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·论著·

骨源性碱性磷酸酶预测骨质疏松骨折患者再骨折的意义

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中图分类号:R683 **文献标识码**:A **文章编号**:1006-7108(2014)06-0640-04

摘要:**目的** 探讨骨质疏松患者初次骨折后发生再骨折的影响因素,分析血清骨源性碱性磷酸酶(BALP)对预测再发骨折的临床价值。**方法** 前瞻性队列研究纳入我院 178 例确诊的 50 岁以上骨质疏松性骨折患者。初次骨折时检测患者血清 BALP 水平、骨密度值(BMD)、钙、磷及临床一般资料等,跟踪随访 4 年,以患者再发骨折为随访终点事件。采用 Kaplan-Meier 分析和多元 Cox 回归模型进行再发骨折的风险因素研究,受试者工作特征(ROC)曲线用于评判 BALP 的预测价值。**结果** 178 例骨质疏松性骨折患者 4 年内 30(16.9%)例发生再次骨折。Cox 回归分析结果显示 BALP、年龄、性别和 BMD 是患者再发骨折的独立影响因素。以 BALP 为预测标准,ROC 曲线下面积为 0.757,诊断临界点为 29.0 μg/L,灵敏度及特异度分别为 84.3%、63.8%。Kaplan-Meier 分析显示 BALP>29.0 μg/L 患者骨折再发率较 BALP≤29.0 μg/L 更高($p=0.026$)。**结论** 骨质疏松骨折患者发生再骨折的风险较高,检测血清 BALP 水平是有效可行的预测指标。

关键词:骨源性碱性磷酸酶;骨质疏松;骨折;ROC 曲线

The predictive significance of bone alkaline phosphatase on the second fracture in patients with osteoporotic fractures

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Abstract: **Objective** To explore the risk factors of re-fracture in patients with osteoporotic fractures, and to evaluate the value of serum bone alkaline phosphatase (BALP) as a prognostic indicator in patients with re-fractures. **Methods** A prospective cohort study including 178 patients, who were over 50 years old and diagnosed with osteoporotic fractures and in our hospital, was performed. The serum levels of BALP, calcium, and phosphorus were determined at the time with initial fracture. The bone mineral density (BMD) was detected. And other clinical general data were also collected and analyzed. All the patients were followed up for 4 years. The occurrence of re-fracture or death was defined as end-point event. Kaplan-Meier analysis and multivariate Cox regression model were used for the analysis of risk factors. Receiver operating characteristic curve (ROC curve) was used to evaluate the predictive value of BALP. **Results** Among all these 178 patients, 30 (16.9%) had re-fractures in 4 years. Cox regression analysis showed that BALP level, age, gender, and BMD were independent and important factors for re-fracture. Using BALP as a forecast standard, the ROC area under the curve (AUC) was 0.757, and diagnose critical point was 29.0 μg/L. The sensitivity and specificity were 84.3% and 63.8%, respectively. Kaplan-Meier analysis revealed that patients with serum BALP > 29.0 μg/L had a higher re-fracture incidence than patients with serum BALP ≤ 29.0 μg/L ($P=0.026$). **Conclusion** The prevalence of second fracture is high in patients with osteoporotic fractures. The serum BALP level is an effective and suitable predictor.

Key words: Bone alkaline phosphatase; Osteoporosis; Fracture; ROC curve

骨质疏松症(osteoporosis)是骨量减少、骨的微观结构退化,致骨脆性增加的一种全身性骨骼疾病。骨折是其常见的并发症,严重影响老年人的生活质量,特别是并发骨折时明显增加患者死亡风险[1]。然而,骨质疏松患者初次骨折后,其再骨折率仍偏高。最新的 NOREPOS 研究数据显示[2],骨质疏松

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性骨折患者 10 年内再发骨折率男女比例约为 11% 和 15%。血清骨源性碱性磷酸酶(Bone-specific Alkaline Phosphatase, BALP)是早期反映骨形成的重要指标。本研究将分析其对预测患者再骨折发生率的意义。

1 材料和方法

1.1 研究对象与方法

选择 2007 年 8 月至 2009 年 8 月在我院诊断的骨质疏松骨折患者。入选标准:年龄≥50 岁发生非暴力骨折;排除患有肿瘤、骨代谢相关的疾病及长期服用激素等病例。随访终点事件为再发骨折,除外死亡的病例,所有入选患者至少随访 4 年。按照是否再发骨折分为再骨折组和无再骨折组。

1.2 临床指标

骨密度(BMD)检测采用美国 GE 公司生产的双能 X 线 BMD 检测仪(DXA),测定腰椎 L_1-L_4、L_2-L_4 和股骨颈的 BMD 值,计算总平均值为 BMD-T 值;血清 BALP 水平值采用酶联免疫吸附(ELISA)法测定;钙、磷、血红蛋白、白蛋白、碱性磷酸酶等生化指标采用自动生化仪检测;PTH 采用放射免疫法测定;以上指标均为初次骨折后次日基线水平。

1.3 统计学处理

采用 SPSS 19.0 进行统计分析。计数资料采用 $\bar{x} \pm s$ 表示,单因素比较用 t 或 χ^2 检验。Pearson 相关分析两变量间的关系,Kaplan-Meier 分析法计算累计事件率,Cox 多元回归分析危险因素。受试者工作特征(ROC)曲线评判指标的预测价值。$P<0.05$ 认为有统计学意义。

2 结果

2.1 一般基本数据

对纳入患者跟踪随访,随访时间至少为 4 年,剔除失访数据,共入选 178 例。其中男性 66(37.1%),女性 112(62.9%),所有患者平均年龄为 67.2 ± 10.5 岁。4 年随访时间中共计 30 例发生再骨折,再骨折发生率为 16.9%。骨折类型以椎体骨折后再次骨折最多 12 (40%)例,其次为股骨近端骨折 9(30%) 例。再骨折发生时间平均为 36.4 ± 10.7 月。

2.2 再骨折组与无再骨折组临床资料比较

178 例骨质疏松骨折患者分为无再骨折组与再骨折组。单因素分析结果示:与无再骨折组患者比较,再次骨折患者平均年龄大于无再骨折组,女性比例更高;血清 BALP 水平值更大,BMD-T 值更小($P<0.05$);而糖尿病比例、BMI、血红蛋白、白蛋白、碱性磷酸酶、血钙、血磷、PTH、吸烟比例、饮酒比例及功能锻炼比例两组之间无显著性差异($P>0.05$),见表 1。Pearson 相关分析显示所有患者 BALP 值与 BMD-T 值呈负相关($r=-0.573$, $P=0.034$);与年龄呈正相关($r=0.531$, $P=0.039$)。

表 1 再骨折组与无再骨折组患者一般资料比较

Table 1 Comparison of the general characteristics between the re-fracture group and the non-re-fracture group

项目	再骨折组 ($n=30$)	无再骨折组 ($n=148$)	t/χ^2	P 值
年龄(岁)	73.8 ± 9.3	68.4 ± 10.9	2.532	0.012
男/女	6/24	60/88	4.511	0.034
糖尿病(是/否)	11/19	32/116	3.082	0.079
吸烟(是/否)	3/27	20/128	0.274	0.601
饮酒(是/否)	3/27	23/125	0.614	0.433
功能锻炼(有/无)	12/18	80/69	1.874	0.171
BMI (kg/m^2)	22.8 ± 5.4	23.7 ± 3.1	1.255	0.211
血红蛋白(g/L)	148.8 ± 22.5	153.3 ± 26.2	0.877	0.381
白蛋白(g/L)	33.1 ± 6.4	34.8 ± 5.5	1.501	0.135
碱性磷酸酶(U/L)	74.7 ± 14.8	69.8 ± 17.3	1.447	0.150
血钙(mmol/L)	1.76 ± 0.35	1.81 ± 0.26	0.902	0.368
血磷(mmol/L)	1.25 ± 0.47	1.41 ± 0.72	1.166	0.245
PTH(pg/ml)	37.9 ± 10.6	41.7 ± 13.9	1.415	0.159
BALP(μg/L)	29.9 ± 7.1	26.8 ± 6.7	2.289	0.023
BMD-T 值	−2.59 ± 0.47	−2.35 ± 0.57	2.161	0.032

2.3 BALP 对再骨折的预测

ROC 曲线显示,血清 BALP 水平值对患者的骨折再发有预测意义:ROC 曲线下面积(AUC)为 0.757,诊断临界点为 29.0 μg/L,灵敏度及特异度分别为 84.3%、63.8%,见图 1。

2.4 BALP 对再骨折的影响

根据 ROC 曲线诊断界点 29.0 μg/L,将所有 178 例患者分为 >29.0 μg/L 及≤29.0 μg/L 两组,采用 Kaplan-Meier 分析比较两组患者骨折后再发骨折率情况,Log-Rank 检验结果为统计量 $\chi^2=4.936$, $P=0.026$,两组事件函数的差异有统计学意义。BALP >29.0 μg/L 患者再发骨折显著高于 BALP≤29.0 μg/L 患者,两组的事件发生率曲线见图 2。

2.5 再骨折的多因素 Cox 分析

将 BALP 水平、年龄、性别、BMD-T 值、BMI、骨折部位、是否糖尿病、是否抽烟、是否饮酒、是否独居、是否功能锻炼等因素为自变量代入 Cox 比例风险模型,调整了以上各种影响因素后,与 BALP≤29.0 μg/L 组相比,BALP >29.0 μg/L 患者再骨折风险明显增加($RR=1.938$, $P=0.011$)(表 2),且

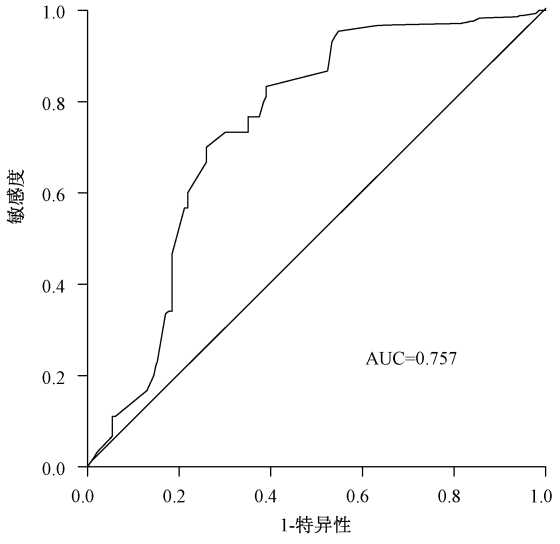

图 1 BALP 预测骨质疏松骨折后再骨折的 ROC 曲线

Fig. 1 The ROC curve of BALP for the prediction of re-fracture after osteoporotic fractures

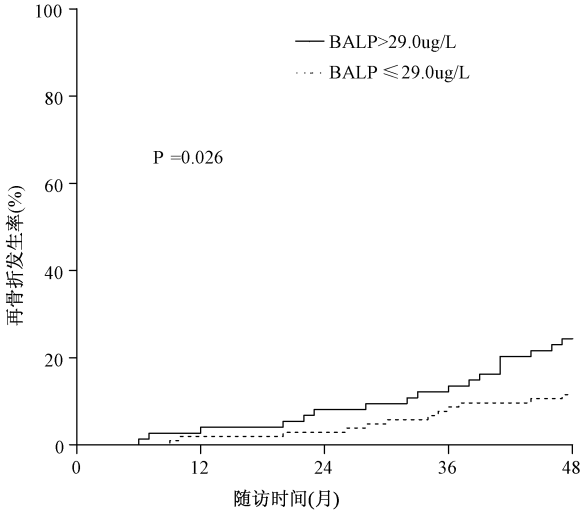

图 2 BALP 预测骨质疏松骨折后再骨折的事件曲线

Fig. 2 The event curve of BALP for the prediction of re-fracture after osteoporotic fractures

独立于女性、高龄、低 BMD-T 等因素。

表 2 骨质疏松骨折后再骨折的多因素 Cox 分析

Table 2 The multivariate Cox analysis of re-fractures after osteoporotic fractures

变量	赋值方法	*RR*	*P* 值	95% *CI*
BALP(μg/L)	>29.0:≤29.0	1.938	0.011	1.193~4.573
女性	女性:男性	1.852	0.019	1.016~2.133
年龄(岁)	>75:≤75	1.567	0.037	0.860~2.979
BMD-T 值	>-2.5:≤-2.5	0.763	0.028	0.129~1.362

3 讨论

骨质疏松骨折严重影响患者生活质量及生存率[3]。骨折后骨骼重建是由成骨细胞介导的新骨形成和破骨细胞介导的骨吸收相互偶联的过程。通过研究骨代谢的生化指标及骨质疏松骨折的临床特点,可为预防再骨折的发生提供有力依据。

BALP 由成骨细胞分泌,其生理功能主要是在成骨过程中水解磷酸酯和焦磷酸盐,发生骨质疏松骨折时静止的成骨细胞转变为活跃的成骨细胞,由于骨吸收亢进而出现代偿性骨形成增加致 BALP 增加[4]。BALP 的变化反映了骨转换过程中的骨形成程度。

Veitch 等[5]证实,骨折后局部骨量减少、骨转换增加,骨折围手术期同时启动骨愈合机制,在成骨活跃期开始即有骨形成的生化指标的变化。我们的数据显示,以骨折时次日血清 BALP 值为标准,预测再发骨折事件的 ROC 曲线 AUC 为 0.757,灵敏度及特异度分别为 84.3%、63.8%,显示具有较好的临床价值。Kaplan-Meier 分析得出 BALP 大小与预后相关,BALP >29.0 μg/L 者再发骨折率显著更高(P = 0.026)。

我们认为较高的骨代谢指标浓度常与较低的 BMD 相关联,较高的骨代谢指标浓度提示较高的骨代谢转换水平[6]。BMD 可以反映骨强度,但不能反映骨小梁结构因素,对早期骨量减少不够灵敏,提供的资料是非动态及局部性的[7]。在骨质疏松骨折中,BMD 的低下反映骨质量减低、骨量减少的骨骼机体基础状况,在骨折发生后,成骨细胞的再生能力可能影响其再次发生骨折的风险。而 BALP 是能监测骨代谢微小变化最敏感的指标。越高的血清 BALP 水平提示更高得骨转换,将消耗成骨细胞的再生能力,加速成骨细胞的凋亡,导致微骨折不能修复,增加再骨折发生[8]。本文 Pearson 相关分析显示血清 BALP 水平与 BMD-T 值呈负相关(r = -0.573, P = 0.034)。因此,BALP 与 BMD 两者结合可能具有更好的预测意义。

本研究样本数相对较少,尚需大样本、多中心调查。我们随访时间为 4 年,而骨质疏松性骨折随时间的进展,再发骨折风险明显增加[9]。因此,对于更长远预测骨折再发生率,有待进一步随访观察。此外反映骨代谢的标志物如 I 型胶原 C 端肽(CTX)、I 型胶原交联氨基末端肽(NTX)、骨钙素(OC)、25-羟基维生素 D3、抗酒石酸酸性磷酸酶

(TRACP)等,其预测价值尚需进一步证实。

总之,骨质疏松骨折患者易发生再骨折,检测骨折后血清 BALP 水平是简单有效的指标。对于预测患者骨折再发生率具有重要的临床意义。

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