Journal of Diabetes Science and Technology
Volume 7, Issue 3, May 2013

ORIGINAL ARTICLE

Impact of Glucose Measurement Processing Delays on Clinical Accuracy and Relevance

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Abstract

Background:

In a hospital setting, glucose is often measured from venous blood in the clinical laboratory. However, laboratory glucose measurements are typically not available in real time. In practice, turn-around times for laboratory measurements can be minutes to hours. This analysis assesses the impact of turn-around time on the effective clinical accuracy of laboratory measurements.

Methods:

Data obtained from an earlier study with 58 subjects with type 1 diabetes mellitus (T1DM) were used for this analysis. In the study, glucose measurements using a YSI glucose analyzer were obtained from venous blood samples every 15 min while the subjects were at the health care facility. To simulate delayed laboratory results, each YSI glucose value from a subject was paired with one from a later time point (from the same subject) separated by 15, 30, 45, and 60 min. To assess the clinical accuracy of a delayed YSI result relative to a real-time result, the percentage of YSI pairs that meet the International Organization for Standardization (ISO) 15197:2003(E) standard for glucose measurement accuracy (±15 mg/dl for blood glucose < 75 mg/dl, ±20% for blood glucose ≥ 75 mg/dl) was calculated.

Results:

It was observed that delays of 15 min or more reduce clinical accuracy below the ISO 15197:2003(E) recommendation of 95%. The accuracy was less than 65% for delays of 60 min.

Conclusion:

This analysis suggests that processing delays in glucose measurements reduce the clinical relevance of results in patients with T1DM and may similarly degrade the clinical value of measurements in other patient populations.

J Diabetes Sci Technol 2013;7(3):660–668

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Abbreviations: (ISO) International Organization for Standardization, (MARD) mean absolute relative difference, (POC) point of care, (T1DM) type 1 diabetes mellitus

Keywords: clinical accuracy, glucose rate of change, time delay, turn-around time, YSI

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Introduction

Tight glycemic control has been demonstrated to improve outcomes in critically ill patients,[1] though a large multicenter trial was unable to demonstrate similar outcomes.[2] Nevertheless, it is standard practice to utilize intensive insulin therapy for hyperglycemia in critically ill patients.[3] It has been reported that point-of-care (POC) meters do not have the same accuracy and precision as laboratory analyzers and are not recommended for management of critically ill patients.[4,5] However, an important source of glucose measurement error is the *delay* in providing actionable glucose measurements to the clinician. That is, the longer the time between collecting a glucose specimen and reporting its glucose value to the clinician, the more likely the patient's glucose level has significantly changed. An advantage of using POC meters over laboratory analyzers is that, in general, this delay, or turn-around time, is much shorter.

Typical clinical laboratory workflows include pre-analytical, analytical, and post-analytical phases. The pre-analytical phase includes specimen collection, transport, and receipt. The analytical phase includes the laboratory test and interpretation of results, while the post-analytical phase includes result reporting and specimen management.[6] This workflow in many situations leads to long turn-around times. A study of 722 institutions and 2763 clinicians reported that the median turn-around time for glucose is 30 min.[7] In another study, it was reported that the mean in-laboratory turn-around time (analytic phase) alone was 24–36 min for glucose results.[8] One study performed in a large university-associated urban emergency department reported turn-around times up to 2 h for central-laboratory-based glucose testing, with majority of the time spent in the pre-analytical phase.[9] In contrast, it has also been reported elsewhere that turn-around times can be as short as 10 min.[10]

Long laboratory turn-around times can pose a risk when timely therapeutic decisions are required. Interventions or treatments based on a patient's *previous* clinical state rather than the *current* state may compromise care. In order to assess the validity of the treatment decision, it is important to understand how much time transpired between blood sample collection and treatment intervention.

Clinical laboratory measurement of blood glucose using YSI analyzers is commonly accepted as a standard method.[11] In this report, we retrospectively assess the clinical accuracy of time-delayed glucose measurements (relative to a real-time result) obtained using a YSI analyzer in people with T1DM during periods of typical glucose management and during insulin and glucose challenges. We evaluate the accuracy of time-delayed glucose results in terms of meeting International Organization for Standardization (ISO) 15197:2003(E) criteria.[12]

Methods

Study Population

Study data were collected for the purposes of assessing the accuracy of the FreeStyle Navigator continuous glucose monitoring system, as reported elsewhere.[13] A total of 58 subjects with T1DM who were not critically ill and over 18 years of age were enrolled in the study. The average age of the subjects was 41 ± 11 (average ± standard deviation) years and the range was 18–64 years.

Study Design

Subjects spent a total of 50 h (in two or three sessions) of the 5-day study period at the health care facility, during which venous blood samples were collected at 15 min intervals via an intravenous angiocatheter. Glucose was measured in duplicate from single blood samples using the YSI 2300 STAT Plus Glucose and Lactate Analyzer (Yellow Springs Instruments Inc., Yellow Springs, OH). The YSI analyzer uses a biosensor with glucose oxidase that measures hydrogen peroxide (released when glucose is oxidized) using a platinum electrode. The YSI analyzer has a manufacturer-reported precision of ±2% of a reading or 2.5 mg/dl (whichever is larger). Measurements were multiplied by a factor of 1.12 to obtain plasma equivalent values. Subjects were given insulin and glucose challenges on separate days to collect enough data during periods of rapidly changing glucose. The insulin challenges were individualized to each subject to bring the glucose level down to 60 mg/dl. The glucose challenges were orally administered and fixed at

75 g of glucose. Subjects were free to perform their daily activities except during the challenges. Subjects followed their previously established medication regimen.

Data Analysis

For this retrospective analysis, only the YSI measurements were used. Prior to analysis, YSI duplicate results that differed by more than 4% (≥100 mg/dl) or 4 mg/dl (<100 mg/dl) were excluded per guidance from ISO 15197. In addition, YSI duplicate results were excluded if they indicated nonphysiological rate of change (>4.4 mg/dl/min) or if operators noted time delays between duplicates, errors, or suspect samples. Acceptable duplicate YSI measurements were averaged to get a total of 10,010 YSI measurements. To simulate delayed laboratory results, each YSI result from each subject was paired with one from a later time point from the same subject separated by time delays of 15, 30, 45, or 60 min. A pair of YSI glucose results consisted of measurements made at times t_1 and t_2, where $t_2 = t_1$ + time delay. Using pairs of YSI results, the %A, %B, %C, %D, and %E of the Clarke error grid[14] were calculated. Mean absolute relative difference (MARD) was calculated by taking the average (for all pairs) of the absolute difference of two YSI results in a pair relative to the first YSI result in the pair. Clinical accuracy, defined as percentage of conformity with ISO 15197:2003(E), was calculated (±15 mg/dl for glucose <75mg/dl and ±20% for glucose ≥75 mg/dl). The same analysis was conducted once using all data and again on two different subsets of data. The first subset was intended to eliminate the relative impact of the glucose and insulin challenges by excluding points in the 5 h time period after each challenge. The second subset was intended to eliminate the relative impact of rapid glucose change by excluding points that showed rate of change ≥2 mg/dl/min. Rate of change in mg/dl/min was calculated by determining the first derivative at every point using a finite forward difference formula as shown:

$$Rate\ of\ change_t = \frac{Glucose_{t+15} - Glucose_t}{15}$$

Results

A typical YSI glucose profile obtained from a subject is shown in **Figure 1**. The subject was given glucose and insulin challenges as indicated.

Analysis of All Data with No Exclusions

Figure 2 and **Table 1** summarize the effect of delay in delivery of glucose results on clinical accuracy when all points were used for the analysis. The number of pairs decreases with increase in time delay because fewer pairs are available for larger time delays at the end of the clinic visit period. It was observed that glucose data points separated by as little as 15 min had a clinical accuracy of 91.5%, which is less than the 95% accuracy defined by ISO 15197:2003(E). As expected, clinical accuracy further degrades as the delay increases. **Figure 2** shows the corresponding Clarke error grid plots.

Analysis of Data after Excluding Insulin and Glucose Challenges

In order to assess the impact of glucose and insulin challenges on accuracy, blood glucose data in the 5 h period after glucose and insulin challenges were removed and the analysis was repeated, with results shown in **Figure 3** and **Table 2.**

It was observed that the clinical accuracy was still less than 95% if a result was delayed by 15 min or more. The corresponding Clarke error grid plots are shown in **Figure 3**.

Analysis of Data after Excluding Rapid Rate of Change

In order to further assess the impact of rapidly changing glucose on delayed result accuracy, points associated with an absolute rate of change greater than or equal to 2 mg/dl/min were excluded from the full data set and the analysis was repeated. The results are presented in **Figure 4** and **Table 3**.

It was observed that, when rapidly changing glucose regions were excluded, for a time delay of 15 min, the clinical accuracy is better than 95%. However, for longer delays, the clinical accuracy is below 95%.

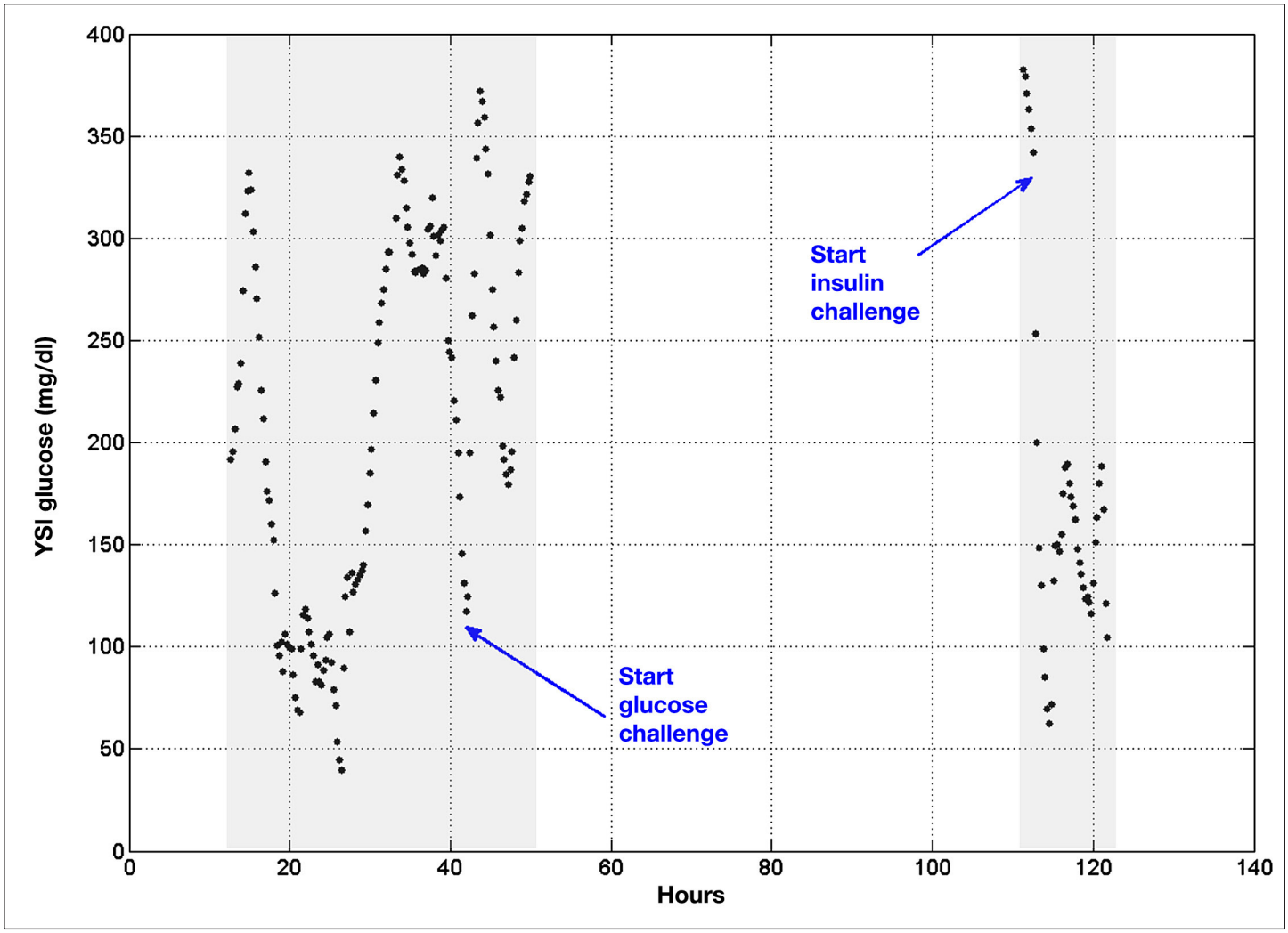

Figure 1. Example of a 50 h YSI profile obtained from a subject. The areas shaded in gray indicate the time the subject was at the health care facility. Outside of clinic hours, subjects were at home and were free to perform their usual activities.

The clinical accuracy results are summarized in **Figure 5** as a function of delay time and for the different degrees of glucose rate-of-change. In the figure, we show that clinical accuracy worsens with increasing time delay. For analysis performed excluding glucose and insulin challenges, it was observed that a delay of 13 min (based on interpolation) or more can reduce clinical accuracy below the ISO 15197:2003(E) recommendation of 95%. Accuracy is further reduced when delay is coupled with a high glucose rate of change. The analysis showed that, at 15 min of delay, the clinical accuracy ranged from 91.5% to 97.4%, depending on the degree of glucose rate of change. Further degradation of accuracy is observed for delays larger than 15 min. Accuracy recommended by ISO 15197:2003(E) at a 15 min delay is achieved only when measurements associated with glucose rate of change of greater than 2 mg/dl/min are excluded. Interpolation (at a fixed Y value of 95%) can be used to ascertain the time delay that can be tolerated to achieve the ISO criteria for the three analysis categories. It can be seen in **Figure 5** that a delay of 10–18 min can be tolerated before the accuracy falls below ISO criteria.

Discussion

It is not unusual for patients with diabetes to have glucose rates of change greater than 2 mg/dl/min. Glucose rates of change have been observed to be greater than 2 mg/dl/min around 20% of the time in two separate studies in (1) a candidate for islet transplantation and (2) the control group of a clinical trial for pramlintide in type 1 diabetes mellitus (T1DM) subjects.[16] Thus it is reasonable to assume that glucose rates of change in excess of 2 mg/dl/min are

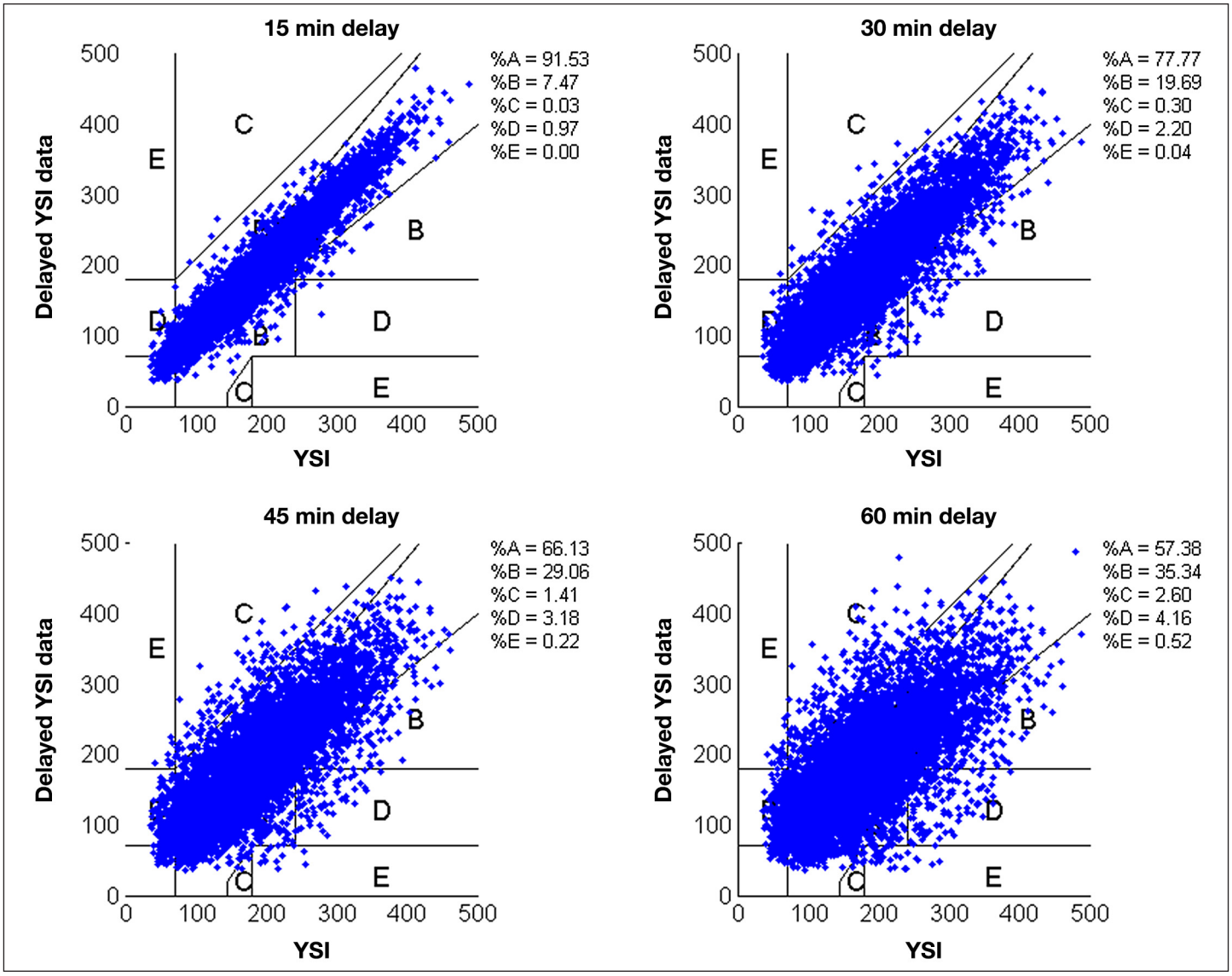

Figure 2. Clarke error grid analysis of delayed YSI glucose measurements when no data points were excluded from the analysis.

Table 1.
Clinical Accuracy Defined by ISO 15197:2003(E); %A, %B, %C, %D, and %E of Clarke Error Grid; and Mean Absolute Relative Difference of Delayed Laboratory Measurements When No Data Points Were Excluded from the Analysis

Time delay (min)	Number of pairs (count)	Clinical accuracy (%)	%A	%B	%C	%D	%E	%MARD
15	9142	91.46	91.53	7.47	0.03	0.97	0.00	8.20
30	8951	77.75	77.77	19.69	0.30	2.20	0.04	14.69
45	8799	66.14	66.13	29.06	1.41	3.18	0.22	20.47
60	8645	57.40	57.38	35.34	2.60	4.16	0.52	25.66

experienced in a hospital setting. For comparison, **Figure 5** also shows a shaded region and two bold dots representing reported accuracy for a typical POC meter in non-intensive care unit and intensive care unit patients[15] of 97.5% and 89%, respectively. This illustrates the clinical accuracy comparison between POC meters and laboratory instruments with delay; as the delay increases, the effective accuracy of the laboratory instrument is quickly degraded so that, after approximately 5–12 min delay (depending on glucose rate of change), it is comparable to the accuracy of a typical

POC meter. In this study, only errors due to time delay relative to real-time results were studied. It is likely that other analytical errors could result when blood samples are not immediately analyzed after collection.

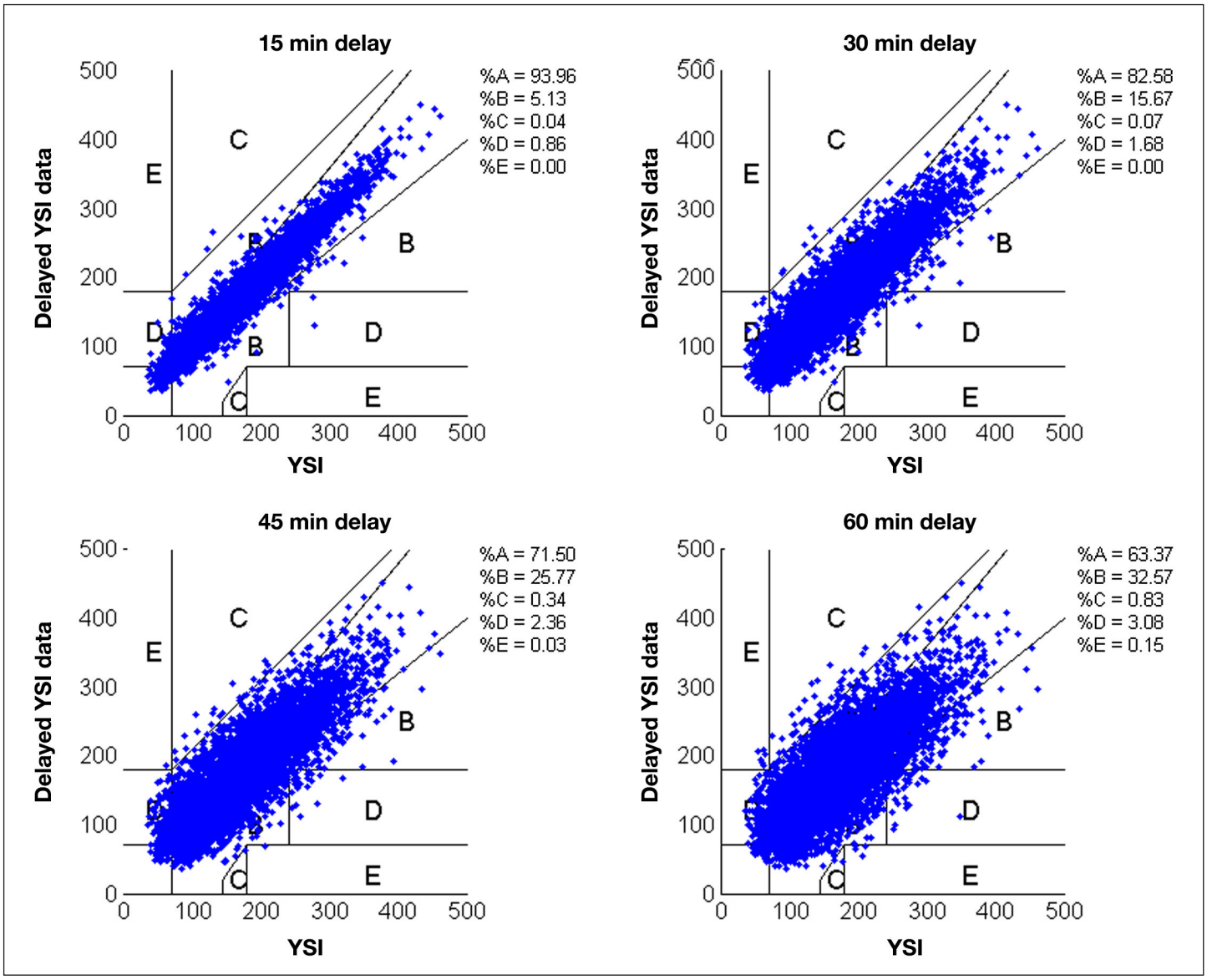

Figure 3. Clarke error grid analysis of delayed laboratory glucose measurements after exclusion of data within 5 h after insulin and glucose challenges.

Table 2.
Clinical Accuracy Defined by ISO 15197:2003(E); %A, %B, %C, %D, and %E of Clarke Error Grid; and Mean Absolute Relative Difference of Delayed Laboratory Measurements When Data Points within a 5 h Period after Insulin and Glucose Challenges Were Excluded

Time delay (min)	Number of pairs (count)	Clinical accuracy (%)	%A	%B	%C	%D	%E	%MARD
15	7203	93.93	93.96	5.13	0.04	0.86	0.00	7.15
30	6946	82.52	82.58	15.67	0.07	1.68	0.00	12.54
45	6738	71.49	71.50	25.77	0.34	2.36	0.03	17.26
60	6528	63.42	63.37	32.57	0.83	3.08	0.15	21.36

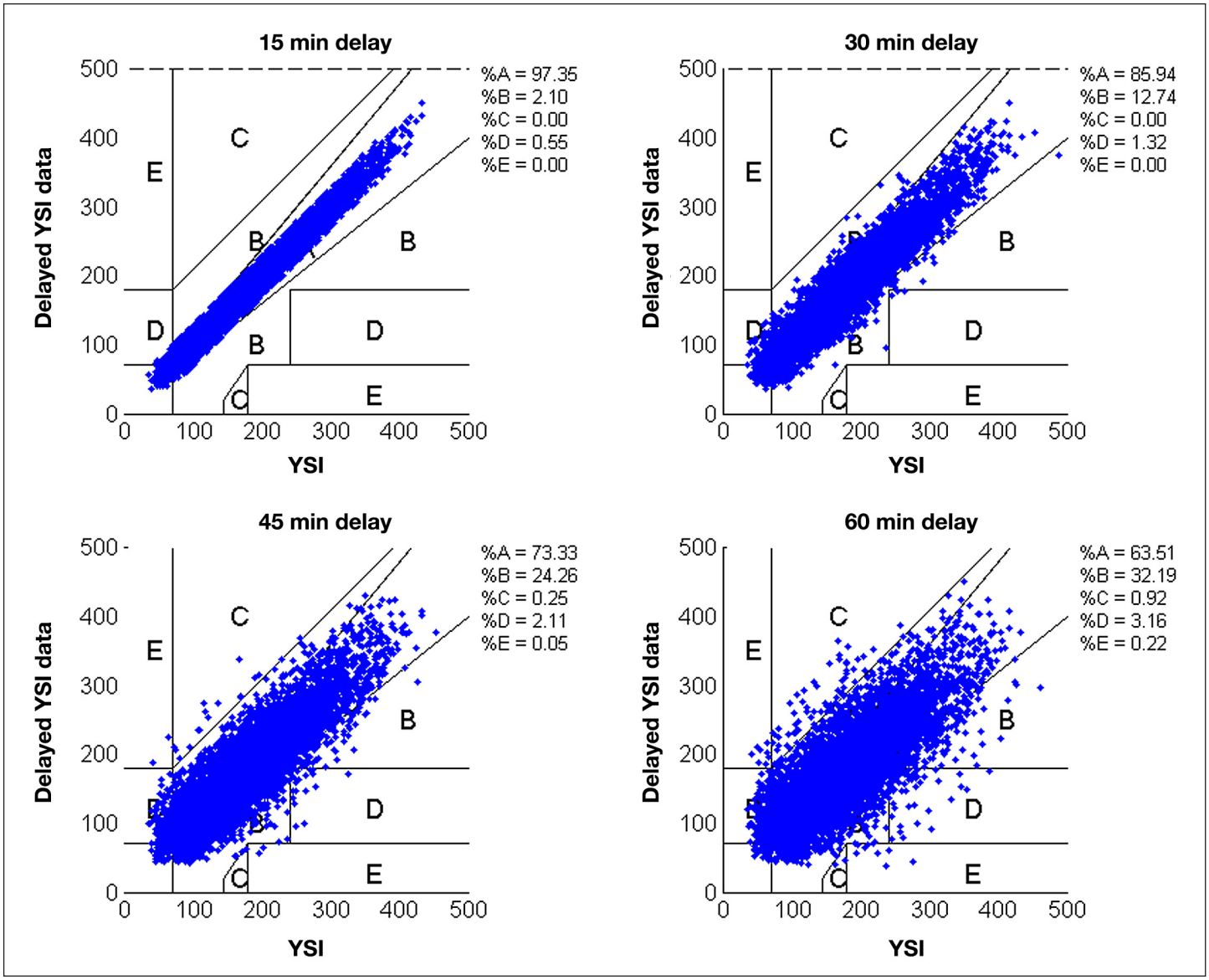

Figure 4. Clarke error grid analysis of delayed laboratory glucose measurements after removal of rapidly changing (≥2 mg/dl/min) glucose data.

Table 3.
Clinical Accuracy Defined by ISO 15197:2003(E); %A, %B, %C, %D, and %E of Clarke Grid; and Mean Absolute Relative Difference of Delayed Laboratory Measurements after Exclusion of rapidly Changing Glucose Data

Time delay (min)	Number of pairs (count)	Clinical accuracy (%)	%A	%B	%C	%D	%E	%MARD
15	7761	97.36	97.35	2.10	0.00	0.55	0.00	5.84
30	7473	85.88	85.94	12.74	0.05	1.32	0.00	11.01
45	7298	73.34	73.33	24.26	0.25	2.11	0.05	16.32
60	7152	63.52	63.51	32.19	0.92	3.16	0.22	21.39

Reported clinical laboratory turn-around times for glucose measurement in hospitals from sample collection to glucose result is in the range of 10–120 min.[7–10] It can be seen that this could have a large impact on effective clinical accuracy. This analysis provides a quantitative means for hospitals to trade off accuracy, measurement cost, and logistics cost when it comes to using the clinical laboratory versus POC instruments for measuring glucose.

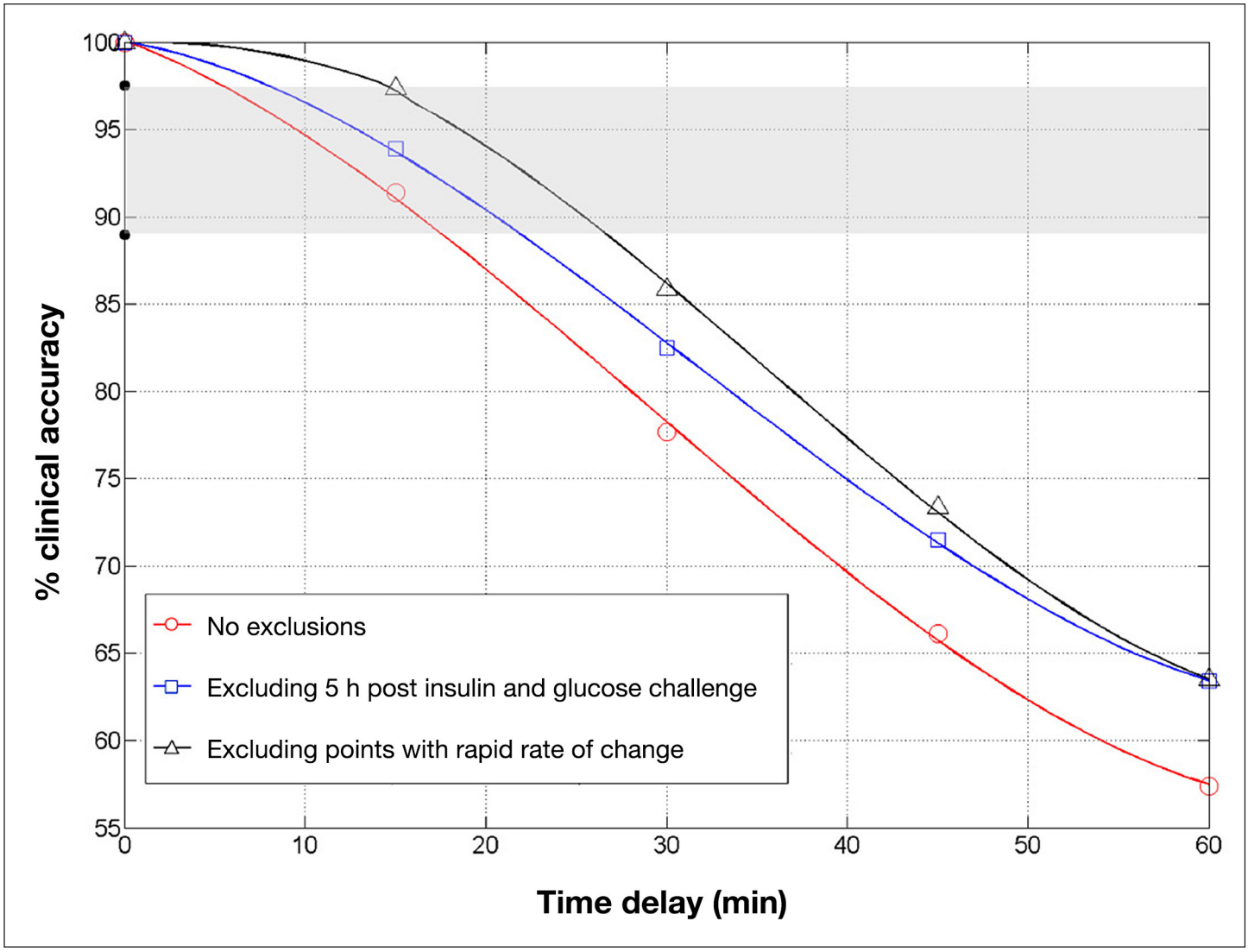

Figure 5. Plots of clinical accuracy (*y* axis) as per ISO 15197:2003(E) versus the delay time between paired points (*x* axis). The shaded region within the bold dots indicates POC meter accuracy of 89% for intensive care unit patients and 97.5% for non-intensive care unit patients.[15] The trend line was drawn using polynomial fits to obtained data. A zero-delay accuracy of 100% was calculated based on YSI manufacturer's specifications.

For this analysis, only subjects with T1DM were available from the study. T1DM patients have been known to have larger excursions from a euglycemic state than type 2 diabetes or nondiabetic patients[17] and thus may have worse accuracy for a given turn-around time. Further studies are needed to understand glucose excursions for non-T1DM patients in a hospital setting (critically ill or not) to generally characterize glucose variability and its impact on measurement accuracy. This should be an additional consideration when implementing glucose measurement procedures in hospitals or in specific departments of hospitals. Hospital glucose measurement procedures may benefit from combining laboratory, POC, and sensor-based continuous glucose monitoring in order to capitalize on their respective strengths. Laboratory measurements have the highest point accuracy but the slowest turn-around time, whereas POC meters have lower point accuracy but instantaneous (less than 3 min) turn-around time. Sensor glucose measurements have lower point accuracy but instantaneous and high-quality rate-of-change measurement[18,19] and may be used to guide when higher point-accuracy measurements are required for clinical action.

Conclusion

Though laboratory instruments are more accurate than POC glucose meters, delayed laboratory results undermine the inherent accuracy of laboratory instruments. To maintain an acceptable level of clinical accuracy as defined by

ISO 15197:2003(E), laboratory glucose measurements must be available and acted upon within 10–18 min of the patient blood draw in the case of T1DM patients. Longer delays degrade accuracy to an extent that the ISO 15197:2003(E) standard criteria are no longer met and, at some point, compare unfavorably with POC meter accuracy. Further studies are required in non-T1DM patients to understand the impact of time delay on glucose measurement accuracy.

Funding:

This work was funded by Abbott Diabetes Care Inc., Alameda, CA.

Disclosure:

The authors are full-time employees of Abbott Diabetes Care Inc.

Acknowledgments:

The authors thank Royce Cheng (formerly at Abbott Diabetes Care Inc.) for initial data analysis and Scott Harper, Ken Doniger, and Erwin Budiman for technical input.

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