·临床研究·

益生菌制剂对方舱医院新型冠状病毒感染轻型患者的临床应用

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【摘 要】 目的 观察益生菌对奥密克戎变异株新型冠状病毒感染(COVID-19)轻型患者病程的影响。**方法** 回顾性分析2022年5月2日至12日上海国家会展中心方舱医院三分院病区收治的133例COVID-19轻型患者病历资料,根据是否接受了益生菌(枯草杆菌二联活菌肠溶胶囊)辅助治疗,在成年(18~59岁)和老年(≥60岁)两个年龄段分别设对照组和益生菌组,成年段共79例,其中对照组40例,益生菌组39例;老年段共54例,其中对照组28例,益生菌组26例。比较对照组和益生菌组新型冠状病毒感染核酸转阴时间、住院天数、*ORFlab*基因和*N*基因清除速率以及主要症缓解情况。采用SPSS 26.0软件统计分析。根据数据类型采用*t*检验、*Wilcoxon*秩和检验,χ^2检验或*Fisher*确切概率法检验。**结果** 成年段对照组和益生菌组间核酸转阴时间、住院天数、*ORFlab*基因及*N*基因清除速率、主要症状缓解情况的差异均无统计学意义;老年段对照组和益生菌组核酸转阴时间[11.0(9.0,13.0)和8.0(6.0,10.0)d]、住院天数[10.5(9.0,13.0)和8.0(6.0,10.0)d]的差异有统计学意义($P<0.05$),*ORFlab*基因及*N*基因清除速率、主要症状缓解情况的差异无统计学意义。核酸转阴Kaplan-Meier曲线显示,成年段对照组和益生菌组中位转阴时间(7.0和6.0 d),差异无统计学意义;老年段对照组和益生菌组中位转阴时间(11.0和8.0 d),差异有统计学意义($P=0.001$)。**结论** 益生菌辅助治疗可以促进老年奥密克戎变异株COVID-19轻型患者核酸转阴。

【关键词】 老年人;益生菌;新型冠状病毒感染;奥密克戎变异株;核酸转阴时间
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Clinical application of probiotics in patients with mild COVID-19 in a Fangcang shelter hospital

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【Abstract】 Objective To observe the effects of probiotics on the course of mild coronavirus disease 2019 (COVID-19) caused by Omicron variant. **Methods** A retrospective analysis was performed of the medical data of 133 COVID-19 patients admitted to the third ward of Fangcang shelter hospital located in the National Exhibition and Convention Center (Shanghai) from May 2 to May 12, 2022. The patients were divided into two age cohorts: adult (18-59 years old, $n=79$) and elderly (≥60 years old, $n=54$). Each cohort was further divided into control group and probiotics group according to whether they received the adjuvant treatment of probiotics (subtilis bifunctional enteric-coated capsule). Of the adult cohort, 40 patients were in the control group and 39 in the probiotics group; of the elderly cohort, 28 were in the control group and 26 in the probiotics group. The two groups in both age cohorts were compared in negative conversion time of the SARS-CoV-2 nucleic acid, length of hospital stay, clearance rates of *ORFlab* gene and *N* gene, and relief of main symptoms. SPSS 26.0 was used for statistical analysis. According to the data type, *t*-test, *Wilcoxon* rank sum test, χ^2 test, or *Fisher* exact probability method was used for inter-group comparison. **Results** In the adult cohort, there was no statistically significant difference in negative conversion time of the nucleic acid, length of hospital stay, *ORFlab* gene clearance rate, *N* gene clearance rate, and relief of main symptoms between the control group and the probiotics group. In the elderly cohort, there were statistically significant differences between the two groups in negative conversion time of the nucleic acid [11.0 (9.0, 13.0) *vs* 8.0 (6.0, 10.0) d] and the length of hospital stay [10.5 (9.0, 13.0) *vs* 8.0 (6.0, 10.0) d] ($P<0.05$ for both), but there was no statistically significant difference in the clearance rate of *ORFlab* gene and *N* gene. The Kaplan-Meier curves showed that there was no statistically significant difference in

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the median conversion time between the two groups in the adult cohort (7.0 *vs* 6.0 d; $P=0.383$), and that there was a statistically significant difference in the elderly cohort (11.0 *vs* 8.0 d). **Conclusion** The adjuvant treatment of probiotics can enhance negative conversion of the nucleic acid in the elderly patients with mild COVID-19 caused by Omicron variant.

【Key words】 aged; probiotics; coronavirus disease 2019; omicron variant; negative conversion time, nucleic acid

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2022年4月,上海出现新一轮新型冠状病毒感染(coronavirus disease 2019, COVID-19)疫情。病毒测序显示为奥密克戎变异株BA.2型和BA.2.2型,传播力更强,更容易突破疫苗防线[1]。研究报道,益生菌可通过肠-肺轴影响免疫功能,提高COVID-19患者病毒清除率[2,3],然而益生菌对奥密克戎变异株的作用目前尚不清楚。上海国家会展中心方舱医院三分院病区收治的部分轻型患者在常规治疗基础上接受了益生菌辅助治疗,本研究首次观察益生菌制剂对方舱医院COVID-19轻型患者病程的影响。

1 对象与方法

1.1 研究对象

回顾性分析2022年5月2日至12日于上海国家会展中心方舱医院三分院病区收治的COVID-19轻型患者的病历资料。诊断、分型及出院标准依据《新型冠状病毒肺炎诊疗方案(试行第九版)》[4]。疑似病例具备以下病原学或血清学证据之一者可确诊:(1)新型冠状病毒核酸检测阳性;(2)未接种新型冠状病毒疫苗者新型冠状病毒特异性免疫球蛋白M(immunoglobulin M, IgM)和免疫球蛋白G(immunoglobulin G, IgG)均为阳性。同时达到以下3条标准者可出院:(1)体温恢复正常3 d以上;(2)呼吸道症状明显好转;(3)连续2次新型冠状病毒核酸检测*N*基因和*ORFlab*基因的循环阈值(cycle threshold, Ct)均≥35(荧光定量聚合酶链式反应方法,界限值为40,采样时间至少间隔24 h)。纳入标准:(1)诊断为COVID-19轻型;(2)年龄≥18岁。排除标准:(1)伴有其他急性疾病或慢病急性加重;(2)妊娠期和哺乳期妇女。轻型患者指临床症状轻微,影像学未见肺炎表现的患者。

1.2 方法

共纳入患者133例,分为成年(18~59岁)和老年(≥60岁)两个年龄段,各年龄段内患者根据是否接受了益生菌辅助治疗分为对照组和益生菌组。成年段共79例,其中对照组40例,益生菌组39例;老年段共54例,其中对照组28例,益生菌组26例。对照组患者接受了与症状相应的对症治疗,包括连花清瘟颗粒、荆银固表方、银黄含片、复方甘草合剂、蒙脱石散、黄连素等;益生菌组患者在对症治疗基础上接受了益生菌辅助治疗。益生菌辅助治疗方法:枯草杆菌二联活菌肠溶胶囊(美常安,250 mg/粒,含活菌5亿个,其中包括屎肠球菌4.5×10^8个和枯草杆菌5.0×10^7个)口服,3次/d,每次2粒,入院当天开始服用,疗程7 d,住院时间短于7 d的患者用至出院。

1.3 观察指标

(1)核酸转阴时间,指从入院前核酸筛查阳性到住院后核酸转阴的时间;(2)住院天数;(3)*ORFlab*基因清除速率,指Ct值≥35的连续2次核酸检测中第1次的*ORFlab*基因Ct值与入院首次核酸检测Ct值之差值除以间隔天数;(4)*N*基因清除速率,指Ct值≥35的连续2次核酸检测中第1次的*N*基因Ct值与入院首次核酸检测Ct值之差除以间隔天数;(5)治疗7 d后主要症状缓解情况。

1.4 病历资料采集

采用excel软件从病例系统摘录患者性别、年龄、合并症、疫苗接种、入院前核酸阳性天数、症状、用药、核酸检测结果等信息,并进行双人校对。

1.5 统计学处理

采用SPSS 26.0统计软件进行数据分析。符合正态分布的计量资料用均数±标准差($\bar{x}\pm s$)表示,采用*t*检验;非正态分布的计量资料,用中位数(四分位数间距)[$M(Q_1,Q_3)$]表示,采用*Wilcoxon*秩和检验。计数资料用例数(百分率)表示,采用χ^2或*Fisher*确切概率法检验。描绘各年龄段对照组和益生菌组的核酸转阴Kaplan-Meier曲线,用*Log-rank*检验。$P<0.05$为差异有统计学意义。

2 结 果

2.1 各年龄段对照组和益生菌组基线资料比较

各年龄段对照组和益生菌组的性别、年龄、合并症、疫苗接种、症状和用药情况等均衡性良好,差异均无统计学意义(表1),具有可比性。

2.2 观察指标比较

成年对照组中因出现肺炎表现转至其他病区患

者 1 例,其余患者均转阴出院。成年段对照组和益生菌组核酸转阴时间、住院天数、*ORFlab* 基因及 *N* 基因清除速率比较,差异均无统计学意义。老年段益生菌组核酸转阴时间、住院天数均短于对照组,差异均有统计学意义(均 $P<0.05$);*ORFlab* 基因及 *N* 基因清除速率差异无统计学意义(表 2)。

治疗 7 d 后各年龄段对照组和益生菌组间主要症状缓解比例的差异均无统计学意义(表 3)。

表 1 各年龄段对照组和益生菌组基线资料比较

Table 1 Comparison of baseline data between control group and probiotics group in different age cohorts

Item	Adult cohort			Elderly cohort		
	Control group (n=40)	Probiotics group (n=39)	P value	Control group (n=28)	Probiotics group (n=26)	P value
Gender[n(%)]			0.900			0.793
Male	22(55.0)	22(56.4)		15(53.6)	13(50.0)	
Female	18(45.0)	17(43.6)		13(46.4)	13(50.0)	
Age[years, $M(Q_1, Q_3)$]	41.0(32.3, 47.8)	44.0(26.0, 53.0)	>0.900	65.0(64.0, 68.0)	66.0(63.8, 68.0)	0.834
Chronic diseases[n(%)]						
Diabetes mellitus	0(0.0)	0(0.0)	>0.900	4(14.3)	2(7.7)	0.736
Hypertension	1(2.5)	0(0.0)	>0.900	6(21.4)	3(11.5)	0.543
Vaccination[n(%)]			>0.900			0.576
Unvaccinated	15(37.5)	14(35.9)		11(39.3)	7(26.9)	
1 dose had been given	1(2.5)	1(2.6)		0(0.0)	0(0.0)	
2 doses had been given	11(27.5)	11(28.2)		6(21.4)	8(30.8)	
3 doses had been given	13(32.5)	13(33.3)		11(39.3)	11(42.2)	
Nucleic acid positive duration before admission[d, $M(Q_1, Q_3)$]	1.0(0,1.0)	1.0(1.0,2.0)	0.091	2.0(2.0,2.8)	2.0(2.0,3.0)	0.609
Symptom[n(%)]						
Pharyngalgia	18(45.0)	17(43.6)	0.900	8(28.5)	11(42.3)	0.291
Cough and expectoration	19(47.5)	20(51.3)	0.737	14(50.0)	10(38.5)	0.394
Nasal congestion and runny nose	15(37.5)	17(43.6)	0.581	7(25.0)	6(23.1)	0.869
Hyposmia	4(10.0)	7(17.9)	0.308	2(7.1)	2(7.7)	>0.900
Hypogeusia	5(12.5)	4(10.3)	>0.900	3(10.7)	2(7.7)	>0.900
Malaise	22(55.0)	22(56.4)	0.900	22(78.6)	21(80.8)	0.841
Nausea and vomitting	7(17.5)	2(5.1)	0.169	7(25.0)	10(38.5)	0.287
Abdominalgia and diarrhoea	5(12.5)	4(10.3)	>0.900	11(39.3)	7(26.9)	0.336
Constipation	0(0.0)	1(2.6)	0.494	6(21.4)	5(19.2)	0.841
Medication status[n(%)]						
Lianhua Qingwen granules	33(82.5)	34(87.2)	0.562	25(89.3)	25(96.2)	0.658
Jingyin Gubiao prescription	30(75.0)	28(71.8)	0.747	–	–	–
Yinhuang Buccal tablet	22(55.0)	20(51.3)	0.741	10(35.7)	13(50.0)	0.289
Compound Liquorice	13(32.5)	11(28.2)	0.678	21(75.0)	20(76.9)	0.869
Montmorillonite	3(7.5)	1(2.6)	0.626	7(25.0)	5(19.2)	0.610
Berberine	3(7.5)	1(2.6)	0.626	5(17.9)	4(15.4)	>0.900

–: no datum.

表 2 各年龄段对照组和益生菌组间核酸转阴时间、住院天数、*ORFlab* 基因及 *N* 基因清除速率比较

Table 2 Comparison of nucleic acid conversion time, length of hospital stay, *ORFlab* gene and *N* gene clearance rate between control group and probiotics group in different age cohorts [d, $M(Q_1, Q_3)$]

Item	Adult cohort			Elderly cohort		
	Control group (n=40)	Probiotics group (n=39)	P value	Control group (n=28)	Probiotics group (n=26)	P value
Nucleic acid negative conversion time	7.0(6.0,9.0)	6.0(5.0,9.0)	0.211	11.0(9.0,13.0)	8.0(6.0,10.0)	0.001
Length of hospital stay	9.0(7.0,9.0)	7.0(6.0,9.0)	0.116	10.5(9.0,13.0)	8.0(6.0,10.0)	0.001
Clearance rate of *ORFlab* gene	3.49(1.96,6.27)	2.66(1.76,3.72)	0.062	2.16(1.49,2.82)	2.35(1.66,3.73)	0.307
Clearance rate of *N* gene	3.89(2.14,6.84)	3.04(1.98,4.45)	0.108	2.01(1.68,2.78)	2.62(1.91,4.82)	0.083

表3 各年龄段对照组和益生菌组主要症状缓解比例的比较

Table 3 Comparison of main symptom relief proportion between control group and probiotics group in different age cohorts

[n(%)]

Symptom	Adult cohort			Elderly cohort		
	Control group (n=40)	Probiotics group (n=39)	P value	Control group (n=28)	Probiotics group (n=26)	P value
Pharyngalgia	14/18(77.8)	14/17(82.4)	>0.900	5/8(62.5)	7/11(63.6)	>0.900
Cough and expectoration	14/19(73.7)	16/20(80.0)	0.716	8/14(57.1)	6/10(60.0)	>0.900
Nasal congestion and runny nose	11/15(73.3)	13/17(76.5)	>0.900	5/7(71.4)	5/6(83.3)	>0.900
Malaise	18/22(81.8)	16/22(72.7)	0.721	15/22(68.2)	16/21(76.2)	0.736
Nausea and vomitting	7/7(100.0)	2/2(100.0)	>0.900	6/7(85.7)	8/10(80.0)	>0.900
Abdominalgia and diarrhoea	5/5(100.0)	4/4(100.0)	>0.900	5/6(83.3)	5/5(100.0)	>0.900

2.3 核酸转阴 Kaplan-Meier 曲线

成年段对照组中位转阴时间为7.0 d，益生菌组为6.0 d，差异无统计学意义（*Log-rank* $\chi^2=0.761$，$P=0.383$）；老年段对照组中位转阴时间为11.0 d，益生菌组为8.0 d，差异有统计学意义（*Log-rank* $\chi^2=10.107$，$P=0.001$；图1）。

2.4 成年段与老年段间核酸转阴时间比较

成年患者共79例，老年患者共54例，核酸转阴时间分别为7.0(5.0,9.0) d和10.0(7.0,12.0) d，差异有统计学意义（$P<0.05$）。

3 讨 论

本研究结果显示老年段益生菌组核酸转阴时间短于对照组，差异有统计学意义，成年段2组转阴时间差异无统计学意义，提示益生菌制剂对老年奥密克戎变异株COVID-19轻型患者核酸转阴有促进作用，而对成年患者无明显影响。两个年龄段中，主要症状缓解情况在对照组和益生菌组间的差异均无统计学意义，但由于有症状的例数少，检验效能低，症状缓解率的比较结果存疑，不能确定益生菌是否对症状缓解起作用。

目前COVID-19主要流行毒株依然是奥密克戎[4]。与德尔塔毒株相比，奥密克戎具有显著的增殖优势，导致传播迅速，发病率更高[5]。以往临床研究结果显示，接受双歧杆菌治疗的COVID-19患者，血清白细胞介素-6水平下降，死亡率从25%下降至5%[6]。补充益生菌不仅可定植并黏附在肠上皮表面，直接阻断病毒附着[7]，而且可通过触发抗病毒免疫促进病毒清除[8]。复合益生菌可显著减少COVID-19患者鼻咽部病毒载量、肺部浸润以及消化道和非消化道症状的持续时间，提高病毒清除率[9]，使呼吸衰竭的发生风险降低了8倍[10]。

益生菌使COVID-19患者获益的机制目前尚不清楚，肠-肺轴可能在其中发挥重要作用[2,3]。宏基因组测序结果显示，COVID-19患者肠道微生物组中有益菌（如粪杆菌等）丰度明显降低[11]，而且会导致病菌（如黏性放线菌等）增加[12]。补充益生菌有助于恢复肠道微生物组平衡，维持肠道屏障功能。益生菌还具有调节免疫、抗炎、抗氧化作用[13]。Gutiérrez-Castrellón等[9]发现益生菌补充剂显著增加了针对新型冠状病毒的特异性IgM和IgG，而粪便微生物群成分没有显著变化，提示益生菌主要通过调节宿主免疫系统发挥作用。因此，益生菌有可能成为COVID-19的预防或治疗策略[14]。

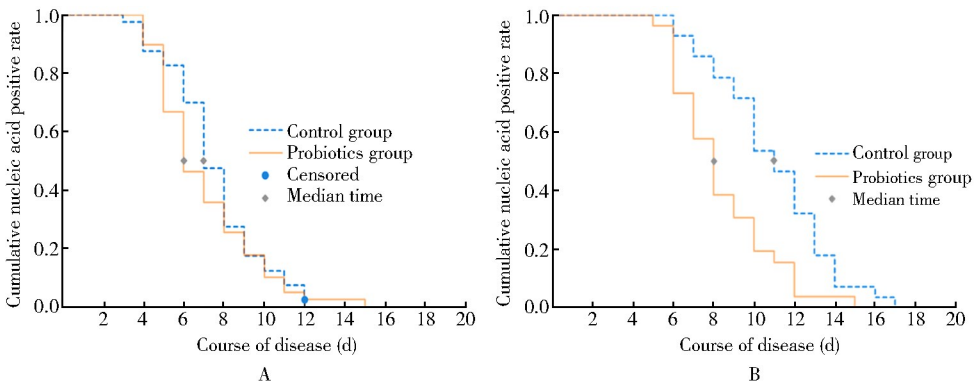

图1 各年龄段对照组和益生菌组累积核酸阳性率

Figure 1 Cumulative nucleic acid positive rate between the control group and probiotics group in different age cohorts

A: adult cohort; B: elderly cohort.

本研究中老年患者核酸中位转阴时间在益生菌组较对照组缩短 3 d,差异有统计学意义。老年人合并慢病多,肠道微生物群失调,免疫系统功能衰退[15],细胞和体液免疫反应能力受损,存在全身低度炎症状态和大量循环促炎细胞因子[16]。炎症反应在导致“细胞因子风暴”的过程中起关键作用,老年 COVID-19 更容易向重型转化[17]。老年人肠道屏障功能降低,肠道菌群失调,因此有消化道症状的老年 COVID-19 患者较多,肠-肺轴的调节机制也受到影响。补充益生菌后,肠道菌群得到一定程度调节,屏障功能提高,通过免疫调节影响肠-肺轴的作用,进而调节呼吸道微生物群,促进呼吸道病毒清除,另外益生菌可能通过免疫调节作用提高了体液免疫和细胞免疫应答水平,从而加快病毒的清除。成年患者中益生菌组核酸转阴时间短于对照组,但差异无统计学意义。益生菌对成年患者的作用不明显,可能因为成年人机体免疫系统功能较强,自身的免疫应答足以应对新冠病毒的侵袭,肠道微生物群平衡状态良好,屏障功能多正常,肠道微生物群通过肠-肺轴对呼吸道微生物群的调节作用受影响较小,因此补充益生菌后作用不明显。本研究中成年患者整体中位转阴时间明显短于老年患者,差异有统计学意义,这也印证了以上观点。

老年患者中,益生菌组 *ORFlab* 基因和 *N* 基因清除速率也大于对照组,但差异无统计学意义。可能有以下原因:(1)Ct 值是基因扩增的循环阈值,是一个指数概念,本研究将其简化为线性,取 2 次 Ct 值之差除以天数作为基因清除速率,能够反映核酸转阴趋势,但并非实际的速率值,可能对结果造成一定影响;(2)本研究筛选出的病例数较少,检验效能不够高,以至结果虽有差异但无统计学意义。

目前关于益生菌对 COVID-19 影响的相关研究不多,方舱医院内接受益生菌辅助治疗的 COVID-19 患者有限。受方舱医院条件限制,轻型患者除核酸检测外未做其他实验室检查,无法收集更多数据资料。未来需开展样本量更大、设计更严谨的前瞻性研究,验证本研究的发现,并进一步评估益生菌对 COVID-19 患者肠道微生物组稳态的影响,以及对免疫功能和肠黏膜炎症的作用。

综上,益生菌制剂对老年奥密克戎变异株 COVID-19 轻型患者具有较好的临床疗效,能显著缩短患者的核酸转阴时间,可以作为 COVID-19 的一种临床辅助治疗,更好地促进老年轻型患者恢复健康。

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