

·临床研究·

影响超低出生体重儿住院期间死亡风险评估的相关因素分析

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摘要:【目的】探究影响不同新生儿危重评分对超低出生体重儿(ELBWI)死亡风险准确预测的相关因素。【方法】自2019年1月1日至2021年1月1日南京医科大学附属儿童医院和东南大学附属中大医院溧水分院新生儿科收治的ELBWI 186例,经纳入和排除标准筛选后最终纳入125名ELBWI。其中死亡组47例、存活组78例。收集围生期一般资料以及新生儿急性生理学评分-II(SNAP-II)、新生儿急性生理学评分围生期补充-II(SNAPPE-II)、新生儿临床危险指数(CRIB)、新生儿临床危险指数-II(CRIB-II)以及国内开发的新生儿危重病例评分(NCIS)其包含的所有评分条目内容进行单变量、多变量统计,并绘制列线图及受试者工作曲线(ROC)进行分析。【结果】产后收缩压、最大吸入氧浓度、BE值和出生体重是影响ELBWI死亡风险准确评估的重要因素[收缩压OR值0.968,95%CI:0.938-0.999, $P=0.043$;最大吸入氧浓度OR值1.020,95%CI:1.006-1.034, $P=0.006$;BE的OR值0.868,95%CI:0.786-0.959, $P=0.005$;出生体重OR值0.994,95%CI:0.991-0.997, $P=0.000$],ROC示以上四者的综合曲线下面积0.71、95%可信区间0.610-0.799,优于CRIB评分。【结论】较低收缩压、较高吸入氧浓度、较大BE值、较小出生体重为影响ELBWI死亡风险准确评估的关键因素。在新评分的开发中,推荐将以上四者纳入评估条目可得到效率更优的ELBWI危重评分预测体系。

关键词:危重疾病评分;超低出生体重儿;死亡;影响因素;预测

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Analysis of Related Factors Affecting the Risk Assessment of Death during Hospitalization of Extremely Low Birth Weight Infants

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Abstract:【Objective】To explore the influencing factors of different scores on predicting death risk of extremely low birth weight infants (ELBWI).【Methods】A total of 186 cases of ELBWI admitted by the Children's Hospital affiliated to Nanjing Medical University and the Lishui Branch of the Affiliated Zhongda Hospital of Southeast University were admitted from January 1, 2019 to January 1, 2021, and 125 ELBWIs were finally included after screening by inclusion and exclusion criteria. There were 47 cases in the death group and 78 cases in the survival group. General data and the items of score for neonatal acute physiology version II (SNAP-II), simplified version of the score for neonatal acute physiology perinatal extension (SNAPPE-II), clinical risk index for babies (CRIB), clinical risk index for babies II (CRIB-II) and the national critical illness score (NCIS) were collected. Univariate and multivariate analysis was performed and nomogram

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was evaluated using receiver operating characteristic curve (ROC).【Results】It was found that systolic blood pressure, maximum inhaled oxygen concentration, BE value and birth weight were important factors in ELBWI mortality risk assessment [systolic blood pressure OR: 0.968, 95%CI: 0.938–0.999, $P=0.043$; maximum inhaled oxygen concentration OR: 1.020, 95%CI: 1.006–1.034, $P=0.006$; BE OR: 0.868, 95%CI: 0.786–0.959, $P=0.005$; birth weight OR: 0.994, 95%CI: 0.991–0.997, $P=0.000$]. ROC showed that the area under the curve of the above four variables is 0.71, and the 95% confidence interval is 0.610–0.799, which is better than CRIB score.【Conclusion】Lower systolic blood pressure, higher inhaled oxygen concentration, higher BE and lower birthweight are important influencing factors to predict the death risk of ELBWI. The above four items should be included in the newly developed score assessment to obtain a more effective ELBWI prediction system.

Key words: illness severity score; extremely low birth weight infants; death; influencing factor; prediction

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超低出生体质量儿(extremely low birth weight infant, ELBWI)由于其出生体质量低、胎龄小、脏器发育不成熟,故合并症发生率及死亡率较高^[1-2]。如何在住院期间甚至生后早期精确评估其预后、了解其死亡风险对于临床医师进行治疗干预及家长救治抉择有重要意义。迄今有多种新生儿危重评分在临床予以应用,如新生儿临床危险指数(clinical risk index for babies, CRIB)、新生儿临床危险指数-Ⅱ(clinical risk index for babies-Ⅱ, CRIB-Ⅱ)、新生儿急性生理学评分-Ⅱ(score for neonatal acute physiology version Ⅱ, SNAP-Ⅱ)、新生儿急性生理学评分围生期补充-Ⅱ(simplified version of the score for neonatal acute physiology perinatal extension, SNAPPE-Ⅱ)以及我国研制的新生儿危重病例评分(neonatal critical illness score, NCIS)^[3-7]。但上述评分研制于不同国家、不同时代,应用于不同胎龄、不同种族人群,故理论上有关其对ELBWI的最佳预测价值需进行仔细比较判别,本课题组在之前的研究中已发现虽然CRIB曲线下面积(area under curve, AUC)最大,但其预测价值仍有待提高,且各个评分AUC差异明显^[8],因此存在影响新生儿危重评分准确评估的多种关联因素。鉴于以上,本文重点寻求影响SNAP-Ⅱ、SNAPPE-Ⅱ、CRIB、CRIB-Ⅱ及NCIS五种临床常用评分对ELBWI死亡风险精确预测的相关因素并进行分析,以探寻哪些指标对于ELBWI死亡风险更具有重要价值,从而为未来构建更佳的ELBWI死亡风险的评分体系提供科学依据。

1 材料与方法

1.1 对象来源

回顾性分析南京医科大学附属儿童医院新生儿科和东南大学附属中大医院溧水分院儿科自2019年1月1日至2021年1月1日三年来收治的所有ELBWI。纳入标准:入院年龄小于生后1 h,胎龄小于32周,出生体质量小于1 000 g的患儿。入院24 h后放弃治疗出院死亡者亦统计入死亡病例。排除标准:CRIB、CRIB-Ⅱ、SNAP-Ⅱ、SNAPPE-Ⅱ以及我国NCIS评分指标资料不全者。

1.2 临床数据收集

所有研究对象汇总后由两人分别收集临床资料,并交由第三名研究者核对、录入。临床资料包含:基线资料(日龄、出生体质量、胎龄、性别、羊水性质、孕母感染情况、复苏及Apgar评分情况)、临床诊断(入院诊断及出院诊断)、SNAP-Ⅱ评分资料[细则含:平均动脉压、最低体温、动脉氧分压/吸入氧浓度(arterial partial pressure of oxygen/inhalation oxygen concentration, $\text{PaO}_2/\text{FiO}_2$)、PH值、惊厥、尿量;根据生后12 h内临床数据评分]、SNAPPE-Ⅱ评分资料(细则含:平均动脉压、最低体温、 $\text{PaO}_2/\text{FiO}_2$ 、PH值、惊厥、尿量、出生体质量、5 min Apgar评分、小于胎龄儿;根据生后12 h内临床数据评分)、CRIB评分资料[细则含:出生体质量、胎龄、先天畸形、最大碱剩余(base excess, BE)、最小吸入氧浓度、最大吸入氧浓度;根据生后12 h内临床数据评分]、CRIB-Ⅱ评分资料(细则含:出生体质量、胎龄、最大碱剩余、最低体温;根据生后

1 h内临床数据评分)以及NCIS评分资料(细则包含:心率、收缩压、呼吸、氧分压、PH值、血钠、血钾、血肌酐、血尿素氮、红细胞压积、胃肠道表现;根据生后24 h内临床数据评分)。

1.3 伦理

本回顾性研究经由研究主席单位南京医科大学附属儿童医院伦理委员会审批(NJCH202107071-1)。因回顾性研究设计,故免除知情同意。数据分析前已经由匿名处理。

1.4 统计学方法

本研究数据分析经由SPSS(17.0)和R语言(4.1)软件完成。首先针对五种评分不同条目进行存活组和死亡组组间比较、开展单变量分析。服从正态分布的定量数据应用均数±标准差($\bar{x} \pm s$)表示,两组间比较采用 t 或 t' 检验。偏态分布的定量数据应用中位数(四分位间距)[$M(P_{25} \sim P_{75})$]表示,两组间比较采用Wilcoxon秩和检验。定性数据采用频数(百分比)[$n(\%)$]表示,两组间比较采用Pearson卡方、校正卡方或Fisher检验。随后,针对单变量分析有统计学差异的变量($P < 0.05$),进一

步收集其进入二分类logistic回归(Forward: LR法)评价差异变量对死亡风险预测的贡献。然后,绘制列线图,具象化上述差异变量对死亡风险的预测价值。最后,绘制受试者工作曲线(receiver operating characteristic curve, ROC),收集曲线下面积(area under curve, AUC)、敏感度、特异度、95%可信区间等,对预测价值进行分析比较。以 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 死亡组与存活组一般资料分析

自2019年1月1日至2021年1月1日共收治ELBWI 186例,其中入院年龄大于等于1 h或胎龄大于等于32周者39例,各项评分所需资料不全者22例,经筛选后最终纳入125名ELBWI。其中死亡组47例(家长担心预后放弃死亡5例、经济原因放弃死亡3例、治疗中死亡39例)、存活组78例。经统计分析,死亡组与存活组在出生体质量、胎龄及Apgar评分差异有统计学意义($P < 0.05$;表1)。

表1 死亡组与存活组一般资料比较

Table 1 Comparison of general data between the death group and the survival group

[($\bar{x} \pm s$), $M(P_{25} \sim P_{75})$, $n(\%)$]

Variable	The survival group($n=78$)	The death group($n=47$)	$Z/t/\chi^2$	P
Admission age / h	0.52(0.14 ~ 0.66)	0.68(0.27 ~ 0.79)	-1.608	0.108
Birthweight/g	845.23±114.68	814.10±122.15	2.814	0.006
Gestational age/week	27.32±1.96	26.56±1.93	3.414	0.001
Male	32(41.03)	26(55.32)	1.745	0.186
Amniotic fluid turbidity	17	7	0.071	0.790
1 min Apgar	7.25±2.26	5.78±2.49	3.763	0.0003
5 min Apgar	8.62±1.71	7.79±1.69	2.755	0.006

2.2 影响超低出生体质量儿死亡风险的单变量分析

针对五种评分细则条目进行归纳、比较,结果收缩压、动脉血气酸碱度、CRIB-II评分BE值、最小吸入氧浓度、最大吸入氧浓度、CRIB评分BE值组间差异均有统计学意义(表2)。

2.3 影响超低出生体质量儿死亡风险的多变量分析

对上述单因素分析有统计学意义($P < 0.05$)的评分指标进一步进行logistic回归分析,发现收缩压、最大吸入氧浓度、CRIB评分BE值、出生体质量

对ELBWI死亡风险评估的贡献值更大[收缩压比值比(odds ratio, OR)值0.968, 95%CI: 0.938-0.999;最大吸入氧浓度OR值1.020, 95%CI: 1.006-1.034; CRIB评分中BE的OR值0.868, 95%CI: 0.786-0.959;出生体质量OR值0.994, 95%CI: 0.991-0.997],其余包括胎龄、5 min Apgar评分、动脉血气PH最异常值、CRIB-II评分BE值、最小吸入氧浓度等进入回归分析后显示差异无统计学意义(表3)。

表2 超低出生体质量儿死亡组与存活组各评分指标值比较

Table 2 Comparison of scoring indicators between the death and survival groups of extremely low birth weight infants

[$(\bar{x} \pm s)$, $M(P_{25} \sim P_{75})$, $n(\%)$]

Variable	The survival group (n=78)	The death group (n=47)	Z/t/ χ^2 /Fisher	P
The lowest temperature in SNAP- II and SNAPPE- II / $^{\circ}\text{C}$	35.87 \pm 0.73	35.85 \pm 0.66	0.175	0.862
The most abnormal value of PaO ₂ /FiO ₂ upon admission in SNAP- II and SNAPPE- II	1.99(1.12 ~ 3.12)	1.60(0.87 ~ 2.77)	-1.838	0.066
Seizure in SNAP- II and SNAPPE- II	0 (0.00)	1 (2.13)	/	0.376
Mean arterial pressure in SNAP- II and SNAPPE- II /mmHg	38.63 \pm 8.54	37.39 \pm 10.99	0.781	0.437
SGA in SNAPPE- II	26(33.33)	13(27.66)	0.440	0.507
The most abnormal PH value of arterial blood gas in SNAP- II , SNAPPE- II , CRIB, CRIB- II , and NCIS	7.26 \pm 0.10	7.18 \pm 0.13	4.250	0.0004
The most abnormal HR value upon admission in NCIS/(t/min)	143.98 \pm 13.39	138.63 \pm 23.50	1.710	0.091
The most abnormal RR value upon admission in NCIS/(t/min)	56.74 \pm 8.56	57.81 \pm 10.33	-0.751	0.454
Minimum arterial oxygen partial pressure upon admission in NCIS/ mmHg	66.73 \pm 28.62	69.89 \pm 37.20	-0.641	0.523
The most abnormal Na ⁺ value upon admission in NCIS/(mmol/L)	136.73 \pm 5.88	136.72 \pm 4.64	0.011	0.991
The most abnormal K ⁺ value upon admission in NCIS/(mmol/L)	5.04 \pm 1.24	4.74 \pm 1.36	1.495	0.137
The most abnormal value of peripheral hematocrit in NCIS	0.49 \pm 0.07	0.47 \pm 0.07	1.902	0.059
The most abnormal value of blood creatinine in NCIS/(mmol/L)	50.55 \pm 25.13	54.72 \pm 24.97	-0.919	0.360
The most abnormal value of urea nitrogen in NCIS/(mmol/L)	4.25(2.95 ~ 7.05)	5.36(2.92 ~ 7.34)	-0.454	0.650
Urine output in NCIS/[mL/(kg·h)]	2.77(1.89 ~ 3.65)	2.43(1.50 ~ 3.96)	-0.726	0.468
Systolic pressure in NCIS/ mmHg	55.48 \pm 11.44	51.60 \pm 11.99	0.146	0.033
Gastrointestinal manifestations in NCIS	10(12.82)	3(6.38)	0.705	0.401
The most abnormal value of BE in CRIB- II /(mmol/L)	-5.35(-7.53 ~ -3.65)	-7.60(-11.10 ~ -4.60)	-3.625	0.0003
Maximum inhaled oxygen concentration in CRIB- II / %	40.87 \pm 20.28	57.93 \pm 21.47	-3.977	0.0001
The most abnormal value of BE in CRIB/(mmol/L)	-5.85(-8.10 ~ -3.90)	-8.30(-11.80 ~ -5.40)	-4.258	0.0002
Congenital malformation in CRIB	3(3.85)	0(0.00)	/	0.290
Minimum inhaled oxygen concentration in CRIB/ %	27.09 \pm 8.89	36.58 \pm 12.22	-3.344	0.001

Abbreviation: SNAP- II : score for neonatal acute physiology version II ; SNAPPE- II : simplified version of the score for neonatal acute physiology perinatal extension; CRIB: clinical risk index for babies; CRIB- II : clinical risk index for babies- II ; NCIS: neonatal critical illness score; HR: heart rate; RR: respiratory rate; PaO₂/FiO₂: arterial partial pressure of oxygen/inhalation oxygen concentration; BE: base excess; SGA: small for gestational age.

表3 评分指标值二分类 logistic 回归分析
Table 3 Binary logistic regression analysis of scoring indicators

Variable	P	OR	OR 95%CI
Systolic pressure	0.043	0.968	(0.938, 0.999)
Maximum inhaled oxygen concentration	0.006	1.020	(1.006, 1.034)
The most abnormal value of BE in CRIB	0.005	0.868	(0.786, 0.959)
Birthweight	0.000	0.994	(0.991, 0.997)
Constant	0.916	0.858	-

OR: odds ratio; CI: confidence interval.

2.4 多变量列线图分析

为了便于分析和比较,将出生体质量划分为≤600 g(设为1)、601~700 g(设为2)、701~800 g(设为3)、801~901 g(设为4)、901~999g(设为5)。列线图左侧为纳入分析变量名,每一个变量对应线段上的标注刻度代表该变量的可取值范围,而线段的长度则反映了该变量单独对结局事件的贡献大小,各变量得分之和的总分可进一步对应不同的死亡风险(Death risk)。由回归分析具象化后的列线图可知具有较低的收缩压、较高的最大吸入氧浓度、较大BE值、较低的出生体质量的ELBWI其死亡风险显著增高(图1)。

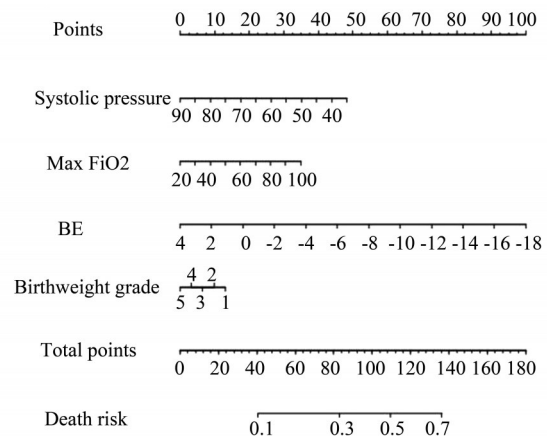


图1 列线图

Fig. 1 Nomographic chart

2.5 受试者工作曲线比较及分析

计算文献报道^[8]五种评分中预测价值最高的CRIB其AUC为0.68,而对上述2.3和2.4中发现的收缩压、最大吸入氧浓度、BE值、出生体质量四个差异变量同样进行ROC分析,可得单一变量AUC

介于0.57~0.66之间,低于CRIB预测效力。但,将四个差异变量进行综合ROC曲线分析,发现四者的综合AUC值为0.71,显著高于CRIB,显示具有更佳的预测价值。(表4、图2)

表4 不同评分、变量的ROC分析比较
Table 4 Comparison of ROC with different variables

Variable	AUC	S.E.	P	95%CI	Sensitivity	Specificity
CRIB	0.68	0.053	0.001	(0.573, 0.779)	0.553	0.782
Systolic pressure	0.58	0.055	0.134	(0.472, 0.688)	0.532	0.641
Maximum inhaled oxygen concentration	0.60	0.055	0.059	(0.492, 0.708)	0.298	0.962
The most abnormal value of BE	0.66	0.051	0.002	(0.563, 0.763)	0.404	0.872
Birthweight	0.57	0.059	0.210	(0.451, 0.683)	0.447	0.744
Integrating the above four variables ¹⁾	0.71	0.048	<0.001	(0.610, 0.799)	0.702	0.603

¹⁾ Here refers to the combination of systolic pressure, maximum inhaled oxygen concentration, BE, and birthweight. Abbreviation: CRIB: clinical risk index for babies; BE: base excess; AUC: arear under curve; SE: standard error; CI: confidence interval.

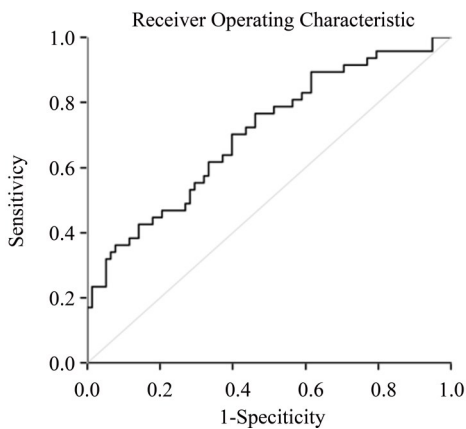


图2 收缩压、最大吸入氧浓度、BE值、出生体质量综合 ROC 曲线

Fig. 2 ROC of combined systolic pressure, maximum inhaled oxygen concentration, BE, and birthweight

3 讨论

随着社会发展,高龄产妇逐渐增多,而由于高龄造成的合并症较多,早产儿尤其是ELBWI越发常见^[9]。ELBWI自身脏器发育不成熟,易罹患多系统疾病,且合并症多,故相较于足月儿抢救难度更大、死亡风险高。基于此,早期对此类人群进行评估、有助于预测死亡风险,也有利于临床抢救和医患沟通。目前新生儿危重评分体系如SNAP- II、SNAPPE- II、NCIS的研究对象主要集中在足月儿、早产儿及极低出生体质量儿^[10-11],而对于超早产儿(胎龄小于28周)或ELBWI而言,有关其死亡风险的预测却仅有零星研究出现。如在课题组前期的探索中发现,相较于NCIS、SNAP- II、SNAPPE- II及CRIB- II,CRIB具有相对更高的预测效力(AUC: 0.787, 95%CI: 0.712-0.862)^[8],但仍有进一步提升改进空间,更为重要的是面对种类如此繁多的新生儿危重评分,究竟哪些因素和条目影响各类评分的预测准确度尚缺乏研究分析。

对于ELBWI,本研究发现CRIB其AUC值为0.68(标准误0.053)。McLeod JS在2020年的meta分析中也显示对于出院前极低出生体质量儿死亡风险,CRIB具有较佳的预测价值[AUC 0.88(0.86-0.90)]^[12]。笔者认为CRIB更为精准其原因与评分条目含有吸入氧浓度、血气BE值及出生体质量密切相关。我们的单因素和多因素logistic回归分析也支持最大吸入氧浓度、BE值及出生体质量对死

亡风险的准确评估影响较大(OR值分别为1.020、0.868和0.994,详见表3)。其中最大吸入氧浓度可以反映ELBWI出生时肺脏发育成熟情况,生后需要较高吸入氧浓度往往说明ELBWI其早期呼吸窘迫越重,有效换气、通气功能减弱,易造成低氧血症,以上可导致多种不良预后。Rantakari等的研究就表明高吸入氧浓度与早产儿脑白质损伤密切相关^[13]。BE值则体现了ELBWI内环境的稳定程度,在重症感染、低血容量、低体温时会引起微循环障碍,从而产生氧债及代谢性酸中毒^[14-15]。严重的代谢性酸中毒与重度颅内出血及肺出血紧密联系,这也是造成ELBWI死亡的重要合并症^[16-17]。而上述较重的肺部病变、低氧血症与代谢性酸中毒又产生了相互影响,增加了ELBWI死亡风险。除此之外,低出生体质量同样是早产儿死亡的重要危险因素^[18]。来自JAMA杂志2022年的报道统计了2013-2018年10 877名胎龄小于28周的新生儿,结果表明积极治疗的ELBWI在23周时存活率为55.8%(535/958),而在22周时的存活率仅为30.0%(60/200)^[19]。

作为CRIB的改良版本,CRIB- II精简了评分内容,其未含有“吸入氧浓度”条目,这会导致反映肺部氧合功能的重要指标缺失。而吸入氧浓度同多种不良预后密切相关,如神经发育障碍、支气管肺发育不良以及死亡^[20-21]。另外,值得注意的是CRIB- II要求评分在生后1 h内完成,相较于其他评分较宽的时间窗(生后12~24 h),较短的评分时间窗会丢失生后后续时间段的重要临床信息,从而造成预测效能下降,因此,适当延长评分窗口并且纳入吸入氧浓度作为评分条目仍是必要的。作为国内开发的新生儿危重评分,NCIS相较于其他评分,只需在生后24 h内完成,评分时间窗较为宽松^[22]。单若冰等对93例早产儿进行了死亡风险评估,发现死亡病例NCIS得分明显低于非死亡病例,差异有显著性($P < 0.01$)^[23]。但由于NCIS评分制订之初参考的对象主要为足月儿,ELBWI数目纳入较少^[6]。另外,NCIS评分虽然含有收缩压条目,但缺少出生体质量、BE、最大吸入氧浓度等其他对死亡风险评估影响较大的条目。而且,NCIS条目达到11项之多,临床评估费时、尚需精简以改善效率。反观SNAP- II及其改良版SNAPPE- II,条目较少、同时也含有血压、氧浓度和出生体质量等重要指标,但同样缺少BE条目,Randolph等^[24]的研究

表明在校正混杂变量后,出生后血气 $\text{PH}<7$ 、 $\text{BE}<-12\text{ mmol/L}$ 与死亡显著相关[$\text{OR}=2.5$, $95\text{CI}(1.6, 4.2)$]。这进一步提示了BE作为评估条目的重要性。

总之,通过本回顾性研究,我们发现收缩压、最大吸入氧浓度、BE值、出生体质量是影响ELBWI死亡风险能否准确评估的重要因素,故在以后新评分

的开发中,推荐将以上四者纳入评估条目可得到效力更优的ELBWI危重评分预测体系。但本研究也有其局限性,如样本量仍较小,另外本研究纳入的两中心其血气、生化仪器并不完全一致,这在一定程度上影响了结果的准确性,有待后续扩大样本量的同时做好质控的统一。

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