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不同类型排斥反应受者血常规及外周血淋巴细胞亚群特征性变化

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[摘要] **目的:** 排斥反应一直是限制移植肾存活的最重要因素。移植肾病理活检是排斥反应诊断的金标准, 但因其局限性并不能作为常规监测手段。近来, 外周血淋巴细胞亚群检测已成为评估机体免疫系统的重要手段, 然而其在肾移植领域的应用价值和策略有待探究; 此外, 常规检验参数的新开发利用也是探索肾移植疾病诊断策略和预测模型的重要手段。本研究旨在结合血常规, 探究外周血淋巴细胞亚群与T细胞介导的排斥反应(T cell-mediated rejection, TCMR)和抗体介导的排斥反应(antibody-mediated rejection, ABMR)的相关性及其协助诊断价值。**方法:** 回顾性分析2021年1至12月就诊于中南大学湘雅二医院且符合纳入标准的154例肾移植受者的基本资料以及临床资料。根据排斥反应是否发生及其类型分为稳定组、TCMR组和ABMR组。比较3组的基本资料, 并将TCMR组和ABMR组排斥反应治疗前的移植肾功能、血常规和外周血淋巴细胞亚群数据与稳定组进行比较。**结果:** 稳定组、TCMR组和ABMR组在免疫抑制维持方案、移植肾来源等方面差异均无统计学意义(均 $P>0.05$), 但ABMR组的肾移植术后时间显著长于稳定组($P<0.001$)和TCMR组($P<0.05$)。在移植肾功能方面, ABMR组的血肌酐值均高于稳定组和TCMR组(均 $P<0.01$), 并且TCMR组也高于稳定组($P<0.01$); TCMR组和ABMR组的尿素氮均显著高于稳定组(均 $P<0.01$), 而TCMR组和ABMR组之间差异无统计学意义($P>0.05$); TCMR组和ABMR组的估算肾小球滤过率(estimated glomerular filtration rate, eGFR)均低于稳定组(均 $P<0.01$)。在血常规方面: ABMR组的血红蛋白、红细胞数和血小板数均低于稳定组(均 $P<0.05$); TCMR组的中性粒细胞比例和数量均高于稳定组(均 $P<0.05$), ABMR组的中性粒细胞比例高于稳定组($P<0.05$); TCMR组的嗜酸性粒细胞比例和数量均低于稳定组和ABMR组(均 $P<0.05$); TCMR组和ABMR组的嗜碱性粒细胞比例和数量、淋巴细胞比例和数量均低于稳定组(均 $P<0.05$); 稳定组、TCMR组和ABMR组的单核细胞比例和数量差异均无统计学意义(均 $P>0.05$)。在淋巴细胞亚群方面: TCMR组和ABMR组的CD4⁺ T细胞数和T细胞数均低于稳定组(均 $P<0.05$); TCMR组的CD4⁺ T细胞数、NK细胞数和B细胞数均低于稳定组(均 $P<0.05$); 稳定组、TCMR组和ABMR组在T细胞比例、CD4⁺ T细胞比例、CD8⁺ T细胞比例和数量、CD4⁺/CD8⁺ T细胞比值、NK细胞比例、B细胞比例方面差异均无统计学意义(均 $P>0.05$)。**结论:** 排斥反应的发生导致移植肾功能受损, 同时会伴有肾移植受者血常规、外周血淋巴细胞亚群部分指标的特征性变化。TCMR和ABMR发生时血常规、外周血淋巴细胞亚群部分指标改变特点的不同可能有助于预测和诊断排斥反应以及二者的鉴别。

[关键词] 肾移植; 抗体介导的排斥反应; T细胞介导的排斥反应; 血常规; 外周血淋巴细胞亚群

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Characteristic changes in blood routine and peripheral blood lymphocyte subpopulations in recipients of different types of rejection

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ABSTRACT

Objective: Rejection remains the most important factor limiting the survival of transplanted kidneys. Although a pathological biopsy of the transplanted kidney is the gold standard for diagnosing rejection, its limitations prevent it from being used as a routine monitoring method. Recently, peripheral blood lymphocyte subpopulation testing has become an important means of assessing the body's immune system, however, its application value and strategy in the field of kidney transplantation need further exploration. Additionally, the development and utilization of routine test parameters are also important methods for exploring diagnostic strategies and predictive models for kidney transplant diseases. This study aims to explore the correlation between peripheral blood lymphocyte subpopulations and T cell-mediated rejection (TCMR) and antibody-mediated rejection (ABMR), as well as their diagnostic value, in conjunction with routine blood tests.

Methods: A total of 154 kidney transplant recipients, who met the inclusion and exclusion criteria and were treated at the Second Xiangya Hospital of Central South University from January to December, 2021, were selected as the study subjects. They were assigned into a stable group, a TCMR group, and an ABMR group, based on the occurrence and type of rejection. The basic and clinical data of these recipients were retrospectively analyzed and compared among the 3 groups. The transplant kidney function, routine blood tests, and peripheral blood lymphocyte subpopulation data of the TCMR group and the ABMR group before rejection treatment were compared with those of the stable group.

Results: The stable, TCMR group, and ABMR group showed no statistically significant differences in immunosuppressive maintenance regimens or sources of transplanted kidneys (all $P > 0.05$). However, the post-transplant duration was significantly longer in the ABMR group compared with the stable group ($P < 0.001$) and the TCMR group ($P < 0.05$). Regarding kidney function, serum creatinine levels in the ABMR group were higher than in the stable group and the TCMR group (both $P < 0.01$), with the TCMR group also showing higher levels than the stable group ($P < 0.01$). Both TCMR and ABMR groups had significantly higher blood urea nitrogen levels than the stable group ($P < 0.01$), with no statistically significant difference between TCMR and ABMR groups ($P > 0.05$). The estimated glomerular filtration rate (eGFR) was lower in both TCMR and ABMR groups compared with the stable group (both $P < 0.01$). In routine blood tests, the ABMR group had

lower hemoglobin, red blood cell count, and platelet count than the stable group (all $P < 0.05$). The TCMR group had higher neutrophil percentage ($P < 0.05$) and count ($P < 0.05$) than the stable group, and the ABMR group had a higher neutrophil percentage than the stable group ($P < 0.05$). The eosinophil percentage and count in the TCMR group were lower than in the stable and ABMR groups (all $P < 0.05$). Both TCMR and ABMR groups had lower basophil percentage and count, as well as lower lymphocyte percentage and count, compared with the stable group (all $P < 0.05$). There were no significant differences in monocyte percentage and count among the 3 groups (all $P > 0.05$). In lymphocyte subpopulations, the TCMR and ABMR groups had lower counts of CD45⁺ cells and T cells compared with the stable group (all $P < 0.05$). The TCMR group also had lower counts of CD4⁺ T cells, NK cells, and B cells than the stable group (all $P < 0.05$). There were no significant differences in the T cell percentage, CD4⁺ T cell percentage, CD8⁺ T cell percentage and their counts, CD4⁺/CD8⁺ T cell ratio, NK cell percentage, and B cell percentage among the stable, TCMR, and ABMR groups (all $P > 0.05$).

Conclusion: The occurrence of rejection leads to impaired transplant kidney function, accompanied by characteristic changes in some parameters of routine blood tests and peripheral blood lymphocyte subpopulations in kidney transplant recipients. The different characteristics of changes in some parameters of routine blood tests and peripheral blood lymphocyte subpopulations during TCMR and ABMR may help predict and diagnose rejection and differentiate between TCMR and ABMR.

KEY WORDS

kidney transplantation; antibody-mediated rejection; T cell-mediated rejection; blood routine; lymphocyte subpopulations

肾移植是治疗终末期肾病的最有效方法, 然而排斥反应一直是限制移植肾长期生存的最重要因素, 尤其是抗体介导的排斥反应(antibody-mediated rejection, ABMR)^[1-2]。移植肾病理是排斥反应诊断的金标准, 但因其有创性等缺点并不能作为常规监测手段。因此, 临床急需一些替代手段, 以期能够协助诊断排斥反应、预测移植肾功能以及体现移植免疫反应状态, 同时又能日常便利开展^[3]。然而, 在开发适用于肾移植受者个体化治疗的评估标志物或预测模型方面, 仍需进一步研究^[4-5]。

新诊断项目的开发和既有项目的重新开发利用是探索肾移植受者疾病诊断策略和风险预测模型的2种重要手段^[6]。排斥反应的本质是机体免疫系统活化从而清除“非我”移植器官的过程, 因此监测受者免疫系统的变化尤为重要^[7]。在众多免疫监测手段当中, 血常规是最常见的检验项目; 此外, 近年来外周血淋巴细胞亚群(又称为TBNK淋巴细胞监测; 以下简称“淋巴细胞亚群”)检测已成为评估机体免疫系统的重要手段^[8]。虽然淋巴细胞亚群检测已被用于肾移植临床, 但目前仍缺乏统一的应用策略^[7,9]。因

此, 本研究旨在通过回顾性分析肾移植受者的血常规、淋巴细胞亚群检测结果, 探究发生T细胞介导的排斥反应(T cell-mediated rejection, TCMR)和ABMR受者之间的异同, 为临床诊治TCMR和ABMR提供帮助。

1 对象与方法

1.1 对象及分组

将2021年1至12月就诊于中南大学湘雅二医院的肾移植受者列为研究对象。纳入对象为: 移植时年龄 ≥ 18 岁、首次肾移植、无排斥反应以外的可能影响机体免疫系统和移植肾功能的疾病, 以及临床资料完善的受者。

根据排斥反应是否发生及其类型将纳入的154名受者分为移植肾功能稳定组(以下简称“稳定组”)、TCMR组和ABMR组。移植肾功能稳定定义为血肌酐低于 $176 \mu\text{mol/L}$ 且无明显感染和排斥反应指征^[10]。TCMR与ABMR均经移植肾病理穿刺活检确诊^[11-12]。本研究经中南大学湘雅二医院伦理委员会批准(审批

号: 临研第 126 号)。

1.2 数据采集

采集研究对象的临床资料, 包括受者一般资料(性别、年龄等), 受者的免疫抑制维持方案, 常规实验室检测指标(血常规、肾功能、免疫抑制药物血药浓度、淋巴细胞亚群检测结果等), 以及群体反应性抗体(panel reactive antibody, PRA)检测和移植肾病理穿刺活检结果等。淋巴细胞亚群检测分别采用 CD45、CD3、CD4、CD8、CD19、CD16、CD56 定义 T 细胞、CD4⁺ T 细胞、CD8⁺ T 细胞、B 细胞和 NK 细胞, 并采用绝对计数管进行计数。对于发生排斥反应的受者, 血常规、淋巴细胞亚群检测、肾功能的检测结果为抗排斥反应治疗前的检测结果。采用肾脏病膳食改良(modification of diet in renal disease, MDRD) 试验公式计算受者的估算肾小球滤过率(estimated glomerular filtration rate, eGFR)^[13]。

1.3 统计学处理

应用 SPSS 22.0 软件和 GraphPad Prism 10.0 软件进行数据统计分析和绘图。计量资料以均数±标准差表示, 计数资料以例数和百分比进行描述。符合正

态分布且方差齐的计量资料采用方差分析进行比较, 否则采用非参数 Whitney U 检验进行分析。计数资料采用 χ^2 检验进行比较, 对于不满足 χ^2 检验应用要求的计数资料采用 Fisher 精确概率法进行比较。P<0.05 为差异具有统计学意义。

2 结果

2.1 患者基本资料的比较

稳定组、TCMR 组和 ABMR 组在年龄、性别、供体类型、免疫抑制维持方案、移植肾来源等方面差异均无统计学意义(均 P>0.05)。在术后时间方面, ABMR 组显著长于稳定组和 TCMR 组(均 P<0.05)。在 PRA 阳性率方面, ABMR 组显著高于 TCMR 组(P<0.01)。在移植肾功能方面, ABMR 组的血肌酐值显著高于稳定组和 TCMR 组(均 P<0.05), 并且 TCMR 组也高于稳定组(P<0.05); TCMR 组和 ABMR 组的尿素氮均显著高于稳定组(均 P<0.05), 而 TCMR 组和 ABMR 组之间差异无统计学意义(P>0.05); TCMR 组和 ABMR 组的 eGFR 值均显著低于稳定组(均 P<0.05), 而 TCMR 组和 ABMR 组之间差异无统计学意义(P>0.05, 表 1)。

表 1 受者基本资料的比较

Table 1 Comparison of the general data from the recipients

基本资料	稳定组(n=133)	TCMR 组(n=9)	ABMR 组(n=12)	P
年龄/岁	37.17±11.85	43.00±8.94	38.67±6.11	0.317
性别(男/女)	72/61	7/2	8/4	0.271
术后时间/月	28.31±32.37	21.67±29.79	66.40±58.03*†	0.001
PRA 阳性/[例(%)]	12(9.02)	2(22.22)	5(41.67)†	0.005
供体类型/例				1.000
尸体供肾	112	8	10	
活体供肾	21	1	2	
免疫抑制维持方案/例				0.128
他克莫司+霉酚酸+激素	119	6	11	
环孢素+霉酚酸+激素	14	3	1	
血肌酐/($\mu\text{mol}\cdot\text{L}^{-1}$)	113.91±29.66	201.67±55.22*	309.32±208.85*†	<0.001
尿素氮/($\text{mmol}\cdot\text{L}^{-1}$)	8.00±3.20	15.26±6.70*	17.58±11.33*	<0.001
尿酸/($\mu\text{mol}\cdot\text{L}^{-1}$)	345.45±88.45	392.22±88.48	389.93±112.03	0.104
eGFR/($\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$)	79.86±27.67	43.98±20.49*	35.75±24.51*	<0.001

*与稳定组比较, P<0.05; †与 TCMR 组比较, P<0.05。eGFR: 估算肾小球滤过率; TCMR: T 细胞介导的排斥反应; ABMR: 抗体介导的排斥反应; PRA: 群体反应性抗体。

2.2 血常规结果比较

稳定组、TCMR 组和 ABMR 组在白细胞数量、

单核细胞的数量和比例方面的差异均无统计学意义(均 P>0.05)。然而, 与稳定组相比, ABMR 组具有更

低的血红蛋白浓度、红细胞数、血小板数(均 $P < 0.05$)。在中性粒细胞方面, TCMR组和ABMR组的中性粒细胞比例均高于稳定组(均 $P < 0.05$), 并且TCMR组的中性粒细胞数量显著高于稳定组($P < 0.01$)。在嗜酸性粒细胞方面, 稳定组和ABMR组的

嗜酸性粒细胞比例和数量均高于TCMR组(均 $P < 0.05$)。在嗜碱性粒细胞方面, TCMR组和ABMR组的嗜碱性粒细胞比例和数量均低于稳定组(均 $P < 0.05$)。在淋巴细胞方面, TCMR组和ABMR组的淋巴细胞比例和数量均低于稳定组(均 $P < 0.05$, 图1)。

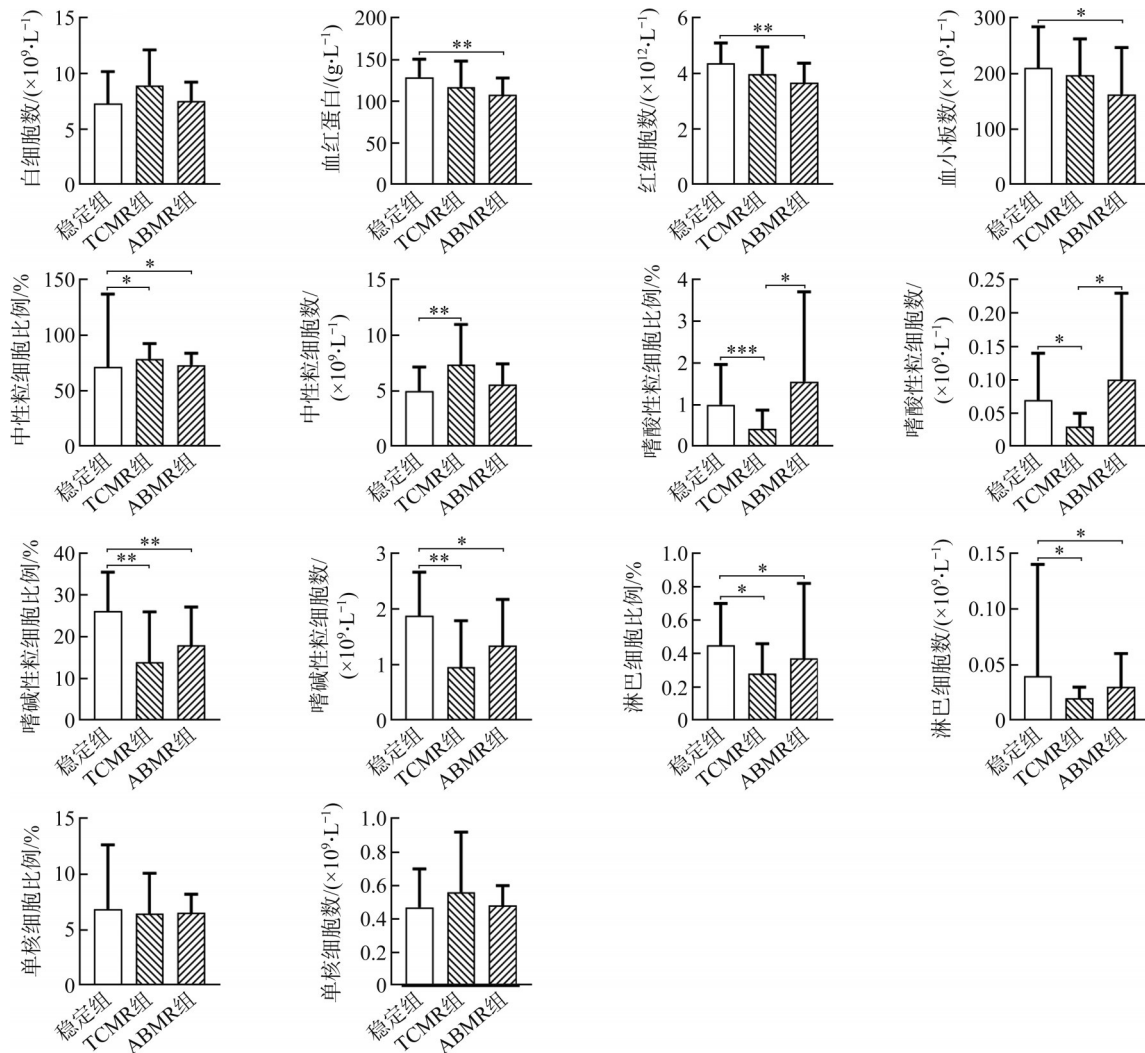


图1 稳定组、TCMR组和ABMR组之间血常规参数的比较

Figure 1 Comparison of blood routine parameters among the stable group, TCMR group, and ABMR group

* $P < 0.05$, ** $P < 0.01$. TCMR: T cell-mediated rejection; ABMR: Antibody-mediated rejection.

2.3 淋巴细胞亚群检测结果比较

与血常规中淋巴细胞数量的结果一致, TCMR组和ABMR组的CD4⁺细胞总数均显著低于稳定组(均 $P < 0.05$)。3组受者的T细胞、CD4⁺T细胞、和CD8⁺T细胞比例和数量差异均无统计学意义(均 $P > 0.05$), 但TCMR组和ABMR组的T细胞数量、TCMR组的CD4⁺T细胞数量均显著低于稳定组(均 $P < 0.05$)。在

CD4⁺/CD8⁺T细胞比值方面, 3组之间的差异无统计学意义($P > 0.05$)。3组NK细胞比例的差异无统计学意义($P > 0.05$), 但TCMR组和ABMR组的NK细胞数量均显著低于稳定组(均 $P < 0.05$)。3组B细胞比例的差异无统计学意义($P > 0.05$); 但在B细胞数量方面, TCMR组显著低于稳定组($P < 0.01$; 图2、图3)。

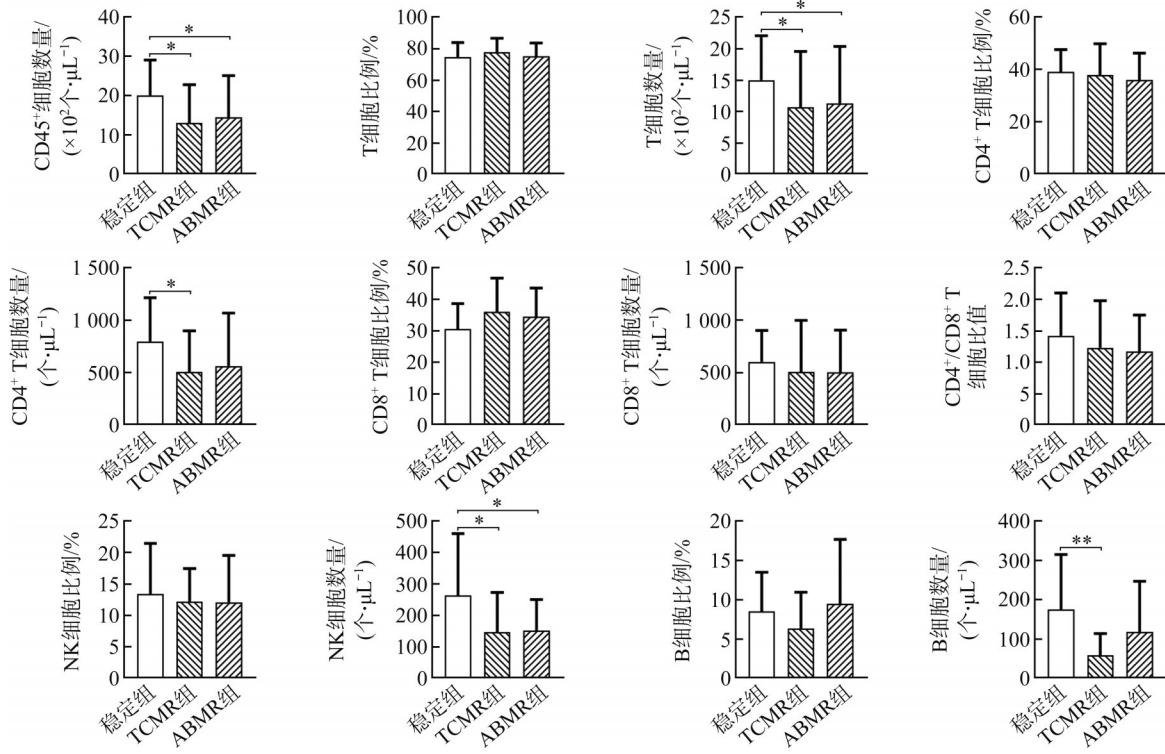


图2 稳定组、TCMR组和ABMR组间外周血淋巴细胞亚群检测结果比较

Figure 2 Comparison of peripheral blood lymphocyte subsets among the stable group, the TCMR group, and the ABMR group

*P<0.05, **P<0.01. TCMR: T cell-mediated rejection; ABMR: Antibody-mediated rejection; NK: Natural killer.

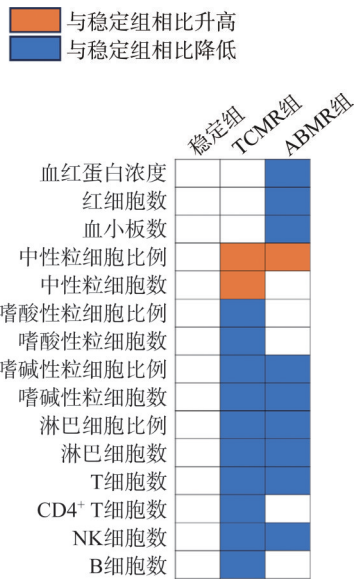


图3 稳定组、TCMR组和ABMR组之间的血常规、淋巴细胞亚群差异性指标的变化趋势

Figure 3 Variation trend of blood routine and lymphocyte subpopulation difference indexes among the stable group, the TCMR group, and the ABMR group

TCMR: T cell-mediated rejection; ABMR: Antibody-mediated rejection; NK: Natural killer.

3 讨论

通过技术手段准确评估和预测患者的免疫功能状态, 有助于实现个体化治疗和提升免疫相关疾病的临床诊疗效果^[14]。精准的免疫风险评估是推动肾移植术后受者个体化管理的关键^[7]。本研究通过分析移植肾功能稳定受者、TCMR受者和ABMR受者的临床资料, 发现排斥反应发生时, TCMR受者和ABMR受者在血常规、淋巴细胞亚群方面存在诸多异同。

在本研究中, ABMR的发生显著晚于TCMR, 并且发生时伴随移植肾功能的减退。TCMR主要发生于肾移植术后早期, 然而随着移植术后时间的延长(>1年), ABMR变成肾移植排斥反应的主要类型^[15]。与发生时间相对应, TCMR是移植术后早期移植肾失功的主要原因, 而ABMR是移植术后晚期移植肾失功的主要原因^[2]。

血常规是临床常规检验项目之一。本研究发现在血常规的各项指标方面, 发生TCMR或ABMR的受者与移植肾功能稳定受者之间存在一些差异。ABMR受者的血红蛋白浓度以及红细胞数显著低于

稳定组, 并且似乎也低于TCMR组(虽然差异无统计学意义)。既往的研究^[16-18]提示ABMR与血红蛋白之间存在交互作用。移植肾功能减退促进贫血的发生; 而低血红蛋白浓度($<10\text{ g/dL}$)是新生供者特异性抗体(donor-specific antibodies, DSA)产生的风险因素, 并且低血红蛋白也是移植肾失功的独立风险因素^[16-18]。研究^[19-20]表明TCMR并不会影响受者的血小板数量, 而ABMR受者会发生血小板数量的降低^[21]。本研究发现ABMR的发生会伴随血小板的降低, 但TCMR发生时不具有此类现象。此外, 血小板在移植肾内聚集是ABMR病理特征之一, 并且血小板的聚集与移植肾的损伤程度相关^[22]。目前对于粒细胞与肾移植排斥反应的研究较少。本研究发现TCMR的发生会伴随中性粒细胞比例和数量的显著升高; ABMR的发生伴随中性粒细胞比例轻微增加。然而, 其他学者^[19]认为TCMR的发生并不会出现中性粒细胞数量的改变。因此, 对于中性粒细胞与排斥反应的关系, 需要更多的研究进行证实。对于嗜酸性粒细胞的变化, 有研究^[23]揭示嗜酸性粒细胞数量 $\geq 0.3 \times 10^9/\text{L}$ 是肾移植术后3个月内发生排斥反应的独立风险因素, 这种风险是嗜酸性粒细胞数量 $< 0.3 \times 10^9/\text{L}$ 受者的3倍。另有研究^[24]认为嗜酸性粒细胞的增加预示着急性排斥反应的预后较差, 嗜酸性粒细胞比例 $\geq 4\%$ 的急性排斥病例中37.9%的病例为不可逆性排斥反应。本研究的数据提示, 在TCMR和ABMR发生时嗜酸性粒细胞比例和数量的改变存在差异, TCMR的发生伴随二者显著减少, 而ABMR的发生伴随二者轻度升高。嗜酸性粒细胞比例和数量的改变或许有助于区分TCMR和ABMR。本研究发现, 发生TCMR和ABMR的受者相较于稳定受者而言具有较低的嗜碱性粒细胞比例和数量。虽然暂无研究揭示嗜碱性粒细胞在肾移植受者长期生存过程中的动态变化特征, 但有研究^[25-26]提示嗜碱性粒细胞的减少与狼疮肾炎的发生存在关联。这提示嗜碱性粒细胞的减少可能与肾损伤存在关联。

目前, 在肾移植排斥反应诊疗方面如何应用淋巴细胞亚群检测结果尚存争议。有研究^[21, 27]发现发生TCMR受者和慢性ABMR受者的外周血淋巴细胞比例和数量显著降低。然而, 也有研究^[19]认为急性TCMR会伴有淋巴细胞比例的显著升高。本研究中的血常规结果和淋巴细胞亚群检测结果均提示TCMR和ABMR受者的淋巴细胞较稳定受者显著减少。

对于T细胞, 本研究数据提示TCMR受者和ABMR受者伴有T细胞减少, 并且TCMR受者伴有 CD4^+ T细胞数量的减少。Zhang等^[28]发现发生急性TCMR受者与发生感染受者之间的 CD4^+ T细胞和

CD8^+ T细胞的数量似乎并无显著差异, 这意味着急性TCMR受者可能具有较低的 CD4^+ T细胞和 CD8^+ T细胞数量。研究发现: 急性排斥反应的发生会导致 CD4^+ T细胞比例升高而 CD8^+ T细胞的比例降低, 从而出现 $\text{CD4}^+/\text{CD8}^+$ T细胞比值升高^[29]; TCMR的发生会导致外周 CD8^+ T细胞比例的升高^[27]; 急性排斥反应的发生会造成受者总T细胞数量、 CD4^+ T细胞数量、 $\text{CD4}^+/\text{CD8}^+$ T细胞比值升高^[30]。有研究^[21, 31]提示DSA的产生和ABMR的发生均不会影响 CD4^+ T细胞和 CD8^+ T细胞的数量。本研究结果与该研究结果相符。而另有研究^[32]认为DSA的出现会导致 CD4^+ T细胞的比例降低, 并且幼稚 CD4^+ T细胞比例增加以及记忆/效应 CD4^+ T细胞比例降低。因此, 目前对于排斥反应的发生与外周血T细胞的改变之间的相关性分歧较大。

对于NK细胞, 本研究发现TCMR和ABMR的发生并不影响外周血NK细胞的比例, 但会伴随NK细胞数量减少。然而, 有研究^[28]提示急性TCMR的发生似乎并不影响NK细胞的数量。也有研究^[29]认为急性排斥反应的发生会造成NK细胞比例的升高。有研究^[31, 33-34]证实ABMR受者出现DSA会导致NK细胞比例和数量的减少, 这种变化也许与ABMR的发生伴随移植肾内细胞毒性NK细胞的募集有关。因此, ABMR的发生伴随受者外周血NK细胞数量减少。

对于B细胞, 有研究^[35]证实急性排斥反应的发生伴有外周血B细胞比例及数量的减少。然而, 不同的观点^[36]认为虽然TCMR发生时移植肾内会浸润大量B细胞, 但这并不影响外周血中B细胞的比例。本研究发现与稳定受者相比, TCMR的发生伴有B细胞数量的减少, 而ABMR的发生似乎并不影响B细胞的比例和数量。对于ABMR受者中B细胞的变化趋势尚不明确, 有研究^[31]发现DSA的出现伴随B细胞比例的降低, 而不同观点^[33]认为DSA的出现不会影响B细胞的比例。结合本研究的发现以及其他研究结论, 笔者推测ABMR的发生并不会导致B细胞数量的增高; 此外B细胞数量的变化也许可以用于TCMR和ABMR的鉴别诊断。

综上所述, 肾移植受者发生排斥反应时会伴有血常规、淋巴细胞亚群检测部分指标的变化, 通过动态评估这些指标的变化可能有助于评估受者发生排斥反应的风险。此外, 在发生TCMR和ABMR时, 受者的血常规、淋巴细胞亚群的部分指标的变化趋势或程度存在不同, 这些指标也许可以辅助鉴别TCMR和ABMR。当然, 本研究也存在一些局限之处: TCMR受者和ABMR受者的样本量较小以至于无法建立预测模型; 基于数据的可及性无法回顾性

分析所纳入受者在排斥反应发生前的血常规、淋巴细胞亚群检测结果的动态变化过程。

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