新型冠状病毒信息简报

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上海科技大学免疫化学研究所

生物医学大数据平台和高通量筛选平台领衔编译制作

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1. 2020 年 4 月 15 日疫情

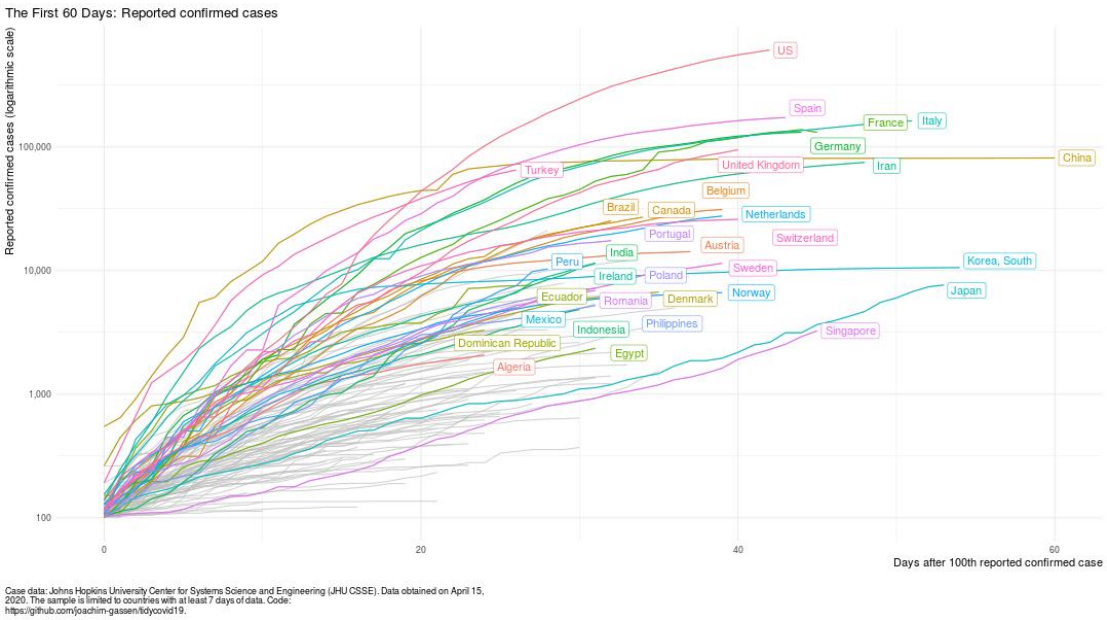
数据来源：WHO

发布时间：2020 年 4 月 15 日北京时间下午 4 点

链接：https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports

根据 WHO 提供的数据，2020 年 4 月 15 日全球累计确诊新型冠状病毒病人 1914916 例，当日新增确诊 70082 例，累计死亡 123010 例，当日新增死亡 5989。

中国累计确诊 83745 例，累计死亡 3352 例，当日新增确诊 49 例，新增死亡 1 例。



重点国家确诊数量曲线（https://jgassen.shinyapps.io/tidycovid19/，数据截止 4 月 15 日北京时间下午 4 点）

全国新型冠状病毒肺炎新增确诊病例分布图（4 月 15 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. COVID-19 在家庭内部的继发率及相关决定因素

Household Secondary Attack Rate of COVID-19 and Associated Determinants

来源：medRxiv
发布时间：2020-04-15
链接：https://www.medrxiv.org/content/10.1101/2020.04.11.20056010v1

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编译者：宋珂

中文摘要：

背景：截至 2020 年 4 月 2 日，全球报告 COVID-19 病例数已累计超过 100 万，死亡人数超过 55000 例。然而，SARS-CoV-2 病毒在家庭内部的传播能力仍然不明确。

方法：基于广州市的综合接触追踪数据，我们在人口层面上估算了病毒的有效复制率；并在个体层面上推算出家庭内部的继发率(SAR)。同时，我们评估了年龄因素对病毒传播的影响，以及潜伏期内 COVID-19 患者的传染性。

结果：共追踪到 212 例原发病例，137 例非原发病例（继发或三次传染）和 1938 例未感染的密切接触者，共分为 195 个无关联的聚类。在假设平均潜伏期为 4 天，最长传染周期为 13 天的条件下，如果将所有近亲都视为家庭接触者，我们估计家庭 SAR 为 13.8%（95% CI：11.1-17.0%）；如果仅将同一住址内的人员视为家庭接触者，则 SAR 为 19.3%（95% CI：15.5-23.9%）。儿童（<20 岁）的感染率仅是老年人（≥60 岁）的 0.26（95% CI：0.13-0.54）。感染风险未发现性别差异，而且 COVID-19 患者在潜伏期至少与发病期间拥有相同的传染性。平均而言，一个 COVID-19 患者可以感染 0.48（95% CI：0.39-0.58）位近亲。如果未实施隔离，则感染人数将增加到 0.62（95% CI：0.51-0.75）。广州市的病毒有效复制率将在大约 1 周内从高于 1 降至低于 0.5。

结论：在家庭内部，SARS-CoV-2 比 SARS-CoV 和 MERS-CoV 具有更高的传播性，并且大于 60 岁的老年人最容易受到传染。仅凭发现和单独隔离患者，可能不足以遏制疫情的扩散，需要同时在广州市内实施严格的人员活动限制。

Abstract:

Background: As of April 2, 2020, the global reported number of COVID-19 cases has crossed over 1 million with more than 55,000 deaths. The household transmissibility of SARS-CoV-2, the causative pathogen, remains elusive. Methods: Based on a comprehensive contact-tracing dataset from Guangzhou, we estimated both the population-level effective reproductive number and individual-level secondary attack rate (SAR) in the household setting. We assessed age effects on transmissibility and the infectivity of COVID-19 cases during their incubation period. Results: A total of 195 unrelated clusters with 212 primary cases, 137 nonprimary (secondary or tertiary) cases and 1938 uninfected close contacts were

traced. We estimated the household SAR to be 13.8% (95% CI: 11.1-17.0%) if household contacts are defined as all close relatives and 19.3% (95% CI: 15.5-23.9%) if household contacts only include those at the same residential address as the cases, assuming a mean incubation period of 4 days and a maximum infectious period of 13 days. The odds of infection among children (<20 years old) was only 0.26 (95% CI: 0.13-0.54) times of that among the elderly (≥60 years old). There was no gender difference in the risk of infection. COVID-19 cases were at least as infectious during their incubation period as during their illness. On average, a COVID-19 case infected 0.48 (95% CI: 0.39-0.58) close contacts. Had isolation not been implemented, this number increases to 0.62 (95% CI: 0.51-0.75). The effective reproductive number in Guangzhou dropped from above 1 to below 0.5 in about 1 week. Conclusion: SARS-CoV-2 is more transmissible in households than SARS-CoV and MERS-CoV, and the elderly ≥60 years old are the most vulnerable to household transmission. Case finding and isolation alone may be inadequate to contain the pandemic and need to be used in conjunction with heightened restriction of human movement as implemented in Guangzhou.

Table 1. Demographic compositions of the study population stratified by case type (primary, nonprimary and non-case) and contact type (household and non-household). Percentages are presented in parentheses. Non-primary incidence is calculated as the number of non-primary cases divided by the sum of non-primary cases and non-cases.

Demographic feature	Category	Primary cases	Nonprimary cases		Non-cases		Overall	Non-primary Attack Rate (%)	
			Household	Non-household	Household	Non-household		Household	Non-household
Age group	<20	10 (5)	9 (9)	1 (3)	162 (24)	72 (6)	254 (11)	5.26 (2.43, 9.76)	1.37 (0.035, 7.4)
	20-59	142 (67)	62 (64)	30 (75)	390 (58)	950 (75)	1574 (69)	13.72 (10.68, 17.24)	3.06 (2.07, 4.34)
	≥60	60 (28)	26 (27)	9 (22)	121 (18)	243 (19)	459 (20)	17.69 (11.89, 24.83)	3.57 (1.65, 6.67)
Gender	Female	105 (50)	56 (58)	20 (50)	340 (51)	617 (49)	1138 (50)	14.14 (10.86, 17.97)	3.14 (1.93, 4.81)
	Male	107 (50)	41 (42)	20 (50)	333 (49)	648 (51)	1149 (50)	10.96 (7.98, 14.58)	2.99 (1.84, 4.59)
Origin	Imported	171 (81)	50 (52)	27 (67)					
	Local	41 (19)	47 (48)	13 (33)					
Total		212 (100)	97 (100)	40 (100)	673 (100)	1265 (100)	2287 (100)	12.60 (10.34, 15.15)	3.06 (2.2, 4.15)

3. 可靠性高的 SARS-CoV-2 等温扩增和检测，包括用粗酶

High-surety isothermal amplification and detection of SARS-CoV-2, including with crude enzymes

来源：bioRxiv

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编译者：宋张悦

中文摘要：

等温核酸扩增方法（iNAT），如环介导等温扩增（LAMP），由于需要的仪器相对简单，所以是基于聚合酶链式反应（PCR）检测方法的很好的选择，特别是在护理点或使用资源有限的情况下。但是，iNATs 会产生假扩增子，特别是在没有目标序列的情况下，导致假阳性结果。如果信号是基于非序列特异性探针，如嵌入式染料或 pH 值变化，则尤其如此。此外，致病菌经常被证明是移动的、进化的目标，而且会积累突变，这将导致无效的引物结合，从而产生假阴性结果。针对目标序列不同区域的内部冗余检测有助于减少这种假阴性。在文中，研

究人员描述了三种先前已报道的依赖于非序列特异性读取结果的 SARS-CoV-2 LAMP 检测方法，快速转化为可以用序列特异性荧光寡核苷酸链置换(OSD)探针可视化读取的检测方法。研究人员还评估了一管化操作单个和多重 LAMP-OSD 的检测方法，并证明了用 LAMP-OSD 方法可以在人唾液中检测到 SARS-CoV-2 病毒。

研究人员选了文献中已经报道的三组 LAMP 扩增引物，分别命名为 Tholoth、Lamb 和 NB 引物组，扩增的目标序列是 SARS-CoV-2 的 ORF1AB 和 N 基因，针对三组引物，研究人员分别设计了三个序列特异性的 OSD 探针，探针由一条 5’带 FAM 荧光标记的长链和一条 3’带猝灭基团的互补短链组成。Tholoth 和 NB OSD 探针的结合区域与正向环引物(LF)重叠，所以要去掉原先这两组引物中的 LF 引物。Lamb OSD 探针与原先的 LF 引物没有重叠，所以研究人员做了两组实验，分别是去掉 LF（5-primer）以及留下 LF（6 primer Lamb，信号更强）的实验。研究人员还做了单个和多重 LAMP-OSD 检测比较，结果显示 Tholoth 和 NB 两组引物混合检测的信号更强。由于 OSD 探针带荧光信号，所以结果可以在荧光定量 PCR 仪上实时分析，也可以在终点用手机和蓝色 LED 透照器或 BioRad ChemiDoc 相机拍照，可以目测“有/没有”的结果。利用 LAMP-OSD 方法，研究人员证明可以在人的唾液中直接检测到 SARS-CoV-2 病毒（Figure 6）。此外，研究人员还开发了一种开源酶 Bst-LF 来替代商品化的 Bst 酶。

Abstract:

Isothermal nucleic acid amplification tests (iNAT), such as loop-mediated isothermal amplification (LAMP), are good alternatives to polymerase chain reaction (PCR)-based amplification assays, especially for point-of-care and low resource use, in part because they can be carried out with relatively simple instrumentation. However, iNATs can generate spurious amplicons, especially in the absence of target sequences, resulting in false positive results. This is especially true if signals are based on non-sequence-specific probes, such as intercalating dyes or pH changes. In addition, pathogens often prove to be moving, evolving targets, and can accumulate mutations that will lead to inefficient primer binding and thus false negative results. Internally redundant assays targeting different regions of the target sequence can help to reduce such false negatives. Here we describe rapid conversion of three previously described SARS-CoV-2 LAMP assays that relied on non-sequence-specific readout into assays that can be visually read using sequence-specific fluorogenic oligonucleotide strand exchange (OSD) probes. We evaluate one-pot operation of both individual and multiplex LAMP-OSD assays and demonstrate detection of SARS-CoV-2 virions in crude human saliva.

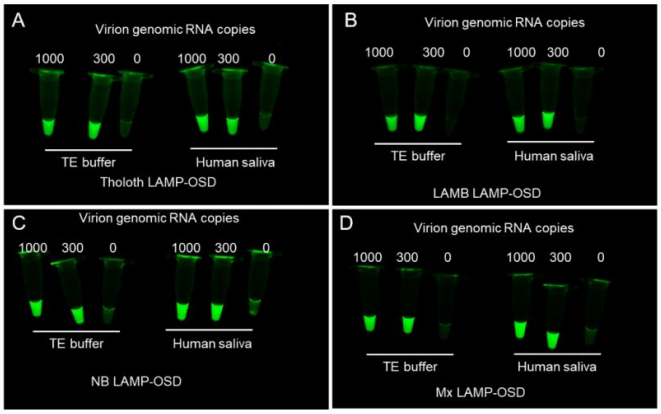

Figure 6. LAMP-OSD analysis of human saliva containing SARS-CoV-2 virions.

Indicated virion amounts were spiked in TE buffer or human saliva and added to individual or multiplex (Mx) LAMP-OSD assays. Endpoint images of OSD fluorescence are depicted for Tholoth (A), 6 primer LAMB (B), and NB(C) individual LAMP-OSD assays and Tholoth+NB Mx LAMP-OSD assays (D).

4. 自行收集的唾液和鼻拭子与临床医生收集的鼻咽拭子相比用于Covid-19检测具有相当的敏感性

Self-Collected Oral Fluid and Nasal Swabs Demonstrate Comparable Sensitivity to Clinician Collected Nasopharyngeal Swabs for Covid-19 Detection

来源：medRxiv

发布时间：2020-04-11

链接：https://www.medrxiv.org/content/10.1101/2020.04.11.20062372v1

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DOI或PUBMED ID：Preprint

编译者：张鹏伟

中文摘要：

背景：目前，由2019年严重急性呼吸综合征冠状病毒2（SARS-CoV-2）引起的大流行导致了Covid-19。作者想比较样本类型和采集方法，以探索一种更简单的收集样本方式是否可以扩大测试的范围。

方法：作者通过一个测试项目（drive-through）招募了一些人进行SARS-CoV-2感染测试。在参与者家中，作者评估了在有或无临床医生监督的情况下自行收集唾液拭子样本的能力，临床医生监督自行采集中鼻甲（鼻）拭子样本，临床医生采集鼻咽拭子样本。他们用验证的逆转录定量聚合酶链反应（PCR）检测标本中的SARS-CoV-2，并测量循环阈值。还记录每个参与者的症状状态和症状开始日期。

结果：作者招募了45名参与者。研究的参与者年龄中位数为42岁（四分位距，31至52岁）。在受试者中，29人是至少有一个样本的SARS-CoV-2检测呈阳性。其中，29人中有21人（73%）出现明显症状。采用标本分型和家庭采集的方法，临床医生监督自取唾液拭子感染标本29例中检出26例（90%），临床医生监督自取鼻腔拭子标本27例中检出23例（85%），临床医生采集鼻咽后拭子标本29例中检出23例（79%），而未经监测的自行采集的唾液拭子样本29份中检出19份（66%）。尽管鼻咽拭子被认为是黄金标准，但4个被临床医生采集的鼻咽拭子的参与者检测为阴性，被其他3种样本检测为阳性。此外，每个样本类型的假阴性结果通常不重叠。

结论：在监督下自行采集的唾液和鼻拭子样本与临床医生采集的鼻咽拭子样本相似（如果不是更好的话），用于检测SARS-CoV-2感染。没有样本类型捕捉到所有SARS-CoV-2感染，这表明个体之间呼吸道不同部位的病毒载量分布存在潜在的异质性。监督下的自我收集与临床医生收集类似，通过减少对训练有素的医护人员的需求，减少医护人员的暴露，以及减少在严重短缺期间用于测试的PPE（个人防护设备）数量，就可以快速扩大美国的检测能力。

Abstract:

Background: Currently, there is a pandemic caused by the 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes Covid-19. We wanted to compare specimen types and collection methods to explore if a simpler to

collect specimen type could expand access to testing.
Methods: We recruited individuals recently tested for SARS-CoV-2 infection through a “drive-through” testing program. In participants’ homes, we assessed the performance of self-collected oral fluid swab specimens with and without clinician supervision, clinician-supervised self-collected mid-turbinate (nasal) swab specimens, and clinician-collected nasopharyngeal swab specimens. We tested specimens with a validated reverse transcription-quantitative polymerase chain reaction assay for the detection of SARS-CoV-2 and measured cycle threshold values. Symptom status and date of onset of symptoms was also recorded for each participant.
Results: We recruited 45 participants. The median age of study participant was 42 years old (Interquartile range, 31 to 52 years). Of the participants, 29 had at least one specimen test positive for SARS-CoV-2. Of those, 21 (73%) of 29 reported active symptoms. By specimen type and home-based collection method, clinician-supervised self-collected oral fluid swab specimens detected 26 (90%) of 29 infected individuals, clinician-supervised self-collected nasal swab specimens detected 23 (85%) of 27, clinician-collected posterior nasopharyngeal swab specimens detected 23 (79%) of 29, and unmonitored self-collected oral fluid swab specimens detected 19 (66%) of 29. Despite nasopharyngeal swabs being considered the gold standard, 4 participants tested negative by clinician-collected nasopharyngeal swab and positive by the 3 other specimen types. Additionally, false negative results by each sample type were seen to generally not overlap.
Conclusions: Supervised self-collected oral fluid and nasal swab specimens performed similarly to, if not better than clinician-collected nasopharyngeal swab specimens for the detection of SARS-CoV-2 infection. No sample type captured all SARS-CoV-2 infections, suggesting potential heterogeneity in the distribution of viral load in different parts of the respiratory tract between individuals. Supervised self-collection performed comparably to clinician collection and would allow for rapid expansion of testing capacity in the United States by reducing the need for trained healthcare workers, reducing exposure of healthcare workers, and reducing the amount of PPE (personal protective equipment) being used for testing during a critical shortage.

5. COVID-19 患者中的迟发性血小板减少症

Delayed-Phase Thrombocytopenia in Patients of Coronavirus Disease 2019 (COVID-19)
来源：medRxiv
发布时间：2020-04-11
链接：https://www.medrxiv.org/content/10.1101/2020.04.11.20059170v1
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DOI 或 PUBMED ID：Preprint

编译者：刘焕珍

中文摘要：

本文中迟发性血小板减少症的定义是：患者出现症状 14 天后血小板减少症开始出现或恶化。COVID-19 患者的造血系统也可能受到病毒的影响。患者入院时普遍具有血小板减少症，而晚期或延迟期是否具有血小板减少症则不清楚。该可追溯的单中心病例系列分析了 2020 年 1 月 25 日至 3 月 9 日在中国武汉联合医院的 COVID-19 患者，2020 年 3 月 11 日开始分析。患有 COVID-19 相关的迟发性血小板减少症的病人占入院患者的 11.8%。老年患者或入院时淋巴细胞数低的患者很容易得迟发性血小板减少症。迟发性血小板减少症与住院时间延长和 ICU 入院率升高有着显著的关系。延迟期最低点血小板计数与 B 细胞百分比和血清 IL-6 水平呈高度线性负相关。我们还介绍了三例患有延迟性血小板减少症患者的骨髓穿刺病理，显示巨核细胞成熟受损。我们推测迟发性血小板破坏可能是由抗体介导的，并建议对重症患者进行免疫调节治疗以改善病症。此外，临床医生需要注意迟发性血小板减少症，尤其是在症状发作后的 3-4 周。

Abstract:

Delayed-phase thrombocytopenia is defined as thrombocytopenia begins or worsens after 14 days post symptoms appearance. The pandemic COVID-19 pneumonia has engulfed the entire world. Hematopoietic system can also be affected by COVID-19. Thrombocytopenia at admission was prevalent, while late-phase or delayed-phase thrombocytopenia is obscure. This retrospective single-center case series analyzed patients with COVID-19 at the Union Hospital, Wuhan, China, from January 25th to March 9th, 2020. Analysis began on March 11th, 2020. COVID-19 associated delayed-phase thrombocytopenia was occurred in 11.8% percent of enrolled patients. The delayed-phase thrombocytopenia in COVID-19 is prone to develop in elderly patients or patients with low lymphocyte count on admission. The delayed-phase thrombocytopenia is significantly associated with increased length of hospital stay and higher ICU admission rate. Delayed-phase nadir platelet counts demonstrated a high and significantly negative linear correlation with B cell percentages and serum IL-6 levels. We also presented bone marrow aspiration pathology of three patients with delayed-phase thrombocytopenia, showing impaired maturation of megakaryocytes. We speculated that the delayed-phase platelet destruction might be mediated by antibodies, and suggest immunoregulatory treatment in severe patients to improve outcomes. Besides, clinicians need to pay attention to the delayed-phase thrombocytopenia especially at 3-4 weeks after symptom onset.

6. COVID-19 死亡病例临床特点及死因分析

The clinical characteristics and mortal causes analysis of COVID-19 death patients

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DOI 或 PUBMED ID：
编译者：王玮
中文摘要：
目的：目前，COVID-19 在全球范围内造成了大量的死亡。但是，很少有研究关注死亡患者的临床特征。本文对我国 COVID-19 死亡患者的临床特点及死因进行了回顾性分析。
患者与方法：该文章收集了我国地方卫生行政部门公布的 COVID-19 死亡病例临床资料。从 GTEx 数据库中搜集了病毒受体在人体不同器官中的表达。
结果：本研究共收集了来自中国 24 个省份的 159 例患者信息，其中 60 岁以下青年患者 26 例，60 岁及以上老年患者 133 例。中位年龄为 71 岁，这表明大多数死亡患者是老年人。男性死于 COVID-19 的患者多于女性（1.65 倍）。从发病到死亡的中间天数是 15 天（四分位数范围 10-20 天）。高血压是最常见的并存疾病（56.90%），呼吸衰竭是最常见的直接死因（47.39%）。以发热（71.19%）和咳嗽（55.08%）为主要症状。死亡患者中有一例为无症状（*无典型 COVID-19 症状）的病人，该病人 80 岁，同时患有严重心衰和肾功能衰竭。此外，通过对年轻人和老年人的比较，发现心脏病是老年人死亡的重要危险因素。以 ACE2 和 TMPRSS2 是 SARS-CoV-2 的受体，该文章分析了它们在不同器官中的表达。TMPRSS2 和 ACE2 在死亡患者具有相应临床特征的器官中高表达。
结论：男性、年龄、心脏病是死亡的主要危险因素。此外，严重并存疾病的无症状患者也可能死于 SARS-CoV-2。因此，在治疗中应重视老年心脏病患者和无症状患者。

Abstract:
Purpose: Currently, COVID-19 is causing a large number of deaths globally. However, few researches focused on the clinical features of death patients. This study conducted a retrospective analysis of clinical characteristics and mortal causes in Chinese COVID-19 death patients.
Patients and methods: The clinical characteristics of death patients were collected from publicized by local health authorities in China. Expressions of virus targets in human organs were obtained from GTEx database.
Results: 159 patients from 24 provinces in China were recruited in our study, including 26 young patients under 60 and 133 aged 60 or older. The median age was 71 years, which indicated that most death patients were elderly. More male patients died of COVID-19 than females (1.65 fold). Hypertension was the most common coexisting disorder and respiratory failure was the most common direct cause of death. Fever (71.19%) and cough (55.08%) were the predominant presenting symptoms. There was one asymptomatic patient. In addition, by comparing young and old patients, heart disease was identified as an important risk factor for death in the aged patients. ACE2 and TMPRSS2 were the targets of SARS-CoV-2, we analyzed their expression in different organs. TMPRSS2 and ACE2 had a high expression in the organs which had corresponding clinical features in death patients.
Conclusion: Male, age and heart disease were the main risk factors of death. Beside, asymptomatic patients with serious coexisting disorders may also die of SARS-CoV-2. Thus, more attention should be paid to the old patients with heart disease and asymptomatic patients in the treatment.

7. 关于 92 例 COVID－19 死亡患者的分析

Analysis of 92 deceased patients with COVID－19

来源：Journal of Medical Virology
发布时间：2020-04-15
链接：https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25891
第一作者：Fan Yang
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DOI 或 PUBMED ID：10.1002/jmv.25891
编译者：宋张悦

中文摘要：
目的：回顾性分析新冠状病毒病-19 (COVID-19)死亡病例的临床特点及并发症。
方法：收集武汉大学人民医院 2020 年 1 月 6 日至 2 月 25 日期间死亡的 92 例 COVID-19 患者的病历、实验室检查结果、计算机断层扫描 CT 等资料，总结其并发症的临床特点。
结果：92 例患者平均年龄 69.8±14.5 岁（30-97 岁），其中男性 49 例，女性 43 例。发病至死亡的平均生存时间为 14.3±6.0 天。有 91 例死亡患者分别出现了不同的并发症，包括急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)、心肌损伤(31/91)、肝损伤(15/91)、肾功能不全(14/91)、多器官功能障碍综合征(MODS, 14/91)、气胸(1/91)。其中，83 例死亡患者至少有一种并发症。而 1 例死于复发性消化道出血的患者与 COVID-19 无直接关系。65 例死亡患者生前有基础疾病，包括高血压(51/92)、心脏病(16/92)、糖尿病(13/92)、脑血管疾病(10/92)、恶性肿瘤(4/92)、慢性肝病(3/92)、慢性肾功能不全(2/92)、血液系统疾病(2/92)、慢性阻塞性肺疾病(1/92)。本研究还对降钙素原(PCT)、c -反应蛋白(CRP)和血清淀粉样蛋白 A (SAA)等炎症标志物进行了研究，结果显示有 39 例患者的炎症标志物(PCT、CRP、SAA)显著升高。
结论： COVID-19 死亡患者的主要并发症是 ARDS、心肌损伤、肝损伤、肾功能不全及 MODS。SARS-CoV-2 作为一种新发传染病，其感染涉及多器官。ARDS 发病率最高，是最常见的死亡原因。此外，COVID-19 对心肌细胞、肝脏和肾脏均有损伤。危重患者以高龄(>60 岁)、基础疾病、多脏器病变为共同特征。早期诊断和治疗将有助于预防并发症和降低死亡率。

Abstract:
Objective: This retrospective study aimed to analysis the clinical characteristics and complications in death cases with novel coronavirus disease-19 (COVID-19). Method: We collected the medical records of 92 patients with COVID-19 in Renmin Hospital of Wuhan University who died during January 6th to February 25th, 2020, summarized the clinical characteristics of complications. Results: There were 91 death cases who developed different complications including acute respiratory distress syndrome (ARDS) (73/91), myocardial injury (31/91), liver injury (15/91), renal insufficiency (14/91), multiple organ dysfunction syndrome (MODS) (14/91) and pneumothorax (1/91). Among these patients, 83 patients had at least one complication. While 1 patient who died of recurrent gastrointestinal bleeding was not directly linked to COVID-19. Conclusion: The main complications of deceased patients with COVID-19 were ARDS, myocardial injury, liver injury, renal insufficiency and MODS.

8. 静脉注射免疫球蛋白治疗 COVID-19 危重症患者的临床疗效:一项多中心回顾性队列研究

Clinical Efficacy of Intravenous Immunoglobulin Therapy in Critical Patients with COVID-19: A multicenter retrospective cohort study

来源：medRxiv

发布时间：2020.04.11

链接：https://www.medrxiv.org/content/10.1101/2020.04.11.20061739v1

第一作者：Zi yun Shao

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DOI 或 PUBMED ID：Preprint

编译者：孔娟

中文摘要：

目的：确定静脉注射免疫球蛋白(IVIG)治疗 COVID-19 的临床疗效。

方法：多中心回顾性队列研究。在 2019 年 12 月 23 日至 2020 年 3 月 31 日在中国设立的 8 个政府指定的 COVID-19 治疗中心纳入 325 例患者，其中 174 例分配给 IVIG 治疗组，151 例分配给对照组。评价的主要结果是 28 天和 60 天的死亡率，次要结果是住院总时间和疾病总持续时间，同时对炎症反应及患者器官功能进行了检测。根据 COVID-19 的临床分类、IVIG 剂量和开始治疗时间进行亚组分类，风险因素由 COX 比例风险模型确定。

结果：本研究 325 例患者，其中 222 例(68%)重症型，103 例(32%)危重症型。住院 28 天内死亡 42 例(13%)，60 天内死亡 54 例(17%)，重症死亡 6 例(3%)，危重症死亡 48 例(47%)。174 例使用 IVIG，151 例不使用。研究者首先对两组 COVID-19 危重患者的详细人口统计学和临床概况进行了统计，IVIG 组患者和对照组相比具有较高的急性生理和慢性健康评估(APACHII)评分，器官功能衰竭评估(SOFA)评分，同时白细胞介素-6 和乳酸水平较高。而淋巴细胞计数和氧合指数和对照组相比较低(均 P<0.05)。当所有的 COVID-19 患者都被纳入时 IVIG 组的 28 天和 60 天死亡率没有改善。多变量回归显示 COVID-19 患者分类和 IVIG 使用都与死亡危险因素相关，临床分类(危险比 0.126，95%可信区间 0.039-0.413，P=0.001)，IVIG (危险比 0.252，95%可信区间 0.107-0.591，P=0.002)。亚组分析显示，仅在危重型患者中，IVIG 可显著降低 28 天死亡率，降低炎症反应并改善某些器官功能(均 p<0.05),早期(入院≤7 天)和大剂量(>15g/d)使用 IVIG 可显著降低 60 天死亡率。

解释：早期和高剂量的 IVIG 治疗只能改善危重型 COVID-19 患者的预后，为 SARS-COV-2 感染 IVIG 治疗人群的选择和方法提供临床依据。

Abstract

Background Coronavirus disease 2019 (COVID-19) has spread all over the world, causing more than 1.5 million infections and over ten thousands of deaths in a short period of time. However, little is known about its pathological mechanism, and there are still no clinical study reports on specific treatment. The purpose of this study is to determine the clinical efficacy of intravenous immunoglobulin (IVIG) therapy on COVID-19.

Methods In this multicenter retrospective cohort study, adult critical COVID-19 patients (including severe type and critical type, according to the clinical classification defined by National Health Commission of China) in 8 government designated treatment center in China from Dec 23, 2019 to Mar 31, 2020 were enrolled. Demographic, clinical, treatment, and laboratory data, prognosis were

extracted from electronic medical records, and IVIG was exposure factor. Primary outcomes were the 28 days and 60 days mortality, and secondary outcomes were the total length of in-hospital and the total duration of the disease. Meanwhile, the parameters of inflammation response and organ function were detected. The risk factors were determined by COX proportional hazards model. The subgroup analysis was carried out according to clinical classification of COVID-19, IVIG dosage and timing.

Findings 325patients were included in this study, of whom 222 (68%) were severe type, 103 (32%) were critical type. 42 (13%) died in 28 days within hospitalization, total 54 (17%) died in 60 days, and 6 (3%) died in severe type, 48 (47%) died in critical type. 174 cases were used IVIG, and 151 cases were not. Compared with the baseline characteristics between two groups, the results showed that the patients in IVIG group had higher Acute Physiology and Chronic Health Evaluation (APACHII) score, Sequential Organ Failure Assessment (SOFA) score, IL-6 and lactate level, lower lymphocyte count and oxygenation index (all $P<0.05$). The 28 day and 60 day mortality did not improve with IVIG in overall patients. The in-hospital stay and the total duration of disease were longer in IVIG group ($p<0.001$). Risk factors were clinical classification (hazards ratio 0.126, 95% confidence interval 0.039-0.413, $P=0.001$), and using IVIG (hazards ratio 0.252, 95% confidence interval 0.107-0.591, $P=0.002$) with COX regression. Subgroup analysis showed that only in patients with critical type, IVIG could significantly reduce the 28 day mortality, decrease the inflammatory response and improve some organ functions (all $p<0.05$), and 60-day mortality reduced significantly by using IVIG in the early stage (admission≤7 days) and with high dose (>15 g/d).

Interpretation Early and high dose of IVIG therapy may improve the prognosis of COVID-19 patients only in critical type, which provides the clinical basis for the choice of treatment population and method of IVIG therapy for the SARS-CoV-2 infection.

9. 唾液酸酶在 COVID-19 确证性临床试验中入组第一例受试者

来源：雅虎财经，礼来亚洲资本

发布时间：2020-04-15

链接：https://finance.yahoo.com/news/ansun-biopharma-enrolls-first-patient-110000268.html，礼来亚洲资本公众号

编译：蒋立春

一家临床期生物制药公司 Ansun Biopharma 宣布在其一个旨在评估 DAS181 药物治疗 COVID-19 的安全性和有效性的确证性临床试验中（POC），成功入组第一例病人。该公司的 DAS181 是一项研究阶段的重组唾液酸酶。这项随机双盲实验 hi 将会在全美 12 个研究中心总共招募 22 例病人。对数据进行临时检查分析后，第二期将会在美国和欧洲再招募约 60 名病人。4 月早期，DAA181 在治疗 4 名 COVID-19 的重症患者中表现出显著疗效。

Ansun Biopharma 也在和多个学术机构合作者开展体外研究以阐明 DAS181 对抗 COVID19 的机制。

DAS181 是一个重组唾液酸酶，会切割人呼吸道上皮细胞表面的唾液算。 is a 很多病毒利

用唾液酸作为感染上皮细胞的受体，DAS181 可以阻断病毒的进入防止病毒感染和扩散。该药开展针对住院的免疫抑制的下呼吸道流感感染的全世界多中心的三期临床。在中国正在开展一项治疗流感重症住院病人的二期 b 临床试验。

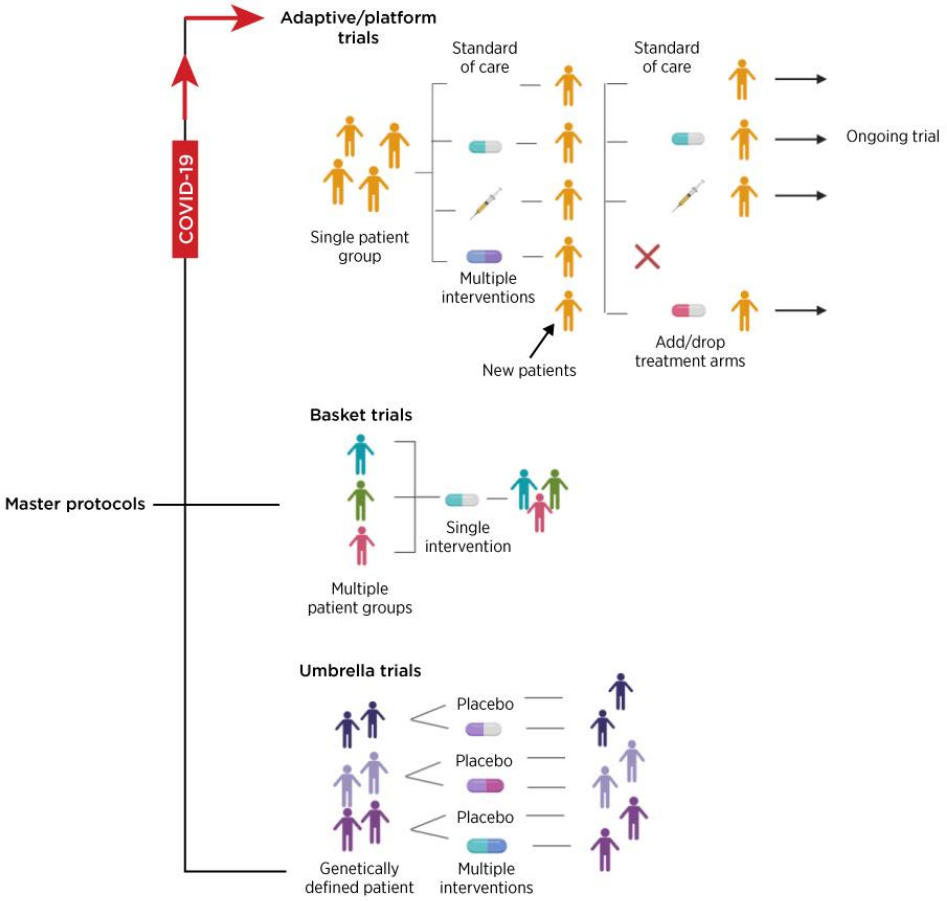
10. 主协议渐渐成为 COVID-19 治疗的关键临床工具

Master protocols emerge as a critical clinical tool against COVID-19

发布时间：2020-04-11

链接：https://www.biocentury.com/article/304898

编译:蒋立春



图（一），主协议下不同的临床设计结构图

主协议临床试验渐渐来到舞台中央，为最快找到安全和有效的治疗 COVID-19 的解决途径.

主协议框架下的大型临床试验会在一个试验中，采用统一的 protocol 在一个试验中同时评价多种治疗方案或者一个治疗方案对多种病人群体的疗效。

这种做法的优势是通过平行测试以及共享一个对照臂或者产生可以在不同治疗中进行比较的数据从而提高临床试验的效率（图一）。因为 COVID-19 是一个新发病，未知因素很多，所以一般会采用 adaptive trial，适应性试验这种模式。这种模式的临床试验中，可以增加或者舍弃不同治疗方案的试验臂。

	RECOVERY	ACTT*	SOLIDARITY	REMAP-CAP
Sponsor	University of Oxford,UK	National Institute of Allergy and Infectious Disease	World Health Organization (WHO)	MJM Bonten, UMC Utrecht, Netherlands
Arms	Lopinavir/ritonavir; Dexamethasone; Hydroxychloroquine; Interferon-β	Remdesivir; placebo	Hydroxychloroquine or chloroquine; Remdesivir; Lopinavir/ritonavir; Interferon-β and lopinavir/ritonavir; Standard of care	Hydroxychloroquine; Hydroxychloroquine plus lopinavir/ritonavir; Interferon-β; Anakinra (IL-1RA antagonist); Standard of care
Trial design	Randomized adaptive trial	Randomized, placebo-controlled adaptive trial	Randomized adaptive trial	Randomized adaptive trial
Primary endpoint	In-hospital mortality, 28 days	Disease severity, measured by 8-point scale	Disease severity	Days alive and outside ICU
Target enrollment	5000	400 (Initial)	Undetermined	6800
Location	U.K.	International	International	International

表 1，已经启动的主协议临床试验

**On 2020 Apr 10, On Friday, Eli Lilly and Co. announced the study would add an arm to treat patients with Olumiant baricitinib, a JAK1/JAK2 inhibitor approved to treat rheumatoid arthritis (RA).

11. 转载：JAMA 综述：治疗新冠病毒，近 10 款老药新用和 3 种辅助疗法的最新证据

来源：医学新视点微信公众号

概述：

尽管目前我们还没有针对新冠病毒（SARS-CoV-2）的特效药，但在医药行业的努力下，科学和临床发现正在迅速发展。《美国医学会杂志》（*JAMA*）最新发表来自德克萨斯大学西南医学中心（University of Texas Southwestern Medical Center）团队的综述，**总结了新冠病毒感染的病理和潜在治疗靶点，以及氯喹、瑞德西韦、洛匹那韦/利托那韦等主要在研药物和临床现有支持性治疗的最新证据。**

综述认为，目前最有前景的在研疗法是瑞德西韦，但仍有待随机试验的检验。辅助治疗中，抗细胞因子或免疫调节药物，以及康复者血浆疗法的作用值得关注，但不推荐使用皮质类固醇激素。

中文报道来源：

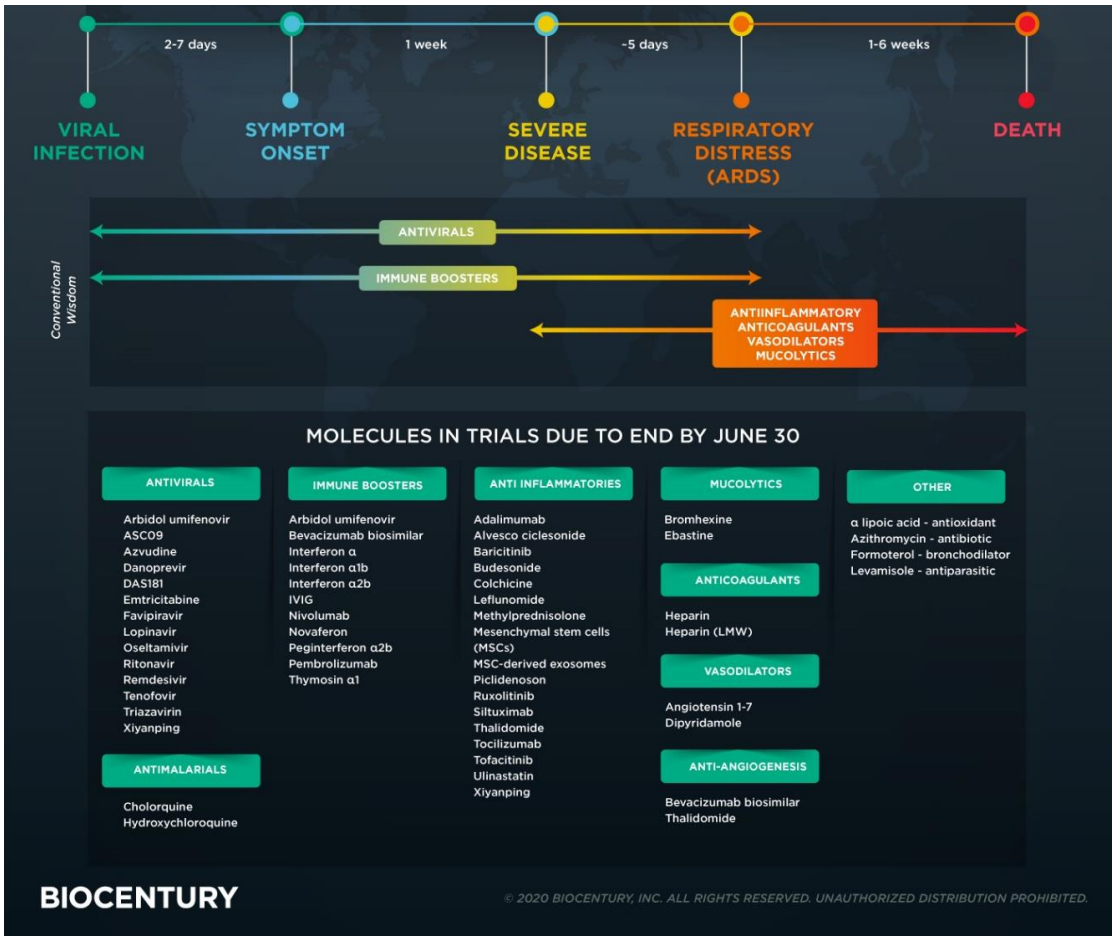
https://mp.weixin.qq.com/s?__biz=MzAxOTU2OTU4MQ==&mid=2649914673&idx=1&sn=311b86d680725de19ab30318f6c66af5&chksm=83c3d3f3b4b45ae5823bb33e91509ea34b464878c7e7a094e3c05390cd8eeeb983344660a13f&mpshare=1&scene=1&srcid=&sharer_sharetime=1587020783560&sharer_shareid=80f78c62f02832698f0a70d54f98b491&key=d2a5d91993b9552202e899e851ef616bc0454b4b3beed04abb27ad93b31635176c969a95581f4d48864465600f85b3c0210dedb766f0ae684aa876b293e158ec7c65864665ade9a987fd8bb43441623b&ascene=1&uin=MjgxMjY4NjgxNQ%3D%3D&devicetype=Windows+10&version=62080085&lang=zh_CN&exportkey=AwEXIEUERD7ZqhXiDOVzfZc%3D&pass_ticket=GaskctPQ8NnOXyAcBgOzwNLdSRUeK5NlXigeNJfYPgUHzQUXf4Ry16ATwj1gQfm5

Original article from JAMA:

Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19) A REVIEW

URL:https://jamanetwork.com/journals/jama/fullarticle/2764727

相关阅读：COVID-19: closing in on matching therapeutic mechanism to disease stage
COVID-19,靠近将治疗机制和疾病发病阶段相匹配
链接：https://www.biocentury.com/article/304896
该评论综合了 COVID-19 疾病发展不同阶段对应的治疗药物以及相应机制，并对今年 6 月 30 前会结束的临床试验进行了总结。



12. 老鼠、仓鼠、雪貂、猴子——哪些实验动物可以帮助战胜新的冠状病毒？

Mice, hamsters, ferrets, monkeys. Which lab animals can help defeat the new coronavirus?

来源：Science 新闻稿
发布时间：2020-04-13
链接：https://www.sciencemag.org/news/2020/04/mice-hamsters-ferrets-monkeys-which-lab-animals-can-help-defeat-new-coronavirus
通讯作者：Jon Cohen
通讯作者单位：Science 专栏作者
DOI 或 PUBMED ID：10.1126/science.abc2335
编译者：张丽双
中文摘要：
目前研究者们正在努力寻找合适的 SARS-CoV-2 感染动物模型。
小鼠（Mice）——众多动物模型当中最常见。人 ACE2 受体在与病毒结合的关键区域的 29 个

氨基酸中，有 11 个氨基酸与小鼠 ACE2 不同，所以 SARS-CoV-2 很难感染小鼠。一个思路是将人 ACE2 受体转入小鼠建立 hACE2 转基因小鼠模型；还有利用 CRISPR 基因编辑技术，鉴定使小鼠更易感或更不易感的基因、采用免疫缺陷的小鼠模型帮助筛选小鼠适应株或使用其他病原体（如重组 hACE2 的腺病毒载体）将人 ACE2 基因表达进小鼠体内。但小鼠模型症状较轻，更合适的小鼠模型仍在探索当中。

仓鼠（Hamsters）——ACE2 受体在与病毒结合的关键区域的 29 个氨基酸中，人与仓鼠仅有 4 个氨基酸不同。研究人员发现仓鼠被 SARS-CoV-2 感染后，体重减轻、嗜睡、翘毛、驼背以及呼吸急促等症状，另外在仓鼠的肺部和肠道发现了高水平的 SARS-CoV-2，这些发现与人上下呼吸道感染的表型非常相似。还发现将感染 SARS-CoV-2 的仓鼠和未感染的仓鼠放在一起，未感染的仓鼠也会受到感染。仓鼠模型将有助于研究 SARS-CoV-2 的可能传播途径。

大鼠（Rats）——ACE2 受体在与病毒结合的关键区域的 29 个氨基酸中，人与大鼠有 13 个氨基酸不同。在 SARS-CoV 和 SARS-CoV-2 的易感性方面，大鼠同样不具有优势。但大鼠的体型较大，在很多需要重复取血的实验当中具有较大优势。MIRIMUS 公司正与其他研究组合作，利用 CRISPR 基因编辑技术建立 hACE2 的大鼠模型，用以评估不同剂量的疫苗对宿主产生的抗体反应，实际上，很多药物试验包括毒理学研究等也都是从大鼠身上开始研究的。

雪貂（Ferrets）——其上下呼吸道解剖比例、支气管壁粘膜下腺体的密度等都与人呼吸道状况非常接近。此前的研究表明，SARS-CoV 能够有效感染雪貂，引起轻度症状，并可以在雪貂之间进行传染。但在 SARS-CoV-2 的感染上，确实会被感染，并导致体温升高，但似乎并不能复制到高水平。研究人员进一步发现了雪貂可以经飞沫传播。值得注意的是，SARS-CoV-2 对老年人的影响更大。研究者在一种可以引起血小板减少的病毒感染雪貂模型中也观察到了类似的现象，年轻的雪貂被该病毒感染后没有症状，但在年老的雪貂被感染后死亡率达 93%。基于此，雪貂或许可以作为可能的 SARS-CoV-2 模型。

猴子——在评估潜在药物和疫苗时，最具有说服力的动物模型是猴子模型，猴子模型的缺点时昂贵并且难以操作，但在遗传学上与人极其近的亲缘关系往往使猴子试验成为开展药物和疫苗临床试验的最后一步。很多团队正在进行对于恒河猴模型的研究，发现恒河猴在感染 SARS-CoV-2 后，病情轻微，体重稍有减轻，但无发烧现象，肺部显示与人相似的病理学症状。

动物模型的名单可能很快就会增加。例如，《科学》杂志 4 月 8 日在网上发表的一项最新研究报告称，这种病毒可以感染猫。尸检显示，感染导致他们的鼻腔、气管和肺部出现“大量”病变。

Abstract:

Beloved as pets, Syrian hamsters are winning another kind of attention from scientists trying to understand and defeat COVID-19. Fifteen years ago, scientists found the hamsters could readily be infected with the coronavirus that causes severe acute respiratory syndrome (SARS). Their symptoms were subtle, so the animals didn’t get much traction as a model for the disease. But with COVID-19, caused by a related virus, SARS-CoV-2, the model’s prospects appear brighter.