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在线全文

·临床研究·

重症急性胰腺炎多器官功能衰竭患者早期发生毛细血管渗漏综合征的临床表征研究*

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【摘要】 目的 探讨重症急性胰腺炎（severe acute pancreatitis, SAP）患者毛细血管渗漏综合征（capillary leak syndrome, CLS）早期生物标志物的动态变化临床表征及与多器官功能衰竭（multiple organ failure, MOF）相关性。**方法** 选取2019年9月1日–2020年12月31日四川大学华西医院胰腺炎中心收治的171例SAP患者作为研究对象，根据入院5 d内是否发生MOF分为MOF组和Non-MOF组，并进一步根据是否合并中重度腹腔高压（intra-abdominal hypertension, IAH）进行亚组分析。通过动态监测患者血液生物标志物〔血红细胞比容（hematocrit, HCT）、尿素氮（blood urea nitrogen, BUN）、肌酐（creatinine, Cr）〕、血浆蛋白〔白蛋白（albumin, Alb）、总蛋白（total protein,TP）、非白蛋白血浆蛋白（non-albumin plasma proteins, NAPP）〕及腹腔内压的变化，综合分析这些指标在不同分组中的变化趋势。**结果** 两组基线资料差异无统计学意义，具有可比性；MOF组患者持续48 h的全身炎症反应综合征（systemic inflammatory response syndrome, SIRS），发生率（71.8% vs. 91.3%）、ICU转入率（17.6% vs. 70.4%）、平均住院时间〔（19.0±12.2）d vs.（32±17.7）d〕均高于Non-MOF组（P<0.05）；MOF组的呼吸、循环和肾功能衰竭的发生率均高于Non-MOF组，其中循环衰竭（69% vs. 3.5%）和肾功能衰竭（65.5% vs. 3.5%）发生率差异有统计学意义（P<0.05）。与Non-MOF组相比，MOF组患者的入院后5 d内BUN和Cr水平升高，而Alb、TP入院后快速下降后逐渐回升，NAPP水平在入院后持续下降，且入院后第3天NAPP水平低于Non-MOF组，差异有统计学意义（P<0.001）；Alb/NAPP入院后第1天显著下降后再迅速上升，入院后第3、4天两组差异有统计学意义（P=0.001）。合并中重度IAH的患者亚组分析，各项指标的动态变化趋势与总体趋势变化类似，且差异更为显著。混合线性模型显示MOF合并IAP组HCT、BUN、Alb/NAPP和Alb/TP平均水平更高并且随着时间的推移而增加（P<0.001）。**结论** SAP患者CLS模型具有合理性，证实CLS是从SIRS到MOF发生的关键因素，NAPP的丢失是CLS持续并向MOF进展的早期重要指标，中重度IAH也会促使MOF进一步恶化，为阐明MOF潜在机制提供依据，也有待前瞻性大样本的进一步验证。

【关键词】 重症急性胰腺炎　多器官衰竭　毛细血管渗漏综合征　腹腔高压　生物标志物

Clinical Manifestations of Early-Onset Capillary Leak Syndrome in Patients With Multiple Organ Failure Due to Severe Acute Pancreatitis

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[Abstract] Objective To investigate the early dynamic changes of biomarkers associated with capillary leak syndrome (CLS) in patients with severe acute pancreatitis (SAP) and their correlation with multiple organ failure (MOF). **Methods** A total of 171 SAP patients admitted to the West China Centre of Excellence for Pancreatitis, West China Hospital, Sichuan University between September 1, 2019 and December 31, 2020 were enrolled for this study. The patients were divided into MOF and non-MOF groups based on the occurrence of MOF in the first 5 days of hospitalization, and were further divided into subgroups based on the presence of moderate-to-severe intra-abdominal hypertension (IAH). We performed dynamic monitoring of the blood biomarkers (hematocrit [HCT], blood urea nitrogen [BUN], and creatinine [Cr]), plasma proteins (albumin [Alb], total protein [TP], and non-albumin plasma proteins [NAPP]), and intra-abdominal pressure. Trends in these indicators across groups were analyzed comprehensively. **Results** No significant differences in baseline data between the two groups were observed. The baseline data of the 2 groups were comparable. The MOF group had significantly higher rates of persistent systemic inflammatory response syndrome (SIRS) lasting 48 hours (91.3% vs. 71.8%), ICU admission (70.4% vs. 17.6%), and length-of-stay ([32 ± 17.7] days vs. [19.0 ±

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12.2] days) compared to those of the non-MOF group ($P < 0.05$). The incidences of respiratory, circulatory, and renal failures were higher in the MOF group than those in the non-MOF group, showing significant differences in circulatory failure (69% vs. 3.5%) and renal failure (65.5% vs. 3.5%) ($P < 0.05$). In the first 5 days of hospitalization, the MOF group showed significantly elevated BUN and Cr levels, while Alb and TP levels dropped rapidly upon admission and then gradually recovered. The NAPP level of the MOF group continued to decrease after admission, and on the third day after admission, the NAPP level was lower than that of the Non-MOF group, showing statistically significant difference ($P < 0.001$). The Alb/NAPP ratio of the MOF group decreased significantly on day 1 and then rapidly increased, showing significant differences between the groups on days 3 and 4 ($P = 0.001$). Subgroup analysis of MOF patients with moderate-to-severe IAH revealed similar trends in the dynamic changes and the overall changes in the indicators, and the difference was even more pronounced. The mixed linear model showed that the average levels of HCT, BUN, Alb/NAPP, and Alb/TP were higher and increased over time in the MOF combined with IAP subgroup ($P < 0.001$). **Conclusion** The CLS model of SAP patients is validated, confirming that CLS is a key factor in the progression from SIRS to MOF. The loss of NAPP is an early and important indicator of CLS persistence and progression to MOF. Additionally, moderate-to-severe IAH accelerates the deterioration of MOF. These findings provide valuable insights into the potential mechanisms of MOF and warrant further validation through large-scale prospective studies.

[Key words] Severe acute pancreatitis Multiple organ failure Capillary leakage syndrome Abdominal hypertension Biomarkers

急性胰腺炎(acute pancreatitis, AP)是一种常见的消化系统疾病,随着社会生活方式和饮食结构的改变,该病在全球的发病率逐年上升[1-2]。约20%的AP患者会发展成为重症急性胰腺炎(severe acute pancreatitis, SAP),通常伴有全身炎症反应综合征(systemic inflammatory response syndrome, SIRS),多器官功能衰竭(multiple organ failure, MOF),病死率可高达30%~47%[3-5],其中大多数合并症和死亡都与MOF相关。AP的发病机制尚未完全明确,目前认为腺泡细胞内胰酶过早活化、核转录因子的激活以及细胞程序性死亡和损伤相关分子模式的释放,进一步激活炎症通路和免疫细胞。大量炎性介质、细胞因子和趋化因子的释放,不仅加剧了局部胰腺的损伤,而且激活炎症级联反应,然而临床研究发现合并SIRS的AP患者大约一半都不会进展到MOF,而细胞因子以及血管活性物质比如血小板活化因子、一氧化氮、缓激肽、内皮素等破坏血管内皮屏障导致毛细血管渗漏是向MOF进展的重要环节[4,6-9],也是造成早期液体复苏补液不足和过负荷的主要原因[10]。2020年美国匹兹堡的一项研究采用尿素氮(blood urea nitrogen, BUN)、肌酐(creatinine, Cr)、血红细胞比容(hematocrit, HCT)、白蛋白(albumin, Alb)等作为生物标志物模拟SAP发生时毛细血管渗漏综合征(capillary leak syndrome, CLS)间隔室模型,初步发现大分子血浆蛋白丢失的失调和CLS是SAP导致MOF最可能的机制[11]。另外,腹腔高压(intra-abdominal hypertension, IAH)/腹腔间隔室综合征(abdominal compartment syndrome, ACS)是SAP最常见的并发症之一,IAH发生率约为30%~70%,ACS发生率约为10%~27%[12-13],合并ACS病死率可高达50%~70%[14],CLS发生,腹腔液体积聚增加、血浆胶体渗透压降低,导致腹腔内压持续升高,腹部器官血流灌注减少,导致组织器官缺氧和组织损伤,出现肺、心、肾和胃肠功能不全甚至衰竭[15]。IAH的发生伴随血管壁压力增大和血流动力学改变,可能加剧毛细血管渗漏,导致水、电解质和大分子蛋白外渗,加重CLS。此外,IAH还可能通过加重SIRS和细胞因子的释放(如TNF-α、IL-6等)进而导致MOF和死亡[16-17]。本研究从国内SAP患者的回顾性队列研究中根据是否发生MOF以及合并IAH亚组的临床特征进行比较,拟验证该MOF动态发展模型,以期提供早期可预警CLS发生的生物标志物,为早期发现及治疗提供思路。

1 资料与方法

1.1 一般资料

本研究通过四川大学华西医院生物医学伦理审查委员会审查,批件号:2022年审(837)号。纳入2019年9月1日–2020年12月31日四川大学华西医院胰腺炎中心收治的所有AP患者。纳入标准:①诊断明确的AP患者,诊断标准参考2012修订版亚特兰大指南[18]:a. 腹痛;b.血淀粉酶或脂肪酶升高至少正常值三倍以上;c. 腹部CT或超声符合AP影像学特征表现。符合上述3项中的2项即确诊。②发病时间≤72 h;③受试者充分知情同意。排除标准:①年龄<18岁;②入院后需立即转入重症监护病房(intensive care unit, ICU);③慢性胰腺炎;④精神异常患者;⑤疾病终末期患者;⑥因各种原因无法配合者;⑦数据不完整。采集所纳入患者的基线资料,包括性别、年龄、体质量指数(body mass index, BMI)、病因、吸烟史、饮酒史、糖尿病病史、高血压病史;记录从入院当天至入

院后第4天的生化指标〔HCT、BUN、Cr、Alb、总蛋白(total protein, TP)、非白蛋白血浆蛋白(non-albumin plasma proteins, NAPP)〕、SIRS评分、改良Marshall评分。入院当天至入院第4天连续每天监测膀胱压, 记录当天最大值。IAH诊断及分级参考2013年指南[19], 根据腹腔内压12 ~ 15 mmHg(1 mmHg= 0.133 kPa)、16 ~ 20 mmHg、21 ~ 25 mmHg、> 25 mmHg分为Ⅰ ~ Ⅳ级。Ⅰ级为轻度, Ⅱ ~ Ⅳ级为中重度。AP分级标准、胰腺坏死评估、MOF诊断参考2012修订版亚特兰大指南[18], 观察指标为: 持续SIRS发生率、胰腺坏死发生率、平均住院天数、ICU转入率、各器官功能衰竭发生率、病死率等临床结局。将患者按入院5天内是否发生MOF分为MOF组和Non-MOF组进行总体比较; 再根据患者入院时是否合并中重度IAH, 将SAP患者进行亚组分析。

1.2　统计学方法和轨迹分析

连续性变量资料使用$\bar{x}\pm s$(正态分布)和M(P_{25}, P_{75})(非正态分布)表示; 分类变量资料使用百分比表示。连续性变量组间比较采用Mann-Whitney *U*检验和Kruskal Wallis *H*试验比较。分类变量采用卡方检验或Fisher精确检验。双侧检验$P<0.05$为有统计学意义。使用线性混合效应模型评估临床生化指标的动态变化趋势, 每个受试者随机截距, Admission Day和MOF被作为固定效应变量纳入模型, Day-by-MOF interaction交互项纳入模型。模型表达式如下:

$$\text{Biomarker}_{ijk}=\beta_0+\beta_1\cdot\text{day}_i+\beta_2\cdot\text{MOF}_j+\beta_3\cdot(\text{day}_i\times\text{MOF}_j)+u_{i+}\epsilon_{ijk}$$

所有统计检验均采用R 4.4.1软件对数据进行分析。

2　结果

2.1　基线资料

结果见表1。本研究共纳入SAP患者171例, 男129例, 女42例。其中Non-MOF组142例, MOF组29例。两组患者平均年龄分别为45.3岁和47.1岁; 两组男性占比分别为73.9%、82.8%; MOF组的BMI、吸烟史、饮酒史和糖尿病史的比例均高于Non-MOF组, 两组的病因前三位依次为高脂血症、胆源性、特发性, 但差异均无统计学意义。两组基线资料具有可比性。

表 1　SAP患者Non-MOF组和MOF组的基线资料比较

Table 1　Comparation of baseline data of SAP patients between Non-MOF and MOF groups

Index	Non-MOF (*n*=142)	MOF (*n*=29)	*P*
Age/yr., $\bar{x}\pm s$	45.3±11.8	47.1±13.7	0.459
Man/case (%)	105 (73.9)	24 (82.8)	0.442
Body mass index/(kg/m^2), $\bar{x}\pm s$	26.56±3.42	27.36±4.03	0.271
Smoking history/case (%)	32 (35.2)	12 (57.1)	0.107
Drinking history/case (%)	36 (39.6)	11 (52.4)	0.408
Hypertension/case (%)	11 (12.1)	2 (9.5)	0.629
Diabetes/case (%)	5 (7.9)	5 (10.2)	1.000
Etiology/case (%)			0.162
Biliary	58 (40.8)	16 (55.2)	
Hyperlipidemia	58 (40.8)	13 (44.8)	
Alcohol	6 (4.2)	0 (0.0)	
Idiopathic	14 (9.9)	0 (0.0)	
Other	6 (4.2)	0 (0.0)	

2.2　临床结局

结果见表2。MOF组患者持续48 hSIRS发生率、ICU转入率、平均住院时间均高于Non-MOF组, 且差异有统计学意义($P<0.05$)。从器官功能衰竭情况来看, MOF组的呼吸、循环和肾功能衰竭的发生率均高于Non-MOF组, 其中循环衰竭和肾功能衰竭发生率差异有统计学意义($P<0.05$)。与Non-MOF组比较, MOF组胰腺坏死超过30%占比和死亡患者均更高, 但差异无统计学意义($P>0.05$)。MOF合并IAH亚组临床结局比较, 与Non-MOF IAH组比较, 合并中重度IAH的MOF组患者ICU转

表 2　SAP患者及SAP患者合并中重度IAH亚组Non-MOF组和MOF组的临床结局比较

Table 2　Comparation of clinical outcomes of SAP patients and SAP patients with moderate and severe IAH subgroup between Non-MOF and MOF groups

Clinical outcomes	Non-MOF (*n*=142)	MOF (*n*=29)	*P*	Non-MOF with IAH (*n*=56)	MOF with IAH (*n*=20)	*P*
SIRS-positive within 48 h/case (%)	102 (71.8)	27 (93.1)	0.029	45 (80.4)	19 (95.0)	0.236
Pancreatic necrosis > 30%/case (%)	16 (11.3)	7 (24.1)	0.074	41 (73.2)	16 (80.0)	0.153
Hospitalization days ($\bar{x}\pm s$)	19.0±12.2	32.0±17.7	<0.001	18.9±7.4	34.8±18.2	<0.001
ICU admission/case (%)	25 (17.6)	19 (70.4)	<0.001	8 (14.3)	12 (66.7)	<0.001
Organ failure/case (%)						
Respiratory failure	131 (92.3)	29 (100.0)	0.257	56 (100.0)	20 (100.0)	/
Circulatory failure	5 (3.5)	20 (69.0)	<0.001	0 (0.0)	11 (55.0)	<0.001
Renal failure	5 (3.5)	19 (65.5)	<0.001	0 (0.0)	15 (75.0)	<0.001
Death/case (%)	3 (2.7)	6 (10.3)	0.077	1 (1.8)	6 (27.3)	0.002

入率、死亡率、平均住院时间、循环衰竭和肾功能衰竭发生率均增加($P<0.05$)。

2.3 Non-MOF组与MOF组及亚组各生化指标变化

2.3.1 HCT

结果见图1、图2和表3。两组患者入院时HCT水平均偏高,在入院后2 d内迅速下降,此后 MOF组HCT水平下降比Non-MOF组更快,在入院后第4天小于Non-MOF组,差异有统计学意义($P=0.02$),该趋势变化在合并中重度IAH的SAP患者中类似,在入院后第3天两组差异有统计学意义($P=0.016$)。

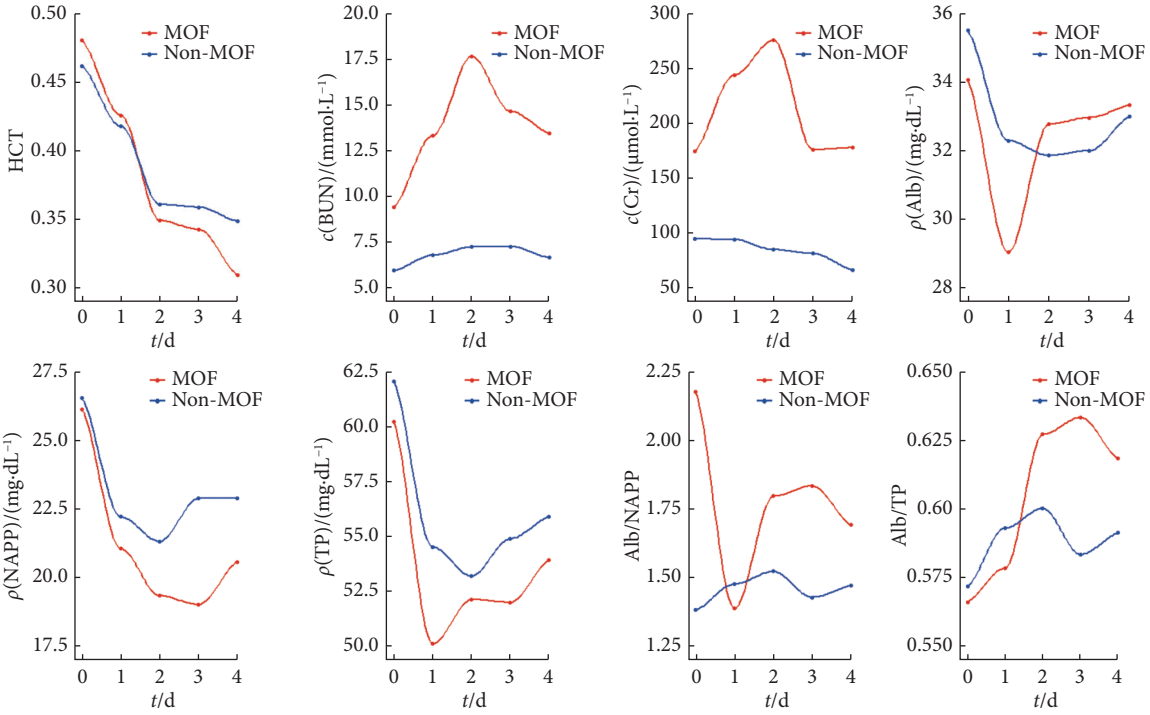

图 1 Non-MOF组和MOF组生化指标变化趋势图

Fig 1 The trends of changes in the biomarkers of in the Non-MOF and MOF groups

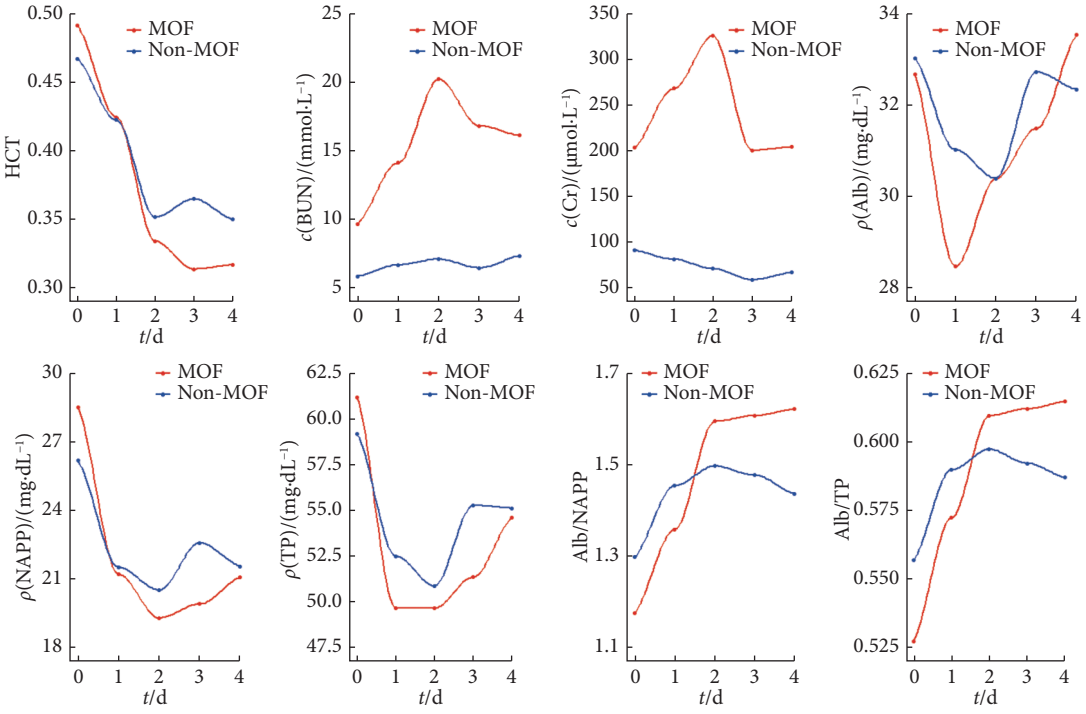

图 2 SAP合并中重度IAH亚组患者Non-MOF和MOF两组的生化指标变化趋势图

Fig 2 Trends of changes in the biomarkers of the subgroup of SAP patients combined with moderate and severe IAH in the Non-MOF and MOF groups

表 3　SAP合并中重度IAH亚组患者Non-MOF和MOF两组混合线性模型的结果

Table 3　Mixed linear model results for the subgroup of SAP patients with moderate and severe IAH in Non-MOF and MOF groups

Coefficient	HCT		BUN		Cr		Alb	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Intercept	0.44 (0.43 to 0.46)	<0.001*	6.57 (5.51 to 7.64)	<0.001*	104.38 (85.38 to 123.39)	<0.001*	32.02 (30.42 to 33.60)	<0.001*
MOF	0.034 (0.005 to 0.064)	<0.001*	4.94 (2.66 to 7.22)	<0.001*	106.02 (66.94 to 145.08)	<0.001*	−2.00 (−4.70 to 0.69)	0.153
Admission day	−0.030 (−0.035 to −0.026)	0.02*	0.19 (−0.11 to 0.49)	0.22	−6.83 (−11.17 to −2.48)	0.002*	−0.15 (−0.85 to 0.54)	0.167
Day-by-MOF interaction	−0.014 (−0.023 to −0.005)	0.002*	0.84 (0.24 to 1.44)	0.007*	−2.296 (−6.30 to 10.91)	0.60	0.78 (0.19 to 1.75)	0.167

Coefficient	TP		NAPP		Alb/NAPP		Alb/TP	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Intercept	55.64 (53.47 to 57.81)	<0.001*	24.52 (23.46 to 25.58)	<0.001*	1.39 (1.30 to 1.48)	<0.001*	0.575 8 (0.559 6 to 0.59)	<0.001*
MOF	−0.48 (−4.15 to 3.19)	0.8	1.13 (−0.812 to 3.04)	0.257	−0.16 (−0.309 to −0.010)	0.04*	−0.034 (−0.06 to 0.075)	0.014*
Admission day	−0.86 (−1.88 to 0.16)	0.101	−0.998 (−1.51 to −0.49)	<0.001*	0.033 (−0.005 to 0.072)	0.09	0.007 (0 to 0.014)	0.056
Day-by-MOF interaction	−0.36 (−1.99 to 1.26)	0.67	−0.81 (−1.69 to 0.07)	0.07	0.10 (0.042 to 0.16)	0.001*	0.019 (0.000 8 to 0.030)	0.001*

OR: odds ratio; CI: confidence interval. * $P < 0.05$, the mixed linear model showed that the MOF group had increased mean levels of HCT, BUN, and Cr as well as increased HCT and BUN levels over time as shown in the interaction term "Day-by-MOF interaction."

2.3.2　BUN和Cr

MOF组患者入院当天的BUN和Cr水平高于Non-MOF组，差异均有统计学意义（$P<0.001$）。并且入院后5 d内，MOF组的BUN和Cr水平仍持续上升，而Non-MOF组增加幅度不大，差异有统计学意义（$P<0.001$）（图1）。在合并中重度IAH亚组患者中，变化趋势一致，入院当天至第4天，MOF组的BUN和Cr水平高于Non-MOF组（$P<0.001$）（图2和表3）。线性模型分析结果也证实在合并IAH亚组的患者中，MOF组与Non-MOF组Cr和BUN比值比（odds ratio, OR）及95%置信区间（confidence interval, CI）分别是4.94（2.66 ~ 7.22）和106.02（66.94 ~ 145.08），差异有统计学意义（表3）。

2.3.3　Alb、NAPP和TP

两组Alb、TP水平均在入院后开始迅速下降，前者第1天跌至最低，MOF组下降速度更快，且差异有统计学意义（$P=0.001$），后续Alb、TP水平逐渐升高。与Alb和TP不同，NAPP水平在入院后第1、2、3天均下降，且MOF组入院后第3天低于Non-MOF组（$P<0.001$）（图1）。与Non-MOF组Alb/TP比较，MOF组入院时小于前者，入院后第2天该比值增大，但仅第3天两组差异有统计学意义（$P=0.001$）；而MOF组入院时Alb/NAPP高于Non-MOF组，入院后第1天该比值显著下降后迅速上升，在入院后第3、4天两组差异有统计学意义（$P=0.001$），反映出MOF组中NAPP的丢失更大（图1）。在SAP合并中重度IAH亚组患者中（图2），Alb、TP、NAPP、Alb/TP均表现出类似趋势变化，MOF组入院后第1天Alb水平，入院后第3天TP、NAPP水平低于Non-MOF组，差异有统计学意义（$P<0.05$）。而Alb/NAPP变化趋势不同，与Non-MOF组比较，入院时合并中重度IAH的MOF组增高，在入院后第1天该值降低后开始逐渐升高，于入院后第2天超过Non-MOF组，但差异无统计学意义。线性模型分析结果也证实在合并IAH亚组的患者中，MOF组与Non-MOF组Cr〔OR（95%CI）：4.94（2.66 ~ 7.22），$P<0.001$〕和BUN〔*OR*（95%CI）：106.02（66.94 ~ 145.08），$P<0.001$〕差异有统计学意义（表3）。

3　讨论

毛细血管渗漏被认为是包括SAP、脓毒症、烧伤等急性重症疾病从炎症向多器官损伤进展的重要机制，而MOF是影响SAP病死率权重最大的因素（OR= 16.7）[20]。近年来陆续有研究报道血管内皮生长因子、血管生成素-1、血管生成素-2、E-选择素、E-钙黏蛋白、细胞间粘附分子-1等生物标志物可反映内皮功能损伤，并预测AP病情严重程度，但目前尚未在临床常规开展[21-22]。2020年美国KOMARA等[11]提出的CLS模型纳入能反映循环（血液浓缩情况，HCT）、内皮功能（Alb、TP和NAPP）、胰腺灌注情况（胰腺坏死）和肾脏功能（BUN、Cr）的指标，认为Alb、TP和NAPP水平的动态变化可以作为反映CLS的生物标志物，NAPP丢失是CLS导致重症患者发生MOF最可能的机制。然而该研究样本量较小，仅57例，且

尚无外部验证。本研究共纳入SAP患者171例,结果显示与KOMARA等研究一致,无论是否发生MOF,入院当天HCT水平均较高,意味着均存在血液浓缩,但本研究两组差异无统计学意义,可能与本研究患者发病时间为48 h以内,美国研究纳入的患者发病时间更早有关。相比于单器官衰竭,MOF组并发肾脏衰竭的比例明显升高,本研究中Cr与BUN作为反映肾脏灌注不足和滤过减少的生物标志物,其水平明显高于Non-MOF组,且发生时间早持续时间长,线性模型分析结果也证实在合并IAH亚组的患者中,MOF组与Non-MOF组Cr和BUN水平的差异有统计学意义,进一步明确了肾脏功能评估是早期识别CLS发生的前哨器官。

MOF组入院后Alb、NAPP、TP水平开始快速下降并持续,意味着早期内皮细胞严重损伤。而Alb和TP水平在Non-MOF组中从入院后第2天开始逐渐回升,意味着毛细血管渗漏得到调控,MOF组的毛细血管渗漏入院后第1天即出现失调,且随着病情进展持续存在。在SAP并发IAH患者亚组分析中,与Non-MOF组相比,MOF组Alb/NAPP的变化意味着该组患者中NAPP的丢失发生更早、更严重、持续时间更长(图2)。并且线性模型分析结果显示Alb/NAPP在两个亚组间模型和随时间变化趋势比较,差异均有统计学意义〔OR(95%CI):−0.16(−0.309 ~ −0.010),P= 0.04〕(表3)。上述结果均证实了血浆蛋白,尤其是大分子的NAPP水平变化是Non-MOF组与MOF组及合并IAH亚组趋势变化的显著差异性生物标志物。炎症导致内皮损伤是血管渗漏发生的主要机制,最早从血管内漏出的小分子蛋白为Alb,而当渗漏调控失调即表现为血管内NAPP为主的丢失[23]。NAPP包括免疫球蛋白、载脂蛋白、纤维蛋白原等,它们在免疫反应、凝血和修复过程中起着重要作用。当NAPP开始大量丢失时,毛细血管渗漏已难以调节,而NAPP(如球蛋白、免疫球蛋白、纤维蛋白原等)的渗出增大淋巴系统负担,加重回流障碍,第三间隙内液体积聚不断增加,有效血容量不足,以及腹腔内压力增加,均加重器官组织灌注不良,缺血缺氧难以纠正,以AKI最为常见。NAPP的丢失还会激活免疫系统,通过增加毛细血管的通透性、改变血液流变性,血液黏度上升,红细胞变形能力下降,加重微循环障碍,同时亦加重炎症,促MOF进展。综上,本研究结果证实该CLS模型合理,CLS可能是从SIRS进展到MOF过程中关键机制。早期液体复苏是SAP最重要的支持治疗之一,然而目前尚无公认的合理补液策略。本研究结果为早期识别CLS提供一些证据,在液体复苏过程中上述指标的变化也可能作为液体复苏治疗效果的评估及为后续补液方案提供指导,另外,对于合并休克或液体无反应性的重症患者,适当的液体复苏早期联合使用血管活性药物也许是未来值得研究的方向,也期待若能针对NAPP丢失的机制更深入地研究,挖掘潜在的靶点阻断血管渗漏[24]。

本研究具有一定的局限性。首先,本研究所观察入院后连续5 d的常见生化指标为建模参数,无法全面反映整个疾病发展动态过程,有一定的局限性。其次,本研究关注了血浆蛋白水平变化,但并未采集Alb补充情况,可能对结果有一定干扰。再次,尽管以AIH程度分组后,Non-MOF组和MOF组合并AIH的发生率的差异并无统计学意义(结果未展示),可能与测量膀胱压需安置尿管有创操作,故无AIH或轻度AIH患者样本量较少有关。最后,由于本研究采用探索性分析和回顾性队列,存在一定假阳性风险和偏倚。

总之,本研究通过回顾性大样本队列研究证实了NAPP丢失是CLS发生并导致SIRS向MOF进展的重要中间环节,验证了匹兹堡大学提出的SAP患者CLS模型,同时也发现在亚组分析(合并中重度IAH的MOF组)患者中,所有指标及动态变化趋势差异更为显著,该模型也具有合理性,但仍有待大样本前瞻性研究进一步验证。

* * *

作者贡献声明 吴雪滢负责正式分析、初稿写作和审读与编辑写作,李兰负责研究方法和可视化,石佳华负责验证,李洁负责调查研究,李紫钰负责数据审编和软件,林子琦负责提供资源和经费获取,刘婷婷负责项目研究管理,金涛负责论文构思和审读与编辑写作,夏庆负责监督指导。所有作者已经同意将文章提交给本刊,且对将要发表的版本进行最终定稿,并同意对工作的所有方面负责。

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