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论著

联合检测 MPO、IL-6 和 hs-CRP 对冠心病危险分层的价值

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[**摘要**] **目的** 探讨联合检测3种血清炎性标志物对冠心病危险分层的价值。**方法** 对381例住院冠心病患者[急性心肌梗死(acute myocardial infarction, AMI)105例,不稳定性心绞痛(unstable angina pectoris, UAP)162例,稳定性心绞痛(stable angina pectoris, SAP)114例]和337例对照组[非冠心病患者(non-coronary heart disease, NCHD)187例和健康体检者150例],分别用选择抑制法检测血清髓过氧化物酶(myeloperoxidase, MPO)、微粒子化学发光免疫法检测白细胞介素-6(IL-6)、免疫荧光分析法检测超敏C反应蛋白(hs-CRP)。**结果** 急性冠脉综合征(acute coronary syndromes, ACS)组MPO、IL-6、hs-CRP均显著高于SAP、NCHD和健康组($P=0.000$)。MPO以AMI组最高,UAP组其次,SAP组再次,均明显高于NCHD和健康组($P<0.05$)。UAP组与SAP组IL-6水平差异无统计学意义($P>0.05$),但明显低于AMI组,高于NCHD及健康组($P<0.05$)。SAP、NCHD、健康体检者3组间hs-CRP无统计学差异,但显著低于UAP组及AMI组($P<0.05$)。AMI患者MPO多轻度升高(89.52%)并伴IL-6和hs-CRP重度升高(分别达90.48%和96.19%),UAP患者MPO多轻度升高(80.86%)并伴IL-6和hs-CRP中度升高(分别为67.28%和78.40%)。SAP患者MPO和hs-CRP轻度升高率分别为48.25%和53.51%,IL-6中度升高率为54.39%。单项炎性标志物对ACS的诊断灵敏度均较高,但特异性均不理想。串联分析3种炎性标志物诊断ACS的灵敏度、特异性、阳性预测值、阴性预测值和准确度分别为74.53%、79.82%、89.64%、57.23%和76.12%。**结论** 联合检测MPO、IL-6和hs-CRP可鉴别诊断冠心病不同病理阶段,提高诊断ACS的特异性和阳性预测值,有助于冠心病的危险分层。

[**关键词**] 髓过氧化物酶;白细胞介素-6;超敏C反应蛋白;冠心病;危险分层;急性冠脉综合征
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Value of risk stratification of coronary heart disease by combined determination of myeloperoxidase, interleukin-6 and high sensitivity C-reactive protein

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[**Abstract**] **Objective** To study the value of risk stratification of coronary heart disease (CHD) by combined detection of three inflammatory markers of myeloperoxidase (MPO), interleukin-6 (IL-6) and high sensitivity C-reactive protein (hs-CRP). **Methods** Serum levels of MPO, IL-6 and hs-CRP were respectively measured by selective repression method, microparticle chemiluminescent immunoassay and immunofluorescence analysis in 381 CHD patients [105 acute myocardial infarction (AMI), 162 unstable angina pectoris (UAP) and 114 stable angina pectoris (SAP)] and in 337 people who were set as controls [187 non-coronary heart disease (NCHD) and 150 healthy subjects]. **Results** Levels of MPO, IL-6 and hs-CRP in the acute coronary syndromes (ACS) group (AMI group + UAP group) were significantly higher than those in the SAP, NCHD and healthy groups ($P=0.000$). AMI patients had the highest activity of MPO, UAP patients were the second highest, and SAP patients were the third highest as compared with those of the NCHD and healthy groups ($P<0.05$). IL-6 levels of the UAP and SAP groups had no significant difference ($P>0.05$), but were significantly lower than those of the AMI group and higher than those of the NCHD and healthy groups ($P<0.05$). There was no significant difference in serum levels of hs-CRP among the SAP, NCHD and healthy groups, but their hs-CRP levels were significantly lower as compared with those of the UAP and AMI groups ($P<0.05$). About 89.52% AMI patients had slightly elevated MPO with severely elevated IL-6 and hs-CRP

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(90.48% and 96.19%, respectively). Of 80.86% UAP patients had slightly elevated MPO with moderately elevated IL-6 and hs-CRP (67.28% and 78.40%, respectively). SAP patients had slightly elevated of MPO and hs-CRP (48.25% and 53.51%) with moderately elevated IL-6 (54.39%). Each tested inflammatory marker had a high diagnostic sensitivity for ACS, but the specificity was unsatisfactory. The diagnostic efficiency of combined detection of the three inflammatory markers by serial tests for ACS were 74.53% for sensitivity, 79.82% for specificity, 89.64% for positive predictive value, 57.23% for negative predictive value and 76.12% for accuracy, respectively. **Conclusion** Combined detection of MPO, IL-6 and hs-CRP can be used in diagnosis of CHD at different pathological stages and improve the specificity and positive predictive value for diagnosing ACS, which is helpful for the risk stratification of CHD.

[**Key words**] myeloperoxidase; interleukin-6; high sensitivity C-reactive protein; coronary heart disease; risk stratification; acute coronary syndromes

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冠心病(coronary heart disease, CHD)是冠状动脉发生粥样硬化,发生痉挛、斑块破裂及血栓形成导致管腔阻塞,引起冠状动脉供血不足、心肌缺血或梗死的疾病[1]。研究发现,从稳定性心绞痛(stable angina pectoris, SAP)发展到不稳定性心绞痛(unstable angina pectoris, UAP)、再从UAP发展到急性心肌梗死(acute myocardial infarction, AMI)是由轻到重的连续变化病理过程,CHD不同病理阶段,其动脉粥样斑块具有不同的病理特征。易损斑块具有脂质中心大、纤维帽薄、平滑肌细胞少和胶原含量低、炎性细胞及炎性介质水平高等特点[2],是绝大多数急性冠脉综合征(acute coronary syndromes, ACS)共同的病理基础,ACS包括临床上难以截然区分的UAP和AMI[3]。相对于SAP,ACS更需积极干预以延缓或阻止严重冠脉事件发生。本研究检测不同病理阶段冠心病患者血清炎性标志物髓过氧化物酶(myeloperoxidase, MPO)、白细胞介素-6(interleukin-6, IL-6)和超敏C反应蛋白(high sensitivity C-reactive protein, hs-CRP)水平,并以性别、年龄匹配的非冠心病(non-coronary heart disease, NCHD)患者和健康体检者作为对照,以探索MPO、IL-6和hs-CRP在CHD不同病理阶段血清变化特点,以及串联分析该3种炎性标志物在CHD危险分层的价值,报告如下。

1 资料与方法

1.1 研究对象

1.1.1 CHD组 381例血清标本来源于四川省医学科学院·四川省人民医院2010年3-9月的住院CHD患者,其中男性262例,女性119例。吸烟者115例,非吸烟者266例。高龄组(≥51岁)223例,年龄51~91(64.7±8.7)岁;低龄组(<51岁)158例,年龄31~50(38.6±6.4)岁。均进行了冠脉造影检查,并按2007年美国ACC/AHA指南[4-6]诊断为AMI 105例,UAP 162例,SAP 114例。

1.1.2 对照组 337例对照者,包括本院同期187例NCHD患者和150例表观健康体检者,其中男性219例,女性118例。吸烟者89例,非吸烟者248例。高龄组185例,年龄51~88(63.9±7.5)岁;低龄组152例,年龄30~50(39.5±5.8)岁。187例NCHD患者为同期经冠脉造影检查排除CHD的患者。

1.1.3 研究对象排除标准 CHD组和对照组均排除陈旧性心肌梗死,急、慢性感染,脑血管、周围血管疾病(同时患有CHD除外),自身免疫性疾病,近期手术,恶性肿瘤,肝、肾功能疾患,血液病,营养不良及甲状腺功能减退等疾患。

1.2 材料

1.2.1 仪器 HITACHI 7080全自动生化分析仪(日本,日立公司);Beckman-Coulter ACCESS 2全自动微粒子化学发光免疫分析仪(美国,Beckman-Coulter公司);i-CHROMATM Reader免疫荧光分析仪(韩国,Boditech公司);J-6B低温离心机(美国,Beckman公司)。

1.2.2 主要试剂 MPO试剂及校准品,四川省新成生物科技有限责任公司,参考区间1.9~16.0 U/L;IL-6试剂及校准品,美国Beckman-Coulter公司配套产品,参考区间1.9~6.5 ng/L;hs-CRP试剂及校准品,韩国Boditech Diagnostics Inc配套产品,参考区间0~1.0 mg/L。MPO、IL-6、hs-CRP分别以高于参考区间上限1~2倍、2~4倍和>4倍定义为轻度、中度和重度升高。

1.3 样本收集和测定

各组均在入院24 h内清晨空腹采集(含促凝剂真空采血管)静脉血4.0 ml(AMI患者若需溶栓或紧急冠状动脉介入治疗则在治疗前取血,UAP、SAP及NCHD组均在冠状动脉造影前取血),30 min内分离血清(3 000 r/min低温离心10 min),-80 ℃低温冰箱。待样品收集齐后,将血清梯度解冻(-80℃→-20℃放置12 h→2~8 ℃放置3 h→回复至室温),离心取上清液。分别用选择抑制法测定MPO活性,用微粒子化学发光免疫分析法测定IL-6浓度,用免疫荧光法测定hs-CRP水平,操作均严格按使用说明书进行。

1.4 统计学分析

数据以$\bar{x}\pm s$表示,采用SPSS 16.0统计软件。计量资料两组均数比较用t检验;多组均数比较用F分析,当$P<0.05$时再进行两两比较的q检验;计数资料比较用χ^2检验。MPO、IL-6、hs-CRP诊断ACS的灵敏度(sensitivity, SE)、特异性(specificity, SP)、阳性预测值(positive predictive value, PPV)、阴性预测值(negative predictive value, NPV)和准确度(accuracy, AC)用矩阵决策法。

2 结果

2.1 CHD组与对照组一般情况比较

CHD组与对照组高龄、低龄年龄比较差异均无统计学意义。其他临床资料比较见表1。

表1 CHD组、NCHD组和健康组一般资料比较

项目	CHD组 (n=381)	NCHD组 (n=187)	健康组 (n=150)	χ^2值	P值
年龄≥51岁	223(58.53%)	106(56.68%)	79(52.67%)	1.51	>0.05
男性	262(68.77%)	117(62.57%)	102(68.00%)	2.27	>0.05
吸烟	115(30.18%)	46(24.60%)	43(28.67%)	1.93	>0.05
糖尿病	108(28.35%)	13(6.95%)	0	79.41	<0.001
高血压病	242(63.52%)	18(9.63%)	0	265.35	<0.001
高胆固醇血症	148(38.85%)	29(15.51%)	13(8.67%)	65.96	<0.001
高甘油三酯血症	87(22.83%)	14(7.49%)	7(4.67%)	39.09	<0.001
BMI					
无记录	67(17.59%)	15(8.02%)	0		
正常(<25)	122(32.02%)	87(46.52%)	121(80.67%)	102.58	<0.001
超重(25-30)	141(37.01%)	63(33.69%)	23(15.33%)	23.89	<0.001
肥胖(>30)	51(13.39%)	22(11.76%)	6(4.00%)	9.83	<0.01
危险因素个数[a]					
0	42(11.02%)	70(37.43%)	85(56.67%)	125.31	<0.001
1	78(20.47%)	58(31.02%)	40(26.67%)	8.01	<0.05
2	95(24.93%)	36(19.25%)	23(15.33%)	6.61	<0.05
≥3	166(43.57%)	23(12.30)	2(1.33%)	124.82	<0.001

a:分别以吸烟、糖尿病、高血压病、高胆固醇血症、高甘油三酯血症、BMI 6个指标异常计数危险因素个数

2.2 CHD各组与NCHD组及健康组3种炎性标志物检测比较

ACS组3种炎性标志物均显著高于SAP组、NCHD组和健康组,其中均以AMI组最高;SAP组MPO、IL-6均明显高于NCHD组和健康组,但hs-CRP无统计学差异;UAP组IL-6水平与SAP组无显著差异,见表2。

表2 CHD患者与对照组MPO、IL-6、hs-CRP检测结果比较($\bar{x}\pm s$)

组别	n	MPO(U/L)	IL-6(ng/L)	hs-CRP(mg/L)
急性冠脉综合征组	267	21.68±11.86[ace]	24.24±36.42[ace]	11.39±13.95[ace]
急性心肌梗死组	105	24.87±13.66[aceg]	46.62±49.56[aceg]	20.58±17.91[aceg]
不稳定性心绞痛组	162	19.61±10.04[acf]	9.73±8.10[ac]	5.43±4.83[ace]
稳定性心绞痛组	114	17.08±9.91[ac]	8.37±5.88[bd]	2.53±2.86
非冠心病组	187	11.14±3.70	3.04±1.45	1.72±1.37
健康组	150	10.16±3.01	2.25±1.07	1.49±1.31
F值		59.47	59.18	80.00
P值		0.000	0.000	0.000

a:$P<0.01$,b:$P<0.05$,与健康组比较;c:$P<0.01$,d:$P<0.05$,与非冠心病组比较;e:$P<0.01$,f:$P<0.05$,与稳定性心绞痛比较;g:$P<0.01$,与不稳定性心绞痛比较

2.3 CHD各组3种炎性标志物轻度、中度及重度升高发生率

AMI患者MPO多轻度升高(89.52%)并伴IL-6和hs-CRP重度升高(分别达90.48%和96.19%),UAP患者MPO多轻度升高(80.86%)并伴IL-6和hs-CRP中度升高(分别为67.28%和78.40%)。SAP患者MPO和hs-CRP轻度升高率分别为48.25%和53.51%,IL-6中度升高率为54.39%,见图1。

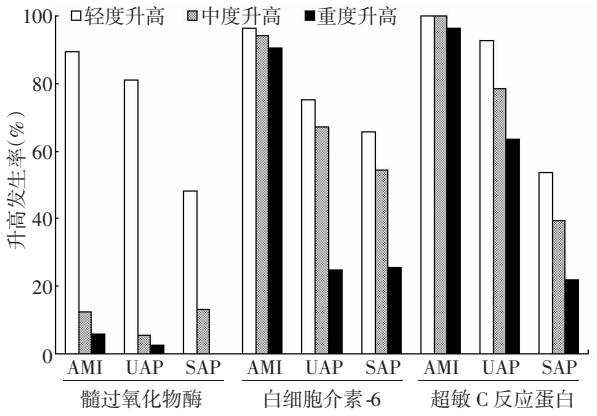


图1 CHD各组3种炎性标志物轻度、中度及重度升高发生率

2.4 串联分析MPO、IL-6、hs-CRP对ACS的诊断效率

如表3所示,单项炎性标志物对ACS的诊断灵敏度均较高,但特异性均不理想。以MPO>16 U/L、IL-6>6.5 ng/L、hs-CRP>1.0 mg/L判定为阳性,采用串联(系列)分析,将MPO、IL-6、hs-CRP进行不同组合,各组合中各项目均阳性才判定为阳性,串联分析3种炎性标志物,可明显提高诊断冠心病患者发生ACS的特异性和阳性预测值($P<0.01$)。

表3 MPO、IL-6、hs-CRP对CHD中ACS的诊断效率(%)

组合方式	ACS组 n	ACS组 阳性数	SAP组 n	SAP组 阳性数	SE	SP	PPV	NPV	AC
MPO	267	222	114	55	83.15[bc]	51.57[a]	80.14[a]	56.73[c]	73.75[d]
IL-6	267	220	114	65	82.40[bc]	42.98[a]	77.19[a]	51.04[c]	70.60[c]
hs-CRP	267	255	114	61	95.51[a]	46.49[a]	80.70[a]	81.54[a]	80.84
MPO+IL-6	267	199	114	27	74.53	76.32	88.05	56.13	75.07
MPO+hs-CRP	267	219	114	34	82.02	70.18	86.56	62.50	78.48
IL-6+hs-CRP	267	218	114	46	81.65	59.65	82.58	58.12	75.07
MPO+IL-6+hs-CRP	267	199	114	23	74.53	79.82	89.64	57.23	76.12

a:$P<0.01$,b:$P<0.05$,与MPO+IL-6+hs-CRP比较;c:$P<0.01$,d:$P<0.05$,与hs-CRP比较

3 讨论

冠心病是心血管系统中最常见的疾病,其病理基础是动脉粥样硬化和血栓形成,易损斑块是引起冠心病急性发作(ACS和冠脉猝死)的冠状动脉斑块。研究证实,炎症反应在动脉粥样硬化的所有阶段均具重要作用,从脂质条纹形成到易损斑块破裂。炎性细胞(中性粒细胞、巨噬细胞、T淋巴细胞、肥大细胞等)在动脉粥样硬化早期病变中起支配地位,其效应分子加速病变进展,引起炎症激活导致易损斑块破裂,引发ACS[7]。越来越多的临床研究证据显示,冠心病病理事件与血清炎症标志物变化紧密相关,炎症标志物在冠心病诊断、危险分层、治疗及预测中均有重要价值[8-9]。

MPO是白细胞的功能和激活标志,为中性粒细胞、巨噬细胞分泌的含血红素辅基的血红素蛋白酶。临床和流行病学研究发现,MPO广泛参与动脉粥样硬化的病理过程:使高密度脂蛋白(high density lipoprotein, HDL)功能失调;催化低密度脂蛋白(low density

lipoprotein, LDL)氧化和氨基甲酰化,导致巨噬细胞对其吞噬增多;损伤载脂蛋白A1(apolipoprotein A1, ApoA1)转运胆固醇向细胞外流出的能力,促进细胞内脂质沉积及泡沫细胞的形成;加速组织损伤和影响粥样硬化斑块稳定性[10-11]。Zhang等[12]最早发现冠心病患者MPO水平明显高于对照组。Wainstein等[13]进一步研究表明MPO与CHD严重程度相关,在不稳定斑块有大量中性粒细胞和巨噬细胞浸润及炎性因子表达。本研究MPO以AMI组最高,UAP组其次,SAP组再次,均明显高于NCHD组和健康组,与上述研究发现相符合。

IL-6又称前炎性细胞因子,是一种作用广泛的细胞因子。其可诱导肝细胞合成CRP,导致宿主防御和组织损伤;激活巨噬细胞分泌趋化蛋白,募集单核细胞进入血管内膜下参与斑块形成;促进巨噬细胞表面LDL受体表达及对LDL的摄取,加速粥样斑块形成;刺激血管平滑肌细胞增生,促进冠脉血栓形成[14-15]。在一项长达6年的前瞻性研究中,Ridker等[16]发现IL-6每增加1个4分位数,发生AMI风险将增加38%,基线IL-6浓度处于最高4分位数者,发生AMI相对危险度是对照者的2.3倍。本研究发现,AMI组IL-6水平明显高于UAP和SAP组,UAP和SAP组明显高于NCHD及健康组,但UAP组与SAP组无显著性差异。提示检测IL-6有助于区别AMI与UAP及SAP,但不能鉴别诊断UAP与SAP。

C-反应蛋白(C-reactive protein, CRP)直接参与动脉粥样硬化斑块的形成过程:CRP与补体C1q结合激活补体途径,通过补体膜攻击位于动脉粥样硬化前期病变上的复合物;CRP刺激巨噬细胞合成IL-6、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)等促炎分子[17-18];CRP还诱导血管细胞黏附分子-1(vascular cell adhesion molecule-1, VCAM-1)和细胞间黏附分子-1(intercellular adhesion molecule-1, ICAM-1)在内皮细胞表达,介导巨噬细胞对LDL的摄取[19]。临床研究证实hs-CRP与冠心病严重程度和急性冠脉事件独立相关[20]。Arima等[21]通过对2 589例40岁以上普通人群进行长达14年的前瞻性队列研究,发现hs-CRP处于最高4分位数者发生冠心病风险比是最低4分位数的2.98倍。本研究发现SAP、NCHD、健康体检者3组间hs-CRP无统计学差异,但均显著低于UAP组及AMI组,表明检测hs-CRP有助于ACS的评判,但在冠心病患者SAP病理阶段,变化并不明显。

从表3可见,MPO、IL-6及hs-CRP单项炎性标志物诊断冠心病患者发生ACS的灵敏度均较高(>82%),但特异性均不理想,仅分别为51.57%、42.98%和46.49%。串联分析3种炎性标志物诊断冠心病患者发生ACS的SE、SP、PPV、NPV和AC分别为74.53%、79.82%、89.64%、57.23%和76.12%。通过串联试验,SE虽有一定降低,但SP和PPV却明显升高($P<0.01$)。本研究中,AMI患者MPO多轻度升高(89.52%)并伴IL-6和hs-CRP重度升高(分别达90.48%和96.19%),UAP患者MPO多轻度升高(80.86%)并伴IL-6和hs-CRP中度升高(分别为67.28%和78.40%)。SAP患者MPO和hs-CRP轻度升高率仅分别为48.25%和53.51%,IL-6中度升高率为54.39%。

综上所述,ACS患者3种血清炎性标志物均显著高于SAP、NCHD和健康组($P=0.000$),并均以ACS中的AMI组为最高。冠心病不同病理阶段各炎性标志物血清水平具有不同的变化特征:AMI患者MPO多轻度升高并伴IL-6和hs-CRP重度升高,UAP患者MPO多轻度升高并伴IL-6和hs-CRP中度升高。单项炎性标志物对ACS的诊断灵敏度较高,但特异性均较低。采用串联分析MPO、IL-6和hs-CRP可较好地鉴别诊断冠心病不同病理阶段,提高诊断ACS的特异性和阳性预测值,有助于冠心病的危险分层。

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经验交流

18例高危胸段食管异物急诊手术治疗临床分析

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[**关键词**] 食管异物;胸部;外科手术
[**中图法分类号**] R655.4 [**文献标志码**] B

食管异物是耳鼻喉科最常见的急症之一,其发病率占耳鼻喉科疾病的18.3%[1]。对于多数食管异物,都能通过内窥镜安全取出,但仍有一些镜下不能取出或取出失败的异物需要外科手术治疗。我科自2000年2月至2009年9月对18例高危胸段食管异物急诊剖胸手术取出,效果良好。现报告如下。

1 资料与方法

1.1 一般资料

本组18例,男性10例,女性8例;年龄18~84岁,平均48.5岁,其中84岁1例。病程4 h至5 d。就诊时均有不同程度吞咽疼痛。明确异物吞服史15例,不明3例,伴发热3例。常规胸正位片+食管X线碘油造影确诊15例,合并食管穿孔2例,1例异物不明但显示食管下段造影剂向左胸外溢;胃镜下确诊2例,胸部CT确诊食管中段异物穿透食管壁并刺入右主肺动脉、合并纵隔气肿1例。异物类型:义齿4例,动物骨头6例,鱼刺4例,金属别针2例,领带夹1例,金属剃须刀片1例。异物部位:胸中上段14例,下段4例。

1.2 手术方法

所有患者均在气管内插管及静脉复合麻醉下手术。1例胸上段食管异物为金属义齿84岁高龄患者采用左颈前切口;13例异物位于食管胸中上段者右侧剖胸手术取出;4例位于下胸段者左侧剖胸。术中轻柔食指探摸食管异物部位,必要时用食管镜或胃镜进一步明确异物所在部位。找到异物后在异物部位稍下正常食管壁缝2根牵引线,切开食管。取出异物后1#丝线连续缝合食管黏膜、分层间断缝合食管肌层,加带蒂胸膜瓣覆盖。合并食管壁穿孔炎症水肿较重或纵隔感染炎症较重者,取出异物后,不修补食管壁,创面稍事修剪清创,予以食管内T管引流、胃造瘘术。所有患者均予以胸腔稀释碘伏反复浸泡冲洗,留置内径较粗胸腔引流管及鼻胃管。

1.3 术后处理

术后早期禁饮食、鼻胃管负压引流、胸膜腔闭式引流,规范抗感染、胃肠内外营养支持。所有患者术后门诊随访。

2 结果

11例内窥镜下取异物失败,转为急诊剖胸手术,7例异物为金属剃须刀片、金属别针、领带夹或鱼刺刺入右肺动脉或合

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