血清肿瘤标志物的参考变化值和参考变化因子应用比较研究

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摘 要:目的 探讨常规肿瘤标志物参考变化值(RCV)和参考变化因子(RCF)单向、双向分别在不同概率下($P<0.05$,$P<0.01$)的应用比较研究。**方法** 根据参考变化值(RCV)及参考变化因子(RCF)公式计算常规肿瘤标志物在不同概率下的数值。**结果** 常规肿瘤标志物的RCV(单向,双向在$P<0.05$时)分别为AFP(30.99%,36.81%),CEA(30.48%,36.21%),CA125(64.30%,76.39%),CA153(15.68%,18.62%),CA199(40.60%,48.23%)和tPSA(43.19%,51.30%)。RCV(单向,双向在$P<0.01$时)分别为AFP(43.76%,48.45%),CEA(43.05%,47.67%),CA125(90.81%,100.55%),CA153(22.14%,24.52%),CA199(57.33%,63.48%)和tPSA(60.99%,67.53%)。RCF(单向,双向在$P<0.05$时)$RCF_{UP-DOWN}$分别为AFP(1.36%,0.74%,1.44%,0.69%),CEA(1.36%,0.74%,1.44%,0.69%),CA125(1.90%,0.53%,2.15%,0.47%),CA153(1.17%,0.85%,1.2%,0.83%),CA199(1.50%,0.67%,1.62%,0.62%)和tPSA(1.54%,0.65%,1.67%,0.60%)。RCF(单向,双向在$P<0.01$)$RCF_{UP-DOWN}$分别为AFP(1.55%,0.65%,1.62%,0.62%),CEA(1.54%,0.65%,1.61%,0.62%),CA125(2.48%,0.40%,2.73%,0.37%),CA153(1.25%,0.80%,1.28%,0.78%),CA199(1.77%,0.56%,1.89%,0.53%)和tPSA(1.84%,0.54%,1.96%,0.51%)。**结论** 在相同概率下,双侧RCV值高于单侧,而RCF值变化不大。参考变化值RCV仅适用两次检测结果之间的分析,在多于两个连续检测结果时应使用RCF,当RCF作为临床决策工具时可对首诊病人做出正面和负面的预测值,为临床诊断提供科学依据。

关键词: 肿瘤标志物;参考变化值;参考变化因子

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Comparative Study on the Reference Change Value and Reference Change Factor of Serum Tumor Markers

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Abstract: Objective To conduct both aunidirectional and bidirectional ($P<0.05$, $P<0.01$) comparison between with reference change value(RCV) and reference change factor (RCF) of conventional tumor markers. **Methods** The values of conventional tumor markers at different probabilities were calculated according to the RCV and RCF formulas. **Results** The RCV values of six conventional tumor markers (unidirectional and bidirectional at $P<0.05$) were calculated as follows: AFP (30.99%, 36.81%), CEA (30.48%, 36.21%), CA125 (64.30%, 76.39%), CA153 (15.68%, 18.62%), CA199 (40.60%, 48.23%) and tPSA (43.19%, 51.30%), respectively. The RCV values of thesixtumor markers were also calculated (unidirectional and bidirectional at $P<0.01$): AFP (43.76%, 48.45%), CEA (43.05%, 47.67%), CA125 (90.81%, 100.55%), CA153 (22.14%, 24.52%), CA199 (57.33%, 63.48%) and tPSA (60.99%, 67.53%). The $RCF_{UP-DOWN}$ of the six conventional tumor markers (unidirectional and bidirectional at $P<0.05$) were calculated as follows: AFP (1.36%, 0.74%, 1.44%, 0.69%), CEA (1.36%, 0.74%, 1.44%, 0.69%), CA125 (1.90%, 0.53%, 2.15%, 0.47%), CA153 (1.17%, 0.85%, 1.2%, 0.83%), CA199 (1.50%, 0.67%, 1.62%, 0.62%) and tPSA (1.54%, 0.65%, 1.67%, 0.60%), respectively. The $RCF_{UP-DOWN}$ of six conventional tumor markers (unidirectional and bidirectional at $P<0.01$) were AFP (1.55%, 0.65%, 1.62%, 0.62%), CEA (1.54%, 0.65%, 1.61%, 0.62%), CA125 (2.48%, 0.40%, 2.73%, 0.37%), CA153 (1.25%, 0.80%, 1.28%, 0.78%), CA199 (1.77%, 0.56%, 1.89%, 0.53%) and tP-

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SA(1.84%,0.54%,1.96%,0.51%), respectively. **Conclusion** Under the same probability, the RCV value on both sides was higher than that on one side, while the RCF value changes little. RCV is only applicable to the analysis between two test results, and should be used when there are more than two consecutive test results. When RCF is used as a clinical decision-making tool, positive and negative predictive values can be made for the first patient to provide scientific basis for clinical diagnosis.

Keywords: tumor markers; reference change value; reference change factor

临床医生监测个体病人的疾病发展过程,最好的办法就是把病人前后一系列检测结果进行比较。而检测结果的变化除了疾病本身所导致的原因外还包括了个体内生物学变异(within-subject biological variation, CV_I)和分析变异(analytical variation, CV_A)[1]。目前临床上推荐使用参考变化值(reference change value, RCV)来评估同一患者两次检测结果的变化是否存在显著性差异,然而在实际工作中往往会存在一系列两次以上的测定值,这时应用RCV会增加假阳性结果。为了解决这个问题,近来国际上采用参考变化因子(reference change factor, RCF)来评价两次以上结果的差异[2]。本研究通过评估常规肿瘤标志物的RCV和RCF计算数值,为临床判读常规肿瘤标志物结果提供科学的依据。

1 材料与方法

1.1 资料来源 分析变异(CV_A)来自于本实验室(2019年1~6月)室内质控累计值。常规肿瘤标志物(AFP,CEA,CA125,CA153,CA199,tPSA)个体内及个体间生物学变异(CV_I及CV_G)来自于2014年Westgard网站生物变异数据库[3]。

1.2 仪器和试剂 雅培i2000SR化学发光微粒子分析仪,试剂及校准品均由雅培有限公司提供。质控物为伯乐高、低双值肿瘤质控品(批号64641,64642)。

1.3 方法 分别计算常规肿瘤标志物(AFP,CEA,CA125,CA153,CA199,tPSA)在不同概率下($P<0.05$,$P<0.01$)时的参考变化值(RCV)和参考变化因子(RCF)单向、双向的数值。

个体指数计算公式:$\text{Ⅱ} = CV_I/CV_G$

个体内生物变异:$CV_I = (CV_{I+A}^2 - CV_A^2)^{1/2}$

RCV计算公式:$RCV = Z \times 2^{1/2} \times (CV_A^2 + CV_I^2)^{1/2}$

RCF上下限计算公式:$RCF_{UP=exp}(Z \times 2^{1/2} \times (CV_A^2 + CV_I^2)^{1/2}/100)$;$RCF_{DOWN} = 1/RCF_{UP}$。

公式中当单向概率取95%即$P<0.05$时Z分数查表取1.65。当单向概率取99%即$P<0.01$时Z分数查表取2.33。当双向概率取95%即$P<0.05$时Z分数查表取1.96。当双向概率取99%即$P<0.01$时Z分数查表取2.58。

2 结果

2.1 常规肿瘤标志物参考变化值(RCV)单向和双向计算值 见表1。

2.2 常规肿瘤标志物的参考变化因子(RCF)及RCF_{UP},RCF_{DOWN}的单向和双向计算值 见表2。

表1 常规肿瘤标志物RCV(单向、双向$P<0.05$,$P<0.01$)计算值

项目	CV_I(%)	CV_g(%)	Ⅱ	CV_A(%)	RCV(%) $P<0.05$ 单向	$P<0.05$ 双向	RCV(%) $P<0.01$ 单向	$P<0.01$ 双向
AFP	12.2	45.6	0.27	5.25	30.99	36.81	43.76	48.45
CEA	12.7	55.6	0.23	3.07	30.48	36.21	43.05	47.67
CA125	24.7	54.6	0.45	12.23	64.30	76.39	90.81	100.55
CA153	6.1	62.9	0.10	2.82	15.68	18.62	22.14	24.52
CA199	16.0	130.5	0.12	6.84	40.60	48.23	57.33	63.48
tPSA	18.1	72.4	0.25	3.88	43.19	51.30	60.99	67.53

表2 常规肿瘤标志物RCF及RCF_{UP},RCF_{DOWN}(单、双向$P<0.05$,$P<0.01$)计算值

项目	CV_I(%)	CV_A(%)	RCF(%) $P<0.05$ 单向 RCF_{UP}	RCF_{DOWN}	双向 RCF_{UP}	RCF_{DOWN}	RCF(%) $P<0.01$ 单向 RCF_{UP}	RCF_{DOWN}	双向 RCF_{UP}	RCF_{DOWN}
AFP	12.2	5.25	1.36	0.74	1.44	0.69	1.55	0.65	1.62	0.62
CEA	12.7	3.07	1.36	0.74	1.44	0.69	1.54	0.65	1.61	0.62
CA125	24.7	12.23	1.90	0.53	2.15	0.47	2.48	0.40	2.73	0.37
CA153	6.1	2.82	1.17	0.85	1.20	0.83	1.25	0.80	1.28	0.78
CA199	16.0	6.84	1.50	0.67	1.62	0.62	1.77	0.56	1.89	0.53
tPSA	18.1	3.88	1.54	0.65	1.67	0.60	1.84	0.54	1.96	0.51

3 讨论

检测结果的变化是临床医生作出医疗决策的重要依据,它的变化会受到疾病本身的情况、分析前变异(preanalysis variation,CV_P)、分析变异(CV_A)和个体内生物学变异(CV_I)的影响,从表1中可以看出当CV_A和个体指数II($II = CV_I/CV_G$)越大时,会使检测人群的肿瘤标志物假阳性率越高[4]。在Harris EK探讨的个体化研究中指出,个体指数II大于1.4时,单个个体的参考值分布几乎涵盖整个个体间变异(between-subject biological variation,CV_G)的区间;个体指数(II)低于0.6时任何项目的参考变值只在个体间变异(CV_G)的小范围波动。以人群为基础的参考区间对个体连续变化评估是有限的,此时的参考范围价值不大[5]。为了降低假阳性率,实验室内部应做好质量控制管理,把室内分析变异(CV_A)做地更小,最好达到行内标准的最佳或最适标准限,同时引入参考变化值(RCV)数据模型用于评估检测结果的变化,如果两次测定结果的差值大于RCV的固有变异值之和,其差值显示具有临床意义[6]。对同一个体单次测定结果与前一次结果的变化结果的解释应基于生物学变异而不是基于群体参考范围[7]。所以临床医生不能仅使用传统参考值作为临床诊断与健康个体的管理。而应使用个体内参考变化值RCV的变化区间作为疾病与健康管理的辅助手段从而避免临床误诊的发生。从表1中还可以计算出两个单向与双向总共四个不同的RCV值,若临床仅重视检验结果的单向增高或降低,则可选择单向的RCV值;若临床医生对检验结果的增高和降低都给予重视,则可选择双向的RCV值。其为临床医生诊断提供更为丰富的策略。

从表2中可以看出当一个肿瘤患者首诊后,到第二次随访时,病人参考变化值可以在单向/双向上下限很大一个范围内波动。用病人的第一个结果乘以这些参考变化因子(RCF),如结果在这个区间范围之外,那么此结果可被看作有临床意义[8]。例如一个病人的肿瘤标志物CEA首诊检测值是9.15ng/ml。如第二次测量值在参考变化因子(RCF)下限×9.15ng/ml与RCF上限×9.15ng/ml,$Z = 1.65$,$P < 0.05$,单向测量值范围内(6.77~12.44ng/ml)或参考变化因子$Z = 1.96$,$P < 0.05$,双向测量值范围内(6.31~13.18 ng/ml)波动时,测量值的变化结果在统计学上没有差异。但是,对于超出此范围的测量值,此时的结果被认为发生了一个重大的变化,提示临床医生应仔细分析患者的临床情况对患者作出正确的诊治,防止风险的发生。可见参考变化因子(RCF)单向和双向上下限预测因子可用于对首诊肿瘤病人作出正面和负面的预测值,同时也适宜健康人群的个人参考值的管理。

因此,参考变化值(RCV)和参考变化因子(RCF)具有疾病的诊断、监测及健康人群个体参考值的管理等优点[6],尤其在监测肿瘤患者时RCV和$RCF_{UP-DOWN}$还可当作临床诊断的工具[7],为临床判读检测结果提供更为科学的参考依据。

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