Clinical consequences of a miscalibrated digoxin immunoassay

Aaron E. Lim, MBBS(Hons), 1 Jillian R. Tate, MSc, 2 David Clarke, BSc, 2 Ross L. Norris, PhD, 3,4,5 Raymond G. Morris, PhD, 6 Jennifer H. Martin, PhD 1,7

1 Translational Research Institute, The University of Queensland, Woolloongabba, Queensland, Australia
2 Department of Chemical Pathology, Pathology Queensland, Royal Brisbane & Women’s Hospital, Herston, Queensland, Australia
3 Mater Research Institute, Raymond Terrace, South Brisbane, Queensland, Australia.
4 School of Pharmacy, Griffith University, Gold Coast, Queensland, Australia
5 School of Pharmacy, The University of Queensland, Woolloongabba, Queensland, Australia
6 Discipline of Pharmacology, The University of Adelaide, Adelaide, South Australia, Australia
7 Division of Internal Medicine, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia

Correspondence:

Dr. Aaron E Lim, BPhrm, MBBS(Hons)
The University of Queensland, Translational Research Institute, 37 Kent St, Woolloongabba, Queensland 4102, Australia
Email: aaron.lim@uqconnect.edu.au

Postal address: 115 Kenna St Aspley 4034 QLD Australia
Phone: +61421351893 Fax: +61730148788

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Abstract

Background: A routine audit revealed that the analytical method used to measure digoxin concentrations by our State-wide pathology provider in 2009 was underestimating digoxin concentrations by 10%. The assay was recalibrated by the manufacturer in 2010 but clinical outcomes of the underestimation were never measured. This is a pilot study to describe the prescribing behaviour around out of range digoxin concentrations, and to assess if miscalibrated digoxin immunoassays contribute to clinically relevant effects as measured by inappropriate alterations in digoxin doses.

Methods: 30,000 digoxin concentrations across the State Hospital system were obtained in two periods before and after recalibration of the digoxin assay. Digoxin concentration means were calculated and compared and were statistically significantly different. Subsequently, a single-centred retrospective review of 50 randomly chosen charts was undertaken to study the clinical implications of the underestimated concentrations.

Results: Mean digoxin concentrations for 2009 and 2011 were significantly different by 8.8% (CI 7.0%-10.6%). After recalculating 2009 concentrations to their ‘corrected’ values, there was a 16% increase in the number of concentrations within the range when compared to 2011 (41.48% vs 48.04%). However, overall this did not cause unnecessary dose changes in patients that were ‘borderline’ or outside of the therapeutic range, when compared to controls (P = 0.10). The majority of decisions were based on the clinical impression rather than concentration alone (85.1% vs. 14.9%), even when the concentration was outside of the ‘therapeutic range’.

Conclusion: Although, recalculating digoxin concentrations measured during 2009 to their ‘corrected’ values produced a significant change in concentration and values inside and outside of the range, this does not appear to have had an influence on patient treatment. Rather, clinicians tended to use the clinical impression to dose digoxin.

Key Words: digoxin, therapeutic drug monitoring, serum concentrations, prescribing behaviour, miscalibrated assay
**Introduction:**

Digoxin is still used in the treatment of atrial fibrillation (AF) and heart failure but requires therapeutic drug monitoring (TDM) due to its narrow therapeutic range (0.8-2.0 µg/L for AF).\(^1,2\)

TDM requires a complex set of people and system resources – pre validation and calibration, analytical aspects, post validation, reporting and interpretation; a set of factors not commonly found all together in one laboratory.

There is evidence to show that measured plasma digoxin concentrations may vary by a clinically significant amount as a result of the use of different methods and/or analysers and from interference from digoxin-like immunoreactive substances (DLIS).\(^3-7\) This can lead to inappropriate digoxin dosing which can potentially lead to serious problems for patients’ health.\(^3,4\)

During an external quality assurance program in 2010, the Beckman Coulter plasma and serum turbidimetric inhibition digoxin immunoassay used by Pathology Queensland in 2009 was found to be approximately 10% lower than the true value (personal communication Jill Tate, senior scientist Chemical Pathology, Pathology Queensland). As a result, the manufacturer re-standardised the method later in 2010 against a higher order reference method; however, the clinical effects of this recalibration were never quantified. For the Beckman Coulter digoxin assay, the laboratory has a between-run precision of 5% coefficient of variation (CV) at a concentration of 2.0 µg/L. Hence, values of 1.8-2.2 µg/L are considered equivalent and within the allowable limits of performance of 10% CV. An additional positive bias of 10% however, will contribute to an extra 0.2 µg/L. This may elevate a value of 2.0 µg/L to 2.4 µg/L (toxic range) or may lower it to 1.6 µg/L (within the therapeutic range) if there was a negative bias. This would seem clinically significant as higher concentrations of digoxin have been associated with an increase in toxicity.\(^8,9\)
The present study considered whether clinicians made decisions based on the patient’s clinical situation or impression and not solely on measured digoxin concentrations. If clinicians based their decisions solely on the clinical impression, then any discordance between measured digoxin concentrations may not have had a significant clinical impact.

A literature review concluded that there are no data on the clinical outcomes of either biased or imprecise plasma digoxin concentration measurements regardless of the cause; whether from variability between analysers or interference from DLIS. However, a New Zealand study has shown that clinicians were more inclined to dose patients based on their clinical situation when serum digoxin concentrations were low, while high digoxin concentrations were deemed to represent toxicity regardless of the patient’s clinical impression. This is consistent with research showing that higher digoxin concentrations may correlate with digoxin toxicity. Nonetheless, data on current digoxin prescribing in Australia are still lacking; and it has been suggested by the literature that future method comparison studies would benefit from protocols that include the effect on clinical decision-making, not solely measures of analytical performance in isolation.

Consequently, this is a pilot study to describe the prescribing behaviour around out of range digoxin concentrations, and to assess if miscalibrated digoxin immunoassays contribute to clinically relevant effects.

Thus, the aims of this study were to firstly ascertain if recalculation of data collected during 2009 to their ‘corrected’ values altered the number of concentrations within the therapeutic range for that year. Secondly, to investigate if unnecessary alterations in digoxin doses occurred after recalculating the 2009 data to the ‘corrected’ concentrations. Lastly, whether clinicians dosed digoxin purely on measured concentrations or their clinical impression (as judged by blinded assessment).
**Materials and Methods:**

**Determining the difference between pre and post calibrated concentrations**

To define the difference in average digoxin concentrations pre (2009) and post calibration (2011), de-identified Pathology Queensland Statewide data for digoxin concentrations were obtained for the two time periods. The mean digoxin concentrations for both years were calculated and a two-sample student T-test was performed for comparison. All concentrations were analysed, including first measurements.

Concentrations from 2009 were then corrected by the percentage of the mean difference found between 2009 and 2011 and the number of concentrations within the range pre and post recalculation were compared using Pearson’s chi-squared analysis. The therapeutic range used was the standard Pathology Queensland range of 0.8–2.0 µg/L which is the accepted range for the treatment of AF.\(^1\)\(^1\)

**Clinical implications of underestimating digoxin concentrations and clinical prescribing behaviour of digoxin**

The second and third aims of this study examined the clinical implications of underestimating digoxin concentrations in 2009. To achieve this, a single-centre retrospective chart review by a clinical expert was devised. Prior ethical approval from the Research and Ethics Committees of Queensland Health Metro South, Pathology Queensland Governance and The University of Queensland was obtained.

**Patient selection for clinical relevance section:**

As this was a pilot study, a smaller sample was chosen for an in depth chart review. 50 charts from the Princess Alexandra Hospital (PAH) of patients who had borderline digoxin concentrations (0.8 or 2.0 µg/L) or were outside of the range (< 0.8 or >2.0 µg/L) during a 6 month period in 2009 were randomly selected by systematic sampling using an equal-probability method. Of these 50 charts, 25 charts had borderline digoxin concentrations with 7
charts in the >2.0 µg/L group and 18 charts in the < 0.8 µg/L group. The other 25 charts had digoxin concentrations outside of the range with 12 charts in the >2.0 µg/L group and 13 charts in the < 0.8 µg/L group. Ten additional charts of patients who had digoxin concentrations within the range were also randomly selected using the same methodology. These ten charts were used as control samples as it was assumed that no changes in dosing were made if concentrations were within the range.

Thus, including controls, 60 charts in total were examined. Charts were excluded if insufficient clinical data were available to make a judgement on whether appropriate management was undertaken; or if the patient was on digoxin for indications other than AF. Patients who were on digoxin for both AF and congestive heart failure were included.

All concentrations were measured using the Beckman DxC (Beckman Coulter, Brea, CA) analyser at the PAH, Queensland, Australia. Patient data collected included age, sex, sampling and dosing times, digoxin concentrations and doses, serum creatinine, serum potassium, weight, co-morbidities, number of medications, signs of under or overdosing and whether patients were concurrently on other anti-arrhythmic drugs. Sampling and dosing times were recorded to ensure digoxin concentrations were sampled at the appropriate times (Table 1). Although creatinine clearance estimations would have been a better estimate of renal function, serum creatinine was used due to the inability to locate patients’ weights in more than half of the charts. The list of recorded data is further detailed in Table 1.

**Study end-points:**

**Clinical implications of underestimating digoxin concentrations**

The second aim of this study was to assess whether unnecessary alterations in digoxin doses would have occurred after recalculating the data collected in 2009 to the corrected concentrations. Thus, clinical charts were examined to assess whether appropriate decisions were made based on the original concentrations prior to instrument recalibration in 2009.
Decisions for that particular concentration were classified as either: appropriate or inappropriate.

An appropriate decision was defined as a change in digoxin dose consistent with the corrected concentration and was the variable of interest. For example, if the corrected concentration was below the range and an increase in dose was recorded, this would be an appropriate decision. However, if the corrected concentration fell below the range and no change in dose was recorded, this would be defined as an inappropriate decision for the purpose of this study. Here, the clinical stability of the patient was not taken into account; only if the corrected concentration warranted a change in dose in the view of the independent expert reviewer.

Concentrations that were borderline and outside the range were compared to concentrations that were within the range (control) using Fisher’s exact tests. Subgroup analysis was also performed comparing whether the difference between appropriate decisions varied between the < 0.8, 0.8, 2.0 and > 2.0 µg/L groups.

**Clinical prescribing behaviour for digoxin**

The third aim was to elucidate whether clinicians tended to dose digoxin based on the measured digoxin concentration or based on a patient’s overall clinical impression. This was of interest as there are currently no digoxin prescribing guidelines available at the PAH. Actions for each digoxin concentration selected were classified into 2 groups: actions based on either concentration or clinical impression. It was agreed that if a clinician used both the patient’s concentration and the clinical impression of the patient, this would be classified under the clinical impression group. This is because it was difficult to ascertain whether concentrations that were out of the range happened coincidently when clinicians altered the dose of patients.

The definitions for the two groups are as follows:

*Concentration only:* Dose changed after concentration selected was out of the therapeutic range without any signs of clinical instability.
Clinical impression: Dose changed or unchanged based on patient’s clinical stability regardless of therapeutic range.

Criteria for toxicity or underdosing are defined in Table 1. Subgroup analysis was performed for < 0.8, 0.8, 2.0 and > 2.0 µg/L groups. Other variables that may have impacted on the clinician’s decision making were also analysed using Fisher’s exact test. This included being on other anti-arrhythmic drugs, patient’s weight, high serum creatinine, potassium concentration, gender, age, appropriate sampling times for dosing (at steady state, or greater than 6 hours), polypharmacy, and other co-morbidities.

Statistical Analysis Summary:
Univariate statistical analysis was performed using Chi-square tests for categorical variables and student’s T-test for normally distributed continuous variables. Fisher’s exact test was used for paired data for aims two and three due to smaller sample sizes. A two-sided P value of < 0.05 was considered to indicate statistical significance. All calculations were performed using MedCalc for Windows, version 12.7.7 (MedCalc Software, Ostend, Belgium).

Results:
Difference between pre and post recalculated digoxin concentrations
In 2009, there were 15,833 measured digoxin concentrations reported from Pathology Queensland laboratories State-wide with a mean concentration of 0.81 ± 0.70 µg/L, while in 2011 there were 15,816 measured concentrations with a mean concentration of 0.88 ± 0.72 µg/L. Student’s T test showed a significant difference of approximately 8.8% (CI 7.0%-10.6%) between the 2009 and 2011 concentrations.

Concentrations in 2009 were then retrospectively recalculated and increased by a factor of 8.8% to reflect the underestimation of the pre 2010 Beckman method. There was no clinically significant difference when recalculating the concentrations by either 8.8% or the proposed 10% (P = 1.00). The proportion of digoxin measurements which were within the range was found to
differ significantly between the 2009 pre (41.48% within the range) and post (48.04% within the range) recalculated measurements (6.19% difference, CI 5.10%–7.29%, \( P < 0.0001 \)). The difference between the number of digoxin concentrations that were within the range for post recalculated 2009 digoxin concentrations and 2011 digoxin concentrations was not statistically significant (48.04% vs. 46.9%, \( P = 0.25 \)). This suggests that recalculated concentrations from 2009 correlated with recalibrated digoxin concentrations from 2011.

Clinical implications of underestimating digoxin concentrations

57 charts in total were examined. Three charts were excluded from the borderline group according to the exclusion criteria. The final number of charts examined per group is summarised in Table 2.

Of the 47 charts examined of patients with concentrations measured in 2009 that were borderline or out of the range, 34 (72.34%) charts had appropriate decisions. There was no significant difference when compared to the controls which had 100% appropriate decisions (\( P = 0.10 \)). Subgroup analysis was also performed comparing whether the difference between appropriate decisions varied between the < 0.8, 0.8, 2.0 and > 2.0 \( \mu \text{g}/\text{L} \) groups. There was a significant difference between the < 0.8 \( \mu \text{g}/\text{L} \) group and the other three groups (0.8 \( \mu \text{g}/\text{L} \): \( P = 0.0003 \), 2.0 \( \mu \text{g}/\text{L} \): \( P = 0.016 \), > 2.0 \( \mu \text{g}/\text{L} \): \( P = 0.009 \)). This was because post recalculated concentrations that were < 0.8 \( \mu \text{g}/\text{L} \) were still below the range but no increase in doses were noted in the majority of these patients. There were no significant changes between the other groups.

Clinical prescribing behaviour of digoxin

Of the 47 charts examined of patients with concentrations that were borderline or out of the range, the majority of decisions were based on clinical impression (85.1%) as opposed to concentration alone (14.9%). However, this was not equal in all groups. Decisions made by concentration only were significant for digoxin concentrations > 2.0 \( \mu \text{g}/\text{L} \) compared to other
groups (≤ 0.8 µg/L: P=0.04, 0.8 µg/L: P=0.02) but not significantly different from the 2.0 µg/L group (P=0.63).

There appeared to be a trend for clinical impression decision making for patients that were on other anti-arrhythmic drugs (OR 3.06, 95% CI 0.53-17.66), however this proved to be not significant (P=0.24). Other variables also did not appear to significantly impact on whether clinicians based their decision on the clinical impression or the digoxin concentration as demonstrated in Table 3. The impact of serum potassium was not analysed as all samples recorded were within the appropriate reference range.1

**Discussion:**

**Difference between pre and post recalculated concentrations**

A significant number of pre recalculated concentrations in 2009 were within the range post recalculation. This validates previous concerns about the clinical significance of underestimating the data collected in 2009. Although the mean difference between concentrations measured 2009 and 2011 was marginally less than expected, this proved not to be statistically significant. Thus, recalculating the 2009 data by 8.8% or the expected 10% would not have affected the results.

**Clinical implications of underestimating digoxin concentrations**

Overall, recalibration of the digoxin assay did not significantly clinically impact on unnecessary decision making. However, there was a significant difference between the ≤ 0.8 µg/L group and the other three groups. This was because post recalculation, concentrations that were ≤ 0.8 µg/L were still below the range but no increases in doses were noted in the majority of them. Clinicians are generally satisfied with a concentration that is below the therapeutic range as long as the patient is clinically stable (as discussed below). One clinician wrote that, “There was no need for repeat digoxin concentrations as the aim for treatment is rate control and the concentrations do not need to be therapeutic”. In another chart of a patient with concomitant
congestive heart failure the clinician wrote that “it was appropriate to aim for low concentrations in congestive heart failure”; a clinical practice which is in fact supported by the literature but for which there is no quoted therapeutic range.\textsuperscript{12-14}

**Clinical prescribing behaviour of digoxin**

The vast majority of decisions when prescribing digoxin were based on the clinical impression as opposed to concentration alone. This was particularly true with concentrations that were below the therapeutic range even when concentrations were very low (0.3 µg/L). However changes based on concentrations were significantly higher in the > 2.0 µg/L group as clinicians appear to be more cautious about toxicity at concentrations above the range. In fact, in charts of two patients who were borderline high (2.0 µg/L), clinicians specifically noted that although the patients were rate controlled, the dose was reduced because the digoxin concentration was close to the upper limit. A possible contributing factor to this finding is the fact that Pathology Queensland has assigned a digoxin concentration of > 2.0 µg/L as a critical result that must be verbally given to the treating team of the patient, thus, giving the treating clinician an additional prompt for action. Nonetheless, although digoxin concentrations may not always correlate well to the clinical impression\textsuperscript{10}, this trend in dosing is probably associated with best clinical practice. This is because digoxin toxicity could potentially be fatal and the clinical benefits of higher concentrations are questionable.\textsuperscript{10} These findings of clinicians having a greater reliance on laboratory results when digoxin concentrations are at or above the upper limit of the therapeutic range demonstrate similarities in prescribing practice between Australia and New Zealand.\textsuperscript{10}

It was also noted that there was a trend towards more decisions being based on the clinical impression rather than on digoxin concentrations for patients who were on other anti-arrhythmic drugs; however, this was not significant. This trend may be explained by the fact that doses of other co-administered anti-arrhythmic drugs were changed concomitantly, while the digoxin dose was unaltered regardless of the concentration measured. Other variables did not appear to
have any significant impact on whether clinicians based their decisions on the clinical picture, clinical impression, or concentration (Table 3).

It can thus be concluded that clinicians generally dosed digoxin based on a patient’s clinical impression when concentrations were < 0.8 µg/L. Conversely, they tended to use both the patient’s clinical impression and digoxin concentrations for concentrations > 2.0 µg/L. Overall however, the majority of clinicians were treating the patient and not the concentration on a test report, even when the concentrations were well outside the ‘therapeutic range’. Whether the heavy reliance on the clinical impression is a result, at least in part, of a clinician’s awareness of the limitations in assay method accuracy or due to influence from local prescribing culture needs to be further investigated. Additionally, it can be implied that perhaps the current prescribing trends may be adequate as improved assay accuracy and performance could possibly result in the increased reliance on TDM.

The fact that clinicians were treating ‘the patient and not the concentration,’ is a reassuring outcome. It suggests that although biases in digoxin assay methods are important to be aware of, inappropriate changes in dosing are unlikely to occur. In particular, increases in the number of digoxin toxicities are unlikely to occur because although clinicians generally dosed the patient according to the clinical impression when digoxin concentrations were low or within the range, they were guided more emphatically by concentrations when above the range. Given the use of low digoxin concentrations to good effect clinically, perhaps the lower limit of the current therapeutic range (0.8 µg/L) needs to be re-evaluated.

Lastly, this pilot study demonstrates current digoxin prescribing trends in a large Australian tertiary hospital and the clinical use of digoxin concentrations. This could guide future studies containing protocols that include the effects on clinical decision-making from discordant drug concentration results from recalibration or altering methods. Furthermore, the study protocol
could potentially be applied to other drugs that require TDM due to their narrow therapeutic ranges such as lithium, cyclosporin and tacrolimus.

**Study limitations**

Some of the limitations of the study relates to its design. Being a retrospective chart review, it can only be assumed from what was written in the charts as to a clinician’s actual thought and practice processes. However, the text was examined by the clinical supervisor in a blinded manner for validation. It is also acknowledged that the smaller sample size means a lower powered study and a higher likelihood for type one and type two errors; thus increasing the risk of spurious results. In addition, analysing paired controls or subgroups in smaller sample sizes causes a further loss in power. This however, is inevitable and can only be addressed by increasing the sample size of similar studies in the future.

**Conclusion**

Although it has been demonstrated that recalculating digoxin concentrations measured in 2009 to their ‘corrected’ values produced a significant change in concentrations and values ‘inside’ and ‘outside’ of the therapeutic range, this does not appear to have had an influence on patient treatment; at least in the eight to ten percent bias range. Our chart analysis study has shown that the majority of clinicians used their clinical impression to dose digoxin, rather than concentration for most patients, with greater reliance on the concentration at or above the upper limit of the therapeutic range. Whilst unexpected, it is a clinically useful finding and consistent with TDM teaching i.e. that a result be used in the total context of the patient’s clinical impression when prescribing a dose of a drug. This work and the study design are likely to be helpful for laboratories when planning research to assess clinical impact when a new instrument or methodology is introduced in the laboratory.

**Acknowledgements**

We acknowledge my colleague Benny Tu for his assistance in the statistical analysis of this
study.
References

## Tables

**Table 1. Patient data collected.**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs of toxicity</td>
<td>Bradycardia (PR: &lt;60 BPM or a drop in baseline &gt;30 BPM).&lt;sup&gt;1&lt;/sup&gt; PR was used as an objective criterion and was consistently recorded in the charts. ECG changes reflecting digoxin toxicity were not used due to the variable availability within charts.&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Signs of underdosing</td>
<td>Tachycardia (PR: &gt;100 BPM) or uncontrolled AF on ECG if available.&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-arrhythmics</td>
<td>Other drugs used for controlling rate and rhythm in AF: atenolol, metoprolol, diltiazem, verapamil, amiodarone and flecainide.&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Appropriate sampling time</td>
<td>Trough sample measured at least 6 hours after a dose to allow for distribution.&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Normal range for Males: 64-108 µmol/L and Females: 46-99 µmol/L&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>IHD, CHF, HTN, Hypercholesterolaemia, T2DM, CVA, COPD, GORD, OA, CKD</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Patients on ≥ 5 medications.&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

PR, pulse rate; ECG, electrocardiogram; AF, atrial fibrillation; IHD, ischaemic heart disease; CHF, congestive heart failure; HTN, hypertension; T2DM, type 2 diabetes mellitus; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; GORD, gastro-oesophageal reflux disease; OA, osteoarthritis; CKD, chronic kidney disease; BPM, beats per minute
Table 2. Summary of the final number of charts examined per group

<table>
<thead>
<tr>
<th>Group (µg/L)</th>
<th>Number of charts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.8</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>0.8</td>
<td>17</td>
<td>30</td>
</tr>
<tr>
<td>0.9-1.9 (Controls)</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>2.0</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>&gt; 2.0</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>57</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
Table 3. Significance of other variables on clinical decision making

<table>
<thead>
<tr>
<th>Other variables that may affect “clinical vs. concentration” groups</th>
<th>OR (95% CI)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-arrhythmic drugs</td>
<td>3.06 (0.53-17.66)</td>
<td>0.25</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.61 (0.12-3.11)</td>
<td>0.69</td>
</tr>
<tr>
<td>Patient’s weight</td>
<td>†</td>
<td>0.31</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>0.75 (0.15-3.80)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age</td>
<td>†</td>
<td>0.84</td>
</tr>
<tr>
<td>Appropriate sampling times</td>
<td>0.80 (0.08-8.19)</td>
<td>1.00</td>
</tr>
<tr>
<td>Poly-pharmacy</td>
<td>0.30 (0.02-5.81)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Co-morbidities:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>0.61 (0.12-3.11)</td>
<td>0.69</td>
</tr>
<tr>
<td>CHF</td>
<td>1.85 (0.09-38.11)</td>
<td>1.00</td>
</tr>
<tr>
<td>HTN</td>
<td>1.63 (0.32-8.25)</td>
<td>0.69</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>0.72 (0.14-3.67)</td>
<td>0.69</td>
</tr>
<tr>
<td>T2DM</td>
<td>5.16 (0.27-98.41)</td>
<td>0.32</td>
</tr>
<tr>
<td>CVA</td>
<td>1.27 (0.13-12.30)</td>
<td>1.00</td>
</tr>
<tr>
<td>COPD</td>
<td>4.52 (0.24-86.71)</td>
<td>0.32</td>
</tr>
<tr>
<td>GORD</td>
<td>0.15 (0.01-2.80)</td>
<td>0.28</td>
</tr>
<tr>
<td>OA</td>
<td>0.67 (0.06-7.03)</td>
<td>0.57</td>
</tr>
<tr>
<td>CKD</td>
<td>5.85 (0.31-110.91)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

† OR not applicable as T-test was performed

IHD, ischaemic heart disease; CHF, congestive heart failure; HTN, hypertension; T2DM, type 2 diabetes mellitus; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; GORD, gastro-oesophageal reflux disease; OA, osteoarthritis; CKD, chronic kidney disease