【临床研究】

血清白细胞介素-10 和中性粒细胞明胶酶相关脂质运载蛋白水平对纤维支气管镜吸痰灌洗治疗重症肺炎患者预后的预测价值

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摘要: **目的**　探讨血清白细胞介素-10(IL-10)、中性粒细胞明胶酶相关脂质运载蛋白(NGAL)水平对纤维支气管镜吸痰灌洗治疗重症肺炎患者预后的预测价值。**方法**　选择 2018 年 7 月到 2021 年 1 月南阳市中医院收治的 89 例重症肺炎患者为研究对象,患者均在常规治疗基础上实施纤维支气管镜吸痰灌洗治疗,连续治疗 7 d 后评估患者预后,根据预后将患者分为预后不良组与预后良好组。比较 2 组患者年龄、性别、入院时急性生理学与慢性健康状况评分 Ⅱ(APACHE Ⅱ)及血清 IL-10、NGAL 水平,采用 logistic 回归分析重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后的相关因素,应用受试者操作特征(ROC)曲线分析入院时血清 IL-10、NGAL 水平对重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后的评估价值,绘制决策曲线分析重症肺炎患者入院时血清 IL-10、NGAL 水平单独或联合评估纤维支气管镜吸痰灌洗治疗预后的净受益率。**结果**　89 例重症肺炎患者中,38 例(42.70%)痊愈、19 例(21.35%)显效、8 例(8.99%)有效、24 例(26.97%)无效;预后良好患者 65 例,预后不良患者 24 例,预后不良发生率为 26.97%。预后不良组与预后良好组患者性别、年龄和入院时收缩压、舒张压比较差异无统计学意义($P > 0.05$);预后不良组患者入院时 APACHE Ⅱ 评分显著高于预后良好组($P < 0.05$);预后不良组患者 IL-10 水平显著低于预后良好组,NGAL 显著高于预后良好组($P < 0.05$)。Logistic 回归分析结果显示,入院时 APACHE Ⅱ 评分与重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后无关($OR = 1.212,P > 0.05$);高 IL-10 水平是重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后不良的保护因素($OR = 0.623,P < 0.05$),高 NGAL 水平是重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后不良的危险因素($OR = 1.125,P < 0.05$)。ROC 曲线分析结果显示,入院时血清 IL-10、NGAL 水平单独及联合预测重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后不良的 AUC 分别为 0.815、0.826、0.868,特异度分别为 0.750、0.708、0.708,灵敏度分别为 0.785、0.831、0.862。决策曲线分析结果显示,在阈值 0.1 ~ 0.7 范围内,重症肺炎患者入院时血清 IL-10 与 NGAL 联合评估纤维支气管镜吸痰灌洗治疗不良预后的净受益率优于单独 IL-10、NGAL,且在高风险阈值 0.0 ~ 1.0 内的净受益率始终大于 0,净受益率最大值为 0.270。**结论**　重症肺炎患者入院时血清 IL-10、NGAL 水平与纤维支气管镜吸痰灌洗治疗预后相关,入院时血清 IL-10、NGAL 水平单独或联合检测对纤维支气管镜吸痰灌洗治疗的不良预后均有一定预测价值,且血清 IL-10 与 NGAL 水平联合评估获得的净受益率更高。

关键词:　重症肺炎;纤维支气管镜;吸痰;灌洗;白细胞介素-10;中性粒细胞明胶酶相关脂质运载蛋白

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Predictive value of serum interleukin-10 and neutrophil gelatinase associated lipocalin levels on the prognosis of patients with severe pneumonia treated with sputum aspiration and lavage by fiberoptic bronchoscopy

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Abstract: **Objective**　To investigate the predictive value of serum interleukin-10 (IL-10) and neutrophil gelatinase associated lipocalin (NGAL) levels on the prognosis of patients with severe pneumonia treated with sputum aspiration and lavage by fiberoptic bronchoscopy. **Methods**　A total of 89 patients with severe pneumonia admitted to Nanyang Hospital of Traditional Chinese Medicine from July 2018 to January 2021 were selected as the study subjects. All patients were treated with sputum aspirationand lavage by fiberoptic bronchoscopy on the basis of routine treatment. The prognosis of patients was evaluated after 7 consecutive days of treatment. According to the prognosis, the patients were divided into poor prognosis group and good prognosis group. The age, sex, acute physiology and chronic health evaluation scoring system Ⅱ(APACHE Ⅱ) and serum IL-10

and NGAL levels of patients at admission between the two groups were compared, the relevant factors of the prognosis of patients with severe pneumonia after sputum aspiration and lavage by fiberoptic bronchoscopy was analyzed by logistic regression, and the predictive value of serum IL-10 and NGAL levels at admission on the prognosis of patients with severe pneumonia after sputum aspiration and lavage by fiberoptic bronchoscopy was analyzed by receiver operator characteristic(ROC) curve, the net benefit rate of serum IL-10 and NGAL levels at admission alone and in combination in evaluation on the prognosis of sputum aspiration and lavage treatment with fiberoptic bronchoscopy was analyzed by the decision curve. **Results**　Among the 89 patients with severe pneumonia, 38 cases (42.70%) were cured, 19 cases (21.35%) were significantly effective, 8 cases (8.99%) were effective, and 24 cases (26.97%) were ineffective; there were 65 patients with good prognosis and 24 patients with poor prognosis, the incidence of poor prognosis was 26.97%. There was no significant difference in gender, age, systolic blood pressure and diastolic blood pressure at admission between poor prognosis group and good prognosis group ($P > 0.05$); APACHE Ⅱ score of patients in the poor prognosis group was significantly higher than that in the good prognosis group ($P < 0.05$). The level of serum IL-10 of patients in the poor prognosis group was significantly lower than that in the good prognosis group, and the level of serum NGAL was significantly higher than that in the good prognosis group ($P < 0.05$). The results of logistic regression analysis showed that APACHE Ⅱ score at admission was not related to the prognosis of patients with severe pneumonia after sputum aspiration and lavage by fiberoptic bronchoscopy ($OR = 1.212, P > 0.05$); the high level of serum IL-10 was a protective factor for the poor prognosis of patients with severe pneumonia treated with sputum aspiration and lavage by fiberoptic bronchoscopy ($OR = 0.623, P < 0.05$), and the high level of serum NGAL was a risk factor for the poor prognosis of patients with severe pneumonia treated with sputum aspiration and lavage by fiberoptic bronchoscopy ($OR = 1.125, P < 0.05$). ROC curve analysis showed that the AUC of serum IL-10 and NGAL levels at admission and their combination in predicting the poor prognosis of patients with severe pneumonia after treatment of sputum aspiration and lavage by fiberoptic bronchoscopy was 0.815, 0.826 and 0.868, respectively; the specificity was 0.750, 0.708 and 0.708, respectively, and the sensitivity was 0.785, 0.831 and 0.862, respectively. The results of decision curve analysis showed that the net benefit rate of serum IL-10 and NGAL at admission in combination to evaluate the poor prognosis of sputum aspiration and lavage by fiberoptic bronchoscopy treatment in patients with severe pneumonia was better than that of IL-10 and NGAL alone within the threshold value of 0.1 − 0.7. Moreover, within the high-risk threshold value of 0.0 − 1.0, the net benefit rate was always greater than 0, the maximum value of the net benefit rate was 0.270. **Conclusion**　The levels of serum IL-10 and NGAL of patients with severe pneumonia at admission are related to the prognosis of sputum aspiration and lavage by fiberoptic bronchoscopy. The detection of serum IL-10 and NGAL levels alone or in combination at admission has certain predictive value for the poor prognosis of sputum aspiration and lavage by fiberoptic bronchoscopy, and the net benefit rate obtained by the combined assessment of serum IL-10 and NGAL level is higher.

Key words：　severe pneumonia; fiberoptic bronchoscope; sputum suction; lavage; interleukin-10; neutrophil gelatinase associated lipocalin

重症肺炎发病迅速且病情进展较快,患者可伴有意识障碍、昏迷、惊厥、呼吸衰竭等症状,病死风险较高。目前,重症肺炎患者治疗现状不佳,单独通过抗生素治疗难以获得理想的效果。纤维支气管镜吸痰灌洗治疗可通过灌洗液灌洗、抽吸气道,清除气道内分泌物,对重症肺炎具有一定的治疗效果[1]。但是,部分重症患者即使采用纤维支气管镜吸痰灌洗治疗也难以获得较好的预后[2]。因此,寻找一种能有效预测纤维支气管镜吸痰灌洗治疗效果的指标,对改善重症肺炎患者的预后十分重要。研究报道,重症肺炎患者存在不同程度的感染,而感染可诱发机体炎症反应,增加炎症因子的释放[3]。白细胞介素(interleukin, IL)-10 是一种常见的炎症因子,参与机体炎症和免疫反应,在感染中具有重要的作用,可能与重症肺炎患者预后有关[4]。中性粒细胞明胶酶相关脂质运载蛋白(neutrophil gelatinase associated lipocalin, NGAL)是一种具有多种生物学作用的分泌

性糖蛋白,与炎症、免疫应答有关[5]。研究表明,NGAL 水平与感染的严重程度有关,可能与重症肺炎患者预后也有一定的关系[6]。基于此,本研究分析血清 IL-10、NGAL 水平与重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后的关系,以期为重症肺炎患者的治疗提供参考。

1　资料与方法

1.1　一般资料　选择 2018 年 7 月至 2021 年 1 月南阳市中医院收治的重症肺炎患者为研究对象。病例纳入标准:(1)符合重症肺炎诊断标准[7];(2)经胸部 CT 检查和 X 线检查确诊;(3)需要机械通气;(4)完成纤维支气管镜吸痰灌洗治疗。病例排除标准:(1)合并肺间质纤维化、肺结核等其他肺部疾病;(2)合并其他部位感染;(3)患有心、肝、肾等其他重要脏器相关疾病;(4)合并免疫系统疾病;(5)长期使用糖皮质激素或免疫抑制剂。本研究共纳入

重症肺炎患者89例,男51例,女38例;年龄51~77(57.96±5.49)岁;急性生理学与慢性健康状况评分Ⅱ(acute physiology and chronic health evaluation scoring system,APACHEⅡ)18~32(27.02±3.66)分。本研究经南阳市中医院医学伦理委员会审核通过,患者和(或)家属知情同意并签署知情同意书。

1.2 方法

1.2.1 基线资料收集 通过查阅病历收集患者的性别、年龄、入院时收缩压和舒张压等一般资料。

1.2.2 APACHEⅡ评分 入院时,采用APACHEⅡ评分问卷[8]进行评估,该问卷共包括急性生理学评分、年龄评分、慢性健康状况评分3个维度,总分71分,评分越高表示患者病情越重。

1.2.3 酶联免疫吸附法检测患者入院时血清IL-10、NGAL水平 患者入院时,采集清晨静脉血3 mL,静置30 min,3 000 r·min⁻¹离心10 min,分离保存血清;采用酶联免疫吸附法检测血清IL-10、NGAL水平,试剂盒均购自上海酶联生物科技有限公司,严格按说明书进行操作。

1.2.4 治疗方法 患者均实施常规机械通气和抗生素治疗,并进行纤维支气管镜吸痰灌洗治疗,对鼻部、咽喉部进行表面麻醉,经鼻腔置入纤维支气管镜,观察主支气管、气管、叶段、亚段支气管情况,吸出痰液,至病变肺段支气管开口处,留取痰液进行细菌培养及药敏试验;病变部位每次用10~20 mL的37 ℃生理盐水灌洗,并依据药敏试验结果选择抗菌药物注入病灶部位,每日3~5次,连续治疗7 d。

1.2.5 预后评估和分组 治疗完成后,参考《呼吸内科诊疗常规(第2版)》[7]评估治疗效果:临床症状、体征、实验室检查及病原学检查均恢复正常则判定为痊愈;病情出现明显好转,但临床症状、体征、实验室检查及病原学检查中有1项以上未完全恢复至正常判定为显效;治疗后病情存在好转,但临床症状、体征、实验室检查及病原学检查均未完全恢复至正常判定为有效;治疗后病情无明显好转,甚至病情加重者则判定为无效。将治疗痊愈、显效、有效患者纳入预后良好组,将治疗无效患者纳入预后不良组。

1.3 统计学处理 应用SPSS 24.0软件进行数据统计与分析。计量资料均经Shapiro-Wilk正态性检验,正态分布计量资料以均数±标准差($\bar{x}±s$)表示,组间比较采用独立样本t检验;计数资料以例数和百分率表示,组间比较采用χ^2检验;将单因素分析结果中有统计学意义指标纳入多因素分析,采用logistic回归分析重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后的影响因素;绘制受试者操作特征(receiver operator characteristic,ROC)曲线,并计算

曲线下面积(area under the cure,AUC)值,评估患者入院时血清IL-10、NGAL水平预测纤维支气管镜吸痰灌洗治疗预后的价值,AUC值>0.90表示预测性能较高,0.71~0.90表示有一定预测性能,0.50~0.70表示预测性能较低,<0.50表示无预测性能;$P<0.05$为差异有统计学意义。应用R4.1.0统计分析软件和"rmda"软件包,以净受益率为纵坐标,高风险阈值为横坐标,绘制决策曲线,分析入院时血清IL-10、NGAL单独及二者联合预测重症肺炎患者纤维支气管镜吸痰灌洗治疗效果的净受益率。

2 结果

2.1 重症肺炎患者治疗的预后 治疗7 d后,38例(42.70%)痊愈、19例(21.35%)显效、8例(8.99%)有效、24例(26.97%)无效;预后良好患者65例,预后不良患者24例,预后不良发生率为26.97%(24/89)。

2.2 2组患者临床资料比较 结果见表1。预后不良组与预后良好组患者性别、年龄和入院时收缩压、舒张压比较差异无统计学意义($P>0.05$);预后不良组患者的入院时APACHEⅡ评分显著高于预后良好组,差异有统计学意义($P<0.05$)。预后不良组患者IL-10水平显著低于预后良好组,NGAL显著高于预后良好组,差异有统计学意义($P<0.05$)。

表1 2组患者临床资料比较

Tab.1 Comparison of clinical data of patients between the two groups

临床资料	预后不良组 ($n=24$)	预后良好组 ($n=65$)	χ^2/t	P
性别				
男/例(%)	14(58.33)	37(56.92)	0.014	0.905
女/例(%)	10(41.67)	28(43.08)		
年龄/岁	58.04±5.20	57.92±5.63	0.090	0.929
APACHEⅡ评分	29.08±3.43	26.26±3.77	3.207	0.002
IL-10/(ng·L⁻¹)	19.07±2.31	22.14±2.64	5.062	0.000
NGAL/(μg·L⁻¹)	141.00±14.78	122.51±12.67	5.837	0.000
入院时收缩压/mm Hg	86.38±5.27	87.17±5.34	0.625	0.534
入院时舒张压/mm Hg	57.79±3.28	56.74±3.19	1.371	0.174

注:1 mm Hg=0.133 kPa。

2.3 重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后的多因素logistic回归分析 结果见表2。入院时APACHEⅡ评分与重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后无关($OR=1.212,P>0.05$);高IL-10水平是重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后不良的保护因素($OR=0.623,P<0.05$),高NGAL水平是重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后不良的危险因素($OR=1.125,P<0.05$)。

表 2　重症肺炎患者经纤维支气管镜吸痰灌洗治疗预后的影响因素 logistic 回归分析结果

Tab. 2　Logistic regression analysis of influencing factors on prognosis of patients with severe pneumonia treated with sputum aspiration and lavage by fiberoptic bronchoscopy

因素	B	SE	$Wald$	P	OR	95%置信区间 下限	95%置信区间 上限
常量	−12.110	6.013	4.056	0.044	–	–	–
APACHE Ⅱ评分	0.192	0.100	3.684	0.055	1.212	0.996	1.474
IL-10	−0.474	0.156	9.194	0.002	0.623	0.458	0.846
NGAL	0.118	0.032	13.559	0.000	1.125	1.057	1.198

2.4　入院时血清 IL-10、NGAL 单独或联合评估重症肺炎患者纤维支气管镜吸痰灌洗治疗预后的价值

　　结果见表 3 和图 1。入院时血清 IL-10、NGAL 水平单独及联合预测重症肺炎患者纤维支气管镜吸痰灌洗治疗预后不良的 AUC 分别为 0.815、0.826、0.868,特异度分别为 0.750、0.708、0.708,灵敏度分别为 0.785、0.831、0.862;入院时血清 IL-10、NGAL 水平单独及联合预测重症肺炎患者纤维支气管镜吸痰灌洗治疗预后不良的 AUC 比较差异无统计学意义($P > 0.05$)。

表 3　重症肺炎患者入院时血清 IL-10、NGAL 单独或联合评估纤维支气管镜吸痰灌洗治疗预后的 ROC 曲线分析

Tab. 3　ROC curve analysis of serum IL-10 and NGAL alone or combination in evaluation of the prognosis of patients with severe pneumonia after treatment of sputum suction and lavage by fiberoptic bronchoscopy

指标	AUC	95%置信区间 下限	95%置信区间 上限	P	特异度	灵敏度	约登指数
IL-10	0.815	0.719	0.911	<0.001	0.750	0.785	0.535
NGAL	0.826	0.726	0.926	<0.001	0.708	0.831	0.539
二者联合	0.868	0.785	0.951	<0.001	0.708	0.862	0.570
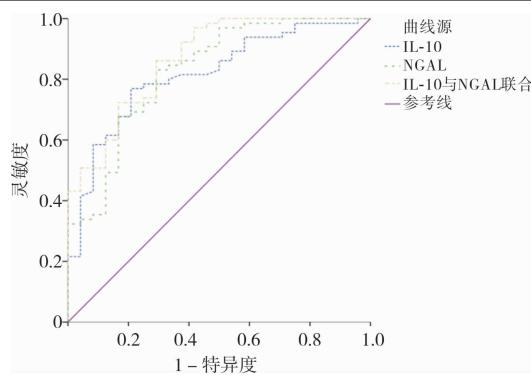
图 1　重症肺炎患者入院时血清 IL-10、NGAL 单独或联合评估纤维支气管镜吸痰灌洗治疗预后的 ROC 曲线

Fig. 1　ROC curve of serum IL-10 and NGAL at admission alone or combination in evaluation of the prognosis of patients with severe pneumonia after treatment of sputum suction and lavage by fiberoptic bronchoscopy

2.5　重症肺炎患者入院时血清 IL-10、NGAL 水平单独和联合评估纤维支气管镜吸痰灌洗治疗预后的决策曲线分析

结果见图 2。在阈值 0.1 ~ 0.7 范围内,重症肺炎患者入院时血清 IL-10 与 NGAL 联合评估纤维支气管镜吸痰灌洗治疗预后不良的净受益率优于 IL-10、NGAL 单独评估,且在高风险阈值 0.0 ~ 1.0 内的净受益率始终大于 0,始终有临床意义,净受益率最大值为 0.270。
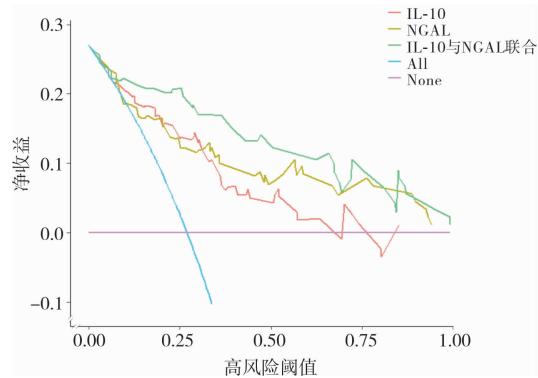

图 2　重症肺炎患者入院时血清 IL-10、NGAL 单独及联合评估纤维支气管镜吸痰灌洗治疗预后的决策曲线

Fig. 2　Decision curve of serum IL-10 and NGAL at admission alone or combination in evaluation of the prognosis of patients with severe pneumonia after treatment of sputum suction and lavage by fiberoptic bronchoscopy

3　讨论

　　重症肺炎的发病率及病死率较高,严重影响患者的生存质量,需及时治疗。纤维支气管镜吸痰灌洗治疗是临床上治疗重症肺炎的有效手段之一,其可在直视状态下清除气道分泌物,将抗生素药物直接注入感染病灶,改善患者通气及换气功能,提高治疗效果,但仍有部分患者治疗无效,预后不佳[9]。本研究结果显示,89 例重症肺炎患者应用纤维支气管镜吸痰灌洗治疗 7 d 后,38 例(42.70%)痊愈、19 例(21.35%)显效、8 例(8.99%)有效、24 例(26.97%)无效,预后不良发生率为 26.97%;说明重症肺炎患者经纤维支气管镜吸痰灌洗治疗后的预后不良的发生风险仍较高,因此,应分析与重症肺炎患者预后有关的因素,从而有效改善患者的治疗和预后。

　　IL-10 是辅助性 T 淋巴细胞分泌的重要细胞因子,能抑制趋化因子及促炎因子的释放,减轻炎症反应[10]。研究证实,IL-10 可能与肺炎患者的病情严重程度有关,也可能会影响重症肺炎患者的预后[11]。NGAL 分泌于炎症损伤中活化的中性粒细胞,在炎症条件下,NGAL 水平明显升高[12]。研究表明,肺癌患者 NGAL 水平明显升高,NGAL 与肺部疾病患者病情具有一定的联系,推测其可能也与重症肺炎患者的预后结局有关[13]。本研究结果显示,预后不良组患者的血清 IL-10 水平显著低于预后良

好组,血清 NGAL 水平显著高于预后良好组;进一步经 logistic 回归分析结果显示,血清 IL-10、NGAL 水平与重症肺炎患者纤维支气管镜吸痰灌洗治疗预后有关,低 IL-10、高 NGAL 可能是重症肺炎患者纤维支气管镜吸痰灌洗治疗预后不良的危险因素。分析原因可能为:重症肺炎患者多合并多种病原菌的感染,疾病进展过程中伴随不同程度的炎症反应[14],而 IL-10 是一种常见的抗炎因子,在重症肺炎的炎症反应过程中具有参与作用,能抑制单核巨噬细胞,减少多种促炎细胞因子的合成与释放,IL-10 分泌缺乏将造成致炎介质的增加和炎症反应的加重,造成持续炎症反应,增加不可逆的组织损伤,从而影响重症肺炎患者的治疗效果,对预后造成不良影响[15-16];IL-10 还能通过辅助 T 细胞调节炎症反应,避免肿瘤坏死因子 α、IL-6 等促炎因子的过度表达,发挥一定的抗炎作用,IL-10 不足可能会影响机体抗炎作用,不利于重症肺炎患者的治疗,增加不良预后发生风险[17]。NGAL 对机体的炎症、免疫反应具有一定的影响,NGAL 能降低中性粒细胞的附着能力和趋化能力,从而抑制机体白细胞的杀菌功能,使炎症反应加重,影响治疗效果,从而增加重症肺炎患者预后不良的风险[18]。NGAL 可以通过共价键绑定至基质金属蛋白酶-9(matrix metalloproteinase-9,MMP-9)前体,维持 MMP-9 的活性,并保护 MMP-9 免受降解[19];而 MMP-9 具有分解肺内、呼吸道内基底膜、细胞外基质等结构复合物的作用,可加重肺炎,诱发肺气肿。另外,NGAL 被证实对肾脏、胰腺具有伤害作用,参与多器官损伤,NGAL 水平异常升高可能会诱发或加重重症肺炎患者的多器官功能障碍综合征,增加治疗难度,影响预后[20]。此外,本研究中 ROC 曲线结果证实,入院时血清 IL-10、NGAL 水平单独及联合对重症肺炎患者纤维支气管镜吸痰灌洗治疗预后不良均有一定预测价值;且决策曲线分析结果显示,重症肺炎患者入院时血清 IL-10 与NGAL 联合评估纤维支气管镜吸痰灌洗治疗预后不良的净受益率优于单独某一指标。

综上所述,重症肺炎患者入院时血清 IL-10、NGAL 水平与纤维支气管镜吸痰灌洗治疗预后有关,其单独或联合检测对纤维支气管镜吸痰灌洗治疗的不良预后均有一定预测价值,且二者联合评估获得的净受益率更高。

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