·临床研究·

老年重症及危重症新型冠状病毒感染患者预后的危险因素分析

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【摘 要】 **目的** 探讨影响老年重症及危重症新型冠状病毒感染患者预后的危险因素。**方法** 选择2020年1月至3月武汉某定点医院某病区收治的61例新型冠状病毒感染老年确诊患者为研究对象,回顾性分析患者的临床资料。采用SPSS 22.0统计软件进行数据分析。根据数据类型,分别采用t检验、秩和检验或χ^2检验进行组间比较。采用Cox回归模型进行患者的生存分析。**结果** 老年重症及危重症新型冠状病毒感染患者病死率为55.7%(34/61)。死亡病例具有以下特征:高龄,女性,发病时间长,合并呼吸困难症状比例高,天门冬氨酸氨基转移酶、碱性磷酸酶、乳酸脱氢酶、尿素氮、肌酐、肌酸激酶同工酶、C反应蛋白、中性粒细胞计数水平高,白蛋白、钙离子和淋巴细胞计数水平低。影响老年重症及危重症患者预后的独立危险因素是肌酸激酶同工酶($P=0.000$,$HR=1.065$,95%CI 1.034~1.096),白蛋白($P=0.001$,$HR=0.867$,95%CI 0.797~0.943),钙离子($P=0.000$,$HR=0.089$,95%CI 0.028~0.279)和呼吸困难($P=0.004$,$HR=6.538$,95%CI 1.840~23.237)。**结论** 影响老年重症及危重症新型冠状病毒感染患者预后的独立危险因素为高肌酸激酶同工酶、低白蛋白、低血钙及存在呼吸困难症状。

【关键词】 老年人;新型冠状病毒;重症及危重症;预后
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Risk factors of prognosis in severe or critically ill elderly patients infected with 2019 novel coronavirus

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【**Abstract**】 **Objective** To explore the risk factors affecting the prognosis of elderly severe or critically ill patients infected with 2019 novel coronavirus. **Methods** A total of 61 old patients (over 60 years old) infected with 2019 novel coronavirus who were admitted to a ward of a designated hospital in Wuhan from January to March 2020 were selected as the research subjects, and their clinical data were collected and retrospectively analyzed. SPSS statistics 22.0 was used for data analysis. According to data types, student's t test, rank sum test or *Chi*-square test was used for intergroup comparison. Cox regression model was used to analyze the survival of patients. **Results** The elderly patients with severe and critical illness had a mortality rate of 55.7% (34/61). The death group showed the following features: very old, female, longer time of onset, high proportion of dyspnea, higher levels of aspartate transaminase, alkaline phosphatase, lactate dehydrogenase, urea nitrogen, creatinine, creatine kinase isoenzyme, C-reactive protein and neutrophilic granulocyte count, and low levels of albumin, calcium and lymphocyte count. The independent risk factors influencing the prognosis of elderly patients with severe and critical diseases were creatine kinase isoenzyme ($P=0.000$, $HR=1.065$, 95%CI 1.034-1.096), albumin ($P=0.001$, $HR=0.867$, 95%CI 0.797-0.943), calcium ($P=0.000$, $HR=0.089$, 95%CI 0.028-0.279), and dyspnea ($P=0.004$, $HR=6.538$, 95%CI 1.840-23.237). **Conclusion** High creatine kinase isoenzyme, low albumin, low blood calcium, and dyspnea are independent risk factors for elderly severe and critically ill patients infected with 2019 novel coronavirus.

【**Key words**】 aged; 2019 novel coronavirus; severe and critical illness; prognosis

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目前新型冠状病毒已演变为全球性大流行,截至2020年11月10日,全球已有超1 420余万人受到感染,世界卫生组织报告超过126万名患者丧生。大多数新型冠状病毒感染患者症状较轻,但约有5%~20%可进展为重症或危重症,其病死率高于普通型和轻型[1,2],是临床诊治的重点人群。老年作为影响新型冠状病毒感染患者预后的独立危险因素已经被大量研究证实,且老年患者病情易发展为重

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症或危重症[2]。然而作为易感人群,基于老年重症及危重症患者的研究报道较少。因此,本研究旨在探讨影响老年重症及危重症新型冠状病毒感染患者预后的危险因素,进而更好地评估该类患者的预后。

1 对象与方法

1.1 研究对象

本研究为单中心回顾性研究,选择2020年1月至3月湖北武汉某定点医院某病区收治的61例新型冠状病毒感染老年确诊患者为研究对象,年龄≥60岁。诊断标准遵循中国国家卫健委制定的《新型冠状病毒肺炎诊疗方案(试行第七版)》。诊断标准简述为综合分析判断符合新型冠状病毒流行病学史及临床表现者,且同时具备病原学或血清学证据之一(反转录酶-聚合酶链锁反应检测新冠病毒核酸阳性或血清特异性抗体阳性)。本研究中纳入的患者均为重型及危重型,且临床治疗完整。临床分型标准同样遵循上述诊疗方案,符合下列任何一条为重型:(1)气促、呼吸频率≥30次/min;(2)静息状态下,指氧饱和度≤93%;(3)氧合指数(动脉血氧分压/吸入氧浓度百分比)≤300 mmHg(1 mmHg=0.133 kPa)。符合下列情况之一者为危重型:(1)呼吸衰竭,且需要机械通气;(2)休克;(3)合并其他器官功能衰竭需重症监护治疗。

1.2 观察指标

收集患者的基本信息及临床资料,包括性别、年龄、现病史、既往史、合并症、生化、血常规等,上述化验检查指标均为入院后首次检查结果,纳入病例的临床结局为好转出院或死亡。对上述资料进行回顾性分析。

1.3 统计学处理

采用SPSS 22.0统计软件进行数据分析。计量资料服从正态分布的采用均数±标准差($\bar{x}\pm s$)表示,组间比较采用t检验;不服从正态分布的采用中位数(四分位数间距)[$M(Q_1, Q_3)$]表示,并进行秩和检验。计数资料以例数(百分率)表示,组间比较采用χ^2检验。采用Cox回归模型进行患者的生存分析。$P<0.05$为差异有统计学意义。

2 结 果

2.1 2组患者临床资料比较

共纳入61例患者,根据临床结局将患者分为好转出院组($n=27$)与死亡组($n=34$)。比较2组临床资料发现死亡病例具有以下特征:高龄,女性,发病时间长,合并呼吸困难症状比例高,天门冬氨酸氨基转移酶、碱性磷酸酶、乳酸脱氢酶、尿素氮、肌酐、肌酸激酶同工酶、C反应蛋白、中性粒细胞计数水平高,白蛋白、钙离子和淋巴细胞计数水平低(表1)。

2.2 多因素回归分析

通过多因素Cox回归方程,将基线资料中存在差异的因素纳入方程,进一步筛选影响患者预后的独立危险因素。结果显示,影响老年重症及危重症患者预后的独立危险因素是肌酸激酶同工酶($P=0.000$, $HR=1.065$, 95% CI 1.034~1.096),白蛋白($P=0.001$, $HR=0.867$, 95%CI 0.797~0.943),钙离子($P=0.000$, $HR=0.089$, 95%CI 0.028~0.279),呼吸困难($P=0.004$, $HR=6.538$, 95% CI 1.840~23.237;表2)。

3 讨 论

新型冠状病毒引起的急性传染病,临床上分为轻型、中型、重型和危重型。其中,重型及危重型患者病情进展更为迅速,严重者出现多器官功能衰竭、脓毒血症、休克等危及生命的并发症,临床预后较其他两型更差[3]。本研究通过回顾性分析61例年龄≥60岁的重症及危重症患者的临床资料,发现死亡率高达55.7%,明显高于既往研究中重症及危重症患者17.0%的病死率[2],这可能与本研究人群为老年人群有关。近期,另一篇来自西班牙的文章报道了与本研究相近的结果,在≥80岁的高龄老年患者中,新型冠状病毒患者病死率为46.9%[4]。因此,本研究中较高的病死率可能与年龄、重症及危重症患者两个特点有关。总之,结合国外相关报道,进一步探究影响老年重症及危重症患者预后的危险因素,有助于及时采取积极有效的治疗措施,降低新型冠状病毒患者的死亡率。

本研究中,我们发现了4个对老年重症及危重症新型冠状病毒患者预后有独立影响的因素。其中肌酸激酶同工酶作为心肌标记物,可以有效反映心肌损伤情况,而超过50%的新型冠状病毒肺炎死亡可能与心肌损伤相关[1,5]。多项研究也证实肌酸激酶同工酶与新型冠状病毒感染患者入住重症监护或院内死亡密切相关[1,6]。目前认为心肌损伤的机制包括直接损伤心肌细胞、全身炎症、心肌间质纤维化、干扰素介导的免疫反应、1型和2型辅助性T细胞过度的细胞因子反应、冠状动脉斑块不稳定和缺氧[7]。

白蛋白下降与新型冠状病毒感染患者预后的关系也有多篇相关报道[8-10]。其机制可能与新冠病毒感染导致肺出现大量渗出物、从而引起白蛋白分布异常有关。此外,老年人群营养摄入不足或正常营养代谢功能的受损也可能降低白蛋白水平[11]。新型冠状病毒肺炎患者血液中不饱和脂肪酸增加,而

表 1 2 组患者临床资料比较

Table 1 Comparison of clinical data between two groups

Item	Discharge group (n=27)	Death group (n=34)	P value
Age (years, $\bar{x}\pm s$)	68.85±7.49	73.32±8.83	0.040
Male [n(%)]	20(74.1)	14(41.2)	0.021
Critically ill patients [n(%)]	3(11.1)	11(32.4)	0.050
Medical history			
Time of onset (d, $\bar{x}\pm s$)	7.07±3.09	14.32±5.99	<0.001
Fever [n(%)]	23(85.2)	33(97.1)	0.093
Fatigue [n(%)]	12(44.4)	23(67.6)	0.119
Cough [n(%)]	15(55.6)	21(61.8)	0.820
Dyspnea [n(%)]	3(11.1)	29(85.3)	<0.001
Sore throat [n(%)]	10(37.0)	12(35.3)	1.000
Diarrhea [n(%)]	3(11.1)	5(14.7)	0.975
Complications [n(%)]			
Hypertension	17(63.0)	19(55.9)	0.767
Diabetes mellitus	8(29.6)	7(20.6)	0.606
Renal insufficiency	5(18.5)	2(5.9)	0.257
CHD	2(7.4)	7(20.6)	0.281
Laboratory examination [$M(Q_1, Q_3)$]			
AST (U/L)	30.50(20.75,36.00)	44.00(31.00,76.75)	0.001
ALT (U/L)	30.50(19.50,43.75)	40.00(23.00,56.00)	0.101
Alkaline phosphatase (U/L)	51.00(41.25,64.75)	74.00(53.25,97.25)	0.008
LDH (U/L)	209.00(184.00,256.75)	541.00(399.50,589.75)	<0.001
Total bilirubin (μmol/L)	12.70(8.20,15.20)	13.65(8.27,18.75)	0.420
Albumin (g/L)	31.50(29.23,33.70)	27.90(24.57,29.40)	<0.001
Urea nitrogen (μmol/L)	4.59(3.65,7.35)	7.78(5.35,14.01)	0.001
Creatinine (μmol/L)	65.05(58.20,77.77)	87.70(70.85,97.27)	0.016
CK-MB (U/L)	11.00(8.00,13.00)	18.00(13.00,32.75)	<0.001
Calcium (mmol/L)	1.95(1.87,2.05)	1.75(1.06,1.88)	<0.001
CRP (mg/L)	7.95(3.25,15.23)	80.55(42.41,114.93)	<0.001
Neutrophil count (G/L)	3.09(2.64,4.06)	7.25(5.73,9.01)	<0.001
Lymphocyte count (G/L)	1.02(0.77,1.36)	0.59(0.41,0.90)	<0.001
Hemoglobin (g/L)	121.00(113.00,143.00)	126.00(104.75,135.00)	0.754

CHD: coronary heart disease; AST: aspartate transaminase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CK-MB: creatine kinase-MB; CRP: C-reactive protein.

表 2 多因素回归分析

Table 2 Multivariate regression analysis

Factor	B	SE	$Wald\ \chi^2$	P value	HR	95.0%CI
CK-MB	0.063	0.015	18.078	0.000	1.065	1.034-1.096
Albumin	-0.143	0.043	11.098	0.001	0.867	0.797-0.943
Calcium	-2.420	0.583	17.241	0.000	0.089	0.028-0.279
Dyspnea	1.878	0.647	8.422	0.004	6.538	1.840-23.237

CK-MB: creatine kinase-MB.

过多的不饱和脂肪酸通过与白蛋白结合,减少了白蛋白浓度[12]。此外,新型冠状病毒肺炎患者常出现严重的肝脏损伤[13],其中白蛋白异常则是入院时最为常见的肝脏生化指标异常[11]。白蛋白水平下降也在一定程度上反映了毛细血管通透性的改变,而新冠肺炎患者的毛细血管通透性的改变与其炎症反应程度相关。因此,白蛋白水平的下降可以反映老年重症或危重症新型冠状动病毒肺炎患者炎症反应、肝脏损伤等多方面的病理生理学改变,可以有效评估患者病情。

既往研究已证实血钙水平减低与病毒性感染或肺炎预后有关[14]。而在新型冠状病毒肺炎患者中,低钙血症也被证实与入住重症监护室、器官损伤及死亡密切相关[15,16]。老年重症或危重症新型冠状病毒肺炎患者出现血钙减低可能与以下机制有关。(1)老年患者常合并营养不良,慢性营养不良会导致维生素 D 缺乏,从而导致低钙血症[17]。(2)组织和器官的缺氧会引起细胞膜的损伤,导致钙内流[18]。(3)新型冠状病毒的包膜 E 蛋白是一种病毒孔蛋白,能形成可渗透钙通道和改变细胞内钙稳

态进而影响血钙水平[19]。(4)重症新型冠状病毒肺炎患者常出现不饱和脂肪酸升高,而不饱和脂肪酸能与钙结合,可引发急性低钙血症[20]。除血钙减低本身可以反映疾病程度外,严重的低钙血症会导致病情严重的神经内分泌和心血管并发症,进而增加死亡率[18]。同时血钙减少影响线粒体功能,导致广泛的组织器官损伤及衰竭[21]。因此在老年重症或危重症新型冠状病毒肺炎患者中密切关注血钙水平变化,及时纠正低钙血症十分重要。

呼吸困难是新型冠状病毒肺炎患者最常见的症状之一。在过去的研究中,呼吸困难多次被报道为新型冠状病毒肺炎患者病情进展为重症或入住重症监护室的预测因素[22,23]。本研究则表明,呼吸困难可预测老年重症及危重症患者的预后,这可能与呼吸困难症状可以直观显示患者缺氧状态、同时可以评估患者对于缺氧的耐受情况有关。综上所述,本研究探讨的4个因素可以综合反映患者器官损伤、缺氧程度、炎症反应等多方面情况,可以有效评估患者预后。因此在针对老年重症及危重症新型冠状病毒感染患者的诊治过程中,密切关注上述指标及症状的变化可有效评估病情进展。

本研究作为单中心回顾性研究存在一定的局限性。首先,样本量相对较小,缺乏生存患者出院后的临床资料,因此无法评估上述因素对新型冠状病毒感染患者长期预后的影响。其次,尽管我们尝试调整许多混杂因素,但其他无法衡量或未知的混杂因素可能也发挥了作用。因此研究结果尚需进一步大规模临床研究明确。

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