Measured creatinine clearance from timed urine collections substantially overestimates glomerular filtration rate in patients with liver cirrhosis: a systematic review and individual patient meta-analysis

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Abstract

Background. Accurate glomerular filtration rate (GFR) assessment in patients with liver cirrhosis is important for prognostication, chronic kidney disease staging, drug dosing and identifying combined liver–kidney transplantation candidates. The objective of this study was to review the accuracy of measured creatinine clearance (MCrCl) from timed urine collections for estimating true GFR.

Methods. A systematic review and individual patient meta-analysis was performed. MEDLINE, old MEDLINE, Index Medicus and Cochrane library bibliographic databases and conference proceedings were searched up to June 2004. Reference lists of relevant studies were searched and experts were contacted. Comparative diagnostic studies describing stable adult patients with cirrhosis categorized according to the Child–Pugh classification were included if a gold standard GFR measurement was performed within 3 days of MCrCl. Individual patient data were abstracted from graphs of primary articles to allow a pooled analysis of agreement between renal measures.

Results. Seven studies of 193 patients from 1974 to 2002 were summarized. MCrCl overestimated inulin clearance (CIn) by a mean of +13 ml/min/1.73 m² and the limits of agreement (mean of the differences±2 SD) were +60 ml/min/1.73 m² and −34 ml/min/1.73 m². This overestimation was highest in patients with lower GFR. The mean clearance ratios [95% confidence interval (CI)] between MCrCl and CIn in the high (≥60 ml/min/1.73 m²) and low (<60 ml/min/1.73 m²) GFR subgroups were 1.18 (1.12–1.23) and 1.49 (1.33–1.66), respectively (P < 0.0001). Fourteen percent of patients with a MCrCl ≥60 ml/min/1.73 m² had a CIn of <30 ml/min/1.73 m².

Conclusions. For patients with liver cirrhosis, MCrCl from timed urine collections consistently overestimates the true GFR. For patients requiring complete clinical evaluation, GFR assessment by CIn is justified.

Keywords: cirrhosis; creatinine; glomerular filtration rate (GFR); inulin; liver diseases; meta-analysis

Introduction

Patients with liver cirrhosis often have a low glomerular filtration rate (GFR) [1]. Accurate assessment of GFR in patients with liver cirrhosis has ramifications for drug prescribing, staging of chronic kidney disease (CKD) and identifying candidates for combined liver–kidney transplantation. It is also a prognostic indicator, with recent studies recognizing an association between elevated pre-orthotopic liver transplant serum creatinine and lower graft and patient survival [1,2]. Direct measurement of GFR in routine clinical practice using inulin clearance (CIn) is not common because of the complexity, expense and limited availability of testing and overall patient inconvenience. Measured creatinine clearance (MCrCl) from timed urine collections is a relatively inexpensive, accessible method used in clinical practice. Although MCrCl has been shown to overestimate GFR in patients with liver cirrhosis, recent
reviews [3] conclude that it is preferable in clinical practice, as it provides a better estimate than serum creatinine or predicted creatinine clearance. Limitations of previous reviews relate to their narrative nature, and failure to provide an overall overestimation or corrective predictive equations. In addition, the potential clinical implications of this overestimation have not been appreciated previously. The objective of this study was to review systematically within a clinical context the relative accuracy of MCrCl for approximating GFR in patients with liver cirrhosis, and its dependency on GFR level and liver cirrhosis severity.

Methods

Studies included in this review

Comparative diagnostic studies were included if two physicians independently agreed an article: (i) included patients 18 years of age or older with liver cirrhosis (as defined by liver biopsy or a compatible clinical profile and biochemical profile) and could be categorized according to the Child–Pugh cirrhosis classification; (ii) described an independent GFR test (inulin, iothalamate or iohexol clearance, technetium DTPA or chromium EDTA) performed within 3 days of MCrCl; and (iii) allowed individual patient data abstraction. Articles were excluded if (i) the GFR marker was measured during or immediately after a studied intervention (i.e. a study drug); (ii) study patients had any of the following diagnoses within 2 weeks prior to the study: (a) gastrointestinal haemorrhage; (b) hypotension; (c) systemic infection; or (d) evidence of volume depletion or expansion; or (iii) study patients had one of the following conditions: (a) hepatorenal syndrome as defined by the International Ascites Club [4]; (b) fulminant hepatic failure; or (c) known primary renal disease.

Finding relevant studies

Citations from MEDLINE (1966 to June 2004), old MEDLINE (1957–1965), Index Medicus (1952–1956) and Cochrane library bibliographic databases were reviewed and relevant full-text English, French, Italian, Spanish and Portuguese language articles were retrieved. The search strategy, developed with an experienced librarian (J.M.), utilized terms sensitive for identifying relevant studies, and was pilot-tested and modified based on relevant articles. The search strategy included the terms ‘jaundice’, ‘liver cirrhosis’, ‘ascites’, ‘glomerular filtration rate’, ‘creatinine clearance’, ‘inulin clearance’, ‘iothalamate clearance’, ‘iohexol’, ‘technetium Tc 99m pentetate’ and ‘edetic acid’.

Supplementary methods of finding studies included a review of relevant article bibliographies, a review of American Society of Nephrology (ASN) meeting abstracts, and information provided by primary study authors. All full-text articles were initially screened for potential relevance by a single physician (N.P.) as citation abstracts often did not report the marker used to determine the GFR. A second physician independently confirmed article inclusion. A third physician resolved disagreements.

Data abstraction from studies

Data relating to study and patient characteristics as well as renal measures were abstracted on standard forms by a single reviewer (N.P.). Individual patient data were obtained from graphs of primary articles. Accuracy of abstraction was confirmed by comparing the summary mean and variance statistics of the abstracted data with information provided in the primary articles. Attempts were made to contact all primary authors of articles included in this review.

Methodological assessment of the primary studies

The quality of diagnostic accuracy for all included articles was assessed according to the main principles of the STARD statement [5].

Statistical analysis

Scatter plot, clearance ratio plot, Pearson’s correlation coefficient (r) and intraclass correlation coefficient (ICC) were used to assess agreement for continuous data. For the scatter plot, a linear regression line was drawn using the least squares method. For the clearance ratio plot, a logarithmic regression line was chosen as it gave the highest $r^2$ value from a group of equations. Subgroup analyses were defined by the Child–Pugh cirrhosis classification and a GFR cut-off of 60 ml/min/1.73 m$^2$. The Wilcoxon rank test was used to compare the high and low GFR subgroups.

Continuous data were converted to CKD stages and drug dose adjustment requirements for MCrCl and CIn. Subsequently, percentages were calculated for various paired CKD stages and drug dose adjustment requirements estimated by MCrCl and CIn. CKD stages were defined by the current KDOQI CKD guidelines (2002) [6] as stage 4–5 (GFR <30 ml/min/1.73 m$^2$) and stage 3 (GFR = 30–59 ml/min/1.73 m$^2$). Stages 1 and 2 were not included as the patient population was not characterized by kidney damage defined as pathological abnormalities or markers of damage. Hence patients with GFR ≥60 ml/min/1.73 m$^2$ were assumed not to have CKD. There was an insufficient amount of data to allow analysis of stages 4 and 5 separately. Referring to the commonly used Sanford Guide® 2003, it was hypothesized that a clinician would be likely to perform a drug dose adjustment for a GFR <10 ml/min/1.73 m$^2$, probably would for a GFR = 10–50 ml/min/1.73 m$^2$ and unlikely to for a GFR >50 ml/min/1.73 m$^2$.

All analyses were performed using SPSS release 7.5.1 software (SPSS Inc., Chicago, IL) and SAS release 8.01 software (SAS Institute, Cary, NC).

Results

Finding and selecting studies

From screening 523 citations and 595 full-text articles (460 MEDLINE, 17 old MEDLINE, 11 Index Medicus and 107 bibliographic references), only 12 articles met the inclusion criteria. The agreement beyond chance between two independent physicians on article inclusion was good (kappa 0.76). Five articles [7–11] were excluded as individual patient data were not
abstractable and, despite attempts at contacting all primary authors of related articles for individual patient data, none replied. Thus, seven articles were included in this review (Figure 1).

Methodological quality assessment

Studies applied similar inclusion and exclusion criteria for eligible participants. Included participants had biopsy-demonstrated liver cirrhosis in 100% of the study patients [12–15], 75% of the study patients [16] and 66% of the study patients [17], and the remainder of the study patients [16–18] had a clinical and biochemical profile compatible with the disease. Exclusion criteria used in the various studies included gastro-intestinal haemorrhage [12,14,16–18], hepatic encephalopathy [12,14,17,18], active infection [16–18] and evidence of a primary renal disease [13,16,17].

All studies prospectively collected baseline data before the index and reference GFR markers were measured. No study explicitly described an independent blind comparison of MCrCl results with Cln results. With the exception of a single study [16], complete diagnostic testing was performed in 100% of study participants.

In all but one study [15], the population was examined in an in-patient setting under supervision. Studies described comparable test protocols. Studies included an equilibration period controlled for energy (range 125–150 kJ/kg per day) and protein intake (range 0.8–1.0 g/kg per day) [12,14,17], discontinued diuretics [17,18], and discontinued other medications known to alter renal function or tubular secretion of creatinine [12–15,17,18]. All studies used Cln as the reference standard. There were differences described in the methods and assays used for Cln and MCrCl; two studies [12,14] measured two consecutive 12 h (8 a.m. to 8 p.m.) urine collections for MCrCl while all others used 24 h urine collections. Clearances were reported as ml/min (23% of patients) [13,18] or ml/min/1.73 m² [12,14–17]. As the latter represents the majority group, clearances are reported as ml/min/1.73 m². Studies performed bladder catheter insertion and one study [16] reported a urinary tract infection which resolved with antibiotics. No other adverse effects were reported in performing the index and reference tests.

Description of studies

The seven articles describe a homogeneous stable group of 193 predominantly male (79%) patients with a weighted mean age of 56 years (range for articles reporting 29–89 years). The majority of patients (81%) were in decompensated Child–Pugh cirrhosis class B or C, with 50% having either a post-hepatitic or post-viral cause of their cirrhosis (Table 1), and most (76%) had ascites.

Ratio of creatinine clearance to inulin clearance and liver cirrhosis severity

For GFR subgroups >50 ml/min/1.73 m², Table 1 demonstrates a clearance ratio range of 1.03–1.41

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**Fig. 1.** Search strategy results.
for patients with compensated Child–Pugh cirrhosis class A and a clearance ratio range of 0.94–1.10 for patients with decompensated Child–Pugh cirrhosis class B or C.

Analysis of continuous data

The scatter plot (Figure 2) demonstrates MCrCl as a function of CIn. The least squares method yielded the linear regression line \( Y = 0.93x + 18.83 \) (Equation 1). The clearance ratio plot (Figure 3) demonstrates the clearance ratio as a function of CIn. The diagram reveals significantly higher clearance ratios at lower GFR values. The mean clearance ratios [95% confidence interval (CI)] in the high GFR subgroup (\( \geq 60 \text{ ml/min/1.73 m}^2 \)) and low GFR subgroup (\(< 60 \text{ ml/min/1.73 m}^2 \)) were 1.18 (1.12–1.23) and 1.49 (1.33–1.66), respectively, \( (P<0.0001) \). In both groups, the ratio was significantly greater than 1 (\( P<0.0001 \)).

Analysis of categorical data

Figure 4 demonstrates percentages for various paired CKD stages estimated by MCrCl and CIn. Considering patients with CKD stage 3 (GFR = 30–59 ml/min/1.73 m²) by CIn, MCrCl overestimated CIn by a mean of 13 ml/min/1.73 m² and the limits of agreement (mean of the differences±2 SD) were +60 ml/min/1.73 m² and –34 ml/min/1.73 m².

Table 1. Studies comparing measured creatinine clearance with inulin clearance in patients with liver cirrhosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients by GFR</th>
<th>Age (years)</th>
<th>Sex (%M)</th>
<th>Child class A/B/C</th>
<th>Cirrhosis cause (%D/E/F/G/H/I)</th>
<th>MCrCl (ml/min/1.73 m²)</th>
<th>CIn (ml/min/1.73 m²)</th>
<th>MCrCl/CIn</th>
</tr>
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<tbody>
<tr>
<td>Arieff [16]</td>
<td>&gt;50 ml/min/1.73 m²:7</td>
<td>NR NR 0/3/14</td>
<td>e 100/0/0/0/0/0</td>
<td>84.4 ± 31.1</td>
<td>84.2 ± 24.6 e 1.00 ± 0.17</td>
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<tr>
<td>&lt;50 ml/min/1.73 m²:10</td>
<td>21.1 ± 17.3 e 1.33 ± 0.97</td>
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<td>Laffi [18]</td>
<td>&gt;50 ml/min/1.73 m²:9</td>
<td>58 ± 7.5</td>
<td>60 0/9/6</td>
<td>67/0/0/13/20</td>
<td>74.2 ± 15.8 e 0.94 ± 0.21</td>
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<tr>
<td>&lt;50 ml/min/1.73 m²:6</td>
<td>63.7 ± 8.0 e 1.69 ± 0.31</td>
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<tr>
<td>Caregaro [17]</td>
<td>&gt;80 ml/min/1.73 m²:29</td>
<td>56 (36–70)</td>
<td>68 8/28/20</td>
<td>59/0/25/0/7/9</td>
<td>121.5 ± 28.8 e 1.10 ± 0.24</td>
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<tr>
<td>&lt;80 ml/min/1.73 m²:27</td>
<td>78.7 ± 39.2 e 1.51 ± 0.31</td>
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<tr>
<td>DeSanto [15]</td>
<td>&gt;50 ml/min/1.73 m²:19</td>
<td>51 ± 1.33</td>
<td>63 19/0/0</td>
<td>0/100/0/0/0/0</td>
<td>122 ± 5.7 e 90 ± 4.4 e 1.41 ± 0.08</td>
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<tr>
<td>&lt;50 ml/min/1.73 m²:9</td>
<td>63.7 ± 8.0 e 1.69 ± 0.31</td>
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<tr>
<td>Roy [13]</td>
<td>&gt;50 ml/min/1.73 m²:17</td>
<td>60 ± 9</td>
<td>80 0/30</td>
<td>73/23/0/3/0/0</td>
<td>77 ± 25 e 74 ± 15</td>
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<tr>
<td>&lt;50 ml/min/1.73 m²:13</td>
<td>64 ± 9</td>
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<tr>
<td>Orlando [14]</td>
<td>&gt;70 ml/min/1.73 m²:20</td>
<td>57 ± 5</td>
<td>100 0/10/0</td>
<td>0/100/0/0/0/0</td>
<td>50 ± 22 a 30 ± 10</td>
<td>1.8 ± 0.7</td>
<td>1.03 (1.01–1.05)</td>
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<tr>
<td>&lt;50 ml/min/1.73 m²:20</td>
<td>50 ± 7</td>
<td></td>
<td>0/10/0</td>
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<tr>
<td>Orlando [12]</td>
<td>&gt;72 ml/min/1.73 m²:19</td>
<td>55 ± 10</td>
<td>100 0/30</td>
<td>0/100/0/0/0/0</td>
<td>106 ± 19 b 97 ± 17</td>
<td>1.09 (1.03–1.15)</td>
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<tr>
<td>&lt;72 ml/min/1.73 m²:17</td>
<td>56 ± 22 b 43 ± 20</td>
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<tr>
<td>Total</td>
<td>193</td>
<td>56 g 37/156</td>
<td>43/24/26/1/3/4</td>
<td>A/B or C</td>
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paired drug dose adjustment requirements estimated by MCrCl and Cl\textsubscript{n} (not illustrated). For those patients likely requiring a drug dose adjustment (for a GFR <10 ml/min/1.73 m\textsuperscript{2} by Cl\textsubscript{n}), MCrCl agreed with this requirement 50% of the time but would have falsely guided the clinician to perform only a probable adjustment 50% of the time. For those patients requiring a probable drug dose adjustment (for a GFR 10–50 ml/min/1.73 m\textsuperscript{2} by Cl\textsubscript{n}), MCrCl agreed with this requirement 54% of the time but would not be likely to guide the physician to perform a drug dose adjustment 44% of the time.

Discussion

Summary of methods used

Performing an individual patient data meta-analysis has avoided potential aggregation bias. This bias is observed when the agreement between methods of measurement using a meta-analysis of summary estimates is mistakenly taken to represent the actual agreement between methods in individuals. There are, however, some limitations in this review. Although data abstraction was done with caution, it was performed by a single reviewer which may impact on precision. In addition, only seven relatively small studies could be included out of 12 articles that had met the inclusion criteria. Finally, no objective method could be used to assess the extent of the heterogeneity between studies as described by some variations in the methods, assays and units used to determine the GFR. Despite this limitation, studies used similar inclusion and exclusion criteria, described a stable population with similar baseline characteristics and used comparable test protocols including Cl\textsubscript{n} as a common reference standard.

Implications of glomerular filtration rate overestimation

To our knowledge, this is the first meta-analysis of patients with cirrhosis illustrating the limited ability of MCrCl to detect small incremental losses of GFR in the lower range where the margins separating stepwise additive complications of CKD are narrow. This limitation was illustrated in Figure 4 whereby 14% of patients were classified as not having CKD when in fact they had GFR levels corresponding to severe renal failure stages. Although the current stages of CKD were not defined specifically to reflect patients with liver cirrhosis, it is reasonable to deduce that misclassification using MCrCl would limit the physician’s ability to suspect and address potential complications of CKD. In addition, MCrCl subclassified patients requiring drug dose adjustment by one level ~50% of the time. Failure to recognize the need to adjust the dosing of medications such as aminoglycosides could potentially expose patients to drug-related toxicity. Furthermore, the inability to identify CKD may prevent appropriate liver transplant risk stratification and optimization as well as the identification of potential combined liver–renal transplant candidates.

Corrective measures and alternative GFR equations and markers

No compelling evidence has identified liver cirrhosis severity as a factor influencing GFR overestimation that could allow for corrective measures. Although DeSanto et al. [15] reported a markedly elevated clearance ratio of 1.41 ± 0.08 in patients with Child–Pugh cirrhosis class A, the study did not include an adequate control group. That the clearance ratio may be higher in compensated liver cirrhosis is contested further by a small controlled study from Orlando et al. [14] showing...
no significant difference in the clearance ratios between Child–Pugh cirrhosis class A and C.

Alternative equations have not been studied extensively in patients with cirrhosis. A single recent study [19] demonstrated that predicted GFR using the MDRD equation significantly overestimates GFR (renal clearance of 

\[ {125 \text{I}} \text{iothalamate} \]) by a mean difference of 18.7 ml/min/1.73 m² in patients with liver cirrhosis. None of the articles in this systematic review mentions the possible use of the arithmetic mean of urea and creatinine clearance as an indicator of low GFR in liver cirrhosis. This mean is recommended in the general population for those with low GFR as it essentially corrects for excessive tubular secretion of creatinine. The proportional increase in tubular secretion of creatinine with lower GFR has been confirmed in patients with liver cirrhosis [13]. This meta-analysis allowed the derivation of a potentially useful predictive formula based on ClN. From Equation 1, predicted GFR (ClN) = 1.08 (MCRCl) – 20.25 (Equation 2). Before Equation 2 can be utilized, however, it would have to be validated prospectively against ClN in a cirrhotic patient population from which it was not derived.

Few articles have examined alternative GFR markers using cystatin C or radioisotopes. Although two studies [19,20] support the use of the renal clearance of cystatin C or radioisotopes. Although two studies [19,20] demonstrated that predicted GFR using the MCRD equation significantly overestimates GFR (renal clearance of 

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\[ {51 \text{Cr}} \text{EDTA} \] or 

\[ {125 \text{I}} \text{iothalamate} \] to estimate GFR in patients with liver cirrhosis, neither used ClN as a control.

In conclusion, this systematic review demonstrates the significant overestimation of the GFR by MCRCl in patients with liver cirrhosis. Physicians need to be aware that this overestimation is substantial especially in the low GFR range where important decisions relative to drug dose adjustment, the staging of CKD and the pre-liver transplant evaluation may be required. This review did not recognize adequate corrective measures or alternative GFR equations or markers for the replacement of ClN. In patients with liver cirrhosis requiring complete clinical evaluation, GFR assessment by ClN is justified.

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