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Post-Mortem Diagnosis of Kidney Impairment: An Experimental Study

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Highlights

- State of renal impairment is important for forensic toxicology interpretation
- Creatinine is commonly analysed clinically but eGFR is better
- eGRF has better sensitivity and specificity for scored renal function
- interpretation of renal function from post mortem samples is difficult

Abstract

The determination of the role that drugs may have played in a death is an important part of the investigation into unexplained deaths. Renal impairment may lead to a reduction in drug excretion rate and therefore an accumulation of drugs or metabolites, leading to possible toxic or lethal effects. Creatinine levels are known to be stable in the post mortem period and in life can give an indication of kidney function. There are however widely reported limitations when using creatinine in isolation and so we investigated the usefulness of using estimated glomerular filtration rate (eGFR) for scoring an individual as having renal

impairment using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. We analysed unpreserved vitreous for creatinine in 812 individuals using an isotope dilution mass spectrometry (ID-MS) traceable enzymatic. We found that the biochemical analysis of post mortem vitreous creatinine and subsequent calculation of eGFR is a useful adjunct to the standard testing that takes place during a post-mortem examination and can assist in death investigation. Using an eGFR of <60 mL/min/1.73 m^2 gave a sensitivity of 94.3% and specificity of 97.3% when scoring an individual as having renal impairment. We therefore recommend the calculation of eGFR for the determination of possible renal impairment in post mortem investigations. It is, of course, always pertinent to interpret any results using a wealth of case information. Extreme caution should be exercised in cases where insufficient clinical information/history is available, particularly in cases in which there is suspected diabetic ketoacidosis, dehydration or hospitalisation prior to death.

1. Introduction

The determination of the role that drugs may have played in a death is an important part of the investigation into unexplained deaths. Renal impairment may lead to a reduction in drug excretion rate and therefore an accumulation of drugs or metabolites, leading to possible toxic or lethal effects. This accumulation is more likely if the usual excretion of drugs or their metabolites is through a urinary route (see table 1). Any renal impairment may or may not have been diagnosed before death, and medical records may or may not be available, therefore a suitable method for post mortem investigation is required in order to identify the presence of renal impairment.

In living patients there are two recognised clinical classifications with diminished kidney function, 1) chronic kidney disease (CKD) and 2) acute kidney injury (AKI) both of which would be expected to reduce renal excretion of some drugs [1]. CKD is a condition characterised by a gradual loss of kidney function over time (months, years, decades) [1]. AKI is a disorder that is characterised by a rapid loss (hours to days) of the kidney's excretory function [2]. Although there are clear guidelines/algorithms for the determination of AKI and CKD in the living, the status of kidney function close to the time of death, without previous medical history is difficult to determine using biochemical analysis of post mortem samples alone. This is because definitive confirmation of both CKD and AKI requires analysis of serum at multiple time points [3].

The clinically acceptable measure of kidney function is the determination of glomerular filtration rate (GFR), this measure is directly related to the number of functioning nephrons in the kidney. Clinically it is common to determine GFR using endogenous biochemical markers such as creatinine [4,5] and urea [6]. In the post mortem environment both creatinine and urea have been shown to be stable in vitreous humour so can potentially be used to determine kidney function close to the time of death [7–11].

Although creatinine was the preferred measure of GFR, creatinine concentration is affected by various factors (such as age, gender, ethnicity, muscle wasting disorders, recent intake of cooked meat and drugs that can block tubular secretion of creatinine [12]). In order to overcome some of these limitations of creatinine measurements alone, equations that estimate GFR (eGFR) from creatinine concentration have been developed (such as the Cockcroft and Gault [13], MDRD [14] and

CKD-EPI [15]). In the UK, the CKD-EPI equation (given below) is the recommended equation for determination of eGFR [16].

$$eGFR = 141 \times \min\left(\frac{SCr \times 0.011312}{k}, 1\right)^{\alpha} \times \max\left(\frac{SCr \times 0.011312}{k}, 1\right)^{-1.209} \times 0.993^{age} \times 1.018[if\ female] \times 1.159\ [if\ black]$$

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2, SCr (standardized serum creatinine) = mg/dL, age = years, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of serum creatinine/κ or 1 and max indicates the maximum of serum creatinine/κ or 1.

Although eGFR is the preferred method to assess kidney function, to date the only study to investigate eGFR in the post mortem environment [17] was limited by sample size and used the MDRD equation, rather than the recommend CKD-EPI equation.

The aim of this study is to determine if eGFR is a suitable method to determine the presence of previously undiagnosed renal impairment for post mortem investigations.

2. Materials and Methods

2.1 Sample Collection

Where available, vitreous humour samples were collected and analysed as part of routine Coronial procedure between January 2014 and

December 2016 at the Forensic Toxicology laboratory, University Hospitals of Leicester (UHL) NHS Trust. Vitreous humour was sampled from both eyes by aspiration using a sterile needle and syringe as part of the autopsy. The sampled vitreous was immediately mixed in a preservative free tube. The vitreous samples were then transported to the analytical laboratory and stored at 4°C for up to 1 week before analysis.

2.2 Sample Population

The case inclusion criteria for the study included a post mortem interval not exceeding 72 hours and the availability of vitreous humour. 812 cases were included in the study (216 females and 596 males; age 18 – 95 years of age). The certified causes of death included: Acute traumatic deaths (6); aircraft accident (6); hit by a train (12); fall from height (49); drowning (14); drug toxicity (172); ethanol toxicity (30); hanging (157); head injury (23); alcoholic ketoacidosis (30); diabetic ketoacidosis (40); road traffic collision (210) and stab wound(s) (32). 37 individuals in the study had known renal impairment (KRI) (as stated in the provided clinical history or medical records) and were not included in any of the other groups.

2.3 Sample Analysis

Immediately before analysis for creatinine the undiluted vitreous samples were centrifuged at 11,000 rpm for 10 minutes. The centrifuged samples then were measured for creatinine using the Siemens standard methodology (Siemens Advia® 2400, Siemens Healthcare, Surrey, UK) based on the method of Tanganelli and

colleagues [18]. This assay is traceable to National Institute for Standards and Technology (NIST) SRM967. The clinical reference ranges for creatinine at University Hospitals of Leicester are 60–120 µmol/L. The eGFR reference ranges are eGFR ≥90 mL/min/1.73 m^2 (normal), 60-89 (mild reduction), 45-59 (mild to moderate reduction) (from reference [19]).

2.5 Determination of "kidney impairment" in post mortem cases.

Without antemortem diagnosis of kidney impairment it is not possible to definitively determine renal impairment from a post mortem analysis. We therefore "scored" individuals as having "kidney impairment" based on either a creatinine concentration of >120 µmol/L or an eGFR of either <60 mL/min/1.73 m^2 or <90 mL/min/1.73 m^2. This allowed the comparison of the prevalence of "kidney impairment" in the living (based on population data [20]) and the deceased (based on samples collected at autopsy).

2.5 Data Analysis

From the analytical results of creatinine eGFR was calculated with the CKD-EPI equation using Microsoft Excel 2013 (Microsoft. Redmond, WA. USA). Data were analysed with GraphPad Prism 6.01 (GraphPad Software, Inc. CA 92037 USA). Before any further analysis, outliers were removed using the GraphPad ROUT method (Q = 1%). Normality of distribution was tested using the D'Agostino-Pearson omnibus normality test. Possible differences between the parameters investigated were tested using nonparametric testing (Kruskal-Wallis test (one-way ANOVA)). Sensitivity and specificity of creatinine and eGFR for the determination of scored renal impairment used KRI (control) and

hanging (patient) data with ROC analysis in GraphPad Prism (95% confidence limits). Statistical significance (α) was set at $p<0.05$ for all tests. As most of the groups in this study were not normally distributed data are given as median with ranges.

3. Results

3.1 Comparison of creatinine concentrations and eGFR compared to cause of death

The ranges of creatinine and eGFR for the KRI group (based on medical history) and the cause of death groups are shown in Fig 1 (creatinine) and Fig 2 (eGFR). There were statistically significant higher creatinine concentrations in the KRI group compared to all other causes of death groups (apart from death from diabetic ketoacidosis) (Table 2). When investigating eGFR the KRI group showed statistically significantly lower eGFR than of all of the other causes of death (apart from diabetic ketoacidosis) similar to creatinine results (Table 2).

3.2 *Accuracy of creatinine and eGFR ranges determining renal impairment in known cases*

In 37 patients there was documented kidney impairment, this allowed a comparison of vitreous creatinine and calculated eGFR to the clinical reference ranges in serum. The median concentration of creatinine in all cases (n = 812) was 66 μmol/L with a range of 3 – 1155 μmol/L; this compared to a median creatinine concentration of 220 μmol/L with a range of 86 – 1155 for KRI cases (n =37). The median eGFR in all cases (n = 812) was 112 mL/min/1.73 m^2 with a range of 2 – 3765 mL/min/1.73

m^2; this compared to a median concentration of 23 μmol/L with a range of 2 – 62 for KRI cases (n = 37).

We determined the accuracy of the creatinine and eGFR reference ranges to score individuals as having “kidney impairment” with individuals with known to have kidney impairment. The creatinine reference range (>120 μmol/L) scored 89% (33/37) of individuals as having kidney impairment with the eGFR of <60 mL/min/1.73 m^2 scoring (97% of cases (36/37) and an eGFR <90 mL/min/1.73 m^2 scoring 100% of cases (37/37).

3.3 Sensitivity and specificity of creatinine and eGFR for determination of scored renal failure

The group of individuals who had died due to hanging were determined to be the group that would be least likely to exhibit altered renal function due to the death process. The individuals in this group were all declared deceased at the scene. This allowed the determination of the sensitivity and specificity of the various reference ranges for renal impairment. The analysis showed that based on an eGFR of <60 mL/min/1.73 m^2 to score renal impairment sensitivity was 94.3 %, specificity 97.3 %. With an eGFR of <90 mL/min/1.73 m^2, sensitivity 86.0 %, specificity 100.0 %. Creatinine >120μmol/L gave a sensitivity 98.6 %, specificity 87.5 %.

3.4 Prevalence of KRI in the general UK population compared to individuals scored as having “kidney impairment” based on post mortem analysis

The prevalence of individuals who were scored as having kidney impairment based on creatinine levels of >120 μmol/L or an eGFR <60 mL/min/1.73 m^2 in post mortem vitreous analysis were compared to the

prevalence in the general population based on age (Fig 3). As expected, there was an increase in the number of individuals who were scored as having renal impairment as age increased. On average 7% more males and 6% more females were scored as being renally impaired compared to the population average when using creatinine as a measure to score renal impairment. This increased to 13% (male) and 18% (female) when eGFR (<60 mL/min/1.73 m^2) was used to score renal impairment and was 32.3% (male) and 30% (female) greater than in the general population when eGFR (<90) mL/min/1.73 m^2 was used.

4. Discussion

In forensic toxicology it is important to ascertain, where possible, the presence of kidney impairment in an individual as this diagnosis may go some way to explain the presence of raised drug concentrations in deceased individuals. Creatinine has previously been demonstrated to be stable in the post mortem period in post humour after death [7–11]. Creatinine has also been shown to be useful for the diagnosis of renal impairment in cases where a medical history is unavailable [7,8,21]. However, the use of creatinine concentration suffers from limitations that in clinical practice have been partially overcome by determining the eGFR of an individual. In this study we looked at a series of 812 deaths in which clinical information and post mortem vitreous humour samples were available. We aimed to determine if eGFR calculated from vitreous creatinine was a better measure than post mortem vitreous creatinine concentrations alone for the determination of possible renal impairment (scoring as renal impairment). We also used these data to compare the prevalence of “kidney impairment” in the normal population and our sample population.

In 37 patients there was documented kidney impairment, which allowed a comparison of vitreous creatinine and calculated eGFR levels in a “control” group. When using the reference ranges and eGFR levels the vitreous creatinine scored 89% of individuals correctly (as having renal impairment) with eGFR scoring between 97-100% of individuals as being renally impaired (depending on the eGFR used). The vitreous humour results for this sample group (KRI) demonstrate that determination of kidney function from post mortem vitreous correlates well with known clinical information. Based on the calculated sensitivity (probability that a test result will be positive when the renal impairment is actually present) eGFR (97-100%) performed better than creatinine (89%). In order to determine the sensitivity and specificity of the eGFR and creatinine reference ranges in scoring renal impairment we used the KRI group and the “hanging” group. The “hanging” cause of death group were determined to be the group that would be least likely to have altered renal function (due to the manner of death). eGFR showed larger sensitivities and specificities than creatinine in the determination of kidney impairment. These data suggest that eGFR is a better method to score kidney impairment from post mortem vitreous samples than creatinine alone. It is important to note that the “hanging” group may not be truly representative of a “negative” group for kidney impairment and ideally group(s) of individuals with a with both positive and negative medical histories for kidney impairment would be used to determine more accurate sensitivities and specificities for the tests.

As mentioned above the interpretation of renal impairment can be complicated by the manner of death and also any co-morbidities present. AKI could manifest as part of the death process, especially if death was not instantaneous and the individual was hospitalised before

death. It has been suggested that deaths that involve burns, fires, hyperthermia and dehydration may result in increased creatinine in the blood due to muscle catabolism or from thermal muscle damage, cases in which increased creatinine could be misinterpreted as renal impairment [7,8].

Clinical guidelines also suggest that AKI, and thus renal impairment, may be present in individuals with heart failure, liver disease, dehydration, hypovolemia (i.e. blood loss, fluid loss), drugs with nephrotoxic potential, hypotension, diabetes, chronic kidney disease, blockage of urinary tract and major surgery [22]. For example, in a study of 1,743 patients treated for renal failure the most commonly associated conditions were sepsis (43.8%), major surgery (39.1%), low cardiac output (29.7%) and hypovolemia (28.2%) [22]. These studies show that the determination of renal impairment from post mortem sample analysis may be problematic. A further indication of the scale of prevalence of AKI can be seen in a study from the UK in which 8 - 16% of people admitted to hospital were found to have AKI [23]; this rate increases with sepsis (prevalence of >40%) [24] and in patients admitted to intensive care (prevalence >60%) [25]. It is more likely than not that individuals who are close to death and admitted to hospital for treatment will have some form of AKI.

As expected, the only cause of death group that was not significantly different from the KRI group are individuals that are known to have suffered from diabetic ketoacidosis. In diabetic ketoacidosis individuals may exhibit dehydration and diabetic nephropathy, both of which are known to raise creatinine levels [26]. Simple post mortem testing can determine diabetic ketoacidosis so this can be identified if had not been previously diagnosed [27]. The diabetic ketoacidosis group illustrates the

medical issues that can cause AKI and also complicate the interpretation of renal impairment from post mortem sample analysis.

As expected an increasing trend in kidney impairment with age was observed in the study data with both the creatinine and eGFR kidney impairment scoring. However the prevalence of individuals scored as having renal impairment was higher than that of individuals in the general population. When using eGFR (<60 mL/min/1.73 m^2), the reference parameter that gave the highest sensitivity and specificity for scoring of renal impairment, there was on average a 13-18% higher prevalence of individuals in this scored as having “renal impairment” compared to the general population. This prevalence was even larger if eGFR (<90 mL/min/1.73 m^2) was used (~30-32% higher). The lowest difference was with creatinine (6-7% higher). These results may show that the death process has a larger influence on the creatinine levels than previously expected and any interpretation of post mortem creatinine should be performed with extreme caution, especially the younger age groupings (<65 years) and also in females (see fig 3).

The interpretation of a post mortem creatinine results may also be complicated by the sample analysed. Various post mortem samples have been reported in the literature as being suitable for the determination of creatinine levels including vitreous, pericardial fluid, cerebrospinal fluid, synovial fluid, post mortem serum and blood [7,8,21,28–30]. Studies have suggested the pericardial fluid creatinine concentrations correlate well with post mortem creatinine serum concentrations and that pericardial fluid should be used if post mortem serum is not available [21]. This study also notes that post mortem vitreous creatinine concentrations are significantly lower than those of

post mortem serum. It is possible that post mortem vitreous gives a creatinine concentration closer to that found at the time of death, as vitreous is sealed from the general circulation and this that may protect vitreous from changes in creatinine due to the death process. For example in animal studies creatinine blood concentrations have been shown to increase after death from ~18 μmol/L at the time of death to ~800 μmol/L 2 hours after death [31]. This increase is most likely due to the release of creatinine from muscles into the blood in the early post mortem period [31,32]. Studies have also shown the shown that serum, blood and pericardial fluid creatinine concentrations are on average higher than the creatinine clinical reference ranges [7,8,21]. These postmortem increases in creatinine other body fluids may not be observed in vitreous as there is a time lag between any changes in the concentration of substances in blood and vitreous [33]. The possible postmortem elevation of creatinine in serum, blood and pericardial fluid in the post mortem period and any potential time lag between increases in vitreous creatinine would need to be confirmed in future studies. The use of serum, blood and pericardial fluid could also be problematic as based on the scored prevalence of renal impairment. In the general population these samples on average would give an increased likelihood of the scoring of the individual as being renally impaired as the median creatinine levels in pericardial fluid/serum values are ~ 4 to 5 fold larger than vitreous creatinine levels [21]. The use of pericardial fluid may also be problematic as this fluid is not routinely collected in all medico-legal centres.

5. Conclusion

The biochemical analysis of post-mortem vitreous creatinine and subsequent calculation of eGFR is a useful adjunct to the standard testing that takes place during a post-mortem examination and can assist in death investigation. The data has shown that using eGFR (<60 mL/min/1.73 m^2) determined from vitreous creatinine, has the highest sensitivity and specificity for scoring renal impairment, but the use of a creatinine level of >120 μmol/L gives a scoring of renal impairment closer to that found in the general population. It is, of course, always pertinent to interpret any results using a wealth of case information. Extreme caution should be exercised in cases where insufficient clinical information/history is available, particularly in cases in which there is suspected diabetic ketoacidosis, dehydration or hospitalisation prior to death.

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Figure 1: Vitreous creatinine concentrations in relation to the cause of death and deaths in which there was known renal impairment. Mean, 25th and 75th percentiles, maximum and minimum. KRI – known renal impairment; RTC – road traffic collision.

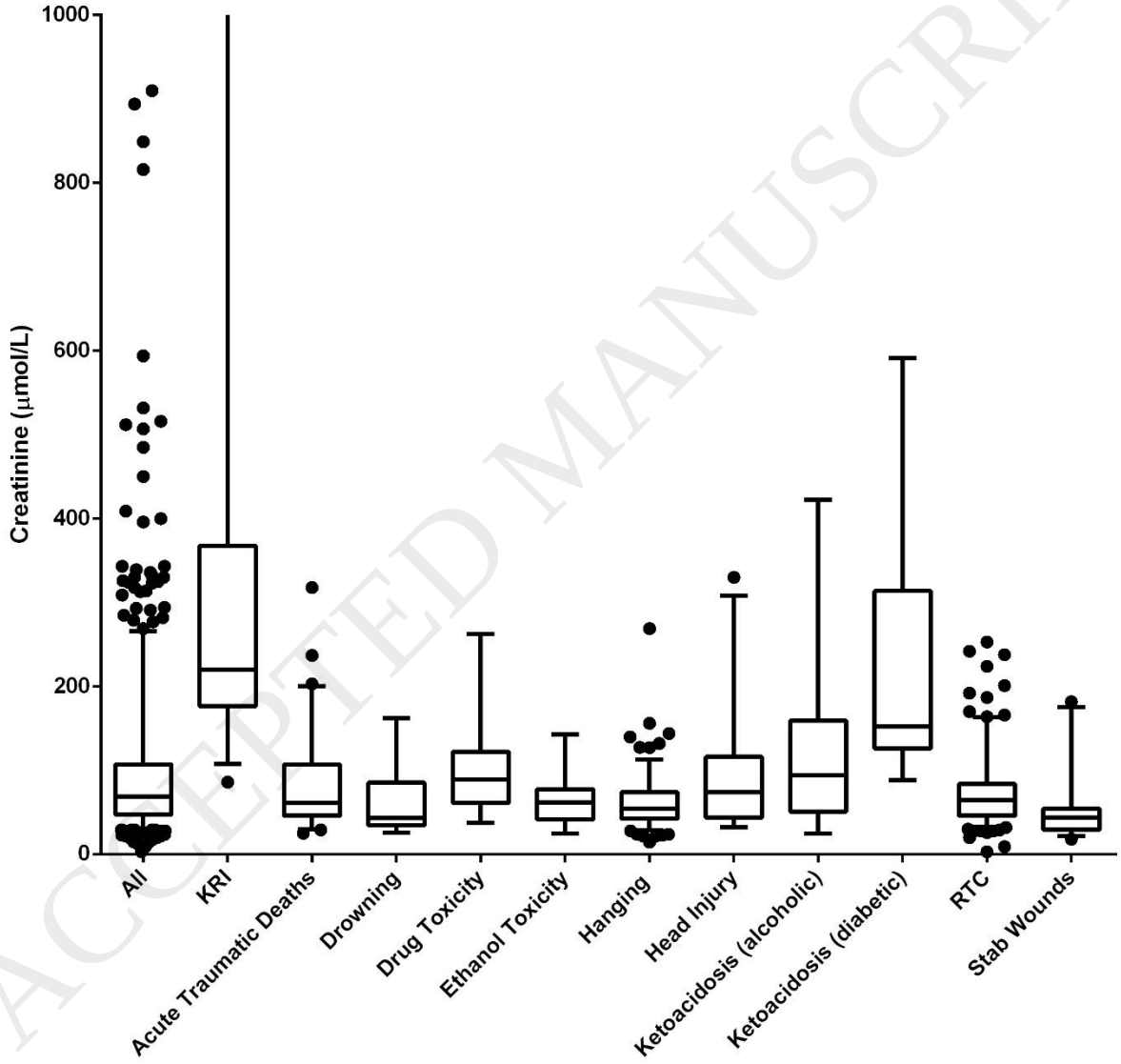


Figure 2: Calculated eGFR concentrations in relation to the cause of death and deaths in which there was known renal impairment.

Mean, 25th and 75th percentiles, maximum and minimum. KRI – known renal impairment; RTC – road traffic collision.

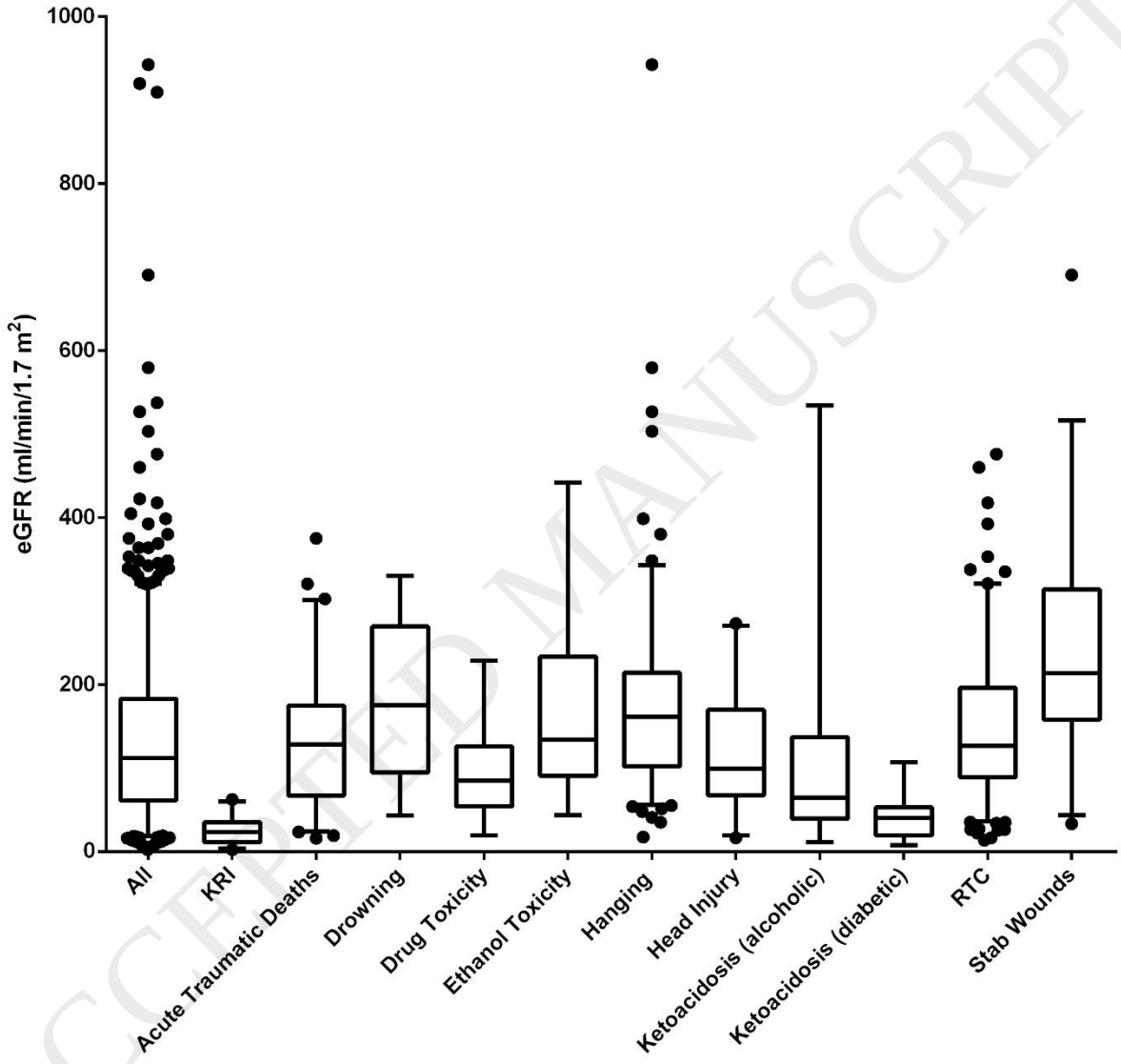
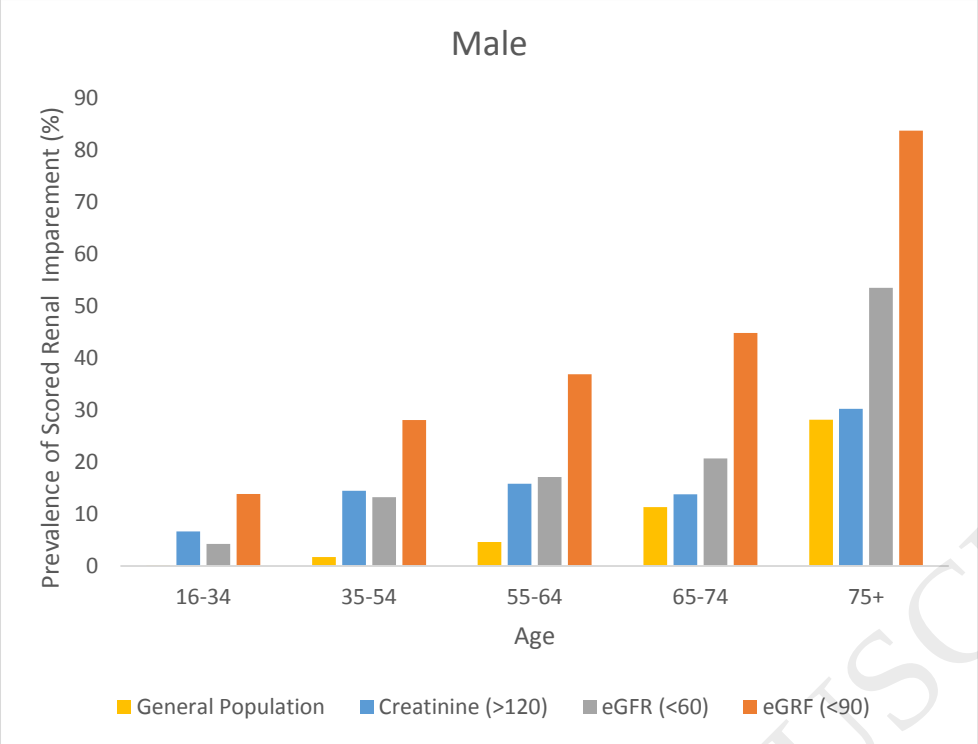


Figure 3: Prevalence of scored kidney impairment in males and females by age group. The individuals were scored as having renal impairment based on either creatinine (> 120 µmol/L) or eGFR (<60mL/min/1.73m^2).



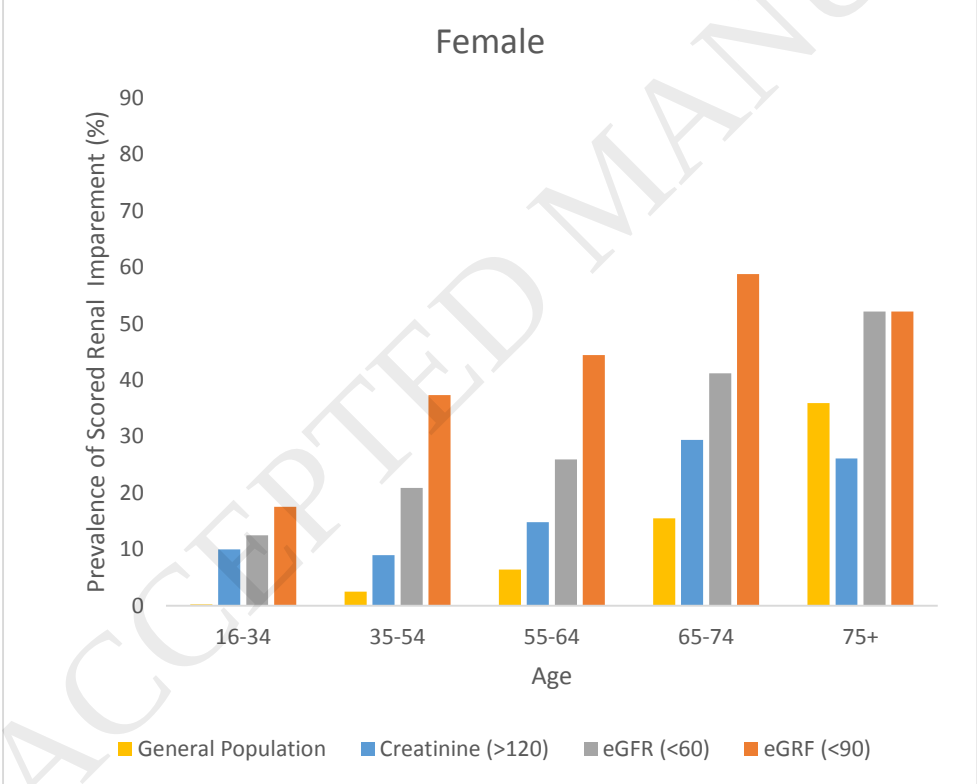


Table 1: Common drugs that may accumulate during kidney impairment. More detailed and wider ranging information about the drugs that are excreted via the renal route can be found in the Renal Drug Handbook [3]. AKI – acute kidney injury, ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, NSAIDS – non-steroidal anti-inflammatory drugs.

Drug	% excreted unchanged in urine	Notes	Reference
ACEi/ARB	-	Known to reduce GFR further in AKI	[3]
Allopurinol		Accumulation of active metabolite oxipurinol	[3]
Amisulpride	50		[3]
Amphetamine	30		[34]
Atenolol	>90		[3]
Benzodiazepines		Risk of accumulation of activate metabolites	[3]
Codeine	-	Accumulation of active metabolite morphine-6-glucuronide	[3]
Digoxin	50 – 75		[3]
Dihydrocodeine	13 - 22	Accumulation of active metabolite	[3]
Dothiepin	56	Accumulation of active metabolites possible	[3]
Diuretics		Risk of hyperkalemia and increase in mortality in AKI	[3,22]
Gabapentin	~100		[3]

Heroin	-	Accumulation of active metabolite morphine-6-glucuronide	[34]
Insulin		Renal metabolism can decrease removal in AKI	[3]
Levetiracetam	66		[3]
Lithium	95		[3]
Methadone	15 – 60		[3]
Metformin	100		[3]
Methamphetamine	43% (4-7% amphetamine)		[34]
Mirtazapine	75		[3]
Morphine	-	Accumulation of active metabolite morphine-6-glucuronide	[3]
NSAIDS		Known to reduce renal function further in AKI	[3]
Pregabalin	92-99		[3]
Tramadol	90		[3]

Table 2: Summary of the result of statistical analysis of known renal impairment group with the various causes of death. Statistical analysis was 1 way ANOVA with Dunn's multiple comparison post-hoc test ($p<0.05$). KRI – known renal impairment; RTC- road traffic collision.

Cause of Death	**Creatinine**		**eGFR**	
	significantly different?	P value summary	significantly different?	P value summary
KRI vs. All	Yes	****	Yes	****
KRI vs. Acute Traumatic Deaths	Yes	****	Yes	****
KRI vs. Drowning	Yes	****	Yes	****
KRI vs. Drug Toxicity	Yes	****	Yes	****
KRI vs. Ethanol Toxicity	Yes	****	Yes	****
KRI vs. Hanging	Yes	****	Yes	****
KRI vs. Head Injury	Yes	****	Yes	****
KRI vs. Ketoacidosis (alcoholic)	Yes	****	Yes	**
KRI vs. Ketoacidosis (diabetic)	No	ns	No	ns
KRI vs. RTC	Yes	****	Yes	****
KRI vs. Stab Wounds	Yes	****	Yes	****