

• 临床研究 •

发热伴血小板减少综合征患者脏器损伤特征研究

张晓敏^{1,2}, 张忠满², 朱轶², 武澎^{3*}

¹无锡市第二人民医院(江南大学附属中心医院)急诊医学科, 江苏 无锡 214002; ²南京医科大学第一附属医院急诊医学科; ³心血管内科, 江苏 南京 210029

[摘要] 目的: 对发热伴血小板减少综合征(severe fever with thrombocytopenia syndrome, SFTS)患者脏器损伤特征进行总结。方法: 回顾性收集2023年1月—2024年12月于南京医科大学第一附属医院就诊并收住入院的SFTS患者, 统计住院期间并发脏器损伤情况, 通过Logistic回归分析探讨脏器损伤与预后相关性, 最终构建基于SFTS患者脏器损伤评估的出院转归预测列线图。结果: 共纳入284例SFTS患者, 共有252(88.7%)例SFTS患者合并脏器损伤, 其中, 心脏是最常累及的脏器。多因素logistic回归分析结果显示, 年龄(OR=1.103, 95%CI: 1.042~1.176, $P=0.001$)、胰腺损伤(OR=3.414, 95%CI: 1.296~9.299, $P=0.014$)、肾损伤(OR=16.365, 95%CI: 5.699~53.234, $P<0.001$)、肺损伤(OR=3.805, 95%CI: 1.494~9.955, $P=0.005$)和脑损伤(OR=3.414, 95%CI: 1.283~9.289, $P=0.014$)可独立增加SFTS患者死亡风险。构建基于SFTS患者脏器损伤评估的出院转归预测列线图可准确预测患者出院转归, Bootstrap抽样1 000次行内部验证显示平均受试者工作特征(receiver operating characteristic, ROC)曲线下面积为0.937(95%CI: 0.910~0.965)。结论: SFTS患者大多合并脏器损伤, 年龄增加和胰腺、肾、肺、脑损伤增加SFTS患者死亡风险。基于脏器损伤的出院转归预测列线图具有良好的临床应用价值。

[关键词] 发热伴血小板减少综合征; 脏器损伤; 列线图

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Characteristics of organ injury in patients with severe fever with thrombocytopenia syndrome

ZHANG Xiaomin^{1,2}, ZHANG Zhongman², ZHU Yi², WU Peng^{3*}

¹Department of Emergency Medicine, Wuxi No.2 People's Hospital (Jiangnan University Medical Center), Wuxi 214002; ²Department of Emergency Medicine; ³Department of Cardiology, the First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China

[Abstract] **Objective:** To summarize the characteristics and patterns of organ injury in patients diagnosed with severe fever with thrombocytopenia syndrome (SFTS). **Methods:** A retrospective analysis was conducted on patients with SFTS admitted to the First Affiliated Hospital of Nanjing Medical University between January 2023 and December 2024. During hospitalization, concurrent organ injuries were recorded and statistically analyzed. Logistic regression analysis was performed to evaluate the association between organ injury and prognosis. Furthermore, a nomogram was developed to predict discharge outcomes based on organ injury assessment in SFTS patients. **Results:** A total of 284 SFTS patients were enrolled in this study, among whom 252 (88.7%) exhibited signs of organ injury. Cardiac injury was most commonly observed. Multivariate logistic regression analysis revealed that age (OR=1.103, 95%CI: 1.042–1.176, $P=0.001$), pancreatic injury (OR=3.414, 95%CI: 1.296–9.299, $P=0.014$), renal injury (OR=16.365, 95%CI: 5.699–53.234, $P<0.001$), pulmonary injury (OR=3.805, 95%CI: 1.494–9.955, $P=0.005$), and cerebral injury (OR=3.414, 95%CI: 1.283–9.289, $P=0.014$) were independently associated with increased risk of in-hospital mortality in SFTS patients. The constructed nomogram demonstrated strong predictive performance for discharge outcomes. Internal validation using the bootstrap method (resampling=1 000) showed an average area under the receiver operating characteristic (ROC) curve of 0.937 (95%CI: 0.910–0.965). **Conclusion:** The majority of SFTS patients experienced concurrent organ injuries. Increased age these, pancreatic, renal, pulmonary, and cerebral injuries were

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*通信作者(Corresponding author), E-mail: wupeng@njmu.edu.cn (ORCID: 0009-0007-7881-0555)

significantly associated with increased mortality risk. The nomogram based on organ injuries for predicting discharge outcomes had good clinical application value.

[Key words] severe fever with thrombocytopenia syndrome; organ injury; nomogram

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发热伴血小板减少综合征(severe fever with thrombocytopenia syndrome, SFTS)是SFTS病毒(又称新型布尼亚病毒)引起的一种传染病,自中国学者首次分离明确病原体后以来,已在东亚多个国家广泛流行^[1-4]。随着诊断技术的提高,我国报告病例数呈现逐年上升趋势,目前已成为一个重要的公共卫生问题。其临床表现以急性发热、血小板减少和白细胞减少为特征,病死率高达5.1%~32.6%^[3-5]。病毒首先在单核-巨噬细胞系统中复制,进而扩散至全身各器官组织,引起血管内皮损伤和系统性炎症反应^[6],最终引发多器官功能障碍综合征,导致不良结局。本研究通过回顾本中心SFTS患者临床数据,对合并脏器损伤的临床特征进行总结,旨在加深医务人员对该疾病的临床认识。

1 对象和方法

1.1 对象

本研究为回顾性观察性研究,收集2023年1月—2024年12月于南京医科大学第一附属医院就诊并收住入院的SFTS患者。排除标准包括:①年龄<18岁;②既往半年内发生过急性冠脉综合征;③慢性肾病、慢性肝病、慢性心功能不全、慢性胰腺炎;④既往神经功能缺陷。根据出院生存状态分为存活组和死亡组。本研究通过了南京医科大学第一附属医院伦理委员会的审核(伦理号:2025-SR-590),患者均知情同意。

1.2 方法

本研究中所有病例均经SFTS病毒核酸检测阳性确诊。心肌损伤诊断标准参照《重症发热伴血小板减少综合征诊治专家共识》^[7]中关于SFTS相关性病毒性心肌炎的具体描述,并将肌钙蛋白(本研究为超敏肌钙蛋白T)升高作为必备要求,肝损伤诊断参照《成人急性肝损伤诊疗急诊专家共识》^[8],胰腺损伤诊断参照《中国急性胰腺炎诊治指南(2021)》中急性胰腺炎诊断标准^[9],肾损伤参照改善全球肾脏病预后组织(KDIGO)制定的急性肾损伤(acute kidney injury, AKI)诊断标准^[10],肺损伤依据急性呼吸窘迫综合征最新定义进行判别^[11]。脑损伤诊断标准参

照《重症发热伴血小板减少综合征诊治专家共识》^[7]中关于SFTS相关脑炎的具体描述并将格拉斯哥昏迷评分(Glasgow coma scale, GCS)<15分作为必要标准。

收集患者一般资料,包括年龄和性别、症状[发热、消化道症状(包括腹痛、腹泻、恶心、呕吐)、呼吸道症状(包括咳嗽、咳痰、胸闷、呼吸困难)、神经系统症状(包括嗜睡、谵妄、肌肉震颤)]、有无显性出血及出血部位、接触史、病毒载量、血小板计数、既往病史、个人史、入室首次及病程中实验室检查(包括血常规、生化、心肌标志物、淀粉酶、凝血功能、动脉血气等)、住院期间影像学检查。

1.3 统计学方法

使用R 4.0软件进行统计学分析,采用Shapiro-Wilk检验对计量资料进行正态性检验,正态分布资料以均数±标准差($\bar{x} \pm s$)表示,偏态资料以中位数(四分位数)[$M(P_{25}, P_{75})$]表示,组间比较分别采用成组 t 检验及Mann-Whitney U 检验。计数资料以频数和构成比表示,组间比较采用卡方检验或Fisher确切概率法。通过多因素Logistic回归探讨各脏器损伤与SFTS患者出院结局的相关性并构建预测列线图,针对预测列线图采用Bootstrap重抽样1000次行内部验证,以受试者工作特征(receiver operating characteristic, ROC)曲线和曲线下面积(area under curve, AUC)评价区分度,校准曲线评价校准度。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 SFTS患者临床特征

共309例患者符合SFTS诊断标准,排除既往半年内发生过急性冠脉综合征6例,慢性肾病1例,慢性肝病3例,慢性心功能不全4例,慢性胰腺炎2例,既往神经功能缺陷5例,同时合并慢性心功能不全与慢性肾病患者2例,同时合并慢性心功能不全与既往神经功能缺陷2例,最终共284例纳入本研究。其中,男156例(54.9%),中位年龄68岁,229例(80.6%)存活出院(表1)。

2.2 SFTS患者合并脏器损伤特征分析

共有252例(88.7%)SFTS患者合并脏器损伤,

表1 SFTS患者临床特征
Table 1 Clinical characteristics of patients with SFTS

Variable	Total(n=284)	Survivor group(n=229)	Death group(n=55)	P
Age[years, $M(P_{25}, P_{75})$]	68(60, 74)	67(59, 72)	73(63, 77)	<0.001
Male[n(%)]	156(54.9)	128(55.9)	28(50.9)	0.505
Main symptoms[n(%)]				
Fever	278(96.9)	224(97.8)	54(98.2)	1.000
Digestive tract symptoms	153(53.9)	125(54.6)	28(50.9)	0.623
Respiratory symptoms	39(13.7)	27(11.8)	12(21.8)	0.052
Neurological symptoms	60(21.1)	37(16.2)	23(41.8)	<0.001
Bleeding	38(13.4)	29(12.7)	9(16.4)	0.469
Tick exposure[n(%)]	64(22.5)	52(22.7)	12(21.8)	0.887
Viral load[$\times 10^5$ copies/mL, $M(P_{25}, P_{75})$]	9.6(1.0, 86.3)	4.6(0.6, 38.5)	3 370.0(32.2, 3 545.0)	<0.001
Temperature[$^{\circ}\text{C}$, $M(P_{25}, P_{75})$]	39.0(38.5, 39.2)	39.0(38.5, 39.2)	39.0(38.5, 39.1)	0.777
Platelet count[$\times 10^9/\text{L}$, $M(P_{25}, P_{75})$]	49(34, 68)	52(37, 75)	39(25, 57)	0.001
Comorbidities[n(%)]				
Hypertension	92(32.4)	66(28.8)	26(47.3)	0.009
Coronary heart disease	7(2.5)	6(2.6)	1(1.8)	0.731
Diabetes	25(8.8)	20(8.7)	5(9.1)	0.933
Stroke	23(8.1)	16(7.0)	7(12.7)	0.161
Smoking[n(%)]	65(22.9)	50(21.8)	15(27.3)	0.389
Alcohol exposure[n(%)]	65(22.9)	50(21.8)	15(27.3)	0.389
Organ injury[n(%)]				
Myocardial injury	222(78.2)	168(73.4)	54(98.2)	<0.001
Liver injury	170(59.9)	124(54.1)	46(83.6)	<0.001
Pancreatic injury	90(31.7)	47(20.5)	43(78.2)	<0.001
Kidney injury	50(17.6)	15(6.6)	35(63.6)	<0.001
Lung injury	62(21.8)	27(11.8)	35(63.6)	<0.001
Brain injury	79(27.8)	39(17.0)	40(72.7)	<0.001

其中,心脏是最常累及的脏器,其次分别为肝脏、胰腺、脑(图1A)。177例(62.3%)合并多脏器损伤(图1B)。图1C为SFTS患者脏器损伤具体类型的频数分布图,图中可见心肌损伤是最常见的脏器损伤类型,其次为心肌损伤合并肝损伤。

2.3 SFTS患者预后危险因素分析

图1B示随损伤累及的脏器数量增加,患者死亡率增加。通过构建多因素 Logistic 回归模型以探讨脏器损伤对SFTS患者预后的影响,在校正了性别、病毒载量、入院血小板计数和高血压病史后,年龄增加和胰腺、肾、肺、脑损伤可独立增加SFTS患者死亡风险(表2)。

2.4 基于SFTS患者脏器损伤的出院转归预测列线图构建

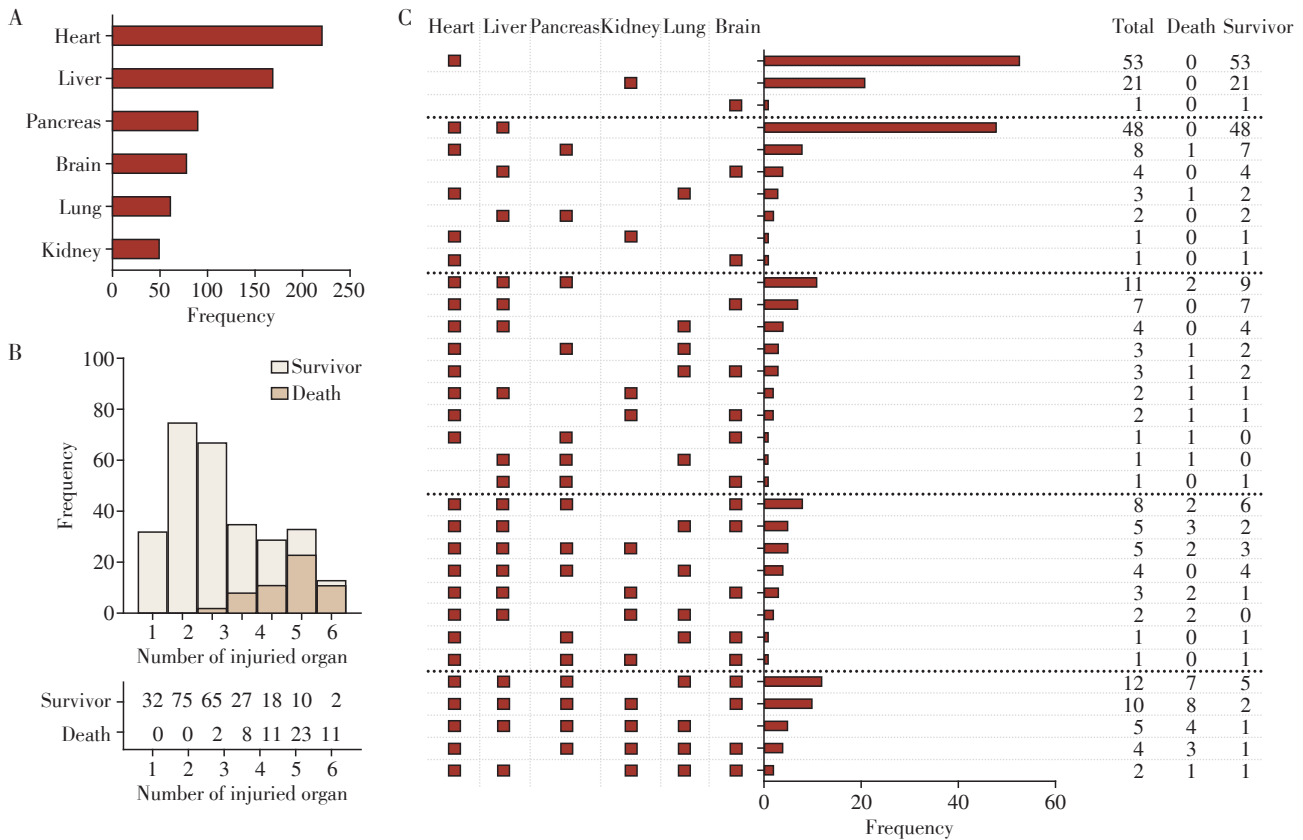
为增加临床实用性,构建基于SFTS患者脏器损伤评估的出院转归预测列线图(图2A),通过评估心、肝、胰、肾、肺、脑6个脏器是否发生损伤,可准确

预测患者出院转归,Bootstrap 内部抽样显示预测模型结果稳定,平均 AUC 为 0.937 (95% CI: 0.910~0.965)(图2B),校准曲线表现良好(图2C)。

3 讨论

SFTSV 侵入人体后常侵犯附近淋巴结,并激活免疫细胞,严重者可引发严重炎症反应和细胞因子风暴,导致多器官功能障碍^[6,12]。本研究通过对 284 例 SFTS 患者脏器损伤特征进行总结,有以下最主要发现:SFTS 患者多合并脏器损伤,其中心肌损伤是最常见类型;年龄增加,胰腺、肾、肺和脑损伤增加 SFTS 患者死亡风险;基于脏器损伤评估构建的出院转归预测列线图具有优异的区分度。

心肌和肝脏是 SFTS 患者最常累及的脏器,这与既往研究发现一致^[13-14]。目前认为 SFTS 相关心肌损伤的致病机制主要包括 SFTS 病毒的直接侵犯和继发免疫相关损伤^[15-16]。在本研究中,78.2%的



A: The frequency distribution of each organ injury in patients with SFTS. B: The frequency distribution of the number of organ injuries in patients with SFTS. C: The specific frequency.

图1 SFTS患者脏器损伤特征总结

Figure 1 Characteristics of organ injury in patients with SFTS

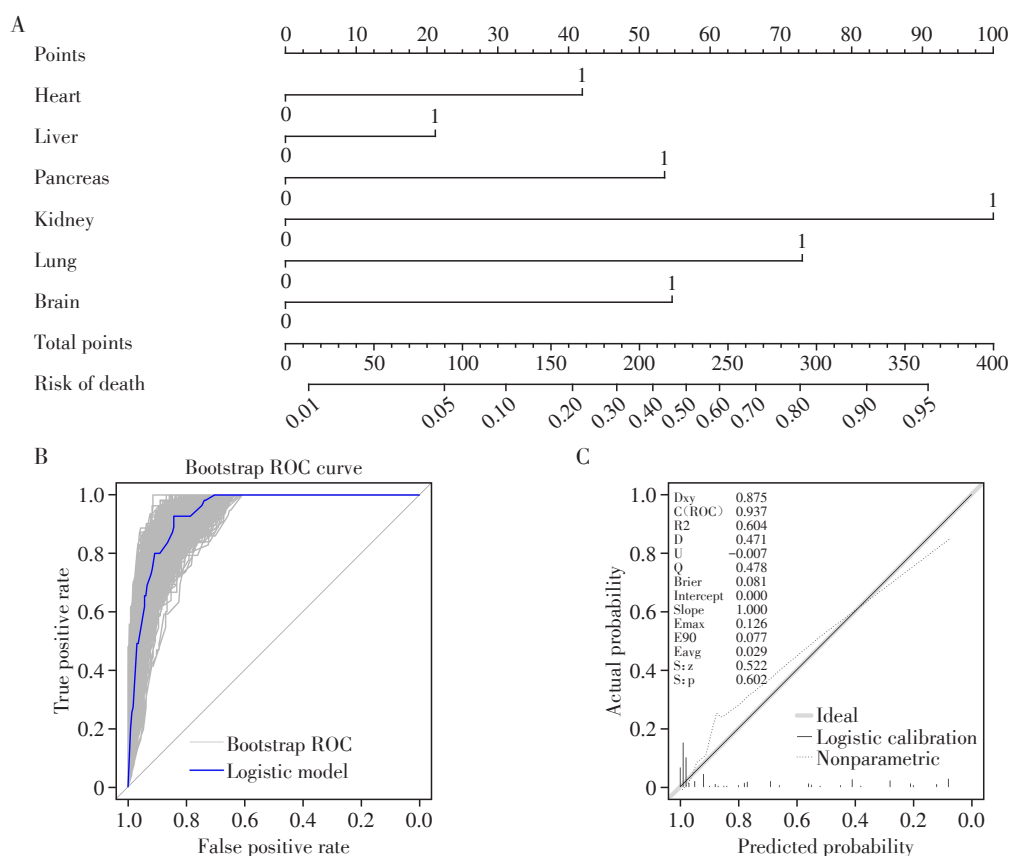
表2 多因素Logistic回归分析结果

Table 2 Multivariate logistic regression analysis

Variable	OR	95%CI	P
Age	1.103	1.042-1.176	0.001
Male	0.716	0.281-1.809	0.479
Viral load	1.000	1.000-1.000	0.976
Platelet count	1.003	0.988-1.019	0.673
Myocardial injury	1.780	0.237-39.133	0.631
Liver injury	1.432	0.471-4.571	0.530
Pancreatic injury	3.414	1.296-9.299	0.014
Kidney injury	16.365	5.699-53.234	<0.001
Lung injury	3.805	1.494-9.955	0.005
Brain injury	3.414	1.283-9.289	0.014
Hypertension	2.455	0.935-6.820	0.073

SFTS患者合并心肌损伤,主要表现为肌钙蛋白的轻度升高。肝损伤最主要的临床特征是转氨酶的异常升高,而胆红素异常升高患者占比较低,在积极治疗后肝脏功能恢复较快。仅合并心肌损伤和/或肝损伤的患者预后良好,未出现死亡病例。

与心肌和肝脏损伤不同,当累及胰腺、肾、肺和中枢神经系统时,SFTS患者死亡风险增加。并且,以上4个脏器的损伤并非孤立存在,而可能是通过炎症网络相互关联:病毒血症导致的内皮损伤是多脏器损伤的共同病理基础^[17],而脑损伤引发的神经内分泌紊乱可进一步加重脏器负担。值得注意的是,胰腺损伤在多脏器衰竭中的作用可能被低估。作为“炎症放大器”,胰腺损伤可通过以下途径加速病情恶化^[18]:①胰酶大量释放,进而激活补体系统,引发全身炎症反应;②胰腺功能障碍后可导致肠道菌群紊乱、移位,加重休克;③作为内分泌器官,胰腺损伤后胰岛素、胰高血糖素分泌异常加剧代谢紊乱。然而在既往研究中,胰腺损伤往往容易被研究者忽视。基于本研究的数据,研究团队认为关于SFTS并发胰腺损伤的专题研究需要进一步开展,以详细刻画该群体的临床特征。与另一种以发热和血小板减少为特征的疾病——肾综合征出血热相比,肾脏损伤并非SFTS患者常见受累器官,这对2种疾病的鉴别诊断有一定帮助。而在本研究中,肾损



A: The nomogram for predicting in-hospital mortality in patients with SFTS. B: The AUC of model and the internal validation using the bootstrap method(resampling=1 000). C: The calibration curve of the predictive model.

图2 基于SFTS患者脏器损伤评估的出院转归预测列线图及评价

Figure 2 Discharge outcome prediction nomogram and evaluation based on organ injury assessment of SFTS patients

伤的发生总是伴随着心肌损伤,因此,肾损伤可能是严重心肌损伤后心源性休克的并发表现。

本研究尚存一定不足:①由于回顾性质的研究特征,部分数据难以获取,本研究未对SFTS患者血液系统损伤,特别是未对并发噬血细胞性淋巴组织细胞增生症进行分析。SFTS相关脑炎目前缺乏统一明确的诊断标准,本研究中主要参照《重症发热伴血小板减少综合征诊治专家共识》中的相关描述进行诊断;②本研究虽行Bootstrap内部验证,但仍需要开展多中心研究以验证列线图在外部队列中的表现;③由于样本量限制,本研究未对脏器损伤严重程度进行分级。④本研究的核心在于揭示SFTS患者脏器损伤的特征,对多因素Logistic回归分析提示年龄为独立危险因素尚未进一步分析,而年龄与脏器损伤的潜在交互作用值得后续研究(如年龄分层分析或机制探索)深入解析。本研究的特色之一是基于脏器损伤评估构建出院转归预测列线图,结果稳定且区分度优异,评分简单易行,临床工作者仅需对SFTS患者脏器损伤进行评估即可计

算出患者死亡风险。SFTS患者大多合并脏器损伤,年龄增加和胰腺、肾、肺、脑损伤增加SFTS患者的死亡风险。基于脏器损伤的出院转归预测列线图具有良好的临床应用价值。

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Author's Contributions:

ZHANG Xiaomin was responsible for research design and draft writing; ZHANG Zhongman was responsible for data collection and analysis; ZHU Yi was responsible for plotting and collecting clinical data; WU Peng was responsible for research design and draft reviewing.

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