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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内容介绍

分类	标题名称
疫情播报	1. 2020 年 5 月 11 日疫情
流行病学	2. COVID-19 在天津的传播异质性与超级传播事件的评价
疾病检测	3. 武汉将开展全员核酸筛查
疾病病理	4. 德国汉堡的一项回顾性队列研究显示，COVID-19 的大多数男性患者在接受重症监护时睾酮水平较低 5. 重症 COVID-19 危重患者急性肾损伤特征 6. 转载：COVID-19 患者胰腺损伤的血清学证据
疾病治疗	7. 对重症 COVID-19 疾病模式的早期检测决定了实时的个性化护理、男性的生物严重性和死亡率下降
疫苗研发	8. COVID-19 疫苗研发的战略途径
临床试验	9. Celebrex 辅助治疗 COVID-19 的实验研究
基础研究	10. SARS-CoV-2 的 Spike 蛋白能够与特定长度和序列的硫酸乙酰肝素结合 11. 一个和 SARS-CoV-2 紧密相关的蝙蝠冠状病毒在刺突的蛋白的 S1/S2 切割位点存在天然插入

1. 2020 年 11 日疫情

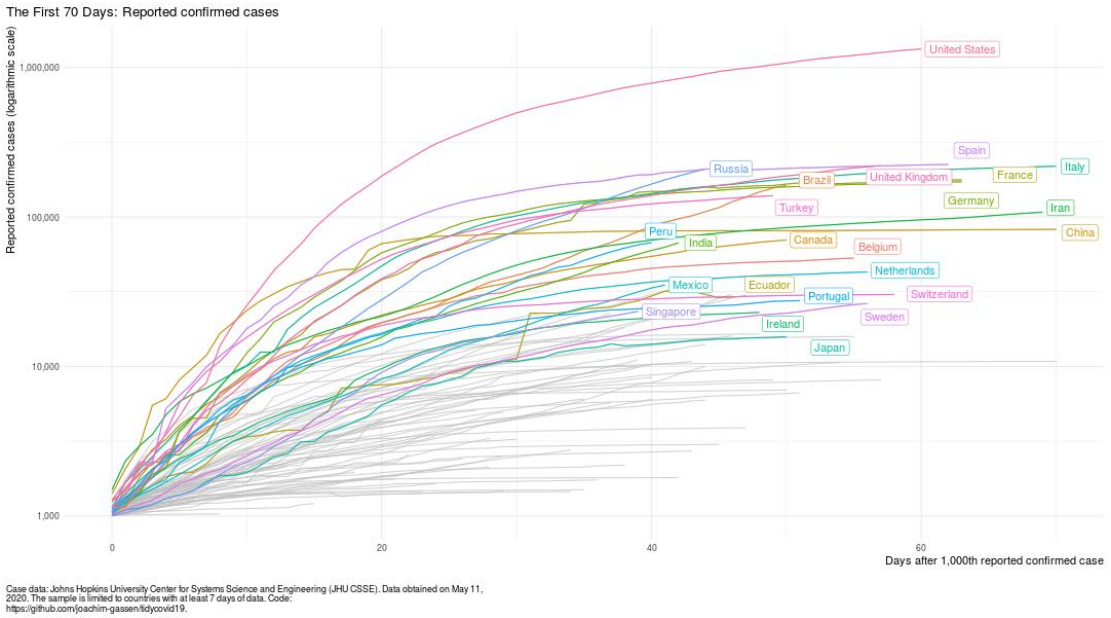
数据来源：WHO

发布时间：2020 年 5 月 11 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 5 月 11 日全球累计确诊新型冠状病毒病人 **4006257 例**，当日新增确诊 88891 例，累计死亡 278892 例，当日新增死亡 4531。

中国累计确诊 84450 例，累计死亡 4643 例，当日新增确诊 20 例，新增死亡 0 例。



重点国家确诊数量曲线（https://jgassen.shinyapps.io/tidycovid19/，数据截止 5 月 11 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（5月11日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. COVID-19 在天津的传播异质性与超级传播事件的评价

Evaluating transmission heterogeneity and super-spreading event of COVID-19 in a metropolis of China

来源：medrxiv
发布时间：2020-05-11
链接：https://www.medrxiv.org/content/10.1101/2020.05.06.20073742v1

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编译者：王玮

中文摘要：

背景：COVID-19 在世界范围内引起了快速的大规模感染。了解其传播特性（包括异质性）对预测和干预未来疫情具有重要意义。此外，传播的异质性通常会引发超级传播事件（super spreading events，SSEs），具体指某些个体会感染大量的继发病例。到目前为止，对 COVID-19 的传播异质性及其潜在原因仍未明确。

方法：收集天津市 2020 年 1 月 21 日至 2 月 26 日期间的所有感染病例资料。利用一个基于分枝过程和负二项式子代分布的异质传递模型，分别估计了表征传染能力和异质性的传染数 R 和离散参数 k。在此基础上，研究了天津市的超级传播事件，并基于异质模型评价了地方政府防控措施的效果。

结果：截至 2020 年 2 月 26 日，天津市共有 135 例确诊病例（其中输入病例 34 例，本地感染 101 例）进入研究。我们将它们分为 43 个传播链，其中最大的一个为 45 个病例，最长的一个为 4 代。估计传染数 R 为 0.67（95%CI:0.54~0.84），离散参数 k 为 0.25（95%CI:0.13~0.88）。一个超级传播者在天津造成了 6 起感染。此外，我们的模拟结果显示，如果天津市自 1 月 28 日以来没有采取防控措施，天津市的疫情将导致 165 例感染，平均持续 7.56 代。

结论：我们的分析提示 COVID-19 的传播能力是临界的（R < 1），但具有明显的异质性，可能引起 SSE。需要更多的研究来验证 COVID-19 在其他人群中的传播异质性及其影响因素，这对于制定有针对性的措施来遏制这一流行病非常重要。

Abstract:

Background: COVID-19 caused rapid mass infection worldwide. Understanding its transmission characteristics including heterogeneity is of vital importance for prediction and intervention of future epidemics. In addition, transmission heterogeneity usually envokes super spreading events (SSEs) where certain individuals infect large numbers of secondary cases. Till now, studies of transmission heterogeneity of COVID-19 and its underlying reason are far from reaching an agreement.

Methods: We collected information of all infected cases between January 21 and February 26, 2020 from official public sources in Tianjin, a metropolis of China. Utilizing a heterogeneous transmission model based on branching process along with a negative binomial offspring distribution, we estimated the reproductive number R and the dispersion parameter k which characterized the transmission potential and heterogeneity, respectively. Furthermore, we studied the SSE in Tianjin outbreak and evaluated the effect of control measures undertaken by local

government based on the heterogeneous model.
Results: A total of 135 confirmed cases (including 34 imported cases and 101 local infections) in Tianjin by February 26th 2020 entered the study. We grouped them into 43 transmission chains with the largest chain of 45 cases and the longest chain of 4 generations. The estimated reproduction number R was at 0.67 (95%CI: 0.54~0.84), and the dispersion parameter k was at 0.25 (95% CI: 0.13~0.88). A super spreader causing six infections in Tianjin, was identified. In addition, our simulation results showed that the outbreak in Tianjin would have caused 165 infections and sustained for 7.56 generations on average if no control measures had been taken by local government since January 28th.
Conclusions: Our analysis suggested that the transmission of COVID-19 was subcritical but with significant heterogeneity and may incur SSE. More efforts are needed to verify the transmission heterogeneity of COVID-19 in other populations and its contributing factors, which is important for developing targeted measures to curb the pandemic.

3. 武汉将开展全员核酸筛查

新闻链接：http://ah.people.com.cn/n2/2020/0512/c358314-34011834.html
根据人民网报道，武汉市 5 月 11 日，武汉市新冠肺炎疫情防控指挥部涉疫大数据与流行病学调查组下发《关于开展全市新冠病毒核酸筛查的紧急通知》，经研究决定，在武汉全市范围内开展全员新冠病毒核酸筛查“十天大会战”。各区按 10 天期限，做好本辖区全员核酸筛查计划安排。
根据其他来源消息，武汉市 4 月底共有 211 家核酸检测点，日检测能力接近 5 万。全市区累计已经完成 103 万核酸检测。估计还有 1000 万常住人口需要进行检测。按照 10 天大会战，日检测量需要达到 100 万例。武汉市是否会采取样品池等检测策略完成检测任务，尚不得知。

4. 德国汉堡的一项回顾性队列研究显示，COVID-19 的大多数男性患者在接受重症监护时睾酮水平较低

The majority of male patients with COVID-19 present low testosterone levels on admission to Intensive Care in Hamburg, Germany a retrospective cohort study
来源：medRxiv
发布时间：2020-05-11
链接：https://www.medrxiv.org/content/10.1101/2020.05.07.20073817v1
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中文摘要：
背景：严重急性呼吸综合征冠状病毒 2（SARS-CoV-2）继续在世界范围内传播，给公众健康造成重大负担。越来越多的证据表明，男性比女性更容易死于 SARS-CoV-2 感染。然而，在 2019 年冠状病毒病（COVID-19）中，造成观察到的性别差异的潜在因素仍然未知。
方法：在这项回顾性队列研究中，纳入了被德国汉堡 Eppendorf 大学医院的重症监护室收治的 COVID-19 患者。研究人员获得了 2020 年 4 月 29 日之前出院或死亡的所有患者的人口统

计数据。系统分析了男性和女性实验室确诊的 SARS-CoV-2 感染患者住院期间的性激素、细胞因子和趋化因子反应。使用单变量和多变量线性回归方法来确定男性和女性疾病严重程度的潜在危险因素。

结果：所有入选的患者（n=45；n=35 男性和 n=10 女性）均表现出高血压为最常见的合并症（男性 45.7%；女性 40%），其次是癌症（男性 35%；女性 40%），肥胖（男性 34.3%，女性 30%），Ⅱ型糖尿病（男性 25.7%，女性 20%）和慢性心脏病（男性 8.6%，女性 0%）。我们发现绝大多数男性 COVID-19 患者呈现低睾酮（68.6%）和低二氢睾酮（48.6%）水平。相比之下，大多数女性 COVID-19 患者的睾酮水平升高（60%），而双氢睾酮水平没有改变。女性和男性 COVID-19 患者都可能出现雌二醇水平升高（男性 45.7%，女性 40%）。SOFA 评分定义的疾病严重程度与男性细胞因子反应（如 IL-6）升高和女性 IL-2 升高相关。在男性 COVID-19 患者中，睾酮水平与炎性 IL-2 和 IFN-γ 呈负相关，而雌二醇水平与炎性细胞因子 IL-6 呈正相关。反之亦然，在女性 COVID-19 患者中，睾酮水平与炎性细胞因子（如 IL-6）呈正相关。

解读：这些数据表明，危重症男性 COVID-19 患者患有严重的睾酮和二氢睾酮缺乏症。需要提升这两种雄激素来促进抗病毒免疫反应以对抗男性感染。

Abstract:

Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread worldwide and pose a major public health burden. There is increasing evidence that men are more likely to die from SARS-CoV-2 infection than women. However, underlying factors that mediate the observed sex bias in coronavirus disease 2019 (COVID-19) remain unknown.

Methods. In this retrospective cohort, we included COVID-19 patients who were admitted to an Intensive Care Unit at the University Hospital Hamburg-Eppendorf, Germany. We obtained demographic data of all patients who were discharged or had died by 29th April 2020. We systematically analyzed sex hormones as well as cytokine and chemokine responses in male and female patients with laboratory-confirmed SARS-CoV-2 infections upon hospital admission. We used uni- and multivariable linear regression methods to identify potential risk factors for disease severity in males and females.

Findings. All enrolled patients (n=45; n=35 males and n=10 females) presented comorbidities with hypertension being the most common (45.7% in males; 40% in females), followed by cancer (35% in males; 40% in females), obesity (34.3% in males and 30% in females), type II diabetes (25.7% in males and 20% in females) and chronic heart diseases (8.6% in males and 0% in females). We detected that the vast majority of male COVID-19 patients present low testosterone (68.6%) and low dihydrotestosterone (48.6%) levels. In contrast, most female COVID-19 patients have elevated testosterone levels (60%) without alterations in dihydrotestosterone levels. Both, female and male COVID-19 patients may present elevated estradiol levels (45.7% in males and 40% in females). Disease severity defined by SOFA score correlates with elevated cytokine responses (e.g. IL-6) in males and IL-2 in females. In male COVID-19 patients, testosterone levels negatively correlate with inflammatory IL-2 and IFN-γ, whereas estradiol levels positively correlate with the inflammatory cytokine IL-6. Vice versa, in female COVID-19 patients, testosterone levels positively correlate with inflammatory cytokines (e.g. IL-6).

Interpretation. We here show that critically ill male COVID-19 patients suffer from severe testosterone and dihydrotestosterone deficiencies. Both androgens are required to mount antiviral immune responses to combat infection in males.
编者注：4 月 25 日简报第 7 条报道过一项基于流行病学和基因组数据的研究提出 Y 染色体丢失引起的 X 染色体单倍体嵌合可能带来免疫缺陷以及心血管病风险可能是男性在 COVID-19 面前更脆弱的原因。

5. 重症 COVID-19 危重患者急性肾损伤特征

Characterisation of Acute Kidney Injury in Critically Ill Patients with Severe Coronavirus Disease-2019 (COVID-19)
来源：medRxiv
发布时间：2020-05-10
链接：https://www.medrxiv.org/content/10.1101/2020.05.06.20069872v1
第一作者：Sébastien Rubin
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通讯作者单位：Néphrologie, Transplantation, Dialyse et Aphérèses Hôpital Pellegrin, Place Amélie Raba-Léon, 33076 BORDEAUX CEDEX
编译者：刘焕珍
中文摘要：
背景：目前尚未报道重症患者中与 COVID-19 相关的急性肾损伤频率、严重程度和特征。
方法：从 2020 年 3 月 3 日至 2020 年 4 月 14 日，单中心队列研究在法国波尔多大学医院的 4 个重症监护病房进行。所有符合 COVID19 和肺部严重程度标准的患者都参加了这项研究。AKI（急性肾损伤）是使用 KDIGO 标准定义的。进行了系统的尿液分析。评估了发病率、严重程度、临床表现、生物学特征（短暂性与持续性急性肾损伤；蛋白尿，血尿和糖尿）和短期预后。
结果：一共 71 例患者参与此项研究，基础血清肌酐为 69±21 μmol/L。入院时，8/71（11%）患者患有 AKI。中位随访时间为 17[12-23]天。研究期间共有 57/71（80%）患者患有 AKI，其中有 35%的急性肾损伤 1 期患者、35%的 2 期患者、30%的 3 期患者；10/57（18%）患者需要肾脏替代治疗。仅有 4/55（7%）患者患有短暂性 AKI，51/55（93%）患者患有持续性 AKI。持续性 AKI 患者的尿蛋白/肌酐中位数为 82 [54-140]（mg / mmol），白蛋白尿/蛋白尿比为 0.23±20，表明主要是肾小管间质损伤。只有 2 例（4%）患者患有糖尿。在 AKI 发生后的第 7 天，有 6 例（11%）患者仍然依赖肾脏替代疗法，其中 9 例（16%）的 SCr> 200 μmol/L，4 例（7%）患者死亡。第 7 天和第 14 天，肾脏的恢复率分别为 28%和 52%。
结论：COVID-19 相关的 AKI 是一种常见的、持续性的、严重的、以几乎完全不伴有糖尿的肾小管间质损伤为特征的疾病。
Abstract:
Background: COVID-19-associated acute kidney injury frequency, severity and characterisation in critically ill patients has not been reported.
Methods: Single-center cohort performed from March 3, 2020, to April 14, 2020 in 4 intensive care units in Bordeaux University Hospital, France. All patients with COVID19 and pulmonary severity criteria were included. AKI was defined using KDIGO criteria. A systematic urinary analysis was performed. The incidence, severity, clinical presentation, biological characterisation (transient vs. persistent acute kidney injury; proteinuria, hematuria and glycosuria), and

short-term outcomes was evaluated.
Results: 71 patients were included, with basal serum creatinine of 69 ± 21 μmol/L. At admission, AKI was present in 8/71 (11%) patients. Median follow-up was 17 [12 - 23] days. AKI developed in a total of 57/71 (80%) patients with 35% Stage 1, 35% Stage 2, and 30% Stage 3 acute kidney injury; 10/57 (18%) required renal replacement therapy. Transient AKI was present in only 4/55 (7%) patients and persistent AKI was observed in 51/55 (93%). Patients with persistent AKI developed a median urine protein/creatinine of 82 [54 - 140] (mg/mmol) with an albuminuria/proteinuria ratio of 0.23 ± 20 indicating predominant tubulo-interstitial injury. Only 2 (4%) patients had glycosuria. At Day 7 onset of after AKI, six (11%) patients remained dependent on renal replacement therapy, nine (16%) had SCr > 200 μmol/L, and four (7%) died. Day 7 and day 14 renal recovery occurred in 28% and 52 % respectively.
Conclusion: COVID-19-associated AKI is frequent, persistent severe and characterised by an almost exclusive tubulo-interstitial injury without glycosuria.

6. 转载：COVID-19 患者胰腺损伤的血清学证据
转载来源：NEJM 医学前沿公众号
链接：
https://mp.weixin.qq.com/s?__biz=MzIxNTc4NzUOMQ==&mid=2247495792&idx=1&sn=da24946c92e9a85eecdd1b3b44b90a27&chksm=9790410aa0e7c81cb0a1a79c6fda94545be5e04cfb16b088db8c8aa0e31831ed17f7eaaa0954&scene=126&sessionid=1589277625&key=0c134eddf9a1aa21b3b49448d00d2cc9fdecf876ebe9d3d1e33e46414dd888bb5869dc5b9d0289b5d1b0a91fec5cb4b68fdfc03472c1c57a8d45d55c216f034c69314b3b13623ef2d2c4ae61037c512a&ascene=1&uin=MjgxMjY4NjgxNQ%3D%3D&devicetype=Windows+10&version=62080085&lang=zh_CN&exportkey=A2vsYuqDzNxYAvUR948wYcc%3D&pass_ticket=xU2HxOxbh1Yh62uxcEBhYCf%2F7BGMyqQJWP%2FcuGYdfTr2KSd6lysw2Cj4YHN9WOkd
该文章来自 NEJM 期刊荟萃（NEJM Journal Watch）
COVID-19 患者胰腺损伤的血清学证据
Serologic Evidence of Pancreatic Injury in COVID-19
评论作者：Douglas G. Adler, MD, FACG, AGAF, FASGE
来自中国一个医疗中心的 COVID-19 肺炎病例系列。
随着 COVID-19 危机的持续，我们逐渐获得了一些关于其胃肠道表现的数据。早期报告指出腹泻是 COVID-19 患者的常见症状（NEJM JW Gastroenterol 2020 Apr 9; [e-pub] and Gastroenterology 2020 Apr 3; [e-pub]）。中国最近的一份报告首次评估了 COVID-19 患者的胰腺损伤。
报告描述了中国一个医疗中心 52 例 COVID-19 肺炎住院患者的血清学检测结果。患者发生了以下器官功能障碍：33%有心脏损伤证据，29%有肝损伤证据，17%有胰腺损伤证据（表现为胰腺实验室检查值升高）。与其他患者相比，胰腺实验室检查值异常的患者有以下情况的可能性较高：入院时有厌食、腹泻和重症疾病；血清肝功能指标异常的严重程度较高；红细胞沉降率较高；CD3+和 CD4+ T 细胞水平较低。在对机械通气或类固醇治疗的需求，以及在至血清转换的时间方面，这些患者与其他患者无显著差异。

7. 对重症 COVID-19 疾病模式的早期检测决定了实时的个性化护理、男性的生物严重性和死亡率下降

Early detection of severe COVID-19 disease patterns define near real-time personalized care, bioseverity in males, and decelerating mortality rates

来源：medRxiv

发布时间：2020-05-11

链接：https://www.medrxiv.org/content/10.1101/2020.05.08.20088393v1

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编译者：孔娟

中文摘要：

背景：COVID-19 已经发展为全球卫生紧急事件。最近的数据显示，英国重症监护病房的死亡率为 50%。研究者报告了一组对 COVID-19 患者实施了新颖的程序和管理方案的单机构的回顾性分析结果，旨在提高感染 COVID-19 住院患者的生存率。

方法：这是一项单机构双中心回顾性分析。研究者利用 Microsoft Azure 中创建的一个新的云数据库，该数据库具有来自电子病历（EPR）的实时记录，在实施决策支持工具和实时数据仪表板后，对需要个性化强化护理的患者进行单机构双中心回顾性分析，重点关注呼吸频率、舒张压、氧合指数、C-反应蛋白、D-二聚体和铁蛋白。不同于常规的方案包括对所有 COVID-19 阳性患者的高剂量预防性抗凝治疗和抗氧化剂处方。

结果：截至 2020 年 4 月 22 日，923 名患者 COVID-19 检测呈阳性。男性 569 例(61.7%)。大多数患者表现为晚期疾病：四分位区间为 C 反应蛋白 44.9-179mg/L，D 二聚体 1070-3802ng/L，铁蛋白 261-1208μg/L。女性的完整病死率为 25.1% [95% CI 20.0, 30.0]，男性为 40.5% [95% CI 35.9, 45.0]。139 名患者入住重症监护室，其中女性当前死亡率为 16.2% [95% CI 3.8, 28.7]，男性为 38.2% [95% CI 28.6, 47.8]，没有种族的差异趋势。这种实时监测仪表板能够使用关键参数对患者进行快速评估，从而加快对管理方案的调整。总共有 513 名(55.6%)患者被定义为血栓栓塞性疾病高风险，超过了定义为呼吸恶化(391 人，42.4%)或细胞因子风暴(68 人，7.4%)的人数。几乎没有证据表明年龄与疾病严重程度相关，但男性的所有仪表盘指数水平较高，尤其是 C 反应蛋白和铁蛋白($p<0.0001$)，并且与年龄无关。

结论：采用的方案(交通灯式实时监控仪表板驱动的个性化护理、基于 D-二聚体>1,000ng/L 和/或 CRP>200 mg/L 的原发性早期抗凝治疗、个性化通气策略和抗氧化剂)能够有效提高 COVID-19 患者的存活率，这种治疗方案值得推广。研究发现男性患严重疾病的风险更大，最有可能的原因是 SRARS-CoV-2 受体位于 X 染色体上，因此需要特别密切的早期关注。

注：集成电子病历的交通信号灯系统在临床仪表板上为每个电子病历提供了实时的决策支持工具。从急诊室入院的第一组观察结果开始，每 10 分钟更新一次。它创建于 2020 年 3 月供 COVID-19 患者使用，并于 2020 年 3 月 20 日启用，并且正在不断开发中。

Abstract:

BACKGROUND: COVID-19 is a global health emergency. Recent data indicate a 50% mortality rate across UK intensive care units.

METHODS: A single institution, two-centre retrospective analysis following implementation of a Decision Support tool and real-time data dashboard for

early detection of patients requiring personalised enhanced care, focussing particularly on respiratory rate, diastolic blood pressure, oxygenation indices, C-reactive protein, D-dimer and ferritin. Protocols differing from conventional practice included high-dose prophylactic anticoagulation for all COVID-19 positive patients and antioxidant prescription.
RESULTS: By 22nd April 2020, 923 patients tested COVID-19 positive. 569 patients (61.7%) were male. The majority presented with advanced disease: interquartile ranges were C-reactive protein 44.9-179mg/L, D-dimer 1070-3802ng/L, and ferritin 261-1208μg/L. Completed case fatality rates were 25.1% [95% CI 20.0, 30.0] in females, 40.5% [95% CI 35.9, 45.0] in males. 139 patients were admitted to intensive care where current death rates are 16.2% [95% CI 3.8, 28.7] in females, 38.2% [95% CI 28.6, 47.8] in males with no trends for differences based on ethnicity. A real-time traffic lights dashboard enabled rapid assessment of patients using critical parameters to accelerate adjustments to management protocols. In total 513 (55.6%) of patients were flagged as high risk for thromboembolic disease, exceeding the numbers flagged for respiratory deteriorations (N=391, 42.4%), or cytokine storm (N=68, 7.4%). There was minimal evidence that age was associated with disease severity, but males had higher levels of all dashboard indices, particularly C-reactive protein and ferritin ($p<0.0001$) which displayed no relationship with age.
CONCLUSIONS: Survival rates are encouraging. Protocols employed (traffic light-driven personalised care, protocolised early therapeutic anticoagulation based on D-dimer>1,000ng/L and/or CRP>200 mg/L, personalised ventilatory strategies and antioxidants) are recommended to other units. Males are at greater risk of severe disease, most likely as the obligate SARS-CoV-2 receptor is on the X-chromosome, and require especially close, and early attention.

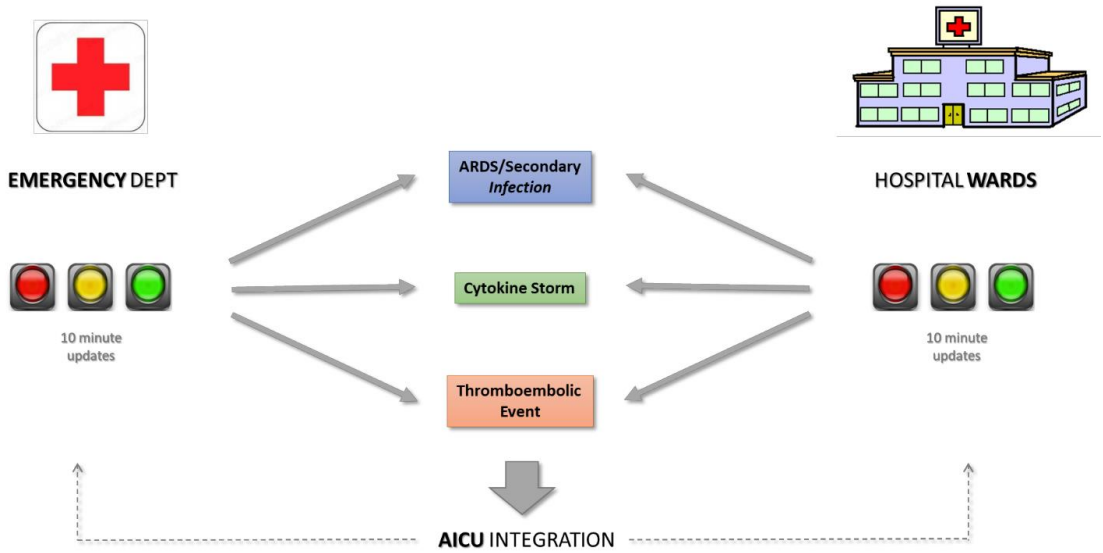

Figure 2: Real time decision support tool highlighting the 3 patterns of disease that were recognised early in the outbreak to be causing mortality.

8. COVID-19 疫苗研发的战略途径

A strategic approach to COVID-19 vaccine R&D

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DOI: 10.1126/science.abc5312
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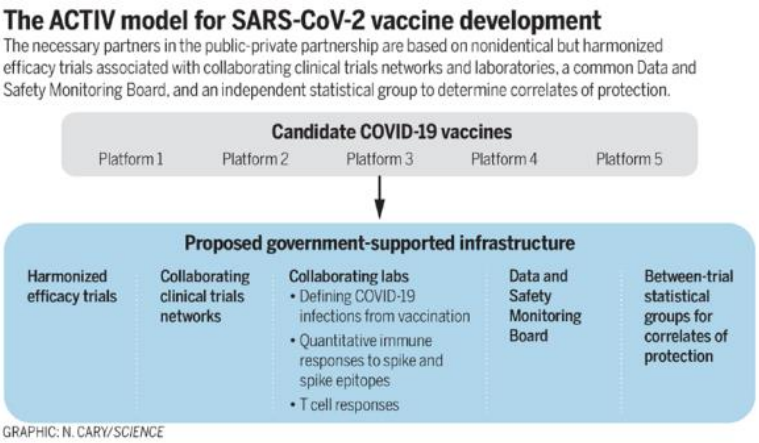
摘要

作者讨论最近出现的一个这样的合作项目:ACTIV(加速 COVID-19 治疗干预和疫苗)公私伙伴关系。在美国国家卫生研究院(NIH)的领导下，这一努力汇集了全球紧急时刻所有部门的力量。作者进一步讨论了开展协调、随机对照疫苗疗效试验的合作平台。该机制旨在同时为几种候选疫苗生成必要的安全性和有效性数据，从而加快疫苗的许可和分发，以预防 COVID-19。

目前对 COVID-19 的保护性免疫反应的构成知之甚少。来自 SARS-CoV-1 患者以及最近感染的 SARS-CoV-2 患者的数据表明，感染后免疫应答水平相对较高，特别是抗体对介导进入宿主细胞的表面(刺突)蛋白的应答。然而，目前尚不清楚保护人体免受随后再感染所需的免疫类型或免疫水平的体内数据，以及这种保护可能持续的时间。SARS-CoV-1 动物模型,免疫接种重组蛋白和病毒核酸疫苗， 以及中和抗体被动转移到刺突蛋白，已被证明对实验感染具有保护作用。这些数据使人乐观地认为，高免疫原性疫苗将引起保护所需的抗体反应的量级和质量。T 细胞免疫在预防早期疾病获得或改善方面的作用，无论是在动物挑战模型中还是在人类冠状病毒疾病中，都尚不清楚，这是必须寻求多种疫苗方法的另一个原因。

高度的安全性是任何广泛使用的疫苗的首要目标,而且理论上存在接种疫苗可能使随后的 SARS-CoV-2 感染更加严重的风险。这已经在猫冠状病毒中报道过，并且在一些接种疫苗的动物模型中观察到 SARS-CoV-1。这些临床前数据表明，与疫苗相关的强化呼吸系统疾病的综合征是由保护性较差的抗体与 T 辅助细胞 2 (TH2) -偏倚免疫反应共同产生免疫复合物沉积所致。最近对疫苗引起的免疫增强的潜在机制和减少这一风险的方法进行了综述。重要的是构建构象正确的抗原,以诱导出功能有效的抗体——这是从接种了福尔马林灭活呼吸道合胞病毒(RSV)疫苗的婴儿，因接种疫苗引起的增强型下呼吸道疾病中得到的教训。目前正在开发 SARS-CoV-2 感染的动物模型，这些模型可用于更好地了解与保护相关的免疫反应。



Abstract

We discuss one such collaborative program that has recently emerged: the ACTIV (Accelerating COVID-19 Therapeutic Interventions and Vaccines) public-private partnership.Spearheaded by the U.S. National Institutes of Health (NIH), this effort brings together the strengths of all sectors at this time of global urgency. We further discuss a collaborative platform for conducting harmonized, randomized controlled vaccine efficacy trials. This mechanism aims to generate essential safety and efficacy data for several candidate vaccines in parallel, so as to accelerate the licensure and distribution of multiple vaccine platforms and vaccines to protect against COVID-19 (coronavirus disease 2019).

We currently know little about what constitutes a protective immune response against COVID-19. Data from SARS-CoV-1 patients as well as recently infected SARS-CoV-2 patients document relatively high levels of immune responses after infection, especially antibody responses to the surface (spike) protein that mediates entry into host cells. However, in vivo data on the type or level of immunity required to protect from subsequent re-infection, and the likely duration of that protection, are currently unknown. In animal models of SARS-CoV-1, immunization with recombinant subunit proteins and viral- and nucleic acid–vectored vaccines, as well as passive transfer of neutralizing antibodies to the spike protein, have been shown to be protective against experimental infection. Endpoints vary from protection of infection to modification of viral replication and disease. These data bring optimism that a highly immunogenic vaccine will elicit the magnitude and quality of antibody responses required for protection. The role that T cell immunity plays in preventing acquisition or amelioration of early disease, either in animal challenge models or in human coronavirus disease, is unclear; this constitutes another reason why a diversity of vaccine approaches must be pursued.。

A high degree of safety is a primary goal for any widely used vaccine, and there is theoretical risk that vaccination could make subsequent SARS-CoV-2 infection more severe. This has been reported for feline coronaviruses and has been observed in some vaccine-challenge animal models of SARS-CoV-1. These preclinical data suggest that the syndrome of vaccine-associated enhanced respiratory disease results from a combination of poorly protective antibodies that produce immune complex deposition together with a T helper cell 2 (TH2)–biased immune response. The potential mechanism behind vaccine-induced immune enhancement and the means to minimize this risk have recently been reviewed . It will be important to construct conformationally correct antigens to elicit functionally effective antibodies—a lesson learned from vaccine-induced enhanced lower respiratory illness among infants receiving a formalin-inactivated respiratory syncytial virus (RSV) vaccine. Animal models of SARS-CoV-2 infection are currently being developed, and these models can be used to better understand the immune responses associated with protection.

9. Celebrex 辅助治疗 COVID-19 的实验研究

Celebrex adjuvant therapy on COVID-19: An experimental study

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DOI 或 PUBMED ID：Preprint

编译者：张鹏伟

中文摘要：

背景：严重急性呼吸综合征冠状病毒 2（SARS-CoV-2）的传播给世界带来了严重威胁，该病毒导致了 2019 年冠状病毒病（COVID-19）。然而，目前还没有有效的药物治疗 COVID-19。通过对现有资料的分析，作者推断 COVID-19 的主要病理基础是环氧化酶-2（COX-2）介导的前列腺素 E_2（PGE_2）过度积聚。

方法：用质谱法测定尿中 PGE2 水平。在常规治疗的基础上，对 Celebrex 治疗 COVID-19 进行了实验研究。共纳入 44 例确诊的 COVID-19 患者（实验组 37 例，对照组 7 例）。实验组给予 Celebrex，每日 1～2 次（0.2g/次），疗程 7～14d。对个人的剂量或持续时间进行了修改。终止 Celebrex 后，通过生命体征、实验室检查和计算机断层扫描评估 Celebrex 辅助治疗的临床结果。

结果：作者发现 COVID-19 患者尿中 PGE_2 浓度明显高于健康人（平均值为 170ng/ml vs 18.8ng/ml，$p<0.01$），且与 COVID-19 的进展呈正相关。在实验组（普通组 29 例，重度组 7 例，危重组 1 例）中，全剂量治疗 25 例，半剂量 Celebrex 治疗 11 例，布洛芬治疗 1 例。全、半、对照组缓解率分别为 100%、82%、57%。Celebrex 显著降低 PGE_2 水平，促进普通或重度 COVID-19 的恢复。

结论：这些研究表明 Celebrex 辅助治疗可能有助于 COVID-19 的治疗。

注：Celebrex，是辉瑞制药有限公司的镇痛药品牌。可有效治疗多种临床常见的急性疼痛：急性创伤/组织损伤（如急性踝扭伤、急性肩腱炎、滑囊炎），慢性疼痛急性发作（如慢性腰背痛急性发作），术后疼痛；也可有效治疗慢性疼痛，如骨关节炎、类风湿关节炎、强直性脊柱炎。

Abstract:

Background: The world is under serious threat with the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the coronavirus disease 2019 (COVID-19). However, there is no effective drug for the treatment of COVID-19. Based on analyses of available data, we deduced that the excessive prostaglandins E_2 (PGE_2) accumulation mediated by cyclooxygenase-2 (COX-2) was the key pathological basis of COVID-19.

Methods: The urine PGE_2 levels were measured by mass spectrometry. An experimental study about Celebrex to treat COVID-19 was conducted based on routine treatment. A total of 44 confirmed COVID-19 patients were enrolled (Experimental group n=37, Control group n=7). Patients in experimental group were given Celebrex once or twice a day (0.2 g/time) for 7-14 days. The dosage or duration was modified for individuals. Clinical outcomes of Celebrex adjuvant therapy were evaluated by vital signs, laboratory tests, and computed

tomography upon the discontinuance of Celebrex. **Results:** We found that the concentrations of PGE_2 in urine samples of COVID-19 patients were significantly higher than that of healthy individuals (mean value is 170 ng/ml vs 18.8 ng/ml, $p<0.01$) and positively correlated with the progression of COVID-19. Among the experimental group (ordinary n=29, severe n=7, critical n=1), 25 cases were treated with full dose and 11 cases with half dose of Celebrex, and 1 case with Ibuprofen. The remission rate were 100%, 82% and 57% in full dose, half dose and control group respectively. Celebrex significantly reduced the PGE_2 levels and promoted recovery of ordinary or severe COVID-19.
Conclusion: Our study suggests that Celebrex adjuvant treatment may be helpful for the therapy of COVID-19.

10. SARS-CoV-2 的 Spike 蛋白能够与特定长度和序列的硫酸乙酰肝素结合

SARS-CoV-2 spike protein binds heparan sulfate in a length- and sequence-dependent manner
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第一作者：Lin Liu，Pradeep Chopra，Xiuru Li
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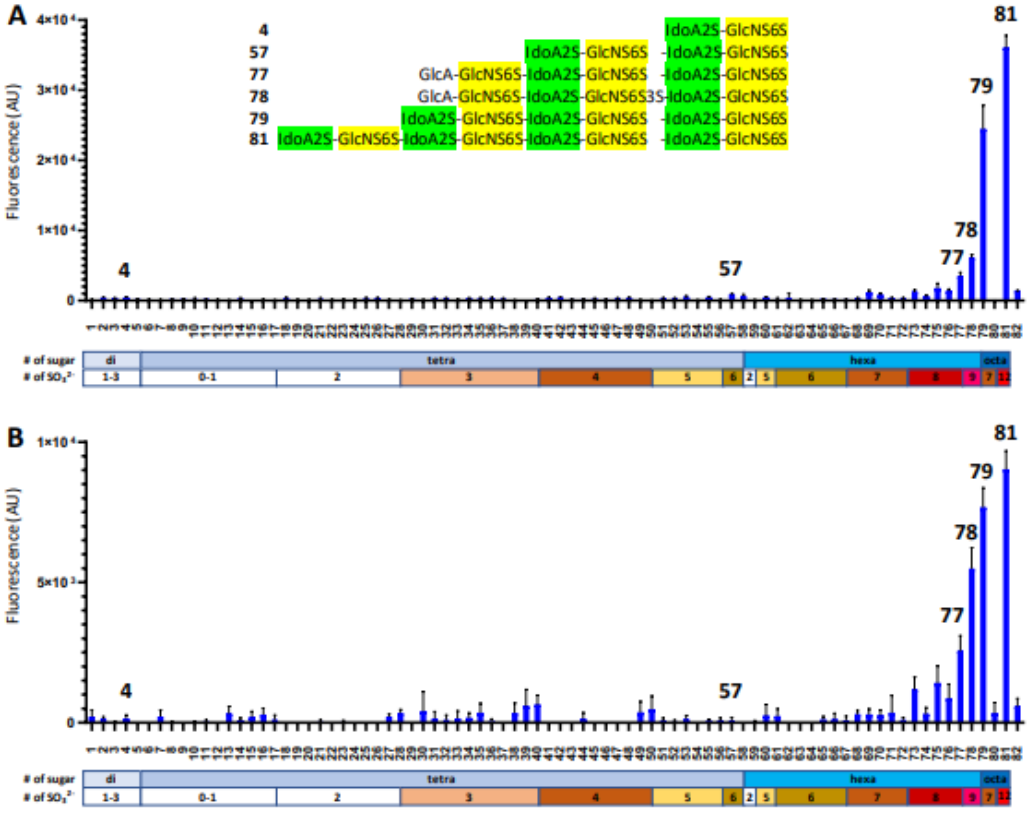
DOI 或 PUBMED ID：
编译者：宋珂
中文摘要：

SARS-CoV-2 病毒在世界范围内造成了空前严重的疫情，急需开发有效的治疗方法。本文中，作者使用大规模的硫酸乙酰肝素(HS)寡聚糖库，对 SARS-CoV-2 的 Spike 蛋白进行了结合能力芯片实验。结果表明，SARS-CoV-2 的 Spike 蛋白能够与特定长度和序列的 HS 结合。其中，由 IdoA2S-GlcNS6S 单体组成的六聚糖和八聚糖的结合能力最强。表面等离子体共振(SPR)实验发现，与单独的受体结构域(RBD，K_D=1uM)相比，SARS-CoV-2 的 Spike 蛋白整体与肝素的亲和力更高(K_D=55nM)。由 IdoA2S-GlcNS6S 组成的八聚糖可以抑制 Spike 与肝素的相互作用，IC50 为 38nM。依据现有数据，作者推测，SARS-CoV-2 的 Spike 蛋白上的 RBD 能够与目标细胞表面表达的特定序列的 HS 结合。同时，HS 在 S1/S2 蛋白水解切割位点的结合，能进一步增强 RDB 与 HS 的结合能力。总体而言，现有结果显示出，利用 HS 寡聚糖作为治疗药物，抑制 SARS-CoV-2 病毒与目标细胞结合的潜力。

Abstract:
Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) is causing an unprecedented global pandemic demanding the urgent development of therapeutic strategies. Microarray binding experiments using an extensive heparan sulfate (HS) oligosaccharide library showed the spike of SARS-CoV-2 can bind HS in a length- and sequence-dependent manner. Hexa- and octasaccharides composed of IdoA2S-GlcNS6S repeating units were identified as optimal ligands. Surface plasma resonance (SPR) showed the SARS-CoV-2 spike protein binds with higher affinity to heparin (K_D=55nM) compared to the receptor binding domain (RBD, K_D=1uM) alone.

An octasaccharide composed of IdoA2S-GlcNS6S could inhibit spike-heparin interaction with an IC50 of 38 nM. Our data supports a model in which the RBD of the spike of SARS-CoV-2 confers sequence specificity for HS expressed by target cells whereas an additional HS binding site in the S1/S2 proteolytic cleavage site enhances the avidity of binding. Collectively, our results highlight the potential of using HS oligosaccharides as a therapeutic agent by inhibiting SARS-CoV-2 binding to target cells.



C

1	IdoA-GlcNAc6S
2	GlcA-GlcNAc6S
3	IdoA2S-GlcNAc6S
4	IdoA2S-GlcNS6S
5	IdoA2S-GlcNS6S
6	GlcA-GlcNAc-GlcA-GlcNAc
7	GlcA-GlcNAc-IdoA-GlcNAc
8	GlcA-GlcNAc-IdoA2S-GlcNAc
9	GlcA-GlcNAc-GlcA2S-GlcNAc
10	GlcA-GlcNAc-IdoA-GlcNAc6S
11	IdoA-GlcNAc6S-GlcA-GlcNAc
12	IdoA2S-GlcNAc-GlcA-GlcNAc
13	IdoA-GlcNAc-IdoA-GlcNAc6S
14	IdoA-GlcNAc6S-IdoA-GlcNAc
15	GlcA-GalNAc-GlcA-GalNAc4S
16	IdoA-GlcNS-IdoA-GlcNAc
17	IdoA-GlcNAc-IdoA-GlcNS
18	IdoA-GlcNAc6S-IdoA-GlcNAc6S
19	IdoA-GlcNAc6S-GlcA-GlcNAc6S
20	GlcA-GlcNAc6S-IdoA-GlcNAc6S
21	GlcA-GlcNAc6S-GlcA-GlcNAc6S
22	GlcA-GlcNAc-GlcA2S-GlcNAc6S
23	GlcA-GlcNAc-IdoA-GlcNS6S
24	GlcA-GlcNAc-IdoA2S-GlcNAc6S
25	IdoA2S-GlcNAc6S-GlcA-GlcNAc
26	GlcA-GlcNS6S-GlcA-GlcNAc
27	GlcA-GlcNS6S-GlcA-GlcNAc
28	IdoA-GlcNS-IdoA-GlcNS
29	GlcA-GlcNAc6S-IdoA2S-GlcNAc6S
30	IdoA-GlcNAc6S-IdoA2S-GlcNAc6S
31	GlcA-GlcNS-IdoA2S-GlcNS
32	GlcA-GlcNS-GlcA2S-GlcNS
33	GlcA-GlcNAc-IdoA2S-GlcNS6S
34	GlcA-GlcNS-IdoA-GlcNS6S
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37	IdoA2S-GlcNS-GlcA-GlcNS
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41	IdoA-GlcNS6S-GlcA-GlcNS6S
42	GlcA-GlcNS6S-IdoA-GlcNS6S
43	GlcA-GlcNS6S-GlcA-GlcNS6S
44	IdoA-GlcNS6S-IdoA-GlcNS6S
45	GlcA-GlcNS-GlcA2S-GlcNS6S
46	GlcA-GlcNS-IdoA2S-GlcNS6S
47	IdoA2S-GlcNS6S-GlcA-GlcNS
48	IdoA2S-GlcNAc6S-IdoA2S-GlcNAc6S
49	IdoA-GlcNS-IdoA2S-GlcNS6S
50	IdoA2S-GlcNS6S-IdoA-GlcNAc6S
51	GlcA-GlcNS6S-IdoA2S-GlcNS6S
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59	GlcA-GlcNAc-IdoA2S-GlcNAc6S-GlcA-GlcNAc
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61	GlcA-GlcNAc-IdoA2S-GlcNS6S-IdoA2S-GlcNS
62	GlcA-GlcNS6S-GlcA-GlcNS6S-GlcA-GlcNS6S
63	GlcA-GlcNS6S-IdoA-GlcNS6S-GlcA-GlcNS6S
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68	GlcA-GlcNS6S-IdoA2S-GlcNS6S-GlcA-GlcNS6S
69	GlcA-GlcNS6S-IdoA2S-GlcNS6S-IdoA-GlcNS6S
70	GlcA-GlcNS6S-GlcA-GlcNS6S-IdoA2S-GlcNS6S
71	GlcA-GlcNS6S-IdoA-GlcNS6S-IdoA2S-GlcNS6S
72	GlcA-GlcNS6S-IdoA2S-GlcNS6S-IdoA2S-GlcNS
73	GlcA-GlcNS6S-IdoA2S-GlcNS3S6S-GlcA-GlcNS6S
74	GlcA-GlcNS6S-IdoA2S-GlcNS3S6S-IdoA-GlcNS6S
75	GlcA-GlcNS6S-GlcA-GlcNS3S6S-IdoA2S-GlcNS6S
76	GlcA-GlcNS6S-IdoA-GlcNS3S6S-IdoA2S-GlcNS6S
77	GlcA-GlcNS6S-IdoA2S-GlcNS6S-IdoA2S-GlcNS6S
78	GlcA-GlcNS6S-IdoA2S-GlcNS3S6S-IdoA2S-GlcNS6S
79	IdoA2S-GlcNS6S-IdoA2S-GlcNS6S-IdoA2S-GlcNS6S
80	GlcA-GlcNS6S-IdoA-GlcNS-IdoA2S-GlcNS6S-IdoA-GlcNAc6S
81	IdoA2S-GlcNS6S-IdoA2S-GlcNS6S-IdoA2S-GlcNS6S-IdoA2S-GlcNS6S
82	Heparin functionalized with primary amine (MW 27KDa)

11. 一个和 SARS-CoV-2 紧密相关的蝙蝠冠状病毒在刺突的蛋白的 S1/S2 切割位点存在天然插入

A novel bat coronavirus closely related to SARS-CoV-2 contains natural insertions at the S1/S2 cleavage site of the spike protein

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编译者：蒋立春

虽然蝙蝠被看作这 SARS-CoV-2 最可能的天然宿主，SARS-CoV-2 的源头仍然未知。作者们对在 2019 年 5 月到 10 月之间从云南采集的 227 个蝙蝠样品进行宏基因组测序，发现了一个全新的蝙蝠来源的冠状病毒 RmYN02。RmYN02 和 SARS-CoV-2 在全基因上有 93.3%的核酸相同（注：之前报道的蝙蝠 RaTG13 和 SARS-CoV-2 整体基因组有约 97%相同，而穿山甲有 91%相同），在 1ab 基因有 97.2%相同。RmYN02 是目前为止和 SARS-CoV-2 在 1ab 基因上最相似的病毒。与之相反，RmYN02 在受体结合区域和 SARS-CoV-2 的序列只有 61.3%相同，可能不和 ACE2 结合。更关键的是，和 SARS-CoV-2 相似，RmYN02 的刺突蛋白的 S1 和 S2 结合处有一个多氨基酸的插入。这为动物来源的 beta 冠状病毒可能在 S1 和 S2 之间天然插入片段提供了强有力的证据（注：SARS-CoV-2 不同于其他 beta 冠状病毒，在 S1 和 S2 亚基之间插入了一个弗林蛋白酶切识别位点，故而成为了“病毒人造说”的理由之一）。

The unprecedented pandemic of pneumonia caused by a novel coronavirus, SARS-CoV-2, in China and beyond has had major public health impacts on a global scale. Although bats are regarded as the most likely natural hosts for SARS-CoV-2, the origins of the virus remain unclear. Here, we report a novel bat-derived coronavirus, denoted RmYN02, identified from a metagenomics analysis of samples from 227 bats collected from Yunnan Province in China between May and October, 2019. Notably, RmYN02 shares 93.3% nucleotide identity with SARS-CoV-2 at the scale of the complete virus genome and 97.2% identity in the 1ab gene, in which it is the closest relative of SARS-CoV-2 reported to date.

In contrast, RmYN02 showed low sequence identity (61.3%) to SARS-CoV-2 in the receptor binding domain (RBD) and might not bind to angiotensin-converting enzyme 2 (ACE2). Critically, and in a similar manner to SARS-CoV-2, RmYN02 was characterized by the insertion of multiple amino acids at the junction site of the S1 and S2 subunits of the spike (S) protein. This provides strong evidence that such insertion events can occur naturally in animal betacoronaviruses.

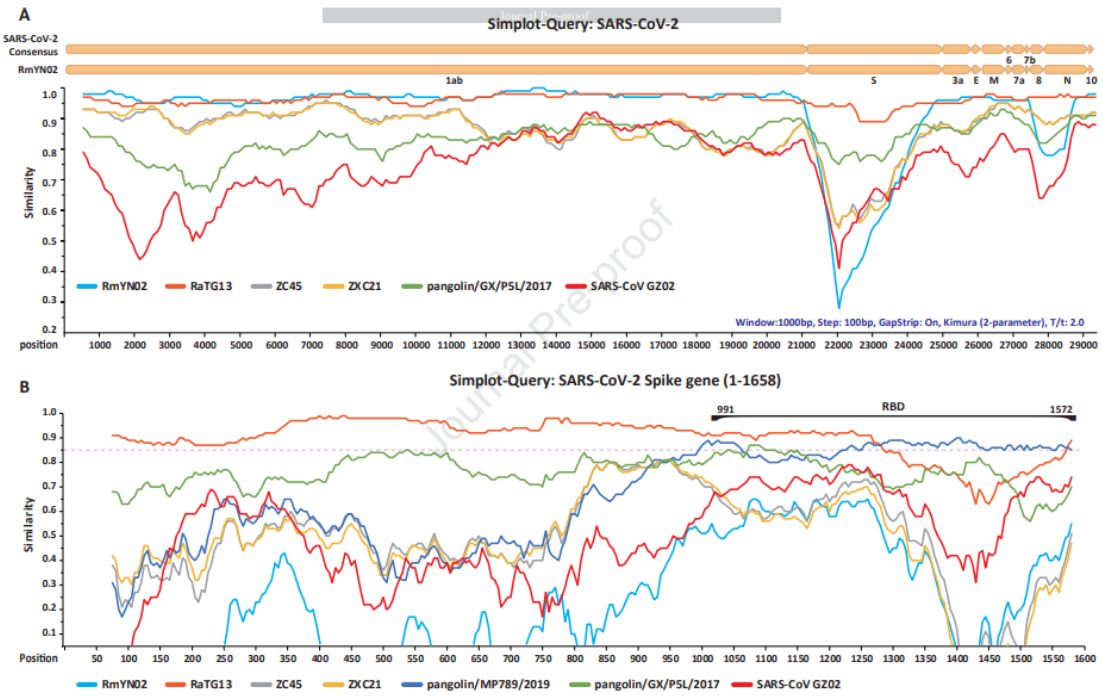

Figure 1. Patterns of sequence identity bet Patterns of sequence identity bet Patterns of sequence identity between the consensus ween the consensus sequences of sequences of SARS-CoV-2 and representative beta and representative beta- and representative beta-CoVs. (A) Whole genome similarity plot between SARS-CoV-2 and representative viruses listed in Table 1. The analysis was performed using Simplot, with a window size of 1000bp and a step size of 100bp. (B) Similarity plot in the spike gene (positions 1-1658) between SARS-CoV-2 and representative viruses listed in Table 1. The analysis was performed using Simplot, with a window size of 150bp and a step size of 5bp.