·临床研究·

高敏C-反应蛋白、白细胞介素-6、溶血磷脂酸及D-二聚体与下肢骨折后深静脉血栓形成的相关性研究

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【摘 要】 **目的** 分析高敏C-反应蛋白(hs-CRP)、白细胞介素-6(IL-6)、溶血磷脂酸(LPA)及D-二聚体(D-Dimer)与下肢骨折后深静脉血栓形成(DVT)的相关性,探讨他们在下肢骨折后DVT中的作用及机制。**方法** 选取海南西部中心医院收治的下肢骨折患者156例,根据术后是否发生DVT将其分为2组:DVT组($n=44$)和非DVT组($n=112$)。监测患者术前1天、术后第1、3、5天的hs-CRP、IL-6、LPA及D-Dimer水平变化。采用SPSS 19.0统计软件进行统计学分析。应用受试者工作特征(ROC)曲线分析术后各时间点hs-CRP、IL-6、LPA及D-Dimer诊断DVT的价值。Pearson相关分析hs-CRP、IL-6、LPA及D-Dimer的相关性。**结果** DVT组术后第1、3、5天的hs-CRP、IL-6、LPA及D-Dimer水平均显著高于非DVT组($P<0.05$)。DVT组术后第3、5天的hs-CRP、IL-6、LPA及D-Dimer水平均显著高于第1天($P<0.05$),且DVT组术后第5天的hs-CRP、IL-6、LPA及D-Dimer水平显著高于第3天($P<0.05$)。非DVT组术后第5天的hs-CRP、IL-6、LPA及D-Dimer水平均显著低于第1天和第3天($P<0.05$)。ROC曲线显示,术后第3天4项联合诊断DVT的AUC(95% *CI*)[0.961(0.896~0.994)]最高,其敏感度和特异度分别为96.8%和90.2%;在单项检测中,术后第3天D-Dimer水平诊断DVT的AUC(95% *CI*)[0.892(0.833~0.952)]较好,其敏感度和特异度分别为84.6%和87.3%。相关分析显示,DVT患者术后第3天hs-CRP与D-Dimer相关性最好($r=0.826$,$P<0.001$)。**结论** hs-CRP、IL-6、LPA及D-Dimer是预测DVT形成的良好指标,术后第3天4项联合诊断DVT的价值较高。

【关键词】 静脉血栓形成;高敏C-反应蛋白;白细胞介素-6;溶血磷脂酸;D-二聚体
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Correlation of high-sensitivity C-reactive protein, interleukin-6, lysophosphatidic acid and D-dimer with formation of deep venous thrombosis after lower limb fracture

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【Abstract】 **Objective** To analyze the correlation of serum levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), lysophosphatidic acid (LPA) and D-dimer with deep venous thrombosis (DVT) after lower limb fracture, and to explore their roles and underlying mechanism in the formation. **Methods** A total of 156 patients with lower limb fracture admitted in our hospital were enrolled in this study. According to whether DVT occurred after operation, they were divided into DVT group ($n=44$) and non-DVT group ($n=112$). The serum levels of hs-CRP, IL-6, LPA and D-dimer were monitored at 1 d before and in 1, 3 and 5 d after operation. SPSS statistics 19.0 was used for statistical analysis. The receiver operating characteristic (ROC) curve was used to analyze the values of hs-CRP, IL-6, LPA and D-dimer in the diagnosis of DVT at various time points after operation. Pearson correlation analysis was employed to analyze the correlation among above indicators. **Results** The serum levels of hs-CRP, IL-6, LPA and D-dimer at 1, 3 and 5 d after operation were significantly higher in the DVT group than in the non-DVT group ($P<0.05$). In the DVT group, the levels of these indicators were notably increased with time elapsing after operation ($P<0.05$). While in the non-DVT group, the levels on the 5th day were obviously lower than those on the 1st and 3rd days ($P<0.05$). The ROC curve analysis showed that the area under ROC curve (AUC=0.961, 95% *CI* 0.896-0.994) for DVT diagnosis when the 4 indicators were combined together was the highest on the 3rd day after operation, with sensitivity of 96.8% and specificity of 90.2%. In the test of single indicator, the level of D-dimer on the 3rd day was best for DVT diagnosis with AUC of 0.892(95% *CI* 0.833-0.952), and sensitivity of 84.6% while specificity

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of 87.3%. Correlation analysis indicated that the hs-CRP level was well correlated with that of D-dimer on the 3rd day after operation in the DVT patients ($r=0.826$, $P<0.001$). **Conclusion** hs-CRP, IL-6, LPA and D-dimer are good indicators to predict the formation of DVT, and the value of combined diagnosis of DVT is quite higher on the 3rd day after operation.

【**Key words**】 venous thrombosis; high-sensitivity C-reactive protein; interleukin-6; lysophosphatidic acid; D-dimer

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深静脉血栓形成(deep vein thrombosis,DVT)是下肢骨折术后常见的并发症,其救治的难度大,病死率较高,对患者生命健康构成极大的威胁[1]。近年来的研究表明,高敏C-反应蛋白(high sensitivity C-reactive protein,hs-CRP)水平升高可促进血栓形成,在DVT的发生、发展过程中发挥着重要作用[2]。白细胞介素6(interleukin-6,IL-6)可诱导纤维蛋白原、凝血因子等激活凝血过程,导致高凝状态,进而促进血栓形成[3]。溶血磷脂酸(lysophosphatidic acid,LPA)是一种多功能的磷脂信使,是血栓形成早期过程的释放物[4]。D-二聚体(D-Dimer)是反映体内血液高凝和纤溶亢进的标志物,对血栓形成性疾病具有早期诊断价值[5]。本研究通过检测下肢骨折后DVT患者的hs-CRP、IL-6、LPA及D-Dimer水平,探讨他们在DVT中的作用及临床意义,旨在为DVT的早期诊断及防治提供依据。

1 对象与方法

1.1 研究对象

选取2015年1月至2017年6月海南西部中心医院收治并行手术治疗的下肢骨折患者156例,其中男性97例,女性59例,年龄(63.5±6.4)岁,股骨干骨折64例,股骨颈骨折34例,骨盆骨折32例,胫、腓骨骨折26例。入选标准:(1)病历资料完整,受伤情况明确;(2)下肢骨折时间为1周内;(3)未接受过抗血小板聚集或抗凝治疗。排除排除:(1)病理性骨折或非首次创伤;(2)既往有血栓病史或超声明确DVT;(3)长期服用抗凝药物;(4)合并严重的心、肝、肺、肾脏功能不全。本研究由本院伦理委员会批准(批准号:2016AB07058036),且患者或家属均签署了知情同意书。

1.2 方法

1.2.1 分组方法 本研究为前瞻性研究,采用静脉彩色多普勒超声检查作为DVT检查的主要方法,所有患者均于手术前1 d及术后14 d内行静脉彩色多普勒超声检查,DVT的诊断参照DVT的诊断和治疗指南(第3版)[6]。根据术后14 d内是否发生DVT将患者分为2组:DVT组($n=44$)和非DVT组($n=112$)。术前记录患者的性别、年龄、体质量指数(body mass index,BMI)及基础疾病等。

1.2.2 观察指标 所有患者均于术前1天、术后第1、3、5天空腹采集静脉血,分别检测hs-CRP、IL-6、LPA及D-Dimer水平。采用免疫比浊法检测血清hs-CRP(罗氏全自动生化分析仪及配套试剂);酶联免疫吸附试验检测血清IL-6及LPA(试剂盒购自深圳晶美生物技术有限公司);免疫比浊法检测血浆D-Dimer(SSJ-2-2多功能免疫检测仪及配套试剂)。

1.3 统计学处理

采用SPSS 19.0统计软件进行统计学分析。计量资料用均值±标准差($\bar{x}\pm s$)表示,2组间比较采用t检验,组内比较采用重复测量的方差分析。计数资料以百分率表示,2组间比较采用χ^2检验。绘制受试者工作特征(receiver operating characteristic,ROC)曲线分析hs-CRP、IL-6、LPA及D-Dimer对DVT的诊断价值,曲线下面积(area under ROC curve,AUC)比较采用Z检验。相关性分析采用Pearson相关分析。$P<0.05$为差异有统计学意义。

2 结 果

2.1 2组患者一般资料比较

2组患者的性别、年龄、BMI、高血压史、糖尿病史、术前hs-CRP、IL-6、LPA及D-Dimer水平比较,差异均无统计学意义($P>0.05$;表1)。

2.2 2组患者术后各时间点hs-CRP、IL-6、LPA及D-Dimer水平比较

DVT组术后第1、3、5天的hs-CRP、IL-6、LPA及D-Dimer水平均显著高于非DVT组,差异有统计学意义($P<0.05$)。DVT组术后第3、5天的hs-CRP、IL-6、LPA及D-Dimer水平均显著高于第1天($P<0.05$),且DVT组术后第5天的hs-CRP、IL-6、LPA及D-Dimer水平均显著高于第3天($P<0.05$)。非DVT组术后第5天的hs-CRP、IL-6、LPA及D-Dimer水平均显著低于第1天和第3天($P<0.05$;表2)。

2.3 术后各时间点hs-CRP、IL-6、LPA及D-Dimer诊断DVT的价值

术后第1天,4项联合诊断DVT的AUC(95%*CI*)是0.858(0.802~0.920),显著优于hs-CRP、IL-6、LPA及D-Dimer,差异均有统计学意义($Z=6.873$、7.426、9.217、5.214,$P<0.05$)。术后第5天,

表 1 基线资料比较

Table 1 Comparison of baseline data between two groups

Item	Non-DVT group (n = 44)	DVT group (n = 112)	χ^2/t	P value
Gender(male/female, n)	28/16	69/43	0.055	0.814
Age(years, $\bar{x} \pm s$)	61.84 ± 6.52	65.28 ± 6.73	1.815	0.104
BMI(kg/m^2, $\bar{x} \pm s$)	23.57 ± 3.74	23.28 ± 3.62	0.316	0.672
History of hypertension[n(%)]	11(25.0)	33(29.5)	0.311	0.577
History of diabetes[n(%)]	6(13.6)	21(18.8)	0.577	0.447
Preoperative hs-CRP(mg/L, $\bar{x} \pm s$)	7.14 ± 1.48	7.36 ± 1.62	0.914	0.325
Preoperative IL-6(ng/L, $\bar{x} \pm s$)	16.37 ± 3.19	18.24 ± 3.86	0.692	0.402
Preoperative LPA(μmol/L, $\bar{x} \pm s$)	2.08 ± 0.61	2.16 ± 0.68	0.750	0.371
Preoperative D-Dimer(mg/L, $\bar{x} \pm s$)	0.34 ± 0.12	0.39 ± 0.15	1.216	0.208

DVT: deep vein thrombosis; BMI: body mass index; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; LPA: lysophosphatidic acid

表 2 2 组患者术后各时间点 hs-CRP、IL-6、LPA 及 D-Dimer 水平比较

Table 2 Comparison of hs-CRP, IL-6, LPA and D-Dimer between the two groups at different time points after operation

($\bar{x} \pm s$)

Item	Non-DVT group (n = 44)	DVT group (n = 112)	t	P value
hs-CRP(mg/L)				
1st day	8.36 ± 2.14	10.62 ± 2.83$^{\#}$	4.105	0.021
3rd day	8.17 ± 1.92	16.74 ± 3.61*	10.247	<0.001
5th day	5.06 ± 1.25$^{*\#}$	19.85 ± 4.37$^{*\#}$	14.813	<0.001
IL-6(ng/L)				
1st day	25.63 ± 4.28	32.81 ± 5.72$^{\#}$	3.874	0.036
3rd day	28.75 ± 4.61	48.93 ± 7.63*	5.158	0.006
5th day	19.24 ± 3.91$^{*\#}$	60.82 ± 9.52$^{*\#}$	9.874	<0.001
LPA(μmol/L)				
1st day	2.58 ± 0.64	5.13 ± 1.27$^{\#}$	4.463	0.012
3rd day	2.74 ± 0.81	6.83 ± 1.74*	9.726	<0.001
5th day	1.83 ± 0.52$^{*\#}$	9.14 ± 2.28$^{*\#}$	11.763	<0.001
D-Dimer(mg/L)				
1st day	2.41 ± 0.53	3.65 ± 0.72$^{\#}$	4.326	0.015
3rd day	2.48 ± 0.56	4.28 ± 0.83*	12.417	<0.001
5th day	0.52 ± 0.18$^{*\#}$	5.17 ± 0.96$^{*\#}$	18.264	<0.001

DVT: deep vein thrombosis, hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; LPA: lysophosphatidic acid. Compared with 1st day after operation in the same group, $^{*}P < 0.05$; compared with 3rd day after operation in the same group, $^{\#}P < 0.05$

4 项联合诊断 DVT 的 AUC(95%*CI*)是 0.907(0.844 ~ 0.961),显著优于 hs-CRP、IL-6、LPA 及 D-Dimer,差异均有统计学意义(Z = 5.549、8.625、8.108、4.827,P < 0.05)。术后第 3 天,4 项联合诊断 DVT 的 AUC(95%*CI*)是 0.961(0.896 ~ 0.994),显著优于hs-CRP、IL-6、LPA 及 D-Dimer,差异均有统计学意义(Z = 5.637、8.142、7.538、5.108,P < 0.05)。其中术后第 3 天 4 项联合诊断 DVT 的敏感度和特异度最好,分别为 96.8% 和 90.2%(表 3)。

2.4 术后第 3 天 hs-CRP、IL-6、LPA 及 D-Dimer 的相关性分析

Pearson 相关分析显示,DVT 患者术后第 3 天 hs-CRP 与 D-Dimer(r = 0.826, P < 0.001)、IL-6(r = 0.625, P < 0.001)和 LPA(r = 0.672, P < 0.001)呈正相关,D-Dimer 与 IL-6(r = 0.613, P < 0.001)和 LPA(r = 0.724, P < 0.001)呈正相关,IL-6 与 LPA 呈正相关(r = 0.553, P = 0.002)。

3 讨 论

DVT 指血液在病理状态下深静脉腔内聚集形成血栓,阻塞静脉管腔,导致静脉回流障碍的周围血管性疾病。下肢骨折患者由于失血致血容量减少、血流缓慢、止血及手术等,极易发生 DVT。尽管静脉血管造影是诊断 DVT 的金标准,但其存在创伤、费用高及操作不便等缺点,使其在临床应用中受限。因而寻找一种便于临床诊断 DVT 发生的常规指标,对 DVT 的救治有着重要意义。

近期的研究表明,DVT 形成是多基因多因素共同作用的结果,全身性炎症反应与DVT密切相关,

表3 术后各时间点 hs-CRP、IL-6、LPA 及 D-Dimer 诊断 DVT 的价值

Table 3 The value of hs-CRP, IL-6, LPA and D-Dimer in the diagnosis of DVT at various time points after operation

Item	SD	AUC	95% *CI*	*P* value	Sensitivity (%)	Specificity (%)	PP value (%)	NP value (%)
1st day								
hs-CRP	0.062	0.758	0.698 – 0.819	0.016	70.2	68.4	71.6	67.3
IL-6	0.065	0.704	0.646 – 0.765	0.031	67.3	63.5	67.2	64.0
LPA	0.068	0.683	0.617 – 0.745	0.042	64.2	61.3	63.8	62.5
D-Dimer	0.059	0.791	0.729 – 0.854	0.008	72.8	74.5	79.0	68.2
Four joint	0.048	0.858	0.802 – 0.920	<0.001	90.3	75.8	79.2	76.4
3rd day								
hs-CRP	0.044	0.874	0.817 – 0.934	<0.001	86.2	83.0	86.2	83.5
IL-6	0.056	0.805	0.747 – 0.864	0.003	75.2	76.4	79.3	71.8
LPA	0.051	0.836	0.776 – 0.898	<0.001	82.7	80.2	84.6	78.9
D-Dimer	0.041	0.892	0.833 – 0.952	<0.001	84.6	87.3	90.5	81.7
Four joint	0.023	0.961	0.896 – 0.994	<0.001	96.8	90.2	93.7	93.5
5th day								
hs-CRP	0.052	0.827	0.771 – 0.886	<0.001	79.5	78.4	81.3	76.2
IL-6	0.063	0.728	0.672 – 0.788	0.023	68.5	65.0	68.3	64.8
LPA	0.060	0.762	0.705 – 0.825	0.014	71.5	69.3	73.6	68.7
D-Dimer	0.046	0.865	0.807 – 0.928	<0.001	85.3	82.4	86.0	82.6
Four joint	0.037	0.907	0.844 – 0.961	<0.001	92.6	81.7	85.2	88.6

PP: positive predictive; NP: negative predictive; DVT: deep vein thrombosis, hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; LPA: lysophosphatidic acid

一些炎症因子及凝血因子可作为 DVT 的潜在危险因素[7,8]。hs-CRP 是一种非特异性的急性时相蛋白,可诱导单核细胞组织因子表达,激活补体系统,使血管内膜损伤,破坏凝血纤溶系统的平衡,从而促进血栓形成[9]。IL-6 主要通过增加组织因子、纤维蛋白原和凝血因子,激活内皮细胞,增加血小板量和减少凝血抑制因子,诱导机体形成高凝状态,进而增加血栓形成的风险[10]。LPA 是一种细胞膜的脂类衍生物,经过和 G 蛋白耦联受体相互作用对靶细胞的生物功能产生影响,进而引起多种生物学效应的发生。在血栓的形成起始过程中,LPA 发挥着关键的调节控制作用,LPA 可改变血小板的形态,聚集和活化血小板,进而促进血栓形成[11]。D-Dimer 作为交联纤维蛋白的特异降解产物,可特异性反映体内继发性纤溶亢进和高凝状态,因其具有检测快速、操作简便及价格低廉等优点,目前已被广泛应用于 DVT 的排除诊断以及复发风险的预测评估[12]。本研究显示,发生 DVT 患者术后第 1、3、5 天的 hs-CRP、IL-6、LPA 及 D-Dimer 水平均显著高于未发生 DVT 患者;而未发生 DVT 患者的 hs-CRP、IL-6、LPA 及 D-Dimer水平明显下降。提示术后 hs-CRP、IL-6、LPA 及D-Dimer水平持续升高的患者存在高凝状态和炎症反应,发生 DVT 风险较大。Yoo 等[13]研究表明,急性下肢深静脉血栓栓塞症患者血浆 C – 反应蛋白(C-reactive protein, CRP)水平明显升高,并证实炎症因子在 DVT 中起到了重要的作用。徐余兴等[14]研究发现,DVT 急性期血清 CRP 及 IL-6 水平明显升高,CRP 及 IL-6 在 DVT 急性期的发生和发展过程中发挥着重要作用。李玉妹等[15]研究显示,DVT 患者血浆中 LPA 水平明显高于健康者,随着治疗的进行其水平逐渐趋于正常值,LPA 水平变化与 DVT 的发展程度密切相关,可以预警血栓形成在体内的发生。另有研究发现,DVT 组术后第 1、3 天的 D-Dimer 水平明显高于非 DVT 组,动态监测 D-Dimer 水平变化有助于早期发现 DVT[16]。因此,下肢骨折患者术后hs-CRP、IL-6、LPA 及 D-Dimer 水平持续升高,应高度怀疑 DVT。

本研究应用 ROC 曲线分析各指标对 DVT 的诊断价值,结果显示术后不同时间点 hs-CRP、IL-6、LPA 及 D-Dimer 水平诊断 DVT 的敏感度和特异度不同,术后第 3 天 4 项联合诊断 DVT 的敏感度和特异度最好,分别为 96.8% 和 90.2%。在单项检测中,术后第 3 天 D-Dimer [AUC (95% *CI*): 0.892 (0.833 ~ 0.952)] 及 hs-CRP [AUC (95% *CI*): 0.874 (0.817 ~ 0.934)] 水平诊断 DVT 的 AUC 相对较好,其敏感度和特异度分别为 84.6% 和 87.3%,86.2% 和 83.0%。Jeong 等[17]研究表明,hs-CRP 水平升高越明显,血管内壁损伤越严重,发生血栓可能性越大,监测 hs-CRP 水平变化对早期诊断 DVT 有一定的临床价值。另有研究认为,临床上测定血浆 D-Dimer简便、迅速,对于 DVT 的诊断和预后评估具有重要意义[18]。但也有研究发现,术后 D-Dimer 水

平对 DVT 筛查诊断有一定价值,但准确性较低,其 AUC 值为 0.688[19]。分析其原因可能与 D-Dimer 的检测方法、试剂不同以及研究中确诊 DVT 方法不同等因素有关。各指标的相关性分析显示,DVT 患者术后第 3 天 hs-CRP、IL-6、LPA 及 D-Dimer 各指标间均呈正相关,其中 hs-CRP 与 D-Dimer 相关性最好($r=0.826$,$P<0.001$)。这进一步提示 hs-CRP、IL-6、LPA 及 D-Dimer 与下肢骨折患者术后 DVT 密切相关,4 项联合检测有助于提高 DVT 诊断的准确性。

综上所述,hs-CRP、IL-6、LPA 及 D-Dimer 可作为早期预测 DVT 的良好指标,术后第 3 天 4 项联合诊断 DVT 的价值较高。在实际工作中,临床医师可通过监测 hs-CRP、IL-6、LPA 及 D-Dimer 水平变化预测下肢骨折患者术后 DVT,并采取相应的治疗措施,及早控制病情,以降低患者的致残率及病死率。

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