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·论 著·

慢性肾衰竭患者透析起始肾小球滤过率与预后关系的meta分析

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[摘要] **目的** 通过系统回顾与meta分析方法探讨慢性肾衰竭患者开始透析时的肾小球滤过率(GFR)水平与其预后的关系。**方法** 以"dialysis initiation""prognosis/mortality/survival""timing""CKD/CRF/ESRD"为关键词,检索PubMed、Medline、EMBASE、Cochrane Central Registry of Controlled Clinical Trials数据库,根据纳入及排除标准选择纳入的文献并进行meta分析。**结果** 共纳入20篇文献,包含21项研究。总体结果为透析起始GFR每增加1 mL/(min·1.73 m^2),患者的全因死亡风险即升高3.3%(HR=1.033,95% CI:1.026~1.040,$P<0.001$)。对纳入的2项随机对照试验、4项各组生存分析起点设置为相同水平的研究分别进行亚组分析,结果均为透析起始GFR与患者生存率无关(HR=1.001,95%CI:0.983~1.020,$P=0.891$;HR=1.014,95%CI:0.990~1.040,$P=0.260$);对以GFR=10或10.5 mL/(min·1.73 m^2)为分界点将患者分为早期和晚期两组的3项研究进行亚组分析,结果显示两组生存率差异亦无统计学意义(HR=1.062,95%CI:0.691~1.633,$P=0.784$)。**结论** 目前的证据显示,慢性肾衰竭患者透析起始GFR越高,死亡风险越高。但导致患者早期透析的因素较复杂,仍需更多高质量的临床证据来决定合理的透析起始时机。

[关键词] 肾透析;肾小球滤过率;慢性肾衰竭;预后;meta分析
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Relationship between glomerular filtration rate at the initiation of dialysis and prognosis of chronic kidney failure patients: a meta-analysis

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[**Abstract**] **Objective** To investigate the relationship between glomerular filtration rate (GFR) at the initiation of dialysis and the prognosis of chronic renal failure (CRF) patients via systematic review and meta analysis. **Methods** Literature retrieval was conducted using "dialysis initiation", "prognosis/mortality/survival", "timing", and "CKD/CRF/ESRD" as key words in databases including PubMed, Medline, EMBASE and Cochrane Central Registry of Controlled Clinical Trials. Literatures were selected according to the predefined inclusion and exclusion criteria and the data were analyzed using meta analysis. **Results** Finally 20 references containing 21 studies were included in the present study. The overall analysis showed that a 1 mL/(min·1.73 m^2) GFR increment was associated with a 3.3% increase in all-cause mortality (HR=1.033, 95% CI: 1.026-1.040, $P<0.001$). However, the subgroup analysis of two RCTs and four studies with the same survival analysis origin demonstrated no significant correlation between GFR at dialysis initiation and survival rate (HR=1.001, 95%CI: 0.983-1.020, $P=0.891$; HR=1.014, 95%CI: 0.990-1.040, $P=0.260$). In addition, subgroup analysis including studies with 10 or 10.5 mL/(min·1.73 m^2) GFR as the cut-off values between early and late stages also showed no significant differences in the survival rates (HR=1.062, 95%CI: 0.691-1.633, $P=0.784$). **Conclusion** It is indicated that higher GFR at dialysis initiation is associated with increased mortality rate of CRF patients; however, the reason for early dialysis is complicated and more high quality clinical trials are needed to determine the dialysis timing.

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[**Key words**] renal dialysis; glomerular filtration rate; chronic renal failure; prognosis; meta-analysis
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慢性肾衰竭(chronic renal failure, CRF)是多种原发与继发肾脏病发展到终末期的共同结局,患者预后差,生活质量低,且耗费极大的社会资源。随着患者肾小球滤过率(glomerular filtration rate, GFR)的逐步降低,CRF 患者最终需接受肾脏替代治疗。包括血液透析(hemodialysis, HD)和腹膜透析(peritoneal dialysis, PD)在内的透析疗法是重要的肾脏替代治疗方法,挽救了大量 CRF 患者的生命,但对于何时是最佳的透析起始时机在学术界仍存在较大争议。2006 年美国肾脏病基金会工作组制定的指南中,推荐患者在 GFR < 15 mL/(min · 1.73 m^2)时开始透析治疗[1],但对 GFR 低于 15 mL/(min · 1.73 m^2)的患者何时启动透析,在临床实践中仍存在较大的模糊空间。有研究表明,推迟启动透析治疗能够降低患者的全因死亡率、并发症死亡率及并发症发生率,早期开始透析常合并心脑血管等系统并发症[2-13]。也有研究认为,为延缓病程进展并提高患者生存时间,应尽早启动透析治疗[14-15]。另有部分研究则提示,在 GFR 低于 15 mL/(min · 1.73 m^2)的患者中无论何时开始透析都不会影响患者的生存率[16-21]。

本研究应用循证医学的方法,纳入近年发表的最新研究进行系统回顾与 meta 分析,以探讨 CRF 患者透析起始 GFR 与其预后的关系。

1 资料和方法

1.1 *检索方法* 检索数据库包括 PubMed、Medline、EMBASE、Cochrane Central Registry of Controlled Clinical Trials。文献发表时间限定为 2000 年 1 月至 2014 年 6 月。检索关键词包括“dialysis initiation”“prognosis/mortality/survival”“timing”“CKD/CRF/ESRD”。

1.2 *研究纳入和排除标准* 纳入标准:(1)研究设计为随机对照临床试验(randomized controlled trial,RCT)、前瞻性队列研究或回顾性研究;(2)研究对象为因原发或继发肾脏病接受透析治疗且年龄≥18 岁的成年患者。排除标准:(1)文献类型为综述、评论等;(2)重复发表;(3)无法获取全文及数据;(4)数据提供不充分;(5)研究对象年龄<18 岁。

1.3 *数据提取及统计学处理* 提取各项研究中透析起始 GFR 分组情况(各组 GFR 的数值范围、各组 GFR 中位数或平均数)、各组样本量、随访期或观察期结束时发生全因死亡事件的例数,各组以最低 GFR 组为对照计算相对危险度(hazard ratio, HR)及其 95%置信区间(confidence interval, CI)。利用广义最小二乘法(generalized least squares for trend estimation)对单项研究进行剂量-反应特点分析[22],得出透析起始 GFR 每增加 1 mL/(min · 1.73 m^2)的 HR 及其 95%CI,再将各项研究进行统计量合并。若总体分析的异质性较大,则根据研究设计等特征对部分研究单独进行亚组分析,观察异质性变化,探讨异质性来源。所有分析均采用 Stata 12.0 软件对资料进行汇总分析并制图。统计量假设检验水准(α)为 0.05。

2 结 果

2.1 *纳入研究的基本情况* 根据检索关键词共检索到英文文献 235 篇,阅读标题及摘要后筛选出 171 篇,进一步阅读全文,最终纳入 20 篇文献,共 21 项研究(Stel 等[7]发表的文章中包含 2 项研究)。(1)研究设计:2 项 RCT,4 项前瞻性队列研究,其余为回顾性研究。2 项 RCT 为同一研究组发表,分别为腹膜透析和血液透析。(2)透析起始 GFR:纳入研究均明确各组患者透析开始时 GFR 估计值(estimated GFR,eGFR)。(3)透析方式:4 项研究为腹膜透析[5,14,18-19],4 项研究为血液透析[11-12,15,17],其余同时包括两种透析方式。(4)研究对象基线资料:部分研究各组间基线资料差异存在统计学意义,2 项回顾性研究应用倾向指数匹配(propensity score matching, PSM)后组间基线资料差异无统计学意义。透析开始时合并疾病多为糖尿病、心血管疾病、脑血管疾病、周围血管疾病等。多数研究在统计学分析中已考虑重要混杂因素,得出经调整后的 HR。(5)生存分析起点:4 项研究将两组生存分析模型起点设置在相同水平。详见表 1。

表 1　纳入研究的基本情况

Tab 1　The baseline characteristics of the included studies

Included study	Study type	*n*	Grouping by GFR	HR (95%CI)	Age	Weight or BMI	Major comorbidity	Laboratory examination
Traynor 2002[2]	RS	235	<8 ≥8	1.00(Ref) 0.62	Older in late stage	Lower in early stage	Early stage: higher Wright/Khan index	Early stage: higher Hb
Beddhu 2003[3]	RS	2 920	GFR+1	1.03(1.02,1.04)	NS	Lower in early stage	Early stage: diabetes, chronic coronary heart diseases, heart failure, cerebrovascular disease	Early stage: lower Alb
Kazmi 2005[4]	RS	302 287	>10.0 7.6-10.0 5.0-7.5 <5.0	1.42(1.38,1.46) 1.19(1.15,1.21) 1.09(1.06,1.12) 1.00(Ref)	Older in early stage	Lower in early stage	Early stage: diabetes, chronic coronary, heart diseases, heart failure, peripheral neuropathy	Early stage: lower Alb
Shiao 2008[5]	RS	275	GFR+1	1.18(1.02,1.37)	Older in early stage	-	Early stage: diabetes, heart failure	Early stage: lower Alb, serum P, Kt/V
Sawhney 2009[6]	RS	7 299	≥15.0 10.0-14.9 5.0-9.9 <5.0	1.65(1.39,1.95) 1.37(1.19,1.59) 1.17(1.02,1.34) 1.00(Ref)	-	-	-	-
Stel 2009a[7]	RS	11 472	≥10.5 8.0-10.5 <8.0	1.45(1.32,1.62) 1.14(1.04,1.25) 1.00(Ref)	-	-	-	-
Stel 2009b[7]	RS	11 472	≥10.5 8.0-10.5 <8.0	1.38(1.19,1.61) 1.17(1.01,1.36) 1.00(Ref)	-	-	-	-
Lassalle 2010[8]	RS	11 685	GFR+1	1.02(1.01,1.03)	Older in early stage	Lower in early stage	Early stage: diabetes, chronic coronary disease, heart failure, peripheral neuropathy	-
Wright 2010[9]	RS	611 913	>15.0 10.1-15.0 5.1-10.0 ≤5.0	1.48(1.47,1.50) 1.16(1.15,1.17) 1.00(Ref) 0.87(0.86,0.88)	Older in early stage	NS	Early stage: diabetes	Early stage: higher Hb
Evans 2011[10]	CS	708	7.5-20.0 <7.5	1.19(0.91,1.56) 1.00(Ref)	Older in early stage	NS	Early stage: more patients with Charlson index=2, angiocardiopathy; Charlson index≥3: NS	Early stage: lower Alb; Hb with NS
Clark 2011[11]	RS	25 910	>10.5 ≤10.5	1.18(1.13,1.23) 1.00(Ref)	Older in early stage	-	Early stage: chronic coronary disease, peripheral neuropathy, cerebrovascular disease, diabetes, lung diseases, malignancies	Early stage: lower median of Alb; NS mean of Alb
Rosansky 2011[12]	RS	81 176	≥15.0 10-14.9 5.0-9.9 <5.0	1.74(1.64,1.85) 1.47(1.41,1.54) 1.23(1.19,1.27) 1.00(Ref)	Older in early stage	Lower in early stage	No comorbidities other than hypertension	Early stage: lower Alb
Yamagata 2012[13]	RS	20 854	≥10.0 8.0-10.0 6.0-8.0 4.0-6.0	1.33(1.08,1.63) 1.41(1.62,1.72) 1.08(0.95,1.24) 1.00(Ref)	NS	-	-	-
Tang 2007[14]	CS	233	GFR+1	0.66(0.45,0.97)	NS	NS	-	-
Hwang 2010[15]	RS	23 551	≥6.52 5.21-6.51 4.28-5.20 3.29-4.27 <3.29	2.44(2.11,2.81) 1.66(1.43,1.93) 1.21(1.04,1.41) 1.18(1.01,1.37) 1.00(Ref)	Older in early stage	-	Early stage: diabetes, heart failure, coronary heart diseases, cerebrovascular disease, hepatocirrhosis, malignancies	Early stage: lower Alb
Korevaar 2001[16]	CS	253	≤10.5 >10.5	1.00(Ref) 0.60(0.35,1.05)	NS	-	NS	-

续表

Included study	Study type	n	Grouping by GFR	HR (95%CI)	Age	Weight or BMI	Major comorbidity	Laboratory examination
Collins 2011[17]	RCT	322	10.0-14.0 5.0-7.0	0.97(0.66,1.41) 1.00(Ref)	NS	NS	NS	Alb, serum P, Hb: NS
Johnson 2012[18]	RCT	828	10.0-14.0 5.0-7.0	1.04(0.79,1.37) 1.00(Ref)	NS	NS	NS	Alb, serum P, Hb: NS
Oh 2012[19]	RS	491	≥7.7 <7.7	0.47(0.16,1.35) 1.00(Ref)	Older in early stage	NS	Early stage: moderate or severe Davies index, diabetes, heart failure	Early stage: higher Hb; Alb: NS
Chang 2012[20]	RS	450	≥7.7 <7.7	1.32(0.87,1.99) 1.00(Ref)	Older in early stage	-	Early stage: diabetes, coronary heart diseases	Early stage: lower Alb, serum P; higher serum Ca, Hb
Crews 2014[21]	CS	652	≥10.0 <10.0	1.59(0.89,2.84) 1.00(Ref)	Older in early stage	Lower in early stage	Early stage: diabetes; NS in other disease	Alb, serum P, Hb: NS

RS: Retrospective study; CS: Cohort study; RCT: Randomized controlled trial; GFR: Glomerular filtration rate, evaluated with mL/(min·1.73 m^2); HR: Hazard ratio; BMI: Body mass index; NS: No significance; Higher or lower: With significant differences between groups; -: No detail; Hb: Hemoglobin; Alb: Albumin

2.2 总体分析结果 在纳入的研究中,2 项研究认为早期透析可以提高患者生存率,12 项研究认为晚期透析可以提高患者生存率,6 项研究认为透析起始 GFR 对患者生存率无明显影响。将所有研究纳入 meta 分析,采用随机效应模型,得出透析起始 GFR 每增加 1 mL/(min·1.73 m^2),患者的全因死亡风险即升高 3.3%(HR=1.033,95% CI:1.026~1.040,$P<0.001$),提示透析起始 GFR 越高,患者死亡风险越高。但异质性检验统计量 $I^2=96.2\%$($P<0.001$),提示纳入研究存在明显异质性(图 1)。

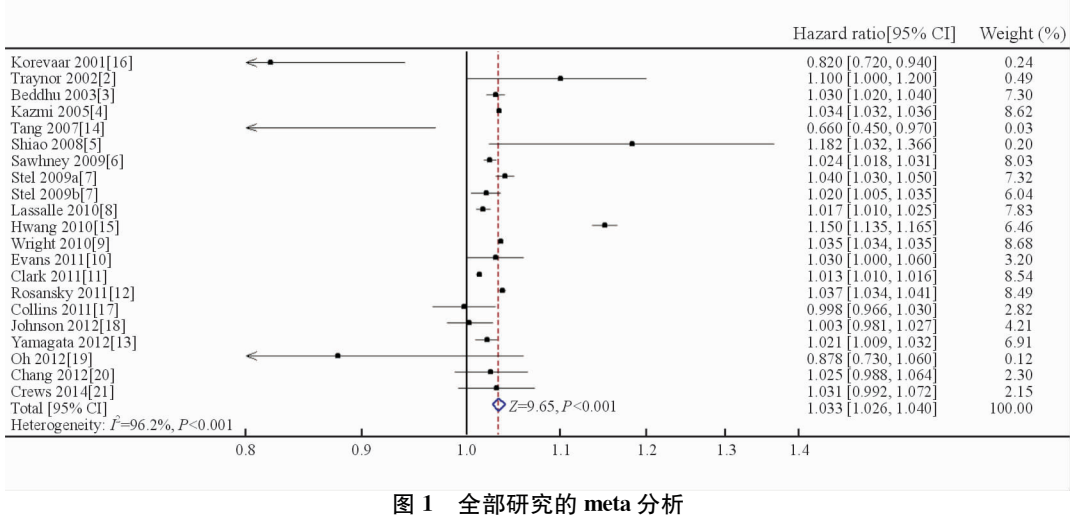

图 1 全部研究的 meta 分析

Fig 1 The meta analysis of all the included studies

2.3 亚组分析结果 由于总体分析异质性较大,因此根据纳入研究的特点进行亚组分析。(1)将 2 项 RCT 进行统计量合并,得出 HR=1.001(95% CI:0.983~1.020,$P=0.891$),提示不同透析起始 GFR 导致的患者生存率差异无统计学意义,透析起始 GFR 并不影响患者的生存率(图 2)。异质性分析统计量 $I^2=0.0\%$($P=0.771$),说明异质性较小,提示研究设计类型可能为重要的异质性来源。(2)将 4 项生存分析起点组间比较相同的研究进行统计量合并,得到 HR=1.014(95% CI:0.990~1.040,$P=0.260$),提示在相同起点进行生存分析后,透析起始 GFR 对生存率无明显影响(图 3)。异质性分析统计量 $I^2=43.8\%$($P=0.149$),说明异质性较小,提示透析起点的设置可能为重要的异质性来源。(3)纳入研究中有 3 项以 GFR=10 或 10.5 mL/(min·1.73 m^2)为分界点将研究对象分为早期和晚期两组,将 3 项研究进行亚组分析,得到 HR=1.060(95%CI:0.690~1.630,$P=0.784$),提示以 10 或

10.5 mL/(min · 1.73 m^2)为分界点的早期透析与晚期透析的患者生存率无明显差异(图 4)。

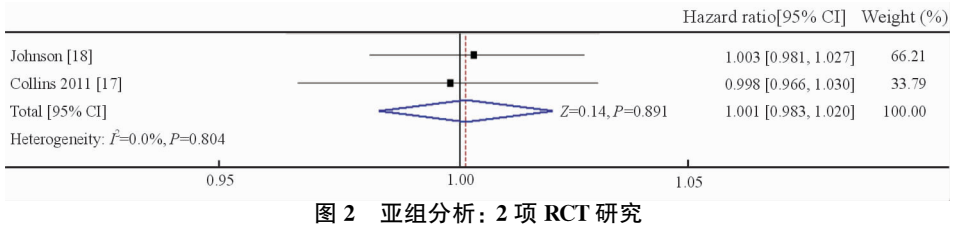

图 2　亚组分析：2 项 RCT 研究

Fig 2　Subgroup analysis of the two RCTs

RCT：Randomized controlled trial

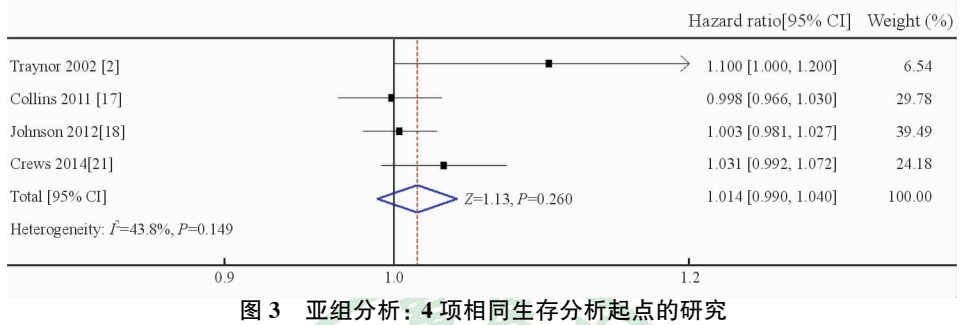

图 3　亚组分析：4 项相同生存分析起点的研究

Fig 3　Subgroup analysis of the four studies with comparable starting point among groups in survival analysis

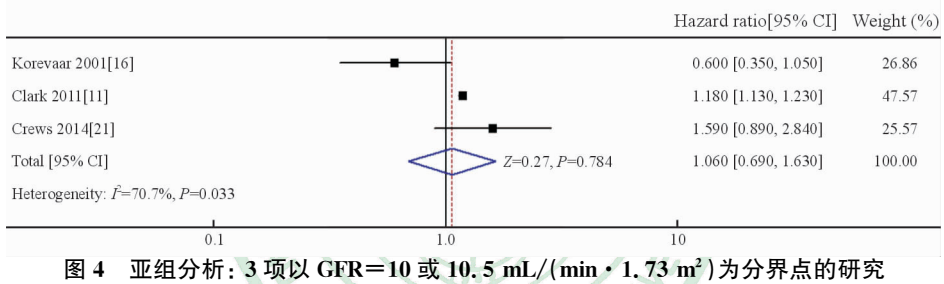

图 4　亚组分析：3 项以 GFR=10 或 10.5 mL/(min · 1.73 m^2)为分界点的研究

Fig 4　Subgroup analysis of the three studies with GFR being 10 or 10.5 mL/(min · 1.73 m^2) as cut-off values among groups

GFR：Glomerular filtration rate

2.4　*发表偏倚评价*　Begg 秩相关法调整统计量 Z=0.03，Pr>|z|=0.976，表明不存在明显发表偏倚。Egger 直线回归法偏倚统计量 t=−0.74，其 95%CI (−3.533 316，1.687 076)包含 0，P>|t|=0.468，同样表明不存在明显发表偏倚。

3　讨　论

本研究纳入了近年发表的 CRF 患者透析起始 GFR 与预后关系的多项研究，结果提示透析起始 GFR 每增加 1 mL/(min · 1.73 m^2)，患者全因死亡风险即升高 3.3%。有研究表明，早期启动透析治疗将会加速肾功能衰竭的进程，对全身代谢功能造成不利影响，从而使得患者预后不佳[23-24]。并且，早期透析使患者更早暴露在发生透析并发症的风险中，如血液透析导致的血液动力学紊乱、滤过膜生物不相容、导管感染以及腹膜透析导致的腹膜炎等，这些同样可能影响患者预后[25]。

然而，符合本研究纳入标准的文献多为回顾性资料，尽管它们拥有较大样本量，但也存在着较高的偏倚风险，且总体分析存在明显的异质性。在回顾性研究的基线资料中，早期透析患者年龄普遍偏大，营养情况较差，血白蛋白较低，且多有糖尿病、心脏病等重要合并症，这些都是对患者预后不利的重要混杂因素(如目前已知 CRF 患者较差的营养状况是造成死亡的主要危险因素[26-27])。它们造成了不同程度的选择偏倚(selection bias)。尽管多数回顾性分析利用统计学方法消除了部分混杂因素的影响，但不能排除未知混杂因素的存在，如未被记录但严重影响预后的重要合并症等。而这些已知的混杂因素与透析起始 GFR 的关联性通常较强，即较高的 GFR 往往与较差的一般情况相伴[3-4,12]；此外约 80%的患者早期启动的透析治疗并非计划中，而是

由于如急性心力衰竭等合并症加重[8,28],因此不能认为回顾性资料中每例早期透析患者皆以较高的 GFR 作为透析指征,无法证明 GFR 与患者死亡风险之间关联的必然性。

RCT 可以通过随机化方法避免混杂因素的干扰,因而本研究针对 2 项 RCT 进行了亚组分析,发现早期透析并不会增加死亡风险,并且研究异质性较小。由此有理由认为早期透析增加死亡风险的结论存在较多干扰因素,需要更多 RCT 来进一步分析透析起始 GFR 与患者死亡风险是否存在必然联系。

此外,多数非随机研究的生存分析起点仅仅设置为透析治疗开始,而这将会带来转诊偏倚(referral bias)和领先时间偏倚(lead-time bias)[18]。本研究纳入了 4 项将生存分析起点组间匹配的研究,它们避免了领先时间偏倚,对它们进行亚组分析后结论为透析起始 GFR 与患者生存率无明显关联,且研究异质性较小,表明生存分析起点的设置可能是重要的研究设计因素。最后,本研究以 GFR=10 或 10.5 mL/(min·1.73 m^2)为分界点进行了亚组分析,结果提示仍需寻找更为合适的透析指征。

综上所述,尽管目前的数据显示 CRF 患者早期透析与患者死亡风险的升高有关,但证据也显示这种关联性较弱,无法证明其为因果关系,仍有待更多高质量的临床证据来决定透析起始时机。此外,考虑到透析起始 GFR 并不能完全代表患者病情程度,在临床实践中仍需综合考虑患者的整体情况,在适当时机给予替代治疗干预。

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