probability of a QC rule is the sum of the probabilities of all acceptance cases, and 1 minus the acceptance probability is the P_{ed} of the rule. Accordingly, P_{ed}(SE) of $1_{3s}/2_{2s}$ rule = 1-(2ab+2ac+bb+2bc), P_{ed}(SE) of $1_{3s}/2_{2S}/R_{4s}$ rule = 1-(2ab+bb+2bc). The P_{ed}(SE) of other multi-rules can be calculated in accordance with the above principles.

2.4. Calculation of ΔP_E

According to the calculation formulas of the above three types of P_{ed}(SE), P_1 and ARL_{ed} in the E(N_{uf}) formula can be obtained. E(N_B) is a non-computational parameter, and E(N_0) is half of E(N_B). ΔP_E is equal to the probability that exceeds the TEa part when the measurement procedure at out-of-control state [P_E(SE)], minus the probability that the measurement procedure exceeds the TEa part in its stable state [P_E(0)] [7], i.e., $\Delta P_E = P_E(SE)\text{-}P_E(0)$. It should be calculated based on the quality requirements TEa and the performance parameters Bias and CV of the

Table 1
Cases of rejection or acceptance of $1_{3s}/2_{2s}$, $1_{3s}/2_{2s}/R_{4s}$ (N=2).

No.	Interval 1 −3s ~ −2s	Interval 2 −2s ~ 2s	Interval 3 2s ~ 3s	Probability	$1_{3s}/2_{2s}$	$1_{3s}/2_{2s}/R_{4s}$
1	AB			aa	Violation of 2_{2s}	Violation of 2_{2s}
2	A	B		ab	Acceptance	Acceptance
3	A		B	ac	Acceptance	Violation of R_{4s}
4	B	A		ab	Acceptance	Acceptance
5		AB		bb	Acceptance	Acceptance
6		A	B	bc	Acceptance	Acceptance
7	B		A	ac	Acceptance	Violation of R_{4s}
8		B	A	bc	Acceptance	Acceptance
9			AB	cc	Violation of 2_{2s}	Violation of 2_{2s}

measurement procedure. The units of the three above-described data should be consistent. The Excel calculation formula is $P_E(SE)$ = NORMSDIST(-TEa/CV-bias/CV-SE)+(1-NORMSDIST(TEa/CV-bias/CV-SE)), $P_E(0)$ = NORMSDIST(-TEa/CV-bias/CV)+(1-NORMSDIST(TEa/CV-bias/CV)).

2.5. Calculation of MaxE(N_{uf})

In brief, the Excel functions for calculating the five parameters of the $E(N_{uf})$ are derived. According to the Parvin's patient risk model, when $E(N_{uf})$ is plotted against the size of the error condition, the maximum $E(N_{uf})$, called MaxE(N_{uf}), will be observed [8]. Thus, the $E(N_{uf})$ value should be calculated within a certain systematic error range to obtain the maximum value. The Excel Auto Fill function can be adopted to calculate the $E(N_{uf})$ in a certain systematic error range (±2.0 times TEa) based on the principle of definite integral, according to a certain systematic error interval (the smaller the interval, the more accurate the result will be). Lastly, the MaxE(N_{uf}) value can be obtained.

3. Results - example applications

3.1. Components of spreadsheet tools

This spreadsheet tool is divided into a single rule tool and a multi rule tool. Its overview page is illustrated in Fig. 1. The first table in the upper left corner is adopted to determine the MaxE(N_{uf}) and Max Run Size result. Another table presents the calculation results of other risk parameters when systematic errors occur. The upper right plot is the Power Function Graph of the candidate QC rule. Two risk diagrams are presented below. The multi rule table tool and the single rule table tool are slightly different on the rule selection page. Click on the drop-down menu in the 1 ks blank in the single rule table tool for selecting the 1_{2s}, $1_{2.5s}$, 1_{3s}, $1_{3.5s}$ rules, and click on the drop-down menu in the N blank to select N = 1, 2, 3, 4. In the selectable rule of the multi-rule table tool, $1_{3s}/2_{2s}$ (N=2),$1_{3s}/2_{2s}/R_{4s}$ (N=2),$1_{3s}/2of3_{2s}$ (N=3),$1_{3s}/2of3_{2s}/R_{4s}$ (N=3),$1_{3s}/2of3_{2s}/R_{4s}/3_{1s}$ (N=3),$1_{3s}/2_{2s}/R_{4s}/4_{1s}$ (N=4), Repeat 1:2s (N=2), and Repeat 1:2s (N=3) rules can be selected. Enter relevant

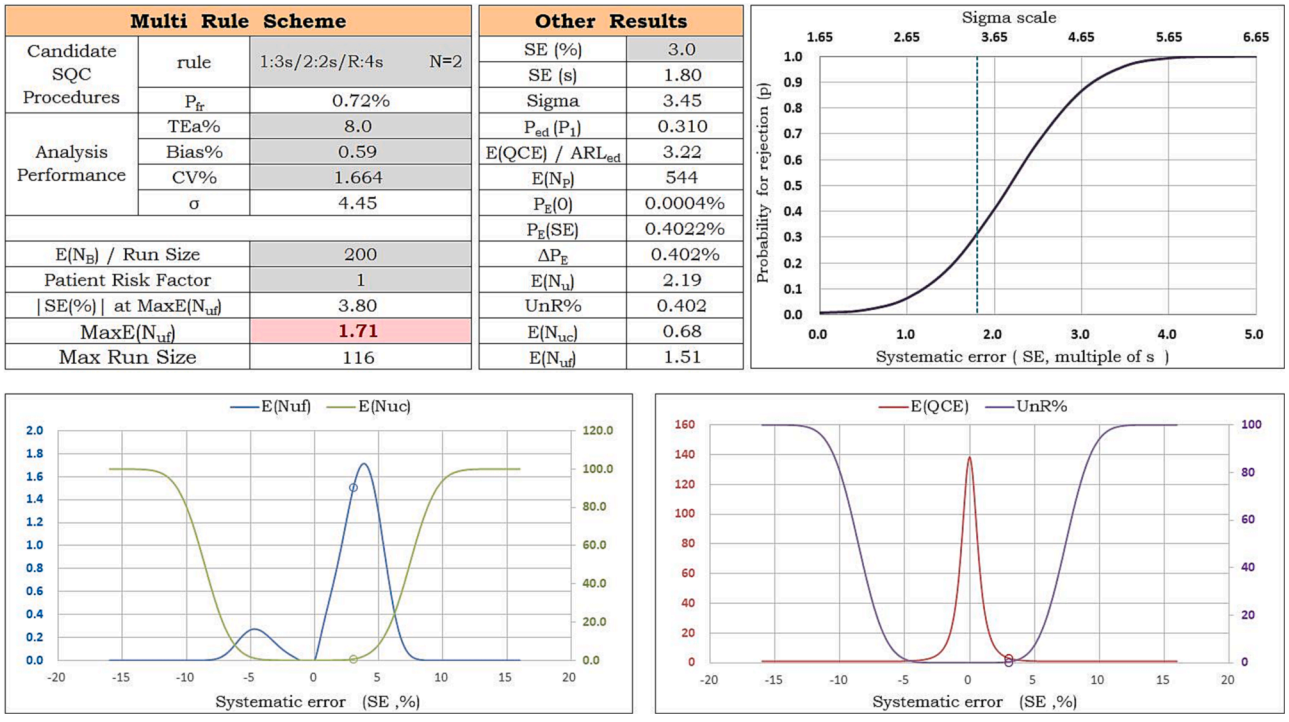

Fig. 1. Spreadsheet Tool overview page.
$E(N_u)$, total expected number of unreliable results; $E(N_{uf})$, expected number of unreliable final results; $E(N_{uc})$, expected number of unreliable correctable results; E(QCE), expected number of QC events to detect a systematic error; $E(N_P)$, expected number of affected patient samples before the detection of a systematic error; $E(N_B)$, expected number of patient specimens tested between QC events; ΔP_E%, increased percentage of results exceeding TEa; UnR%, increased percentage of unreliable results; $P_E(SE)$, proportion of results exceeding TEa at an out-of-control state; $P_E(0)$, proportion of results exceeding TEa at a stable state; P_{fr}, probability of false rejection; P_{ed}, probability of error detection.

information in the blank spaces of TEa%, Bias%, and CV%. The units of the above three parameters must be the same, either percent or concentration unit. Enter the number of patient specimens tested between QC events (practical run size) in the E(N_B) blank. Subsequently, the result of MaxE(N_{uf}) value, maximum run size, probability of false rejection (P_{fr}), sigma value, |SE(%)| at MaxE(N_{uf}) will be calculated. Westgard recommends making an experienced judgment about the relative harm that can result from errors in different tests. Patient Risk Factor is used to correspond to MaxE(N_{uf}) parameter, and a scale of 1–5 is set; if the risk factor increases by 1, the run size will double [13,14]. If the MaxE(N_{uf}) is less than or equal to the risk factor, it will be displayed in green. If the risk factor is exceeded, it will be highlighted in red. If the Max Run Size is >1000, it will be presented as "$>1000''$", whereas the detailed value will not be presented.

3.2. Developing SQC strategy based on risk requirements

Using HbA1c as an example, assume the TEa is 6%, the Bias of a laboratory is 0% and the CV is 1.4%, the calculated sigma value is 4.29. Table 2 shows some candidate SQC strategies of the tool. If the candidate QC rule P_{fr} is > 5% [2], the P_{fr} value in the spreadsheet tool will be highlighted which indicates that the P_{fr} is too high, and the candidate rule should be used with caution. When the designed QC run size is every 100 patient specimens and the laboratory uses the 1_{3s} N2 rule, the MaxE (N_{uf}) under this QC strategy is 2.51, the maximum run size is 39, and the |SE(%)| at MaxE(N_{uf}) value reaches 3.3. That is to say, the maximum E (N_{uf}) value is generated when a systematic error of 3.3% occurs. If the Patient Risk Factor for this item is set to 3, the MaxE(N_{uf}) value should be ≤3, and the QC strategies can conform to the requirements. If the Patient Risk Factor is set to 1, the QC strategy does not meet the requirements, and the spreadsheet tool is highlighted in red. Thus, the QC rule or run size should be adjusted. When the laboratory reduces the run size to 39, it just conforms to the requirement of MaxE(N_{uf}) = 1. To maintain the original run size of 100, it is imperative to increase the frequency of control measurements or use stricter QC limits, e.g., replacing the 1_{3s} N4 rule, for a MaxE(N_{uf}) value of 0.84, or replacing it with the $1_{2.5s}$ N2 rule, for a MaxE(N_{uf}) value of 0.79. Furthermore, the multi-rule scheme can be used in the laboratory. When it is replaced by the $1_{3s}/2_{2s}/R_{4s}$ N2 rule, the MaxE(N_{uf}) value is 1.31, which cannot conform to the requirement of MaxE(N_{uf}). As a result, the run size should be reduced to 76 or less. If the $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ N4 rule or the Repeat 1:2s N2 rule is adopted, the requirements can be met.

3.3. Additional results and diagrams available

Besides the key risk parameter MaxE(N_{uf}), Parvin's patient risk model also includes other closely related risk parameters, e.g., E(N_u), E (N_{uc}), the increased percentage of unreliable patient results (UnR%), the expected number of QC events to detect a systematic error [E(QCE)], and the expected number of affected patient samples before the detection of out-of-control conditions [E(N_P)]. The spreadsheet tool calculates the above risk parameters simultaneously by entering the size of the systematic error that occurred (The SE is limited to ±2 times TEa so as not to exceed the calculation range). With the 1_{3s} N2 scheme in Table 2 as an example, when a systematic error of 3.0% occurs, the P_{ed} of this rule is 0.353, and the QC takes an average of 2.83 times to detect the out-of-control condition. An average of 233 patient samples are examined between the start of the out-of-control state and detection by QC. The increased probability of the patient result exceeding the TEa range reaches 1.604%, thus yielding an average of 3.74 unreliable patient results with an UnR% ratio of 1.604%. The number of correctable unreliable patient results is 1.32, and the number of reported unreliable patient results is 2.42 under the "bracketed QC" mode. ΔP_E% and UnR% are a pair of parameters with the same value but different definitions, which are only related to TEa and SE, not QC rules.

The spreadsheet tool also shows the Power Function Graph, the risk

Table 2
Examples of Spreadsheet Tool Applications.

Parameters	Candidate SQC Strategies																
QC rule	1_{2s} N1	$1_{2.5s}$ N1	$1_{2.5s}$ N2	$1_{2.5s}$ N3	$1_{2.5s}$ N4	1_{3s} N1	1_{3s} N2	1_{3s} N3	1_{3s} N4	$1_{3.5s}$ N2	$1_{3.5s}$ N3	$1_{3s}/2_{2s}$ R_{4s} N2	$1_{3s}/2of3_{2s}$ R_{4s} N3	$1_{3s}/2of3_{2s}/R_{4s}/3_{1s}$ N3	$1_{3s}/2_{2s}/R_{4s}/4_{1s}$ N4	Repeat 1:2s N2	Repeat 1:2s N3
P_{fr}	4.55%	1.24%	2.47%	3.68%	4.88%	0.27%	0.54%	0.81%	1.08%	0.09%	0.14%	0.72%	1.34%	2.08%	2.22%	0.98%	2.22%
TEa%	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Bias%	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CV%	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
σ	4.29	4.29	4.29	4.29	4.29	4.29	4.29	4.29	4.29	4.29	4.29	4.29	4.29	4.29	4.29	4.29	4.29
E(N_B)/ Run Size	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Patient Risk Factor	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
|SE(%)| at MaxE (N_{uf})	3.90	3.90	3.30	2.70	2.40	3.90	3.30	3.00	2.70	3.60	3.00	3.00	2.55	2.25	1.95	2.40	1.80
MaxE(N_{uf})	1.12	2.93	0.79	0.36	0.21	7.46	2.51	1.32	0.84	7.64	4.47	1.31	0.49	0.21	0.18	0.48	0.18
Max Run Size	89	34	126	274	473	13	39	75	119	13	22	76	205	465	564	206	552
SE(%)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
P_{ed}	0.557	0.360	0.591	0.738	0.833	0.196	0.353	0.480	0.581	0.167	0.240	0.482	0.699	0.839	0.891	0.705	0.883
E(QCE)	1.80	2.77	1.69	1.35	1.20	5.11	2.83	2.08	1.72	5.98	4.17	2.07	1.43	1.19	1.12	1.42	1.13
E(N_P)	130	227	119	85	70	461	233	158	122	548	367	157	93	69	62	92	63
ΔP_E%	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604
E(N_u)	2.08	3.65	1.91	1.37	1.12	7.40	3.74	2.54	1.96	8.80	5.89	2.53	1.49	1.11	1.00	1.47	1.01
UnR%	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604	1.604
E(N_{uc})	1.16	1.32	1.13	1.01	0.94	1.45	1.32	1.22	1.14	1.47	1.41	1.22	1.04	0.93	0.89	1.04	0.90
E(N_{uf})	0.92	2.33	0.78	0.36	0.19	5.95	2.42	1.32	0.82	7.33	4.47	1.31	0.45	0.18	0.11	0.43	0.12

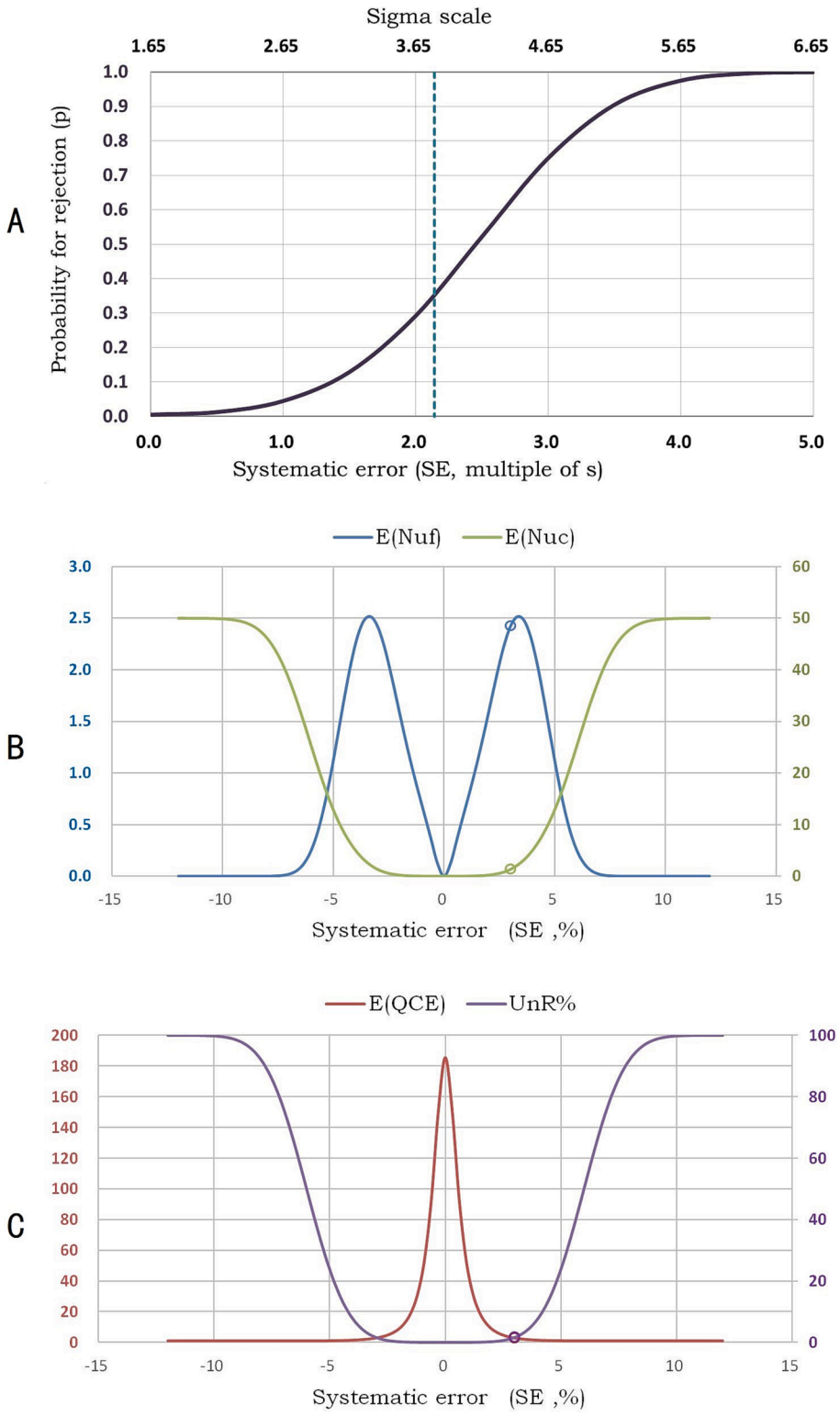

Fig. 2. Power Function Graph and risk diagrams.
TEa: 6%; Bias: 0%; CV: 1.4%; QC rule: 1_{3s} N2; E(N_B): 100; SE: 3.0%.

diagram of E(N_{uf}) and E(N_{uc}) and the risk diagram of E(QCE) and UnR% based on the current QC strategies. As depicted in Fig. 2-A, the rejection rate is illustrated on the Y-axis, the size of the systematic error is represented by the X-axis, the sigma scale is represented by the top X-axis, and the dashed line represents the magnitude of the systematic error. The blue curve in Fig. 2-B represents E(N_{uf}), referring to the left ordinate. The green curve represents E(N_{uc}), referring to the right ordinate. When the measurement procedure is stable (in-control), both are close to 0. With the increase of the systematic error, E(N_{uf}) tends to increase at first and then tends to decrease after reaching the peak value, i.e., MaxE(N_{uf}), and finally approaches 0 again. Accordingly, E(N_{uf}) has a very low value for extremely little or large systematic errors. With the

increase of the systematic error, E(N_{uc}) tends to increase until reaching the maximum value E(N_0). The red curve in Fig. 2-C represents E(QCE), or $ARL_{ed,}$ referring to the left ordinate. The purple curve represents UnR %, referring to the right ordinate. When the measurement procedure is stable (in-control), the value of E(QCE) is the largest, and UnR% is nearly 0. With the increase of the systematic error, E(QCE) decreases significantly to 1, whereas UnR% tends to increase and approaches 100%. The small dots represent the risk position under the current systematic error.

4. Discussion

In CLSI C24-Ed4, the goal of QC in the laboratory is to reduce the risk of harm to a patient due to erroneous results. The application of Parvin's patient risk model illustrates how to achieve the above goal, whereas it is difficult to understand and implement. The patient risk model based on MaxE(N_{uf}) is capable of quantitatively correlating a laboratory's SQC strategy (the number of QC materials to measure, the number of QC results, the QC rule to use at the respective QC event, the frequency of QC events) with the expected number of unreliable patient results produced under an out-of-control condition. The above quantitative methods are associated with numerous parameters and require considerable mathematical calculations. These methods are difficult to complete by hand. A spreadsheet can help with the above-described calculations through a pre-edited program, such that it is adopted to design QC programs based on patient risk.

Traditional SQC design tools, e.g., power function graphs and charts of operating specifications, are not effective in evaluating the risk degree and designing the QC frequency of the measurement procedure. As Parvin's risk model has aroused rising attention, several scholars have conducted in-depth research [15–17] and developed simple tools to design risk-based SQC procedures. Westgard Sigma Rules with Run Sizes [18] refers to a simple qualitative graphics tool. This tool is capable of dividing sigma values into four intervals, each of which provides one QC scheme and the maximum run size. The Sigma-metric SQC run size nomogram [19] tool first determines the intersection point following the vertical line of sigma value and the candidate SQC line. Subsequently, the maximum run size is read on the vertical coordinate based on the intersection point, thus providing up to seven candidate SQC schemes. An internet QC Frequency Calculator tool [20] calculates the run size after transformation by the regression curve formula of SQC line in the nomogram tool; it calculates the maximum run size of 10 candidate QC schemes simultaneously.

The spreadsheet tool, based on the mathematical formula of "E(N_{uf})", can accurately calculate the MaxE(N_{uf}), E(N_u), E(N_{uc}), ARL_{ed} and other risk parameters based on current QC schemes while providing over 20 alternative QC rules. Moreover, a Power Function Graph and two risk diagrams are presented to help laboratory staff gain insights into Parvin's patient risk model. With the use of the above-described tool, laboratories are enabled to intuitively understand the degree of risk of current QC schemes and better evaluate or adjust the schemes.

The core of a QC strategy focusing on patient risk is to limit the number of E(N_{uf}). As depicted in the E(QCE) diagram, relatively large systematic errors are easy to detect; a small out-of-control condition will be difficult to detect, which requires more QC events. This condition may last for a long time, with a greater risk of unreliable results reported. In addition, MaxE(N_{uf}) does not appear under a fixed system error size. As depicted in Table 2 in the "|SE(%)| at MaxE(N_{uf})" values, when the measurement procedure is implemented with different QC strategies, the "|SE(%)| at MaxE(N_{uf})" value will be different. After the design of QC strategy based on MaxE(N_{uf}), it can be ensured that the number of unreliable patient results reported conforms to the requirements of risk control no matter what degree of the systematic error occurs. As depicted in the two risk diagrams in Fig. 1, when bias exists in the measurement procedure, the curves of E(N_{uf}), E(N_{uc}) and UnR% will no longer be symmetrical with the middle line. The reason for the above result is that when a systematic error in the opposite direction of the bias occurs, the systematic error will offset part of the bias, and the number of E(N_{uf}) will be decreased. Accordingly, when there is positive bias, the left E(N_{uf}) curve will decline or be lower than the horizontal coordinate; when there is negative bias, the right E(N_{uf}) curve will decline or be lower than the horizontal coordinate; the E(N_{uc}) and UnR% curves will shift in the opposite direction of the bias. There is more debate about how to determine bias. The CLSI C24-Ed4 document recommends that one option is to assume bias is equal to zero, which aims to identify deviations under stable operating conditions [1].

Maximum run size is primarily adopted to optimize QC frequency in the laboratory, which is directly correlated with MaxE(N_{uf}) and related to multiples of Patient Risk Factor. The relationship between them is expressed as follows: E(N_B)/MaxE(N_{uf}) = Max Run Size/Patient Risk Factor. When Patient Risk Factor is set to 1 and E(N_B) is set to 100, Max Run Size = 100/MaxE(N_{uf}). It is noteworthy that in daily work, the expected number of patient specimens tested between QC events [E(N_B)], i.e., the practical run size, should be determined based on the daily workload, the turn-around-time requirements and desired reporting intervals in the laboratory [13], instead of directly using the maximum run size as the practical run size of the laboratory for daily work.

Sigma values take on a critical significance in selecting QC rules and optimizing QC frequency. For a low-medium sigma level measurement procedure, stricter QC rules and more frequent QC events will increase the cost of laboratory SQC, while reducing the cost to repeat the patient specimen measurements and the risk of issuing corrective reports and harms. For high sigma measurement procedures, the cost of laboratory SQC can be reduced by relaxing the QC limit or by appropriately increasing the run size. At the extremely low sigma value, the MaxE(N_{uf}) value will be higher than the E(N_B) or run size. It is also confirmed from the perspective of patient risk that there may be no appropriate QC strategy to ensure patient safety in the measurement procedure with low sigma levels, such that the laboratory should strive to increase the precision of the measurement procedure to improve the sigma value, or adjust the bias through evaluation [13], or even replace the measurement procedure to ensure patient safety.

5. Conclusions

The size of the risk parameter MaxE(N_{uf}) is recognized as the core of the Parvin patient risk model. The value of this size and the acceptable standard developed by the laboratory determine whether the current QC strategy conforms to the risk requirements, whether the QC rules should be changed, and whether the run size should be adjusted. The data and graphs provided by the spreadsheet tool can provide more insights into the patient risk model and assist laboratories in assessing the risk of QC strategies and designing personalized QC strategies. It simplifies the design of SQC procedures based on patient risk parameters.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2023.03.009.

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