Urodynamic predictor of EGFR in adult LUTs patients.

Abstract

CKD is a growing problem, in an increasingly aged population with an increased propensity for metabolic syndrome. Whilst bladder dysfunction is a logical risk factor for declining renal function, this relationship has not been clearly defined in the adult LUTS population; the predominate group of patients who undergo urodynamics evaluation. By contrast in minority cohorts; patients with neuropathic disease and renal transplant, urodynamic parameters have prognostic value in predicting declining function and determining intervention. The aim of this study was to determine if and how urodynamics can be useful as a predictor of CKD in adult LUTs population.

Methods

Data was gathered from a retrospective urodynamics database of patients who underwent 2 channel filling and voiding cystometry. Patients who had neuropathic disease or renal transplant, or who had inadequate data were excluded from the analysis. Patients most recent EGFR, EGFR prior to urodynamics and earliest EGFR recorded post 2010, upper tract imaging and risk factors for CKD were recorded. Pre urodynamics EGFR was correlated to urodynamic parameters by univariate regression and multivariate regression.

Results

From a database of 403 patients, (278 Male, 125 Female) with mean age 59.3 ± 17.6 (SD), who had pressure flow studies, 48 patients were excluded because a history of neurological disease and 6 were excluded because of renal transplants, leaving 369 patients who were included in the study. Overall, there was no significant change in the mean EGFR pre urodynamics, at the time of urodynamics, and post urodynamics testing. Only 15 out of the 226 patients who had upper tract

imaging had hydronephrosis. So few people had hydronephrosis that overall it was not an important factor for EGFR.

On univariate regression of demographic factors, risk factors for CKD and urodynamic parameters, age hypertension and

upper tract obstruction was associated with reduced EGFR. The only urodynamic factors associated with reduced EGFR were Qmax, and voided volume. The presence of detrusor overacitvity and loss of compliance were not associated with reduced EGFR, leaving no invasive pressure –flow parameters, therefore a novel factor- the detrusor pressure at which patients expressed the normal desire to void (NDP) was evaluated, and this was most strongly correlated with EGFR at the time pf urodynamics ($p=0.000$, $r^2=0.06$). On multivariate regression of all the prognostic factors age, hypertension, and obstruction were independent predictors of EGFR. Detrusor pressure at normal desire had the strongest association with EGFR ($p=0.001$). The only factor that correlated with recovery of EGFR after urodynamics was NDP ($p=0.016$).

Invasive urodynamics provides useful information regarding risk to renal function and this is best evaluated by the detrusor pressure at normal desire.

Introduction

Preservation of renal function is a key concern for urologists and renal physicians. Bladder dysfunction has the potential to cause renal impairment and failure. The most dramatic example is urine retention, but here the most catastrophic loss of renal function usually occurs where there has been the most insidious onset of symptoms. Whilst the diagnosis and initial management of retention is obvious without the need for specialised investigations such as urodynamics, it is beneficial to detect patients who have bladder dysfunction, which places the upper tract at risk, before a decline in EGFR occurs. It is easy to conceive that a prolonged bladder pressure, in the storage phase, either due to detrusor overactivity or loss of bladder compliance in particular, would place the upper tract at risk. Maguire initially demonstrated in myelodysplastic bladders, where a detrusor leak point > 40cm H_2O was strongly correlated with hydronephrosis [1]. This has been corroborated by other investigators [2], though others have propose a lower threshold of DLPP of > 20cm H_2O [3] Likewise in children with myelodysplastic bladders, bladder wall compliance, cystometric capacity and time to maximum flow rate have found to be associated with serum creatinine [4]. In patients with spinal cord injury, maximal detrusor pressure was found to be co associated with reduced effective renal plasma flow on isotope renogram [5].

In renal transplant patients a smaller bladder capacity (though not specifically a urodynamic factor) has been shown to be associated with poorer graft survival [6]. In posterior urethral valves, poor bladder compliance and detrusor overactivity has demonstrated an association with declining renal function [7].

To date however, studies correlating urodynamic parameters to renal function have been unsuccessful in the adults LUTS population, which though individually at lower risk than neuropaths, collectively represent the majority cohort who experience bladder dysfunction and undergo urodynamic testing. In 87 men who had urinary retention, no association between urodynamic parameters in renal function could be determined [8]. In a study of 161 patients with lower urinary

tract symptoms, 42 patients had detrusor overactivity and bladder outflow obstruction; amongst this subgroup, men who had reduced compliance had a higher urea (but not creatinine) than those who had normal compliance [9]. In 359 women who underwent urodynamic investigation, there was no significant difference in EGFR between those with and without DO [10]. It is surprising that our most invasive and sophisticated test has never demonstrated a corollary with renal function in adult LUTS patients. Renal function is off course multifactorial as demonstrated by large population based models where diabetes, hypertension and heart failure are prime risk factors [11,12]. In the adult LUTS population, these risk factors are common place and are usually closely monitored and modified by primary care. Given developed world populations have become increasingly aged with increased risked factors for CKD, overall patients may becoming increasingly susceptible to decline in renal function secondary to bladder dysfunction.

The aim of this study was to determine if bladder dysfunction as characterised by urodynamic parameters where predictive of renal function in the adult LUTS population.

Methods

Patients: A retrospective review of all urodynamic tests undertaken between 5/2014 and 6/2016 was undertaken.

Patients were excluded if they had a history of neuropathic disease or renal transplant or had inadequate data.

Urodynamics: Two channel pressure flow studies was carried out on an MMS solar silver Machine or a genesis pico 3000 machine, in accordance with ICS good practice guidelines [13].

The filling rate sensations, compliance, detrusor overactivity, maximum cystometric capacity, flow rate, voided volume, Q max, pDetQmax, residual and detrusor pressure at normal desire was recorded.

Data Acquisition: Patient demographics, including age gender, risk factors for renal disease, renal imaging and renal function was recorded. Three values of EGFR were recorded for each patient including the most recent, the last prior to urodynamics and the earliest 2010. EGFR was calculated using the MDRD equation.

Statistical Analysis

The relationship between the EGFRS and urodynamic factors, demographic factors and risk factors for CKD were evaluated using univariate and multivariate linear regression. Statistical significance was taken as $p<0.05$. Graphing and statistical analysis was undertaken by minitab v17.

Results

From a database of 403 patients, 48 patients with neuropathic disease (1 with renal transplant) and a further 6 patients were excluded from the study, leaving 369 patients who were included. There were 257 men and 112 women with a mean age of 59.6 ± 16.0. Risk factors for renal dysfunction were obtained from 348 patients (Table 1). Hypertension and hyperlipidaemia were the most prevalent risk factors for CKD. 226 patients had upper tract imaging, off which only 15 had hydronephrosis on u/s. 6 patients had renal disease process and 14 had upper tract obstruction or loss of a renal unit. There was some missing EGFR data, particularly in earlier EGFR recordings. Because if this absent data it was only subsequently possible to construct a model examining change in EGFR post UDS and pre UDS. Overall there was no significant change in EGFR between the 3 time pools.

The most prevalent urodynamic abnormality (n=177), loss of compliance was seen less frequently (n=56). 127 patients demonstrated incontinence during the study, of which 53 had pure stress incontinence, 79 had urge incontinence and 5 patients demonstrated both.

Patients with hydronephrosis had a lower EGFR (Figure 1) 71.4 ± 8.9 (SEM, n=14), versus no hydronephrosis 81.2 ± 1.75 (SEM, n=190) and no upper tract imaging 84.3 ± 2.1 (SEM, n=105). However as only 14 patients with an NDP measurement, had hydronephrosis, this was not statistically significant, p= 0.3 by t test.

The pre urodynamics EGFR was compared to the urodynamic parameters by univariate and multivariate regression (Table 2). Age, hypertension and obstruction of the bladder where associated with reduced EGFR. Those with hypertension had an EGFR 11.3 (ml/min/1.73m^2) less than those without and those with obstruction had a mean EGFR of 14.0 (ml/min/1.73m^2) less than those without. In terms of non-invasive parameters, EGFR was associated with the voided volume (Figure 2a) and the Qmax (Figure 2b). However no association could be found between EGFR and any of the standard invasive storage or voiding parameter. The maximum storage detrusor pressure was not

associated with the EGFR. The normal desire detrusor pressure was the only urodynamic parameter that was associated with EGFR (Figure 3 and Table 2). The size of the effect was that increase in normal desire detrusor pressure by 10cm H_2O was associated with a decrease in EGFR of 2.8 (ml/min/1.73m^2) on univariate regression. Multivariate regression was carried out by forward entry of all of the demographics, CKD risk factor and urodynamic factors listed in Table 2 The predictability of the model was associated with an r^2=0.29. Age hypertension and upper tract obstruction were associated with reduced EGFR. On multivariate evaluation of urodynamic factors, normal desire detrusor pressure was the only urodynamic factor that was associated with a reduced EGFR, again an increase in normal desire detrusor pressure by 10cm H_2O was associated with a decrease in EGFR of 2.8 (ml/min/1.73m^2). Detrusor overactivity was associated with an increased EGFR on multivariate regression, but not univariate regression. When multivariate regression was repeated without NDP, the r^2 of the model decreased to 0.23 and detrusor overactivity was no longer associated with increased EGFR 9not shown)

Figure 3a shows univariate linear regression of pre urodynamics EGFR versus normal desire detrusor pressure (r^2 =0.06, p=0.000). Figure 3b highlights patients who had hydronephrosis. From the patients who had a normal desire detrusor pressure ≥ 20cmH_2O, 35 out of 52 patients had upper tract imaging, of which 6 (21%) had hydronephrosis and 29 (79%) didn't.

Figure 4 and Table 3; the only predictor of increase in EGFR post urodynamics, on either univariate analysis (p= 0.045) or multivariate analysis (p=0.016), was the detrusor pressure at normal desire. This was a small but statistically significant effect such that an increase in NDP by 10 cmH_2O was associated by a rise in EGFR 1.4 of (ml/min/1.73m^2). Overall this model was less predictive than for EGFR presented in Table 2 and was associated with an r^2=0.06.

Table 4 demonstrates how the 52 patients who had NDP ≥ 20 cm H_2O were treated which potentially led to an improvement in their EGFR

Discussion

This paper demonstrates that pressure flow studies have a role to play in evaluating the risk of renal dysfunction in the adult LUTs population. This required the usage of non-standard urodynamics parameter as the primary variables specific to invasive urodynamics showed no correlation with EGFR. On an initial subset of 100 patients, alternative parameters including maximum detrusor and vesical storage pressure, and pressure at first sensation and first desire were evaluated. The recording of the other sensations were associated with a greater amount of missing data therefore it was decided to focus on detrusor pressure at normal desire as the parameter that showed the greatest correlation to EGFR and it was the only variable found to correlate to EGFR in the final cohort. Maximum storage detrusor pressure was included in the final regression models, however this showed no correlation with EGFR on univariate and multivariate regression, indicating that the timing of pressure measurements during the storage phase, rather than the amplitude is more pertinent to the EGFR.

It was not possible to construct a model that examined decline in EGFR prior to urodynamics, as earlier recordings were often unavailable. However a model that looked at recovery of EGFR post urodynamics demonstrated sole correlation to the detrusor pressure at normal desire. Overall there was a trend for a gradual decline in EGFR. It was against this back drop that patients who had an elevated NDP experienced a small but significant increase in their EGFR from interventions, which incorporated pharmacology, surgery and catheterisation as means of improving bladder emptying or reducing the detrusor pressure. 39 out of 52 patients with an NDP ≥ 20 received an intervention. Out of the 13 who didn't, 12 of these patients, were offered treatment for their bladder subsequent to urodynamics. Off course, as this study was retrospective no clinician was looking at the NDP as a means of evaluating the patient, yet, generally speaking, were able to instinctively determine which patients required intervention. How can we know which patients to treat when there are not clear guidelines from existing urodynamic parameters in the adult LUTS population, and detrusor overactivity and loss of compliance, in this and previous studies, has not shown a correlation with

EGFR? This study reaffirms storage pressures as the most pertinent indicator of renal risk but the question is which storage pressure. Loss of compliance would be expected to be a greater risk to renal function than DO but this was not demonstrated in this and previous studies. The problems with compliance as a measure of renal risk is that is primarily a measure of bladder properties as it is not compliance but loss of compliance that causes a rise in pressure as volume is the numerator and pressure the denominator, secondly it depends on the ratio between two values and there is a low threshold for defining loss of compliance i.e. a rise in pressure of 10cm H_20 per 400 ml volume. Furthermore most patients who experience loss of compliance do so at end fill. Urodynamics, by its nature may be a provocative test and whilst it is useful to determine maximum cystometric capacity and to illicit the widest ranges of behaviours patients may be pushed towards volumes that they never experience in day to day life as they have adapted coping strategies that prevent them from experiencing discomfort in real life by voiding or leaking urine at lower volumes. Patients on average experienced normal desire at 2/3 of maximum cystometric capacity. Thus an NDP may be closer to the storage pressures that a patient routinely experiences.

On multivariate regression but not univariate analysis, detrusor overactvity was associated with an improved EGFR. This was because patients with higher storage pressures not due to DO but due to loss of compliance were associated with reduced EGFR, but for the reasons listed above loss of compliance did not predict EGFR. When a multivariate model was constructed without NDP, then DO was no longer and independent predictor of EGFR, indicated that it is linked with the NDP.

NDP is equivalent to the leak point pressure as it is pressure that signal a change from storage to elimination of urine. However it has wider applicability than a leak point pressure (which was rarely undertaken in this cohort), primarily because only 127 out of 359 patients leaked urine, whereas 340 out of 369 patients experienced normal desire during urodynamics. Determining a leak point pressure may be difficult when there is a rapid change in detrusor pressure such as DO, which was a more common finding than loss of compliance in this cohort. It is arguable that DLPP could be

defined in those who didn't leak as being greater than the maximum detrusor pressure encountered during the storage phase, though it has not been traditionally applied in this manner.

Urinary leakage is a double edged as far as risk of declining renal function, as it is associated with elevated storage pressures and weakened outflow tract which increase and decrease the risk to the upper tracts respectively and overall it was not a risk factor for declining renal function (univariate regression p=0.79, data not shown).

The fact that only 15 patients from 360 hydronephrosis demonstrates that bladder dysfunction is an insidious process and the utility in urodynamic assessment in assessing risk to upper tracts.

Conclusion

Urodynamics is useful in evaluating the risk to upper tracts from bladder dysfunction in adult LUTS population. The only urodynamic parameter that independently correlates with EGFR is the detrusor pressure a normal desire.

Table 1; Study patient characteristics.

Characteristics	Mean/ Number of Patients	SD / %
Age	59.6	16.0
Sex	M 257: F 112	69.6%:30.4%
Hypertension n=348	111	31.9%
Hyperlipidaemia n=348	80	23.0%
Diabetes n=348	45	12.9%
IHD n=348	40	11.5%
Renal Disease	6	1.7%
Obstruction/ unilateral kidney loss n=348	14	4.0%
Hydronephrosis n=226	15	6.7%
EGFR post UDS (ml/min/1.73m^2) n=318	81.7	23.8
EGFR pre UDS (ml/min/1.73m^2) n=302	81.8	24.7
Earliest EGFR since 2010 (ml/min/1.73m^2) n=180	81.9	23.6
Detrusor Overactivity n=348	177	50.8%
Loss of compliance	56	16.1%
Urodynamic incontinence	127	36.5%
Stress incontinence	53	15.2%
Urge incontinence	79	22.7%
Stress and urge incontinence	5	1.4%
Normal Desire ml	268	
Maximum cystometric Capacity	388	
Voided Volume	311.7	187.8
Q max	13.1	9.8
Pdet Qmax	55.3	38.5
Normal desire detrusor pressure n=340	11.4	19.3
Maximum Storage detrusor pressure n=340	24.6	36.9

Figure 1 Hydronephrosis verus EGFR- Hydronephrosis (1) EGFR = 71.4 ± 8.9 (SEM), no hydronephrosis (0) EGFR =81.2 ± 1.75 (SEM), No upper tract imaging (*), EGFR = 84.3 ± 2.1 (SEM). p= 0.3 for (0) vs (1) by t test.

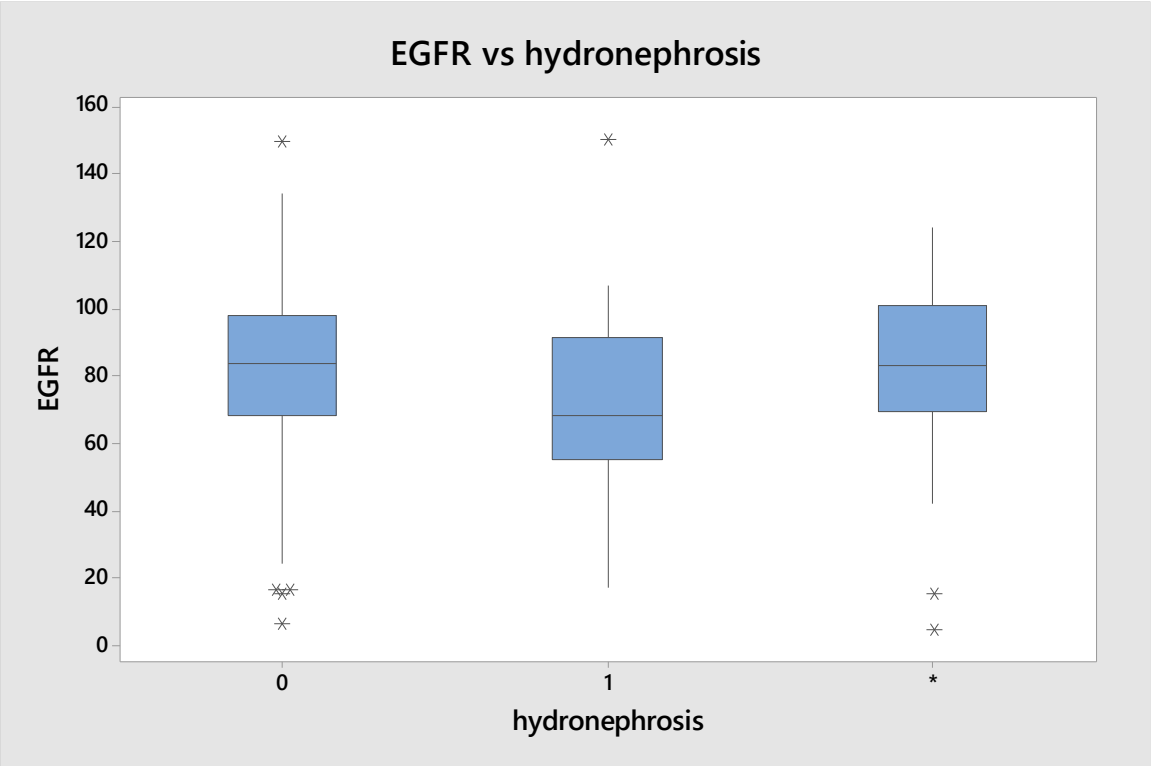
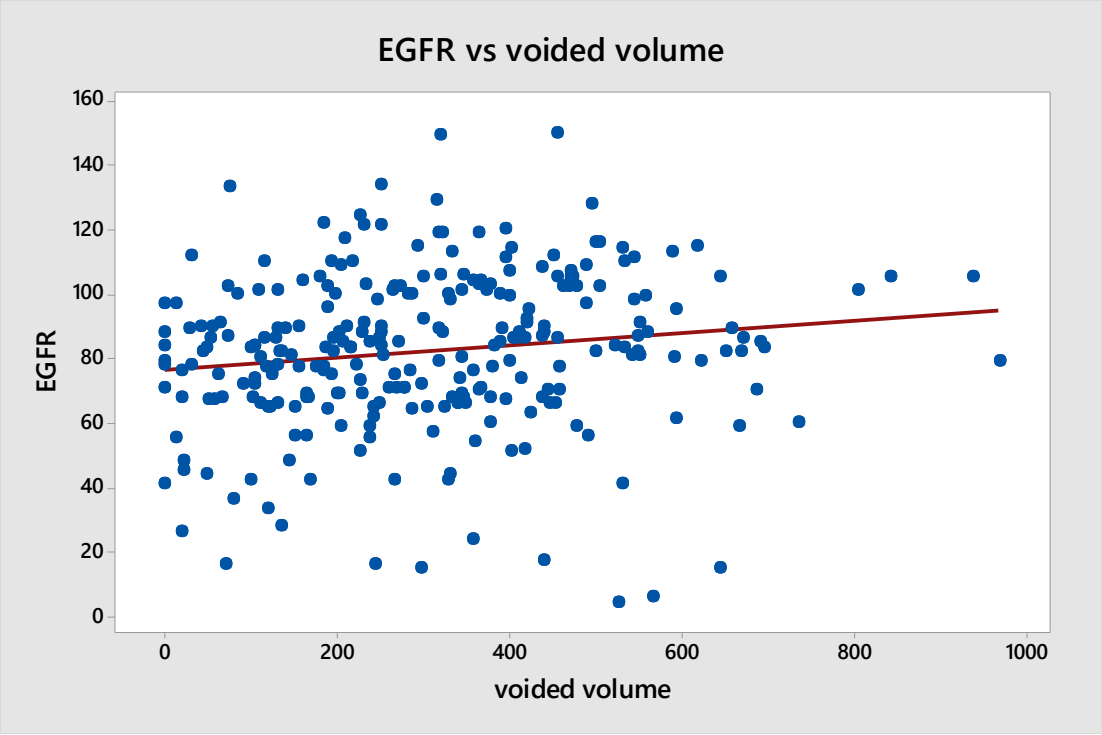


Figure 2a; EGFR vs voided volume and Figure 2b; EGFR vs Qmax.



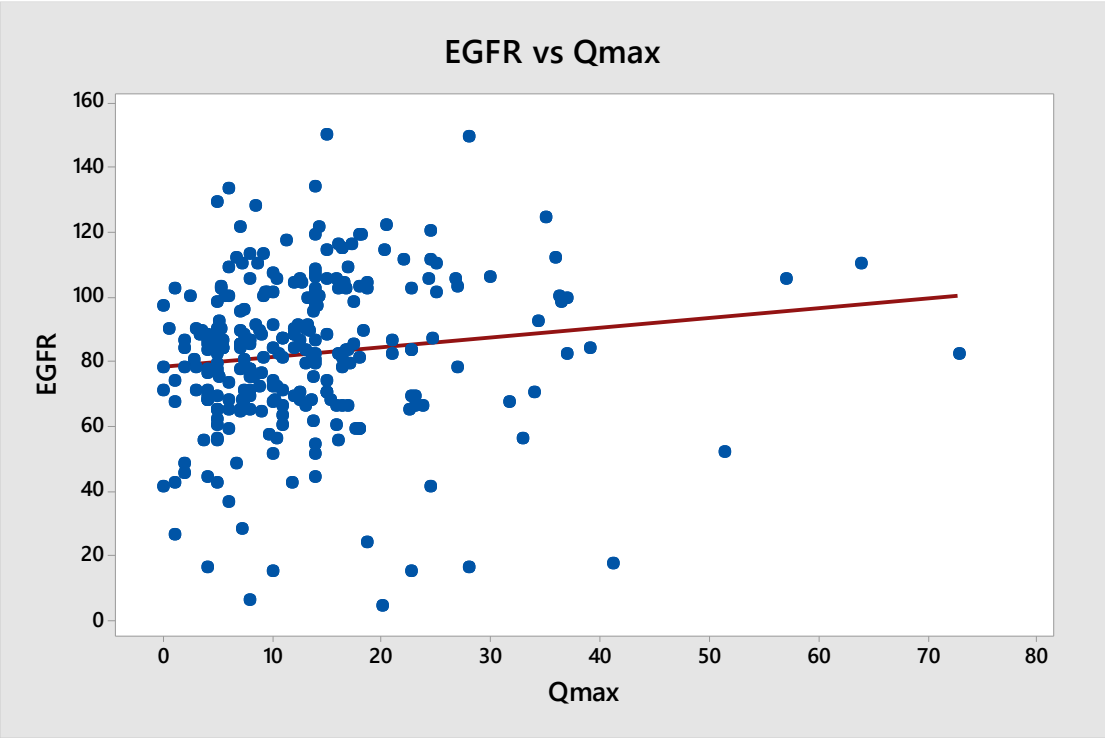
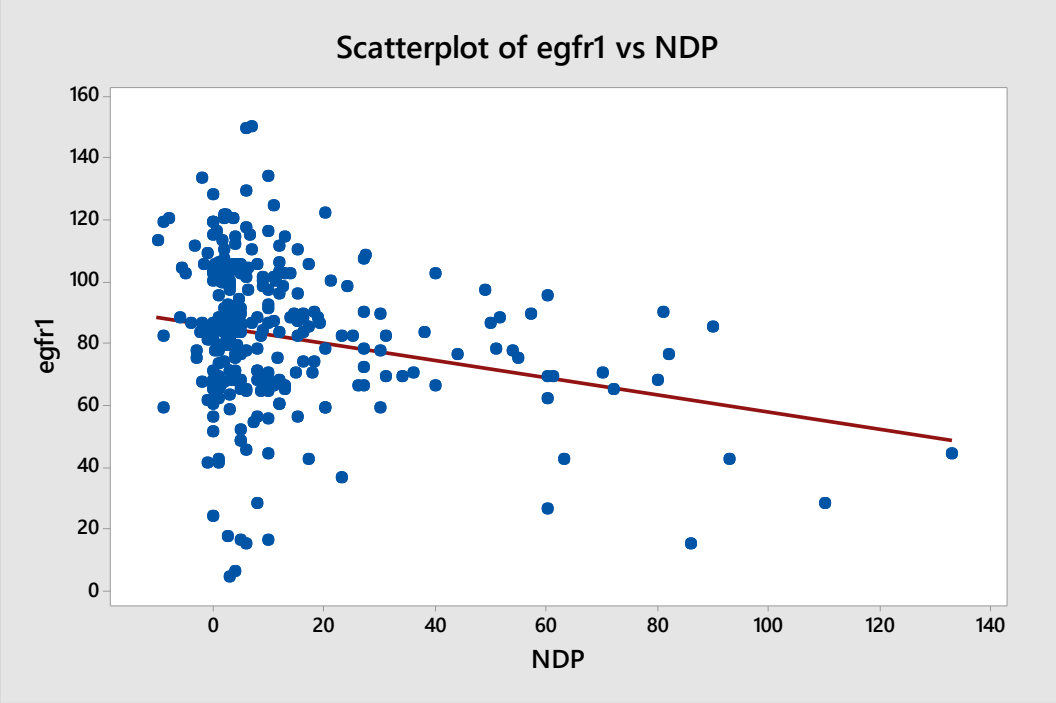


Figure 3a Pre urodynamics EGFR versus normal desire detrusor pressure, 3b the same data coded according to the presence of hydronephrosis on, red=hydronephrosis on u/s /CT, blue = no hydronephrosis, green = no upper tract imaging.



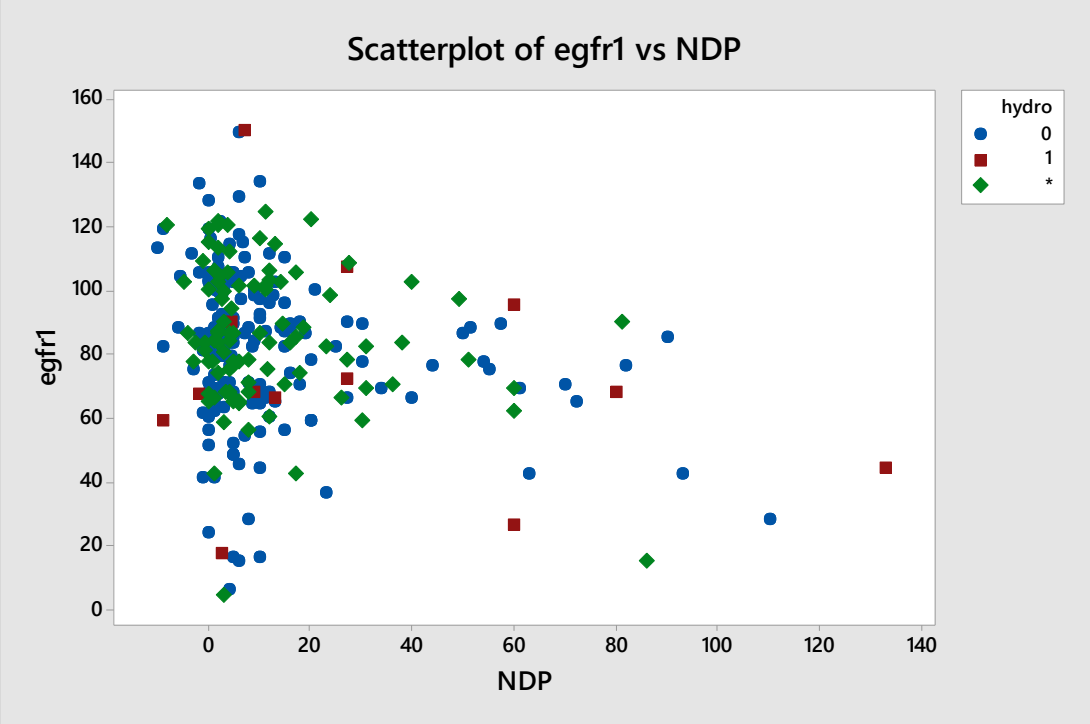


Table 2 Univariate and multivariate regression of demographics, CKD risk factors and urodynamic parameters versus the pre urodynamics EGFR r^2 =0.29.

	Univariate		Multivariate	
Risk Factors	Coefficient	P Value	Coefficient	P Value
Age	-0.418	0.000	-0.458	0.000
Sex	-1.36	0.651	6.310	0.119
Hypertension	-11.3	0.000	-13.260	0.001
Hyperlipidaemia	3.17	0.507	3.180	0.426
Diabetes	4.03	0.024	-4.880	0.333
IHD	-1.47	0.725	9.140	0.067
Renal Disease	9.76	0.378	-8.470	0.366
Obstruction	-14.0	0.031	-26.700	0.001
Detrusor Overactivity	2.86	0.290	8.060	0.016
Loss of compliance	-0.38	0.909	6.330	0.124
Voided Volume	0.018	0.017	0.001	0.270
Q max	0.304	0.035	0.104	0.611
Pdet Qmax	-0.0422	0.268	0.009	0.829
Normal desire detrusor	-0.279	0.000	-0.276	0.001
Maximum Storage Pressure	-0.43	0.271	0.24	0.709

Figure 4 Change in EGFR post urodynamics v

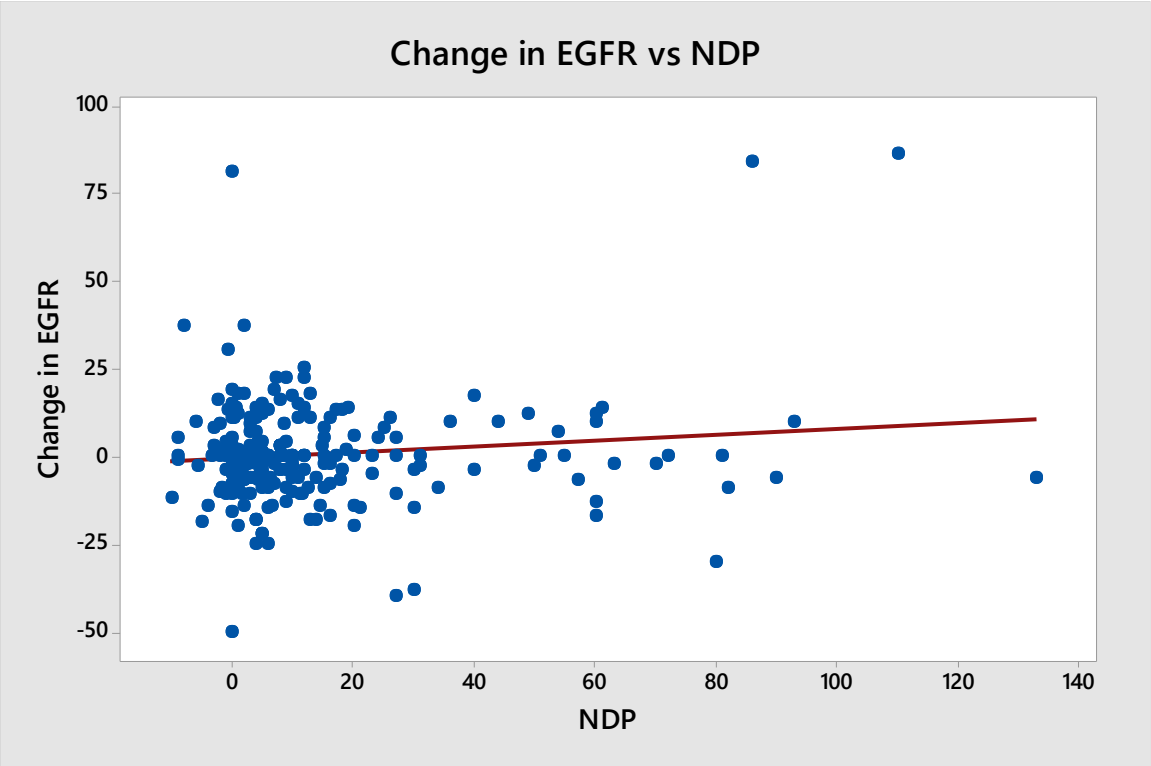


Table 3 Univariate and multivariate regression of demographics, risk factors for CKD and urodynamic parameters versus change in EGFR (Latest- pre urodynamics EGFR, r^2=0.06)

	Univariate		Multivariate	
Risk Factors	Coefficient	P Value	Coefficient	P Value
Age	-0.01	0.831	-0.008	0.927
Sex	-0.91	0.636	-1.53	0.595
Hypertension	1.34	0.460	1.08	0.676
Hyperlipidaemia	-1.55	0.443	-2.57	0.357
Diabetes	-0.07	0.978	2.02	0.568
IHD	-2.16	0.423	-2.28	0.515
Renal Disease	-6.35	0.334	-5.88	0.758
Obstruction	-5.24	0.188	1.63	0.515
Detrusor Overactivity	-1.27	0.483	-3.97	0.088
Loss of compliance	2.33	0.826	-0.06	0.983
Voided Volume	-0.006	0.211	0.001	0.872
Q max	-0.062	0.511	0.057	0.725
Pdet Qmax	0.013	0.590	0.012	0.694
Normal desire detrusor	0.084	0.045	-0.142	0.016
Maximum Storage Pressure	0.44	0.110	0.40	0.446

Table 4. Treatment of patients who had NDP ≥ 20cmH_2O subsequent to urodynamics test (n=52)

Alpha Blockers	**7**
Anticholinergics	8
MIrabegron	7
Botulinum Toxin	5
Posterior nerve stimulation	1
Catheterisation	6
TURP/BNI	6
Clam Cystoplasty	1
DNA/ treatment declined or awaited/ conservative	13

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