·综 述·

不同肾小球滤过率评估公式在老年人中的适用性分析

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【摘 要】 肾小球滤过率(GFR)随年龄增长而下降,在老年人群中,GFR下降并不意味着其一定患有慢性肾脏病。GFR测定是全世界公认的评估肾功能最准确的方法。通过GFR评估公式如Cockcroft-Gault(CG)公式、肾脏病饮食调整研究(MDRD)公式和慢性肾脏病流行病合作研究(CKD-EPI)公式等来获得估算肾小球滤过率(eGFR)已被广泛应用于一般人群中。由于老年人肾脏会发生结构和生理性变化,通常用来评价肾功能的方法并不完全适于这一群体。因此,本文回顾了近年来相关文献资料,就老年人如何选用GFR评估公式作一系统综述。

【关键词】 老年人;肾小球滤过率;慢性肾脏病
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Applicability analyses for glomerular filtration rate evaluation formula in the elderly

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【Abstract】 Chronically reduced glomerular filtration rate (GFR) in old people does not always mean that they suffer from chronic kidney disease (CKD) since their GFR can just be reduced by aging. Measurement of GFR is recognized worldwide as the most accurate way of assessing renal function. GFR equations such as Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) are widely used to estimate GFR in the general population. However, because of the structural and physiological changes in the kidneys of the elderly, the common equations used to evaluate renal function are not entirely suitable for this population group. Therefore, we reviewed relevant literature in recent years, and made a systematic review on how to choose the glomerular filtration rate evaluation formula for the elderly.

【Key words】 aged; glomerular filtration rate; chronic kidney disease
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慢性肾脏病(chronic kidney diseases,CKD)作为一种经济压力和公共卫生事件,正在成为中国面临的一项挑战。2008年,在中国所有CKD患者中,老年人(≥65岁)约占53.07%[1]。社会人口老龄化使得老年人的肾脏问题日益受到人们的关注。肾功能随年龄增长而下降,从40岁开始,肾小球滤过率(glomerular filtration rate,GFR)将以每年0.8~1.1 ml/(min·1.73 m^2)的速度下降[2,3]。老年人不仅会出现增龄性肾功能减退,合并高血压、糖尿病及各种代谢紊乱的比例也比年轻人高,易出现肾功能损害。由于老年人肾脏的结构和生理性变化[4],通常用来评价肾功能的方法并不完全适用于这一群体。因此,本文回顾近几年相关文献资料,以期探讨老年人如何选用GFR评估公式。

1 老年人肾脏结构和功能特点

1.1 老年性肾小球硬化症

从35岁左右开始人体的部分肾单位开始被纤维组织所替代,到70岁时25%的肾单位会受损,肾小球膜增厚近12%,而近髓肾单位的肾小球随着输入袢和输出袢之间直接通路的形成而减少,这种现象叫无肾小球循环[5,6]和因老龄致髓质低灌

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注[5-7],这些改变会导致GFR和肾有效血浆流量(effective renal plasma flow,ERPF)减少。

1.2 血管改变

外周动脉提示因内皮下透明质酸和胶原纤维沉积致使内膜增厚,小动脉内膜因弹性组织增生而增厚,中膜衰退。在低血压或高血压状态下自主血管反应能力老化(与青年人相比减弱),更倾向于损伤肾实质。

1.3 肾小管间质老化

部分肾小管脂肪损伤,致基底膜不规则增厚、纤维化及衰退。近端小管功能在老年人和青年人中相似,但是与青年人相比,老年人在增厚的髓袢升支段的钠重吸收减少,这种现象导致两种重要的后果:钠丢失增多和髓质间质的浓缩作用减弱(髓质低渗透压)。

2 各GFR评估公式的起源

常见的GFR评估公式包括:Cockcroft-Gault(CG)公式、肾脏病饮食调整研究(modification of diet in renal disease,MDRD)公式、慢性肾脏病流行病合作研究(chronic kidney disease epidemiology collaboration,CKD-EPI)公式及柏林倡议研究(Berlin Initiative Study,BIS)公式。

2.1 CG公式

1976年,Cockcroft和Gault等基于249名美国成年人(年龄18~92岁,其中男性占96%)的相关数据资料,以24 h肌酐清除率(creatinine clearance rate,Ccr)为参考标准开发了以年龄、性别、体质量及血肌酐(serum creatinine,SCr)为变量的估算GFR(estimated GFR,eGFR)公式[8],即:

$$Ccr(ml/min)=\frac{(140-年龄)\times 体质量}{72\times SCr(mg/dl)}\ (\times 0.85\ 若为女性)$$

2.2 MDRD公式

1999年,MDRD研究纳入了1628例CKD患者[年龄18~70(50.6±12.7)岁],随机分为试验组(1070例)和验证组(558例),以^{125}I-碘酞酸盐尿液清除率作为参考GFR,开发了一系列估算公式,即MDRD公式[9]。2000年,MDRD工作组对6变量-MDRD公式(包括SCr、白蛋白、尿素氮、年龄、性别以及种族)进行了简化,得到4变量-MDRD公式(SCr、性别、年龄以及种族)。2007年,将SCr标准化后,MDRD公式得以更新[10],并发现4变量-MDRD公式的准确度及精确度与6变量-MDRD公式相似,且优于CG公式[11]。

简化MDRD公式 $GFR[ml/(min\cdot 1.73\ m^2)]=175\times SCr^{-1.154}\times age^{-0.203}$(×0.212,若为黑人)(×0.742,若为女性)(其中SCr单位为mg/dl;age单位为years)

2.3 CKD-EPI公式

2009年,CKD-EPI研究针对受试者(年龄不限,平均年龄47岁)的基线数据开发了CKD-EPI公式,并在另外16个研究中心共3896人(年龄不限,平均年龄50岁)中进行外部验证[12]。由于SCr的产生存在种族差异,2011年,Stevens等[13]开发了四等级种族变量公式。

$GFR[ml/(min\cdot 1.73\ m^2)]=141\times\min(SCr/\kappa,1)^{\alpha}\times\max(SCr/\kappa,1)^{-1.209}\times 0.993^{age}$(×1.018若为女性)(×1.159若为黑人)(若为女性κ:0.7,α:-0.329;若为男性κ:0.9,α:-0.411;SCr单位mg/dl;age单位years)

2.4 BIS公式

2012年,Schaeffner等[14]纳入柏林倡议研究610名居住在柏林的白种人(年龄≥70岁,平均年龄78.5岁),以碘海醇血浆清除率为金标准,开发了2个新公式:基于SCr的BIS-1公式和基于SCr、胱抑素的BIS-2公式,用来估算≥70岁老年人的GFR,并与CG公式、MDRD公式以及CKD-EPI公式对比,发现BIS-1和BIS-2公式准确性更好,尤其在GFR>30 ml/(min·1.73 m^2)人群中。

$BIS\text{-}1=3736\times SCr^{-0.87}\times age^{-0.95}$(×0.82若为女性)

$BIS\text{-}2=767\times Cystatin\ C^{-0.61}\times SCr^{-0.40}\times age^{-0.57}$(×0.87若为女性)

(其中SCr单位mg/dl;Cys C单位mg/L;age单位years)

3 各公式在老年人群的应用

2002年美国肾脏病基金会(National Kidney Fundation,NKF)提出的慢性肾脏病及透析临床实践指南(Kidney Disease Outcome Quality Initiative,KDOQI)基于对众多发表文献的分析,推荐应用CG公式和简化MDRD公式[15]。有研究认为,在老年CKD人群中,MDRD公式与CG公式的一致性低[16]。

尽管美国国家肾脏疾病教育计划(National Kidney Disease Education Program,NKDEP)和其他科学团体推荐应用MDRD公式来评估肾脏功能[9,11],但是大多数药物剂量调整是根据CG公式计算出的Ccr[8]。有文章认为在SCr正常的个体及健康老年人群中,MDRD公式没有优势,CG公式具有从该人群中筛选肾功能下降者的优势,并认为在老年人群中CG公式是更好的选择[17]。除此之外,Tomaszuk-Kazberuk等[18]的前瞻性研究发现,与MDRD公式和CKD-EPI公式相比,CG公式能更好地预测CKD合并急性心肌梗死后的死亡率。相反,另一些研究认为,在老年人群中,MDRD准确性好,CG公式低估

GFR。Lamb等[19]纳入46例老年人[年龄69~92(80.0±4.9)岁],以51 Cr-EDTA为参考GFR,研究发现MDRD公式偏倚小,准确性好,CG公式则明显低估GFR,且准确性差,这与以前多项研究的结果一致[2,20]。

除探讨MDRD和CG公式外,CKD-EPI和BIS公式同样引起了很多研究者的关注。CKD-EPI公式主要包括:基于肌酐的CKD-EPI(Cr)公式、基于胱抑素C的CKD-EPI(Cys C)公式、以及联合肌酐和胱抑素C的CKD-EPI(Cr-Cys C)公式。BIS公式包括基于肌酐的BIS-1公式和基于肌酐及胱抑素的BIS-2公式。

SCr是一般人群中最简单、应用最广的肾功能标志物。SCr浓度受多种因素的影响,包括肌肉质量、小管分泌物和炎症等[21],这些影响因素在老年人中普遍存在。血清胱抑素C是另一种肾功能标志物,一般不常规检测,其不依赖于肌肉质量、性别或年龄,炎症、发热、外分泌、甲状腺疾病及糖皮质激素的使用均不影响其血清浓度[22]。多项研究认为,在中国老年人中,基于肌酐的GFR公式并不能很好地反映GFR[23,24],而Zhu等[25]的验证研究认为,2012年CKD-EPI(Cr-Cys C)方程在中国CKD 3~5期老年人中并不准确,且2012年CKD-EPI(Cys C)方程并不比其他公式表现得更好。此外,一项纳入1165名≥70岁老年女性的前瞻性队列研究也发现,在应用eGFR预测临床预后方面,与CKD-EPI(Cr)公式相比,CKD-EPI(Cr-Cys C)或CKD-EPI(Cys C)公式并不能提高其准确性及预测能力[26]。相反,2016年芬兰的一项纵向流行病学调查指出,在老年人群中,胱抑素C是心血管和非心血管死亡的最佳预测因素,在≥64岁人群中,血清胱抑素C比基于肌酐的eGFR公式和联合肌酐与胱抑素C的CKD-EPI公式在指导临床决策方面更准确[27]。此外,Li等[28]认为,改良的2012年CKD-EPI方程在中国老年人中的应用更准确。

有研究指出,CG公式在方法学上已经过时,而MDRD和CKD-EPI公式应作为首选,在老年人群中亦是如此[29]。David-Neto等[30]纳入70例老年肾移植患者[年龄(65±4)岁]发现,与MDRD公式、CG公式、BIS公式相比,CKD-EPI公式偏倚最小,准确性最高。另一研究也认为CKD-EPI公式比MDRD公式偏倚小,准确性更高[31]。在社区老年人中,亚洲改良CKD-EPI公式和中国改良CKD-EPI公式与临床前期靶器官损害有关,在进行风险评估时可作为首选[32]。而且对合并恶性肿瘤的老年人进行计算机增强断层扫描(contrast-enhanced computed tomography, CECT)检查前肾脏功能评估时,CKD-EPI公式比MDRD公式和CG公式在预测造影剂相关肾病方面更具优势[33]。在中国老年人群中,CG公式及CKD-EPI公式的准确性较好:当GFR≥60 ml/(min·1.73 m^2)时,CKD-EPI(Cr-Cys C)公式准确性较高;当GFR<60 ml/(min·1.73 m^2)时,CG公式则更适合[27]。然而,一项纳入1397名瑞典人(平均年龄61岁)的研究认为,MDRD与CKD-EPI公式会高估GFR[34],而在白种CKD人群中,CKD-EPI(Cr-Cys C)和BIS-2(Cr-Cys C)公式低估GFR,而CKD-EPI(Cys C)则高估GFR[35]。在≥70岁老年人中,同位素稀释质谱法(isotope dilution mass spectrometry, IDMS)-MDRD公式(IDMS-MDRD)及CKD-EPI公式会高估CKD Ⅲ期的GFR,CG公式则无偏倚[36]。

另外,2017年一项横断面研究发现,在评估≥75岁中国CKD人群GFR方面,BIS-2公式比CG、MDRD及CKD-EPI公式更适合[37];在对合并心血管疾病的CKD老年人进行危险分层时,BIS-1比CKD-EPI公式表现更好[38]。而另一研究则发现,在85岁老年人中,BIS公式计算的GFR值低于MDRD-IDMS和CKD-EPI公式,且会使CKD分期更高,尤其是在GFR>29 ml/(min·1.73 m^2)时[39]。

老年人正常肾功能范围存在争议,当eGFR(CG、MDRD、CKD-EPI公式)<60 ml/(min·1.73 m^2)时,不一定代表其患有肾脏疾病。GFR存在增龄问题,从30~40岁以后,GFR大约以每年1 ml/(min·1.73 m^2)的速度下降,65~70岁以后肾功能下降速度加快,到了80岁将下降30%~40%,90岁老年人肾血流量仅为年轻人的50%。在评估老年人肾功能方面,血尿素比SCr更敏感[2,40]。此外,一个新的基于红细胞比容(hemacrit, HCT)、血尿素(urea)以及性别(gender)的公式,即HUGE公式,用来确定GFR<60 ml/(min·1.73 m^2)的老年人是否患有肾脏疾病[41],在CKD[GFR<60 ml/(min·1.73 m^2)]人群中,HUGE公式比eGFR公式(MDRD、CKD-EPI、BIS-1)在区分CKD方面更准确[42,43]。

总之,在SCr正常个体、健康老年人群中筛选肾功能下降者、进行大多数药物剂量调整以及预测CKD合并急性心肌梗死后死亡率时,CG公式是更好的选择。值得注意的是,在本综述引用的文献中,有7篇推荐老年人应用CKD-EPI公式和MDRD公式[2,19,20,28-31],其中3篇认为会高估GFR[34-36],另3篇认为CG公式会低估GFR[2,19,20];另有2篇文献

认为在评估≥70 岁老年人肾功能、对合并心血管疾病的 CKD 老年人进行危险分层时，BIS 公式更合适[37,38]。

GFR 评估公式应用于老年人时并不完全适用，公式的准确性并不仅仅与原发病或基础疾病有关，还与种族、年龄等因素也相关，更与其设计开发时的准确性密切相关。基于老年人肾脏结构及生理特点，以老年人群为研究对象开发全新的 GFR 公式，制定老年人肾功能指标的参考值范围，对于避免虽出现 GFR 下降但实际上并无肾脏损害的老年人群被误诊为 CKD 患者，具有更加现实的意义。

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