Tailoring the sampling time of single-sample GFR measurement according to expected renal function: a multisite audit

Helena McMeekin (h.mcmeekin@nhs.net)
Barts Health NHS Trust https://orcid.org/0000-0002-1717-7043
Sam Townrow
Barts Health NHS Trust
Mark Barnfield
Leeds Teaching Hospitals NHS Trust
Andy Bradley
Manchester University NHS Foundation Trust
Ben Fongenie
Barts Health NHS Trust
Daniel R McGowan
Oxford University Hospitals NHS Foundation Trust
Matthew Memmott
Manchester University NHS Foundation Trust
Charlotte A Porter
Leeds Teaching Hospitals NHS Trust
Fred C Wickham
Royal Free London NHS Foundation Trust
Nick Vennart
South Tyneside and Sunderland NHS Foundation Trust
Maria Burniston
Barts Health NHS Trust

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Abstract

Background

The 2018 BNMS Glomerular Filtration Rate (GFR) guidelines recommend a single-sample technique with the sampling time dictated by the expected renal function, but this is not known with any accuracy before the test. We aimed to assess whether the sampling regime suggested in the guidelines is optimal, and determine the expected error in GFR result if the sample time is chosen incorrectly. We can then infer the degree of flexibility in the sampling regime.

Methods

Data from 8946 patients referred for GFR assessment at 6 different hospitals for a variety of indications were reviewed. The difference between the single-sample (Fleming) GFR result at each sample time and the slope-intercept GFR result at each hospital was calculated. A second dataset of 775 studies from one hospital with nine samples collected from 5 minutes to 8 hours post injection was analysed to provide a reference GFR to which the single sample results were compared.

Results

Recommended single-sample times have been revised: for estimated GFR above 80 ml/min/1.73m^2 a 2 hour sample is recommended, giving mean difference from slope-intercept GFR of -2.08 ml/min/1.73m^2 (1333 GFR tests included). Between 30 and 80 ml/min/1.73m^2 a 4 hour sample is recommended, giving a 1.95 ml/min/1.73m^2 mean difference (2057 GFR tests included). The standard deviation of the differences is 3.50 ml/min/1.73m^2 at 2 hours and 2.56 ml/min/1.73m^2 at 4 hours for GFR results in the recommended range. It is 5.81 ml/min/1.73m^2 at 2 hours and 5.70 ml/min/1.73m^2 at 4 hours for GFR results outside the recommended range.

Conclusion

The results of this multisite study demonstrate a reassuringly wide range of sample times for an acceptably accurate single-sample GFR result. Modified recommended single-sample times have been proposed in line with the results, and the reported errors for both sample times can be used for error analysis of a mistimed sample.

Introduction

The 2018 BNMS GFR guidelines recommend a single-sample technique for routine measurement of GFR. This is a significant change compared with the previous BNMS GFR guidelines, which recommended a slope-intercept technique requiring between two and four samples. The multiple sample slope-intercept technique prevails in UK nuclear medicine departments; a national audit conducted in 2013 reported that 58 out of 59 responding centres employ a multiple sample technique with either two, three, or four samples. Changing practice from multiple to single sample GFR confers many benefits, both in terms of patient comfort and saved departmental resources, but requires logistical changes which could limit compliance with the 2018 guidelines. One of these is the timing of the single blood sample. We aim to address this concern with this paper.

It is well established from theory that the accuracy of a single-sample GFR result depends on the time at which the sample was taken: the lower the GFR the later the sample should be taken for an accurate result. This necessarily means that the expected renal function must be known before the test, a seemingly paradoxical situation. The 2018 BNMS guidelines recommend that the sampling time is set according to the estimated BSA-normalised GFR, giving five ranges with appropriate sampling times (Table 1 in the guidelines). They describe the use of serum creatinine measurements (eGFR), previous GFR measurements, and the patient's history and clinical condition to inform the estimated GFR, and therefore the sampling time. However, we cannot depend on the accuracy of these estimates. In this work we will investigate the range of single sample times for an acceptably accurate GFR result, and quantify the error contributed by a mistimed sample.

Methods

Data from 8946 patients referred for GFR assessment at six UK hospitals for a variety of indications were reviewed. The difference between the single-sample (Fleming) GFR result at each sample time and the slope-intercept GFR result at each hospital was calculated. The slope-intercept calculation method recommended in the previous BNMS guidelines was applied to all GFR measurements, and the results were Brochner-Mortensen and body surface area corrected[2].

To ensure that only good quality data were used in the analysis, data points were excluded if any of the following conditions were met: if any sample was taken outside a twenty-minute window around the intended time; if fewer than three blood samples were taken (minimum of three samples between 2 and 6 hours post injection); if the r^2 correlation coefficient for the fit including all samples was less than 0.97; if the calculated volume of distribution was not in the range of 6 to 12 multiplied by the BSA. Data were also excluded if incomplete information was provided which did not allow for recalculation for the GFR results. The 8946 initial studies were reduced to 5192 after these checks, please see Table 1 for details.

Table 1
Number of GFR results which were excluded from the analysis for QC or methodological reasons.

Check:	R^2	Volume of Distribution	Fewer than three valid samples	Incomplete information
Number of GFR studies removed	467	436	1022	1823

The volume of distribution check was based on the 2004 BNMS guidelines recommendation of 8 times the BSA with a 25% uncertainty margin, however it was found that too many studies were excluded if this was applied, so a 50% upper margin was used. We are not worried that this has influenced the results by including studies with unreliable data: the large inherent variability in the relationship of BSA with volume of distribution is well documented; for example Fleming and colleagues have recommended a 40% margin around the expected volume of distribution for GFR quality control checks.

The same analysis was performed on a dataset from one hospital which included a reference GFR calculated using a nine-sample area-under-the-curve (AUC) calculation, with samples from 5 minutes to 8 hours post injection. The dataset and calculation method have been previously described. The single-sample results were compared to the reference GFR rather than a slope-intercept GFR.

Results

Table 2 gives the number of eligible GFR measurements for the comparison between single-sample GFR and slope-intercept GFR. Table 3 provides the same information for the 9pt AUC reference GFR comparison.

Table 4a and 4b provide respectively the mean and standard deviation of differences in units of ml/min/1.73m^2 between single-sample GFR and the slope-intercept GFR measurements. Table 5a and 5b provide the same results for the comparison with the reference GFR. These data are represented graphically in Figures 1 and 2. For Figure 2 the y-axis scale has been extended compared with Figure 1 to best display the data. A 3D surface plot[i], [ii] of the standard deviation data (the data in Table 3b) is presented in Figure 3.

Slope-intercept GFR mL/min/1.73m^2	Sampling Time (hours)			
	2	3	4	6
30-40	174	125	235	139
40-50	197	182	272	160
50-60	219	313	353	153
60-70	308	506	508	241
70-80	435	680	689	335
80-90	443	716	733	347
90-100	367	628	620	302
100-110	233	367	369	210
110-120	179	257	250	155
120-130	73	95	100	72
130-140	59	73	68	60
140+	26	29	28	24
Total:	2713	3971	4225	2198

Table 2: Number of eligible GFR measurements for the comparison between single-sample GFR and slope-intercept GFR.

9pt AUC Reference GFR mL/min/1.73m^2	All sampling times
30-40	6
40-50	13
50-60	29
60-70	64
70-80	83
80-90	95
90-100	107
100-110	110
110-120	100
120-130	64
130-140	42
140+	62
Total:	775

Table 3: Number of eligible GFR measurements for the comparison between single-sample GFR and the reference GFR. All sample times were present for all measurements.

Slope-intercept GFR mL/min/1.73m^2	Sampling Time (hours)			
	2	3	4	6
30-40	2.22	2.17	2.75	4.65
40-50	0.83	2.02	2.57	5.14
50-60	-0.09	1.40	2.32	5.62
60-70	0.00	0.74	1.94	5.67
70-80	-0.65	-0.05	1.25	4.65
80-90	-0.77	-1.17	0.10	3.01
90-100	-0.98	-2.60	-1.42	0.82
100-110	-1.98	-4.08	-3.16	-1.04
110-120	-3.44	-5.76	-5.44	-3.92
120-130	-5.13	-8.08	-8.94	-7.41
130-140	-7.88	-9.40	-9.51	-8.31
140+	-9.97	-11.31	-11.93	-12.45

Table 4a: Mean differences in units of ml/min/1.73m^2 between single-sample GFR and slope-intercept GFR measurements.

Slope-intercept GFR mL/min/1.73m^2	Sampling Time (hours)			
	2	3	4	6
30-40	8.86	4.77	3.07	**1.39**
40-50	7.13	4.20	2.24	**1.77**
50-60	5.54	2.99	**1.76**	2.44
60-70	5.07	2.61	**2.28**	4.11
70-80	3.57	**2.83**	2.84	4.91
80-90	**3.10**	3.27	3.93	6.19
90-100	**2.73**	3.93	4.78	7.05
100-110	**2.33**	4.38	5.57	7.19
110-120	**2.57**	5.00	6.07	7.73
120-130	**3.12**	4.81	5.71	6.81
130-140	**3.40**	4.76	5.96	8.23
140+	**3.14**	3.69	4.69	7.17

Table 4b: Standard deviation of differences in units of ml/min/1.73m^2 between single-sample GFR and slope-intercept GFR measurements. Lowest values for each row are highlighted in bold text.

9pt AUC Reference GFR mL/min/1.73m^2	Sampling Time (hours)			
	2	3	4	6
30-40	19.2	14.9	11.7	9.6
40-50	4.4	5.5	7.1	11.9
50-60	7.7	9.3	10.2	13.1
60-70	7.1	8.8	9.9	13.1
70-80	5.6	6.4	7.0	11.0
80-90	4.6	5.4	6.6	11.2
90-100	5.2	4.9	5.5	9.4
100-110	2.7	3.3	4.2	7.8
110-120	1.0	0.2	0.6	4.2
120-130	0.1	-0.6	-1.0	2.6
130-140	-2.0	-3.7	-4.2	-2.4
140+	-13.5	-16.5	-17.6	-16.5

Table 5a: Mean differences in units of ml/min/1.73m^2 between single-sample GFR and the reference GFR.

9pt AUC Reference GFR mL/min/1.73m^2	Sampling Time (hours)			
	2	3	4	6
30-40	18.6	10.3	7.0	**3.0**
40-50	9.4	5.1	**3.1**	4.1
50-60	8.7	7.4	**6.0**	4.7
60-70	7.7	6.4	**6.0**	6.8
70-80	7.6	5.5	**5.0**	5.8
80-90	6.3	**5.5**	6.3	7.6
90-100	6.3	**5.3**	5.5	6.7
100-110	**5.4**	5.8	6.5	7.9
110-120	**6.3**	6.4	6.6	7.0
120-130	**5.7**	6.0	6.9	8.2
130-140	**6.6**	7.4	9.2	11.3
140+	**14.1**	15.4	16.7	18.3

Table 5b: Standard deviation of differences in units of ml/min/1.73m^2 between single-sample GFR and the reference GFR. Lowest values for each row are highlighted in bold text.

Discussion

The data supports the approach of the guidelines and demonstrates a reassuringly wide range of sample times for an acceptably accurate single-sample GFR result.

Choosing the optimal sampling time requires a balance between mean absolute difference and standard deviation. For example, it would be unwise to choose 2h as the best sampling time for low GFR, even though the mean difference results are closest to zero, due to the large standard deviation; even if the mean difference is close to zero a high proportion of results will have much larger differences. We looked firstly at the standard deviation when choosing the best sample time for each GFR range, then checked that the mean difference gave suitable accuracy.

The results of this study suggest slightly different recommended single-sample times compared with the 2018 guidelines. For the GFR range where 6h sampling was recommended (30-50 mL/min/1.73m^2), 4h sampling performs significantly better in terms of mean absolute difference, so even though the standard deviation is lower we have recommended 4h sampling for this GFR range. For the 30-40 mL/min/1.73m^2 GFR range the results from the reference GFR comparison indicate that 6h has a slightly lower mean absolute difference also, however only six GFR measurements were present in the data in this range. We recommend that the 6h sample time is replaced with 4h sampling in a revised version of the guidelines in the interests of accuracy and simplified departmental logistics.

The recommended single-sample times on the basis of this study for estimated GFR range are given in Table 5. We have also removed the 3h sample as it conferred a benefit only for one decade of GFR range (see Table 3b), and only by a very small margin. We hope that this simplified sampling regime will increase the routine use of single-sample GFR in UK hospitals. Table 5 does not include the results from previous work which recommends a 24h sample time for GFR less than 25 mL/min/1.73m^2.

Table 5
Proposed recommended single-sample times to use with the Fleming formula based on estimated BSA normalised GFR .

Estimated BSA normalised GFR (mL/min/1.73m^2)	Recommended single-sample time
80+	2h
30-80	4h

One immediately obvious feature from Figures 1 and 2 is how far away the single-sample, and by inference the slope-intercept GFR result, is from the reference GFR: the average differences are much larger and the error bars wider (note: different y-axis scales). We believe this to be due to the overestimation of GFR by the abbreviated techniques; the clearance of tracer from the plasma has not yet reached a terminal exponential at the start of sampling, so the gradient of a slope-intercept measurement flattens as 8h is reached. This is compensated for at high GFR by the inherent underestimation due to the Brochner-Mortensen correction reaching a maximum value. It is not the purpose of this work to propose an improved single-sample formula to correct for this, and such a systematic difference in GFR results would have a far-reaching clinical impact which it is not practical to implement. Our primary focus is to provide an equivalent accuracy single-sample GFR to the slope-intercept method in current clinical use.

To estimate GFR, we recommend using a recent eGFR result calculated from a serum creatinine blood test, if one exists. A 2019 study found that an eGFR threshold of 40 mL/min/1.73m^2 was appropriate for selecting patients where the GFR was subsequently measured as less than 25 mL/min/1.73m^2. Although that study reported a large variation in the accuracy of using eGFR to predict measured GFR, we hope that the results from our study reassure the Nuclear Medicine community that there is a wide range of suitable sample times for an acceptably accurate single-sample GFR result. Pertinent to this discussion is the inherent variability in GFR measurement: estimates of the repeatability of GFR measurement on the same patient over time suggest a variation of approximately 10% and a study by Wilkinson et al. found a coefficient of variation of 12% in duplicate measurements of the same patient when permitted free exercise, and 8% when at rest. The differences we have measured between GFR calculated with slope-intercept and single sample techniques are within these patient dependent variations.

If no previous eGFR measurement is available, the clinical indication for the GFR test can guide the choice. A 2013 UK audit[3] of GFR measurement reported the following referral reasons: oncology patients for assessment pre-chemotherapy (70%); potential live renal donor (16%); monitoring of chronic kidney disease (10%); others (4%). Hopefully it is clear from the referral reason whether reduced renal function is suspected. If the referral is for monitoring of chronic kidney disease then there is reason to expect reduced renal function, whereas if the clinical indication is first assessment pre-chemotherapy or live renal donor then the choice of single-sample time can be guided by the normal range of GFR for the patient age.

It is worth noting here that for a live renal donor where expected GFR is high and the donor is relatively young, a blanket policy of, for example, 4 hour single-sample time could give a significant error in GFR which could affect clinical management in this group, see Table 6 for more details. This would have most clinical impact where the measured GFR was close to the donation threshold, however given the inherent variability of GFR measurement as previously mentioned, decision making of donor eligibility in this GFR range is already tricky. The British Transplant Society Guidelines for Living Donor Kidney Transplantation recommend that the decision of suitability for donation in these cases should be individualised and based on a discussion of the estimated lifetime risk of developing end stage renal disease (ESRD) without donation. An online calculator for ESRD risk is referenced which takes into account additional clinical and demographic factors.

Table 6
Mean difference and standard deviation of differences for single-sample GFR depending on GFR range and single-sample time.

Single-sample time (mL/min/1.73m^2)	n	GFR range (mL/min/1.73m^2)	Mean difference in GFR (mL/min/1.73m^2)	Standard deviation of differences (mL/min/1.73m^2)
2h	1380	80+	-2.08	3.50
	1333	30-80	0.19	5.81
4h	2168	80+	-2.40	5.70
	2057	30-80	1.95	2.56

Conclusion

The results of this multisite study demonstrate a reassuringly wide range of sample times for an acceptably accurate single-sample GFR result. Simplified recommended single-sample times have been proposed in line with the results which should aid clinical implementation. The reported errors for both sample times can be used for error analysis of a mistimed sample.

Declarations

Ethics approval and consent to participate

Ethical approval was not required since this is a retrospective audit of current clinical practice with no impact on clinical management for participants.

Consent for publication

No patient identifiable information is presented in this publication so consent for publication is not required.

Availability of data and material

The datasets analysed in this study are available from the corresponding author on reasonable request.

Competing interests

No authors have a competing interest.

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Authors' contributions

HM wrote the manuscript, performed data analysis, created the graphs, and was a major contributor to the results interpretation and discussion. ST collected and analysed data, contributed to the results interpretation and reviewed the manuscript. MBu designed the study, contributed to results interpretation and manuscript review. DM and FW collected data and reviewed the manuscript. MBa, AB, BF, MM, CP and NV collected data. All authors read and approved the final manuscript.

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Figures

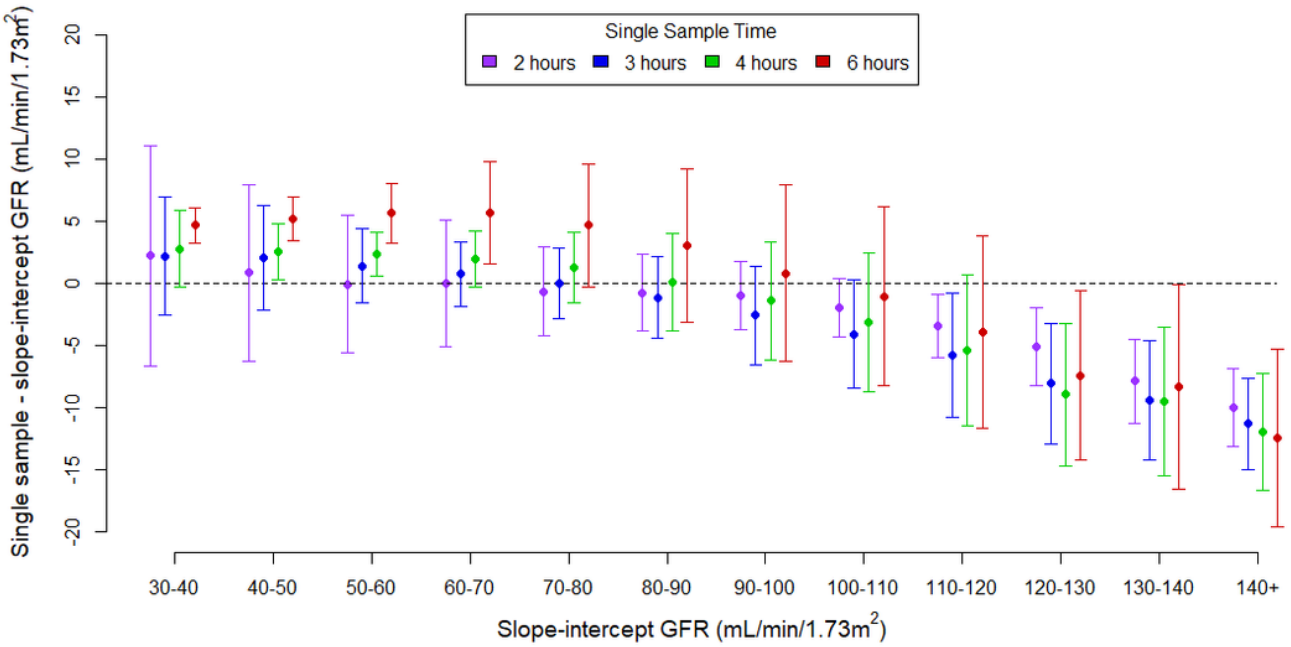

Figure 1

Mean difference in units of ml/min/1.73m2 between single-sample GFR calculated at four time points and the slope-intercept GFR result plotted against slope-intercept GFR. Error bars extend to the standard deviation of the differences.

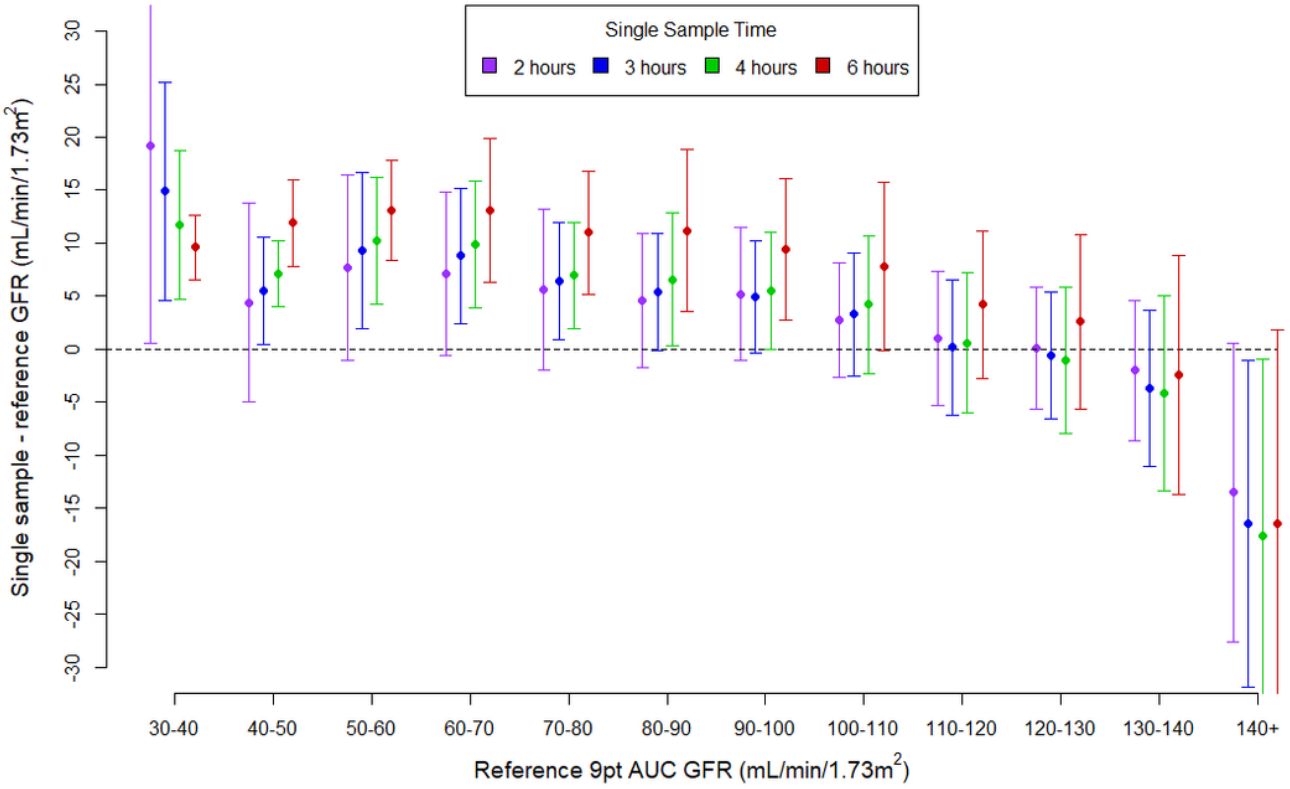

Figure 2

Mean difference in units of ml/min/1.73m2 between single-sample GFR calculated at four time points and the reference GFR calculation plotted against reference GFR. Error bars extend to the standard deviation of the differences. The y-axis scale has been extended compared with Figure 1 to best display the data.

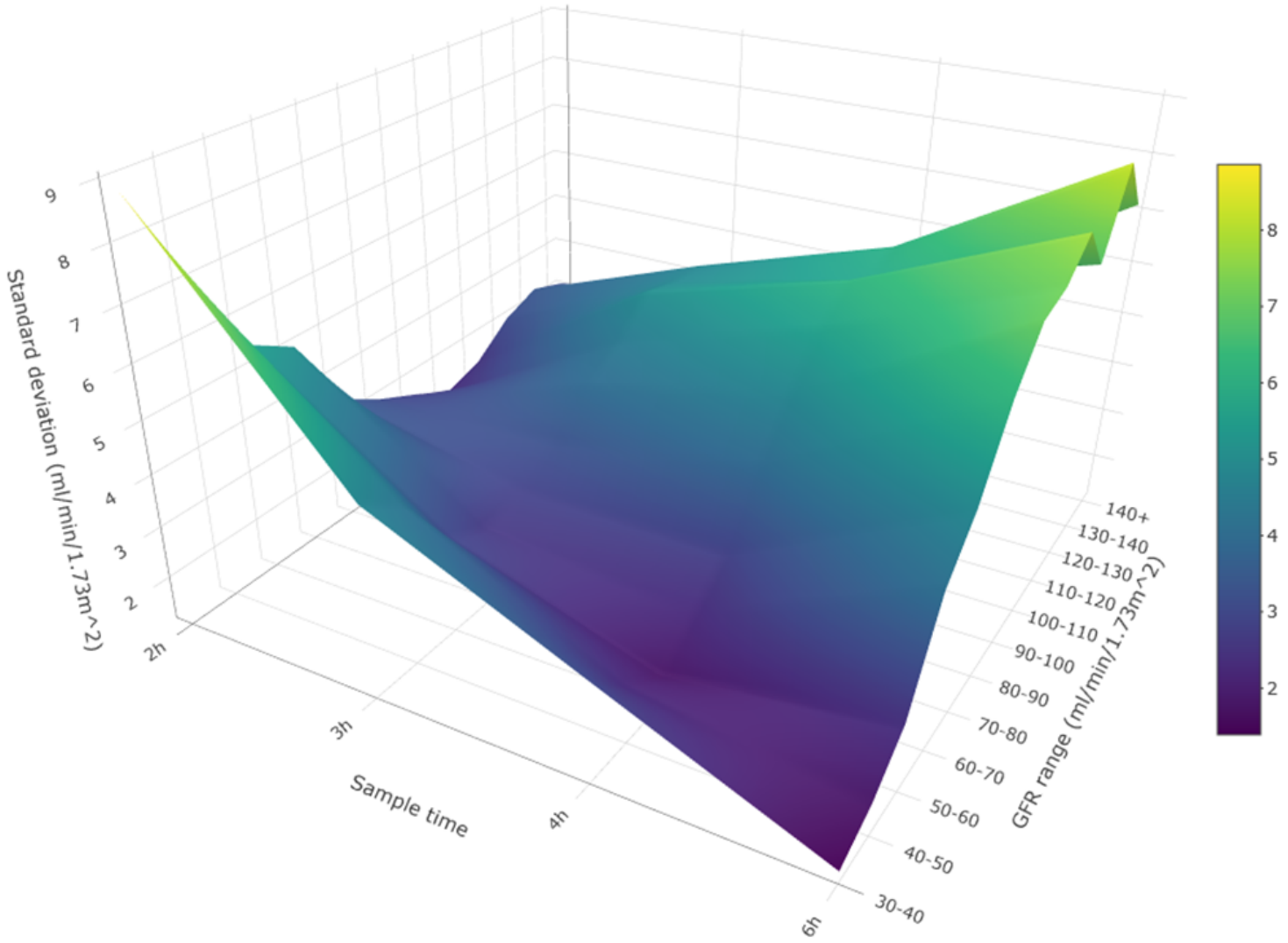

Figure 3

A 3D surface plot showing the standard deviation of differences in units of ml/min/1.73m2 between single-sample GFR and slope-intercept GFR plotted against GFR range and single-sample time. The colours represent increasing standard deviation from purple to yellow on the colour scale.