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# 基于多发性骨髓瘤肾损害早期诊断策略的研究进展

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## 摘　要

**多发性骨髓瘤(Multiple Myeloma, MM)是浆细胞恶性增殖性疾病，因为骨髓中浆细胞的异常增殖，且伴有单克隆免疫球蛋白或轻链的过度产生，造成了多器官受损，其中肾损害是其常见的临床表现。多发性骨髓瘤患者致死率、致残率高，存活期短，而伴肾损害的尤甚，故防治急慢性的肾损害是骨髓瘤患者整体预后的关键。骨髓瘤肾损害的诊断指标有多种，当前评价骨髓瘤患者的肾功能常用临床指标是血肌酐，但其不太灵敏，当发生轻微肾损害时，血肌酐指标尚未变动，而骨髓瘤导致的肾损害需快速、早诊断。因此，本文主要是对多发性骨髓瘤肾损害早期诊断指标的检测及现阶段研究进展进行阐述。**

## 关键词

**多发性骨髓瘤，肾损害，microRNA，血清胱抑素C，血管细胞黏附因子-1**

# Research about Early Diagnosis Strategy in Renal Impairment Due to Multiple Myeloma

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## Abstract

**Multiple Myeloma is plasma cells malignant hyperplastic disease. The multiplication abnormal of plasma cells in bone marrow and excessive production of the monoclonal immunoglobulin or Light**

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**chain, cause multiple organ damage. Renal impairment is the common clinical manifestations. Patients with multiple myeloma have high fatality rate and morbidity, especially these patients with renal damage. Prompt and effective treatment can improve the overall prognosis of these patients with renal damage. There are many diagnostic indicators of myeloma renal damage diagnosis index, the common target is serum creatinine, but it is not too sensitive. Because serum creatinine index has not changed when renal damage is slight. However, MM with Kidney damage requires quick diagnosis in the early time. This article reviews the possible diagnostic indicators and previous research progress of renal damage based on Multiple Myeloma.**

## Keywords

**Multiple Myeloma, Renal Damage, microRNA, Serum Cystatin C, Vascular Cell Adhesion Molecule-1**



## 1. 诊断指标

### 1.1. 血清游离轻链(Free Light Chain, FLC)

轻链是指在免疫球蛋白单体分子中相对于重链而论，分子量较小的多肽链，有 κ、λ 两型。正常浆细胞产生的游离轻链多于重链，轻链被分泌到血液中，被肾小球滤过、肾小管重吸收。[1] 2/3 及以上多发性骨髓瘤患者中，轻链的过量产生超过了肾小管的再吸收能力[2]。研究表明 λ 型肾损害发生概率更高[3]。轻链的检测很早就应用于临床，现已被引入骨髓瘤的诊疗指南中，其特异性高、敏感性强，而且它对初诊骨髓瘤肾损伤的早期诊断意义更大，尤其是在轻链型骨髓瘤中有重要诊断和疗效评估价值[4] [5] [6]。有文献报道，骨髓瘤对肾脏的损害更多的是损伤肾小管，引起肾小管缺血、缺氧等[2] [7]，这些损害都是不可逆的，因为始作俑者是过度增殖的骨髓瘤细胞生成的超出正常量的游离轻链，后者都是有毒性的，甚至可以导致严重的肾功能衰竭[8]。究其原因，考虑是循环中或尿中增加的游离轻链可能与远端肾小管受累(骨髓瘤肾、轻链铸型肾病)或近端肾小管损伤(近端肾小管病变、轻链近端肾小管病变)的范可尼综合征有关[9]。以上病变可单独或同时发生[10]，需要迅速干预，降低游离轻链浓度。多个研究表明，早期和充分化疗结合对症治疗可迅速降低血清轻链浓度。也有文献显示，不间断化疗和延长使用高截断值透析器的血液透析可去除大量游离轻链，但其临床益处还不能做出明确的结论[11] [12] [13]。相信在不久的将来，会有所突破。

### 1.2. microRNA

近年来，microRNA 的研究层出不穷，许多 microRNA 已被证实作为抑癌基因或癌基因参与了肿瘤发生、肿瘤进展和预后。其中，在多发性骨髓瘤中，多种 microRNA 表达显著降低，提示其以抑癌基因发挥作用，部分 microRNA 可能以增加骨髓瘤细胞分泌，发挥癌基因作用，与骨髓瘤早期对器官损害相关[14] [15]。Hongku 等人[16]的研究发现，miR145-3p 的表达下调也与人 MM 的疾病进展有关。MIR145-3p 通过直接靶向骨髓瘤细胞中的组蛋白去乙酰化酶 4 (Histone deacetylase 4, HDAC4)触发细胞自噬凋亡增强。有团队[17]首次在新诊断骨髓瘤队列中证明外泌体 microRNAs 临床意义。相较于许多循环的 microRNAs，外泌体 microRNAs 是由不同类型的细胞(包括癌细胞)在外周血中积极分泌的，更具有生物学相关性，因为它们不是凋亡和坏死的细胞中被动释放出来的。近年来，关于 microRNA 与骨髓瘤相关

的研究层出不穷，而 microRNA 与肾脏疾病也是热点。有学者构建了小鼠缺血/再灌注肾损伤模型，证明人类肾脏中表达的 microRNAs 在肾脏疾病中既有发挥保护作用的种类部分，也有促进损伤部分。[18] [19] [20]同时检验出尿液中也有 6 种 microRNA 可以作为尿液中的急性肾损伤诊断标记物[21] [22]。其中有团队[23]通过基因表达谱证明了 miR-21 在糖尿病肾病中有表达，此外升高的 miR-21 水平还促使肾小球脏层上皮细胞功能下降。相反，体内抑制其表达则可减少糖尿病肾病的发生。由此预测，microRNA 可能成为一种潜在的评估多发性骨髓瘤合并肾损伤早期的生物标记物。而体液中 microRNA 的表达水平可预示病理状况，且其是无创性的诊断方法[24]。当前对它们的调控机制和功能尚未深入阐明，因此，需要进一步的研究来充分阐明这些机制。

### 1.3. *β*2-微球蛋白(*β*2-microglobulin, *β*2-MG)

*β*2-微球蛋白是存在于尿、血浆及一些细胞表面的小分子量血清蛋白质。正常人的含量是动态平衡的，因其产生和排泄是恒定的。很多免疫细胞可分泌 *β*2-微球蛋白，骨髓瘤细胞也可分泌，当其迅速增殖时，合成速度增快，导致血清中其升高，因其只经过肾脏排泄，当排泄不足时，尿中就会大量出现。血清 *β*2-微球蛋白与肾小球滤过率之间存在显著相关性，可作为肾小球滤过率的指标，因此可认为血清 *β*2-微球蛋白作为骨髓瘤肾损害的诊断指标[1]。其中关于骨髓瘤分期与 *β*2-微球蛋白的关系：I 期疾病的定义为 *β*2-微球蛋白 < 3.5 mg/L 和血清白蛋白高于 35 g/L 的患者，中位生存期为 62 个月。III 期疾病，中位生存期为 29 个月，包括 *β*2-微球蛋白高于 5.5 mg/L 的患者。对于不符合其他阶段标准的 II 期疾病患者，中位生存期为 44 个月。[25]

### 1.4. 血清胱抑素 C (Serum cystatin C, CysC)

血清胱抑素 C 是一种细胞外抑制素，属于小分子量的蛋白质，只通过肾脏排泄[26] [27]。它的水平与游离轻链呈正相关，故可作为肾功能的评价指标，它也与晚期疾病相关，是骨髓瘤患者生存的独立预后因素，反映肿瘤负荷，由此可认为其是肾损害的可靠指标[1]。另有文献报道，III 期骨髓瘤患者的胱抑素水平明显高于 I 期和 II 期，而 III 期的患者更多的发生肾功能受损。胱抑素还与 *β*2-微球蛋白呈正相关，前者可以结合 *β*2-微球蛋白在骨髓瘤分期和肾损害预后中起到重要作用。[28]综上，血清胱抑素 C 不仅是肾损害的敏感标志，而且反映肿瘤负担，对骨髓瘤有预后价值。[29] [30] [31]

### 1.5. 血钙水平

血钙水平关系到肾脏功能，两者呈负相关[3]。骨髓瘤细胞和其所在的环境之间发生复杂的作用，经常导致骨破坏，反过来又刺激肿瘤生长，最终加重骨质溶解，这些反应会导致骨痛、肾功能衰竭和高钙血症等[32]。而过高的血钙水平会严重损害肾脏器官，包括降低肾小球滤过率、改变肾血流量以及钙在肾小管和肾间质中沉淀，最终表现为骨髓瘤疾病中肾衰竭的高发生率。[33] [34]

### 1.6. 血管细胞黏附因子-1 (Vascular Cell Adhesion Molecule-1, VCAM-1)和激活素 A

血管细胞黏附因子-1 和激活素 A 作为人体多功能细胞因子，存在于骨髓微环境中，与感染、免疫、肾病等有关。王岩等人的研究发现，肾功能不全患者的血清中细胞黏附因子-1 和激活素 A 水平明显高于正常人。其中，尿激活素 A 还反映了骨髓瘤相关的肾损伤，提示前者有希望应用于早期检测骨髓瘤相关肾损害[35] [36] [37]。由此可见，它们均有可能会成为新靶点来治疗多发性骨髓瘤导致的肾损害。

### 1.7. 蛋白脂蛋白 2 (Protein Lipoprotein 2, PLP2)

蛋白脂蛋白 2 是内质网完整的离子通道膜蛋白。虽然它在正常情况下的确切功能尚不清楚，但对该

蛋白的研究已经揭示了几个特征。它是一个完整的膜蛋白，定位于内质网。其次，有文献表明，它的下调增加细胞凋亡，降低体外肿瘤细胞存活[38] [39]。Hua Bai 等人[40]的研究首次报道了蛋白脂蛋白 2 的表达与骨髓瘤患者预后之间的关系，表明其在高危骨髓瘤患者中过表达，随着病情进展及预后不良而增加。同时，蛋白脂蛋白 2 与骨髓瘤活性标志物(如血清白蛋白水平降低、$\beta$2-微球蛋白、乳酸脱氢酶和 C 反应蛋白水平升高)相关，后者与肾功能受损程度呈正平行，且高危骨髓瘤患者多发生肾功能受损。由此可见，蛋白脂蛋白 2 可能是一种新的预测骨髓瘤肾损伤预后的生物标志物和抗骨髓瘤治疗的治疗靶点，而蛋白脂蛋白 2 低表达的骨髓瘤患者可以获得良好的治疗效果。[41]

## 2. 结论

多发性骨髓瘤是恶性增殖性疾病，男性多于女性，常见于高龄，首发症状多且杂，易造成误诊，虽然化疗明显提高了生存优势，但其仍然是一种复发或难治性疾病[42]。而常见并发症依然是肾脏病变，有研究表明骨髓瘤患者一旦发生肾损害，多发生于 II 期、III 期[1]。因此，寻找灵敏度好、特异性高的血清学指标对骨髓瘤肾损害早期进行诊断及鉴别，并制定针对性的干预措施，对于改善患者预后格外重要[43]。当前研究已证实，以上单克隆蛋白和 $\beta$2-微球蛋白等参数被广泛采用作为标准分期系统，尽管在做出治疗决定方面仍然不充分，相信在不久的将来，这项难题会有所突破。

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