Original article

Urea Percentile Curves in Pre-dialysis children with chronic kidney disease: Efficacy & Limitations.

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Abstract
Introduction: Chronic kidney disease (CKD) carries a lot of co-morbidities. Urea rise may be related to decline in glomerular filtration rate, under nutrition or hyper catabolic state. According to urea percentile curves (UPC), patients with a given glomerular filtration rate show wide range of urea levels. Correlation between urea percentiles and CKD patients’ co-morbidities was suggested in many studies since Montini 2003.

Aim of the study: to evaluate the value of UPCs as a simple tool in monitoring metabolic status and progress of CKD comorbidities.

Methods: Retrospective revision of patients’ files for their urea levels and GFR at the time of diagnosis and long period after (follow-up). Accordingly, each patient was plotted on UPC graph to determine his urea percentile (UP) at each setting. Patients were classified according to their urea percentile as low, moderate and high UP groups, and classified according to urea percentile progress pattern as ascending, descending and stable groups. Correlations between their co-morbidities and their urea percentiles were statistically analysed.

Results: showed correlation between morbidity markers changes in relation to progress course of UP with significant differences in the values of phosphorus rise, bicarbonate changes and frequency of hyperphosphatemia between the 3 groups of urea percentile progress pattern.

Conclusion: Follow up pattern of urea percentile in these children is a simple and helpful tool in monitoring their co-morbidities.

Keywords: Chronic kidney disease; Glomerular filtration rate; Serum urea concentration; Urea percentiles curves.

Running Title: Urea Percentile Curves in Pre-dialysis children with chronic kidney disease.

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INTRODUCTION
Chronic kidney disease (CKD) has many long-term complications related to irreversible deterioration of renal function. Dietary protein intake is metabolized to amino acids and then through the liver to form urea, to be excreted in the urine. Plasma Urea concentration reflects the balance between its production and elimination in urine [1-3]. Uraemia is the main metabolic derangement of CKD. It is a clinical syndrome characterized by elevated concentrations of urea in the blood associated with electrolyte and hormonal imbalances. It is responsible for different clinical co-morbidities that develop in parallel with deterioration of kidney function [4, 5]. The level of urea in the blood is affected by several factors other than renal function deterioration. So, absolute serum urea levels do not correlate well with the development of co-morbidities accompanied with CKD. Estimated glomerular filtration rate (eGFR) reflects a stronger correlation [6].

Regarding urea Percentile in children with CKD, urea metabolism is severely affected by renal failure as, for a given nitrogen intake, serum urea rises roughly in parallel with the fall of glomerular filtration rate (GFR) and absence of significant renal tubular adaptation for urea excretion. There is a correlation between the rise in serum urea and the development of uremic symptoms, such as weakness, malaise, and bleeding due to platelet dysfunction [7].

Repeated evaluations of nitrogen balance would be the most accurate way to predict the metabolic status of a child. In children with CKD the evaluation of metabolic balance has to consider their higher anabolic growth demands. Sufficient protein intake is needed to guarantee adequate growth and satisfactory metabolic control. Identifying a catabolic status or an excessive protein intake is therefore important, but may be difficult [8]. Serum Urea is routinely measured in the clinical setting but they are difficult and time consuming, also the reference data only identify an upper normal value and not a range for different GFR values. Using a large database by the Italian Pediatric Registry of CKD, urea percentile curves were produced for different GFR levels, for the age group between 2–20 years [7]. They provide a reference that can obviate the difficulty in interpreting serum urea. They do not replace nitrogen balance studies, but they represent an additional useful tool. Furthermore, they are very easy and quick to use, and may help to continuously monitor our children with CKD as they help to identify the children with inappropriate serum urea for a given GFR. Further nitrogen balance studies will help to understand why serum urea is elevated [7].

Registry data were used to plot 10th, 25th, 50th, 75th, and 90th percentiles curves on the graphs. Low urea centile patients are those (<25th percentile), moderate (25th-75th percentile), and high (>75th percentile) [7]. “Montini et al. suggested” the association between a high serum urea and poor metabolic control with higher values of phosphorus and parathyroid hormone (PTH) and lower haemoglobin and bicarbonate levels. The lower bicarbonate level in children with high urea concentrations was referred to either high protein intake, catabolism aggravating acidosis or that acidosis
promotes catabolism and thereby production of urea [7]. Patients, who do not comply with dietary recommendations, may also be less compliant with pharmacological therapy. This could also explain the high serum urea, phosphorus, and PTH levels [9]. Levels of azotemia higher than the 75th percentile can reasonably identify those patients with poor metabolic control or an excessive protein intake and suggest the need for careful evaluation of a possible catabolic status in these children. The clinician can utilize these percentiles to evaluate the level of azotaemia for a given GFR and its progression in the same patient more objectively, independent from any worsening of renal function [7]. The aim of this study is to evaluate use of urea percentile curves (UPC) made by Montini et al. [7] as easy accessible tool for identifying subjects with inappropriate serum urea for a given GFR values obtained with Shwartz formula and monitoring pre-dialysis CKD children to predict their metabolic status and to investigate their correlation with important CKD co-morbidities, since Urea percentiles (UP) reflects different ranges for blood urea coincident with each eGFR value [7].

METHODS
A retrospective study was carried out on 100 children of both sexes who were already diagnosed as CKD with primary renal disease and are following at Paediatric Nephrology Outpatient Clinic, Children hospital. The study has been approved by the Research Ethics Committee, Faculty of Medicine, Cairo University (approval code: S-16-2019).

On revising the patients' follow up files, excel sheet was prepared for their laboratory data in order to evaluate their urea metabolic status and markers of studied comorbidities, at two different urea levels with a wide distance of separation {first assessment at the first clinic visit (phase 1) and second assessment at the time of inclusion in the study (phase2)}. Inclusion criteria: age more than 2 years and less than 18 years, GFR <75ml/min/1.73m², on conservative treatment and follow up for at least 1 year. Exclusion criteria: age less than 2 years, children with disease that could affect urea metabolism as metabolic disease, steroid treatment, heart or liver disease.

Laboratory data recorded in the files at phase 1 (basal) and phase 2 (follow up) including; {complete blood count, calcium profile: calcium, phosphorus and alkaline phosphatase (ALP), blood gases, urea and s creatinine} were revised and registered in the sheet. GFR was estimated according to the Schwartz formula [10].

**Patient urea percentiles determination:**
Each patient, according to his urea levels and eGFR values, was plotted on UPC Figure 1 at phase 1 and phase 2 assessment.
Patients were classified according to:

(1) Their urea percentile curves (UPC) into three patterns:
   - Low urea percentile pattern (L) (< 25th percentile)
   - Moderate urea percentile pattern (M) (25th - 75th percentile)
   - High urea percentile pattern (H) (> 75th percentile)

(2) According to changes in UP pattern from phase 1 to phase 2:
   - Group (A) ascending percentile changed to a higher percentile (worsened).
   - Group (B) descending percentile changed to a lower percentile (improved).
   - Group (C) stable remained on the same percentile.

Laboratory markers for studied co-morbidities, were expressed as mean and percentage or frequency for 100 patients (total group) at both basal and follow-up setting Table 1. They included:
- Haemoglobin as a marker for anaemia,
- Phosphorus and ALP as markers for bone disease and bicarbonate as a marker for metabolic acidosis.

Data of the two assessments were related to UP (L, M, H) patterns based on urea levels and eGFR values of each assessment separately, for further data comparison between base and follow-up assessment Table 2, 3. Changes in the laboratory markers values from the first to the second assessment for each patient and then the total group profile, according to (mean level of each laboratory marker and frequency of each co-morbidity) were analysed and related to changing pattern of patient UP (ascending, descending, stable) Table 2, 3.

Statistical analysis:

Data were coded and entered using the statistical package for the Social Sciences. Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons for laboratory markers, between groups (A/B/C) Tables 4 and (A/B) Table 5 were done using analysis of variance (ANOVA) with multiple comparisons post hoc test in normally distributed quantitative variables while non-parametric Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables (Chan, 2003a). For comparing categorical data, Chi square (c2) test was performed. Exact test was used instead when the expected frequency is less than 5 (Chan, 2003b). P-values >0.05 were considered as statistically significant.

RESULTS

[I] Total sample UC patterns & Comorbidities (basal & follow-up):
The study included 100 patients (69 male, 31 female), with primary renal disease already diagnosed as CKD with GFR<75ml/min/m² on conservative
treatment. The median of age of them was 6.6 years with inter-quartile range 4.2: 11.

* Patient’s laboratory markers for the studied clinical co-morbidities in phase 1 and 2 shown in Table1.

* Group profile based on patient UP pattern as Low, Moderate, High (L, M, H) in phase 1 and 2 is shown in Figure 2, 3.

* Group profile based on UP progress pattern according to changes from phase 1 to phase 2 was ascending (A) 36%, descending (B) 18% and stable percentiles (C) 46% groups Figure 4.

[II] Comorbidities in relation to patient Urea percentile Centile Curves UP:
Mean level of laboratory markers and their frequency in relation to UP (L, M, H) are summarised in Tables 2, 3. No statistically significant difference was found between UP patterns (L, M, H) regarding mean level of laboratory markers or frequency of co-morbidities in each assessment (base & follow-up) separately. Statistically significant difference in mean changes in levels of phosphorus, bicarbonate & frequency of hyperphosphatemia were noted between groups when based on progress of UP pattern of patients (A, B, C) Table 4.

[III] Comparison between patient co-morbidities in relation to the urea percentile pattern (A, B, C): Tables 4 and Figure 5, 6.

* Regarding anaemia: there was insignificant difference in the mean values of haemoglobin change and frequency of anaemia between the 3 groups (A, B, C).

* Hyperphosphatemia: showed significant difference in the mean values of phosphorus rise (P value = 0.005) and frequency of hyperphosphatemia (P value = 0.026) between the 3 groups, being highest in the group (A). The highest rate of phosphorus rise is in group (A) compared to the group (B) who showed the highest rate of phosphorus drop and group (C) who showed nearly constant levels of phosphorus as illustrated in Figure 5.

* High Alkaline Phosphatase: there was insignificant difference in the mean values of ALP changes and frequency of its elevation, regarding the 3 groups (A, B, C).

* Metabolic acidosis: there was significant difference in the mean values of bicarbonate changes (P value = 0.038) between the 3 groups being markedly dropped within group (A) as compared to group (B) and (C) who showed better rate in bicarbonate rise and better correction of acidosis as illustrated in Figure 6. But there was insignificant difference in the frequency of metabolic acidosis regarding the 3 groups although frequency of acidosis was highest among group (A).

[IV] Comparison between patient co-morbidities in relation to the type of UP change (A & B only) Table 5:
Phosphorus changes showed significant increase in the frequency of hyperphosphatemia (P value = 0.007) and rate of rise (P value = 0.002) among group (A). Metabolic acidosis showed significant difference in the rate of bicarbonate drop (P value = 0.047) and
insignificant difference in the frequency of acidosis (P value = 0.3) between the two groups although frequency of acidosis was higher among group (A).

Table 1: Total sample comorbidities frequency percentage & mean values of biochemical and haematological parameters in phase (1) & (2)

<table>
<thead>
<tr>
<th></th>
<th>Hb (1) (g/dl)</th>
<th>Hb (2) (g/dl)</th>
<th>Phosph (1) (mg/dl)</th>
<th>Phosph (2) (mg/dl)</th>
<th>ALP (1) (U/L)</th>
<th>ALP (2) (U/L)</th>
<th>HCO3 (1) (mEq/l)</th>
<th>HCO3 (2) (mEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>61.0%</td>
<td>73.0%</td>
<td>16.0%</td>
<td>28.0%</td>
<td>61.0%</td>
<td>67.0%</td>
<td>73.0%</td>
<td>68.0%</td>
</tr>
<tr>
<td>Mean</td>
<td>10.22</td>
<td>10.35</td>
<td>5.06</td>
<td>5.20</td>
<td>574.02</td>
<td>550.92</td>
<td>17.85</td>
<td>19.30</td>
</tr>
</tbody>
</table>

Hb: hemoglobin, Phosph: Phosphorus, ALP: alkaline phosphatase, %: percent, HCO3: bicarbonate

Figure 2: Total sample urea percentile pattern basal assessment phase 1
L: low, M: moderate, H: high

Figure 3: Total sample urea percentile pattern follow-up phase 2

Figure 4: Total sample urea percentile changing pattern.
Table 2: Phase 1 Comparison of co-morbidities (mean and frequency) in relation to urea percentile patterns (L, M, and H)

![Table 2](link-to-table-image)

Table 3: Phase 2 comparison of co-morbidities (mean and frequency) in relation to urea percentile patterns (L, M, and H)

![Table 3](link-to-table-image)

Table 4: Comparison of mean change and frequency of co-morbidities in relation to percentile changes (A, B, and C)

![Table 4](link-to-table-image)

ALP*: alkaline phosphatise, p-value: probability value.

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Figure 5: Statistical comparison between groups (A, B, and C) in relation to phosphorus changes.

Figure 6: Statistical comparison between groups (A, B, and C) in relation to bicarbonate changes.

Table 5: Two groups comparison of co-morbidities (mean change and frequency) in relation to percentile changes (A and B only)

<table>
<thead>
<tr>
<th>Percentile changes (A and B only)</th>
<th>group A (worsened)</th>
<th>group B (improved)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean values of parameter</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<tr>
<td>Haemoglobin change</td>
<td>0.17</td>
<td>2.30</td>
<td>-0.18</td>
</tr>
<tr>
<td>Phosphorus change</td>
<td>0.76</td>
<td>1.88</td>
<td>-0.64</td>
</tr>
<tr>
<td>Alkaline Phosphatase change</td>
<td>16.19</td>
<td>285.77</td>
<td>59.94</td>
</tr>
<tr>
<td>Bicarbonate change</td>
<td>-0.09</td>
<td>4.91</td>
<td>2.48</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Frequency of co-morbidity (A and B only)</th>
<th>group A (worsened)</th>
<th>group B (improved)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Count</td>
<td>Percent</td>
<td>Count</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>52.8%</td>
<td>9</td>
</tr>
<tr>
<td>High phosphorus</td>
<td>24</td>
<td>66.7%</td>
<td>5</td>
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<tr>
<td>High Alkaline Phosphatase</td>
<td>21</td>
<td>58.3%</td>
<td>8</td>
</tr>
<tr>
<td>Low bicarbonate</td>
<td>17</td>
<td>47.2%</td>
<td>6</td>
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DISCUSSION

The current study aimed to evaluate the use of Montini UPC in monitoring children with CKD stages 2-4 on conservative treatment and to correlate them with important clinical and laboratory co-morbidities (anaemia, hyperphosphatemia, high ALP and metabolic acidosis).

[1] Co-morbidities profile of the total group (100 CKD patients pre-dialysis):

Anaemia showed high prevalence through the two assessments (61%, 73%). “Atkinson et al. 2018 reported” increasing prevalence of anaemia in children with CKD as disease stage advances [11]. Its main cause was inadequate production of endogenous erythropoietin that acts on the differentiation and maturation of the red blood cells precursors [12].

Mineral bone disease markers were calcium, phosphorus and ALP. There was high prevalence of hyperphosphatemia through the two assessments (16%, 28%). Similarly, “Mosbah 2019 reported that” calcium and phosphorus metabolism imbalance (hyperphosphatemia and hypocalcaemia) secondary to renal impairment are specially marked in stage 4, 5 CKD result in secondary hyperparathyroidism [13].

“Stanbury and Lumb 1966” correlated plasma phosphorus and bone diseases with uremia in patients with CKD as high serum urea level was associated with increasing frequency of hyperphosphatemia [14]. Similarly, “Montini et al. 2003 reported that” hyperphosphatemia was directly proportionate with CKD progression and uremia. Reduced renal function had deleterious effect on bone and mineral metabolism in children, resulting in renal osteodystrophy [7]. Its mechanisms include reduced renal excretion of phosphate, impaired gastrointestinal and renal reabsorption of calcium, inducing hyperphosphatemia and hypocalcaemia [13].

Frequency of high ALP in the two assessments was (61%, 67%). There was insignificant difference in ALP level between the two assessments. “Mosbah 2019 reported that” total ALP can be used as bone marker, although it is not the best marker for bone turnover [13]. An immunoassay for bone specific ALP is a better marker but not in standard practice. However, it does not confirm more information regarding bone turnover [15]. ALP is an enzyme found in many tissues throughout the body. Unfortunately, the enzyme’s lack of specificity limits its use as a biomarker of disease activity [16]. We could not use PTH to assess the metabolic bone disease associated with CKD as it is not available with the routine follow up laboratory investigations in patients’ files.

Metabolic Acidosis frequency was highly prevalent in the two assessments (73%, 68%). Similarly, “Harambat et al. 2017 found that” children with CKD stages 3-5 with bicarbonate under18 mmol/l had significantly higher risk of CKD progression than those with 22 mmol/L or more. Alkali therapies improve the course of kidney disease [17]. Acidosis is a major metabolic abnormality associated with uraemia. Metabolic acid-base regulation is controlled primarily by tubular cells located in the kidney [18]. On conclusion, the four reported co-morbidities were highly prevalent among the total sample in both assessments with...
insignificant change in the mean or frequency.

[II] Relation between comorbidities and urea percentiles patterns (low, moderate, high): Table 2, 3

Anaemia reported insignificant difference in its frequency or mean haemoglobin on comparing (L, M and H) groups in both assessments. “Montini et al. 2003 found” statistically significant correlation between anaemia and UP patterns (p value = 0.001) and reported that anaemia was marked among patients on high UP pattern [7]. “Phillips et al. 2015 reported that” increasing urea and creatinine concentrations were concurrent with development of anaemia, with a significant negative correlation between haemoglobin and urea concentration. Also, reported that marked anaemia in the presence of elevated erythropoietin suggests inefficient erythropoiesis that’s may be correlated with serum urea concentration [19]. We may attribute the stable level of haemoglobin through our study to the good patient compliance to regular erythropoietin therapy. Also, high level of serum urea in many included patients may be related to factors other than renal deterioration as well; as high protein diet and hypercatabolic status.

Hyperphosphatemia showed insignificant difference in relation to (L, M, H) groups in both assessments. Its prevalence was higher among (M) and (H) groups in both assessments with relative increase in the frequency when comparing first to second assessments but with insignificant relation with UP patterns. This disagreed with “Montini et al. 2003” who found statistically significant correlation between hyperphosphatemia and UP patterns (p value = 0.0001) and reported that patients with the highest serum urea showed the highest values of hyperphosphatemia [7]. It should be noted that hyperphosphatemia can be attributed to excess dietary intake of certain types of food such as red meat, chicken and fish with non adherence of patients to the recommended diet that limits the consumption of them [20]. Hypercatabolic state in severely malnourished patients enhances hyperphosphatemia even with controlled GFR and kidney function [21]. These factors may explain the high prevalence of hyperphosphatemia reported in both assessments in the current study. Also, it is worth to think that regular correction of hypophosphatemia with phosphate binders, hypocalcaemia with calcium supplementation, metabolic acidosis with alkali therapy together with vitamin D supplementation improve the course of kidney disease [18] and may explain the insignificant relation between hyperphosphatemia and UP in the current study.

High ALP was found in both assessments with insignificant correlation with UP pattern. “Montini et al. 2003” used PTH as bone disease marker and found statistically significant correlation between PTH values and the corresponding UP (p value = 0.001). In the current study, we reviewed that ALP is less sensitive for bone disease because it is a biomarker for many diseases and physiologic processes [16].

From metabolic acidosis frequency and mean values of serum bicarbonate, we noticed that in the first assessment the frequency of acidosis was continuously increasing in correspondence to UP pattern but with insignificant relation,
while the mean is nearly constant. In the second assessment, its prevalence was high regardless the corresponding UP pattern with insignificant relation. “Montini et al. 2003” found high prevalence of metabolic acidosis among CKD patients but with significant relation between serum bicarbonate level and UP patterns (p value = 0.0001) as patients with lowest bicarbonate level placed on high UP pattern [7]. “Harambat et al. 2017 reported that” metabolic acidosis is a common complication in paediatric CKD and may be a risk factor for CKD progression [17]. A systematic review and meta-analysis made by “Navaneethan et al. 2019 reported that” treatment of metabolic acidosis with oral alkali supplementation increased serum bicarbonate levels and resulted in a slower decline in eGFR [2]. We can explain the insignificant relation between bicarbonate level and UP patterns in the current study as patients who receive alkali therapy supplementation would improve metabolic acidosis secondary to CKD. Also, absence of regular dialysis would make correction of acidosis by alkali therapy unsatisfactory in reducing elevated serum urea level caused by factors other than renal deterioration. A clinical trial using bicarbonate therapy for CKD stage 3-4 revealed significant rise of bicarbonate without any significant effect on GFR or bone mineral density [22]. We concluded that patients with CKD (pre-dialytic stage), who are plotted on high UP (at a single assessment), are not always associated with the higher prevalence of clinical or laboratory co-morbidities of CKD.

**[III] Relation between patients’ co-morbidities and the percentile changing pattern (ascending, descending and stable percentiles) and 3 group comparison for parameters of significance (hyper phosphatemia, metabolic acidosis): Table 4, Figure 5, 6**

Hyperphosphatemia showed significant increase in the frequency (P value = 0.026) and rate of rise (P value = 0.005) among the worsened group (A) as compared to other 2 groups (B, C). Metabolic acidosis showed significant difference in the rate of bicarbonate drop being highest in group (A) (P value = 0.03) and insignificant difference in the frequency of acidosis between the three groups although the frequency of acidosis was higher among the worsened group (P value = 0.2). Which means, the highest rate of drop in bicarbonate and difficult correction of acidosis occur among the worsened group (A) with mean of (-0.09 ± 4.9mEq/l) while the highest rate of rise and better correction of acidosis occur among the group (B) with mean of (2.4 ± 3.4mEq/l).

**[IV] Comparison between patients’ co-morbidities in relation to the type of percentile change (ascending and descending percentiles): Table 5**

Hyperphosphatemia showed significant increase in the frequency (p value = 0.007) and rate of rise (p value = 0.002) among group (A), hyperphosphatemia correlate with ascending UP pattern confirming the role of phosphorous rich diet and hypercatabolic states in rise of urea & phosphorous [23]. Metabolic acidosis frequency showed insignificant relation with change in UP pattern. But, the mean levels of bicarbonate changes showed significant difference between the two
groups being markedly dropped in group (A) (p value = 0.04).

CONCLUSION
Single assessment of UP does not correlate with clinical and laboratory co-morbidities in CKD2-4. Follow up of UP pattern for the same patient is more predictive and correlated with his co-morbidities that are related to uremia irrespective of its source. With rising UP pattern, we should exclude hyper catabolic states and should not just consider as progression of co-morbidities. Hyperphosphatemia was the most significantly correlated co-morbidity within the three groups (A, B, C). GFR decline enhances phosphorus retention and aggravate uraemia. Metabolic acidosis was significantly related to UP as patients with rising UP reported higher rate of drop in bicarbonate and difficult correction of acidosis as compared to those with descending UP.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ALP</td>
<td>Alkaline Phosphatase</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid Hormone</td>
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<tr>
<td>UP</td>
<td>Urea Percentile</td>
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<tr>
<td>UPC</td>
<td>Urea Percentile Curves</td>
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REFERENCES


AUTHORS’ CONTRIBUTIONS:
The submitted manuscript is the work of the author & co-author. All authors have contributed to authorship, have read and approved the manuscript.

Conception and design of study: 1st author.

Acquisition of data: 2nd & 3rd author.

Analysis and/or interpretation of data: 2nd & 3rd author.

Drafting the manuscript: 1st & 3rd author.

Revising the manuscript critically for important intellectual content: 1st & 3rd author.

Approval of the version of the manuscript to be published: 1st & 3rd author

STATEMENTS

Ethics approval and consent to participate
This study protocol was approved and deemed sufficient by the Ethical Committee of Faculty of Medicine, Cairo University (approval code: S-16-2019).

Consent for publication
“Not applicable”

Availability of data and material
“Not applicable”

Conflict of interest
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