新型冠状病毒信息简报

第 37 期（2020 年 4 月 24 日报）

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 23 日疫情

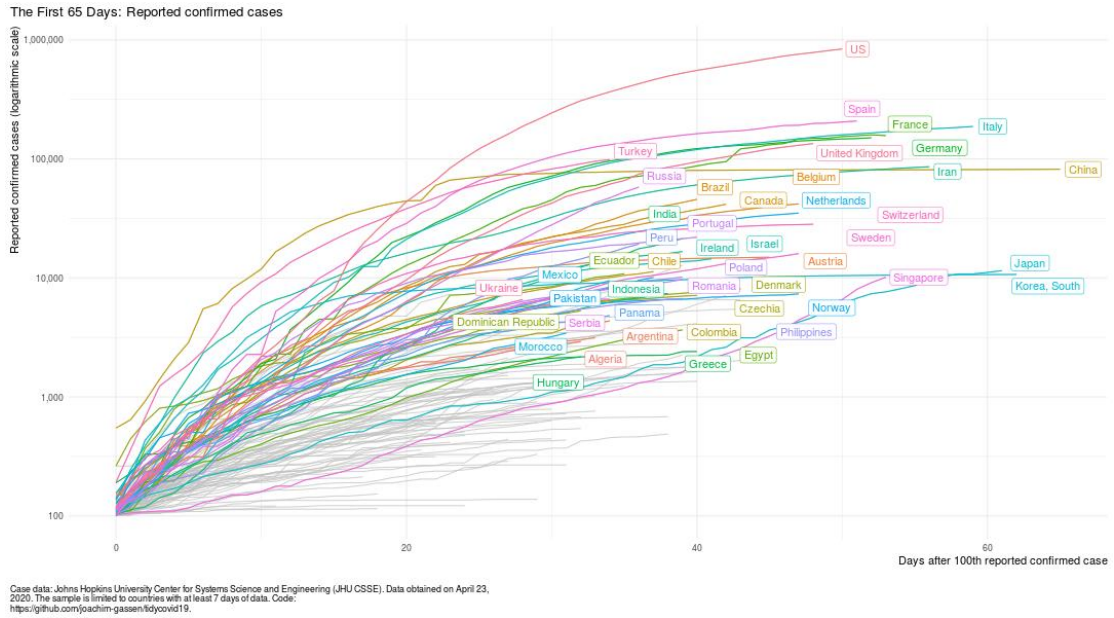
数据来源：WHO

发布时间：2020 年 4 月 23 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 23 日全球累计确诊新型冠状病毒病人 2544792 例，当日新增确诊 73657 例，累计死亡 175694 例，当日新增死亡 6689。

中国累计确诊 84302 例，累计死亡 4642 例，当日新增确诊 15 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 4 月 23 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 23 日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. SARS-CoV-2 在广东省的基因组流行病学

Genomic epidemiology of SARS-CoV-2 in Guangdong Province, China

来源：Cell

发布时间：2020-04-22

链接：

https://www.cell.com/pb-assets/products/coronavirus/CELL_CELL-D-20-00921.pdf

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DOI:

编译者：蒋立春

中文摘要：

截止 2020 年 3 月 19，中国的广东省总共进行新冠病毒检测 160 万次，发现 1388 例核酸阳性病人。为了理解中国的 SARS-CoV-2 的分子流行病学以及病毒的遗传多样性，研究者们采用宏基因组测序以及叠瓦式扩增子测序的方法一共对广东省 53 位病人来源的病毒进行了测序。结合流行病学和分子进化树分析，虽然因为疫情早期病毒的遗传多样性不够导致进化树的聚类存在一定不确定性，研究们发现广东发生了多次独立的病例传入。作者们的研究说明了可能的本地传播链的开始时间、范围以及持续时间是怎样被广东省的大规模的疫情监控以及干预手段所控制的。即便取得了这些成功，因为境外输入病例的增加，广东省的疫情监控工作仍然是必需的。

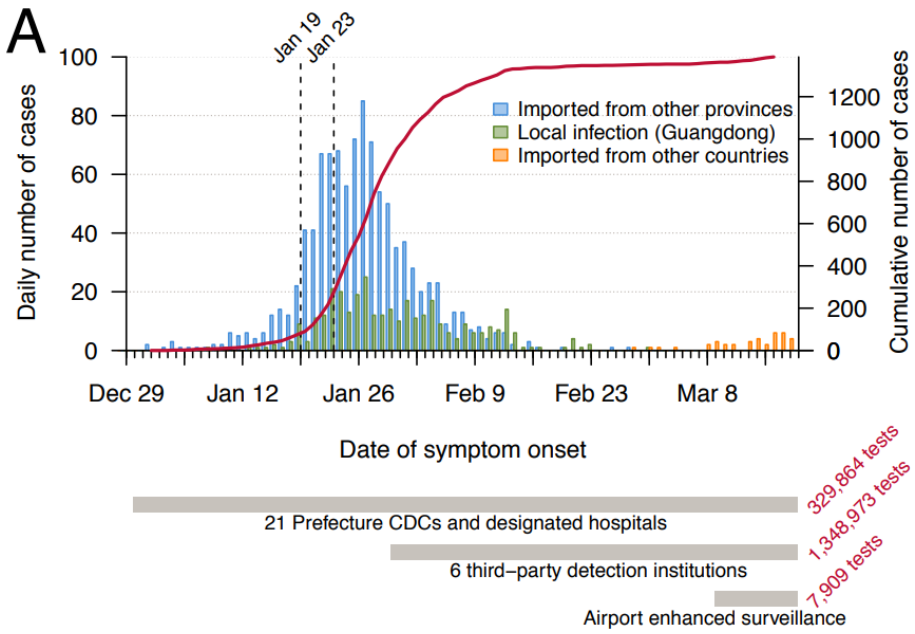

Figure 1: Summary of the COVID-19 epidemic in Guangdong Province, China. (A) Time series of the 1,388 laboratory-confirmed COVID-19 cases in Guangdong until 19th March, by date of onset of illness. Cases are classified according to their likely exposure histories (see inset and main text). The dashed lines indicate the date the first Guangdong case was detected (19th January) and the shutdown of travel from Wuhan (23rd January). An overview of testing and surveillance strategies at different stages of the epidemic are illustrated below the time

series, on the same timescale.

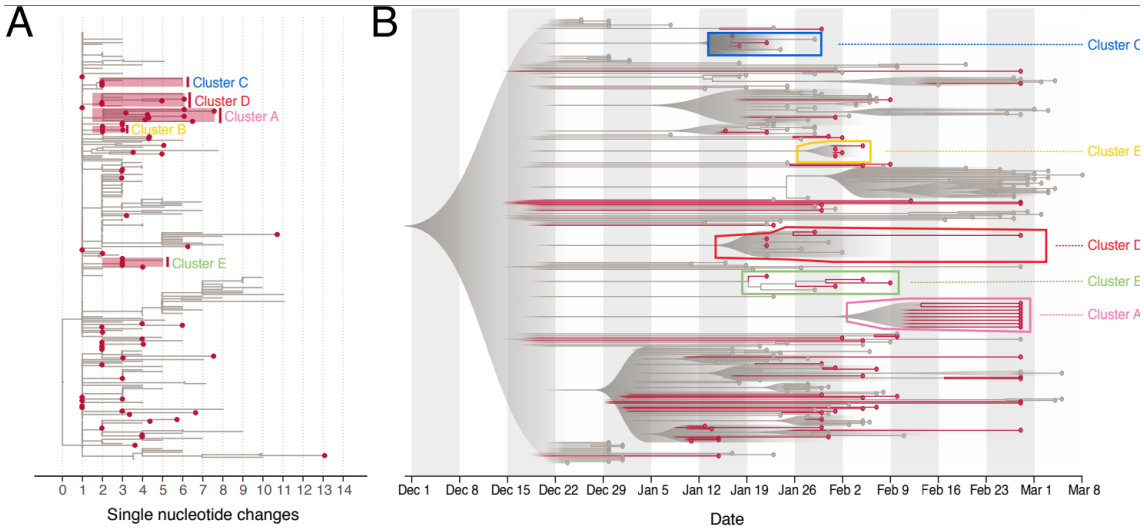

Figure 3: (A) Estimated maximum likelihood phylogeny of SARS-CoV-2 sequences from Guangdong (red circles) and genomes from other countries and provinces (not circled). The axis is in units of nucleotide changes from the inferred root sequence. A phylogenetic bootstrap analysis was not performed due to the low number of phylogenetically informative sites and the number of missing bases (N) in the alignment. The position of clusters A-E discussed in main text are highlighted with red boxes and labelled. (B) Visualization of the corresponding time-scaled maximum clade credibility tree. Sequences from Guangdong and their terminal branches are in red and those from other locations in grey. The clusters (A-E) discussed in main text are highlighted with boxes and labelled. All nodes with posterior probabilities

注：需要了解进化树怎么看，可参考 https://nextstrain.org/help/general/how-to-read-a-tree

Summary

COVID-19 is caused by SARS-CoV-2 infection and was first reported in central China in December 2019. Extensive molecular surveillance in Guangdong, China's most populous province, during early 2020 resulted in 1,388 reported RNA-positive cases from 1.6 million tests. In order to understand the molecular epidemiology and genetic diversity of SARS-CoV-2 in China we generated 53 genomes from infected individuals in Guangdong using a combination of metagenomic sequencing and tiling amplicon approaches. Combined epidemiological and phylogenetic analyses indicate multiple independent introductions to Guangdong, although phylogenetic clustering is uncertain due to low virus genetic variation early in the pandemic. Our results illustrate how the timing, size and duration of putative local transmission chains were constrained by national travel restrictions and by the province's large-scale intensive surveillance and intervention measures. Despite these successes, COVID-19 surveillance in Guangdong is still required as the number of cases imported from other countries has increased.

3. 高精度检测冠状病毒的新方法——双重功能等离子光热生物传感器

Dual-Functional Plasmonic Photothermal Biosensors for Highly Accurate Severe Acute Respiratory Syndrome Coronavirus 2 Detection

来源：ACSNANO

发布时间：2020-04-13

链接：https://pubs.acs.org/doi/pdf/10.1021/acsnano.0c02439

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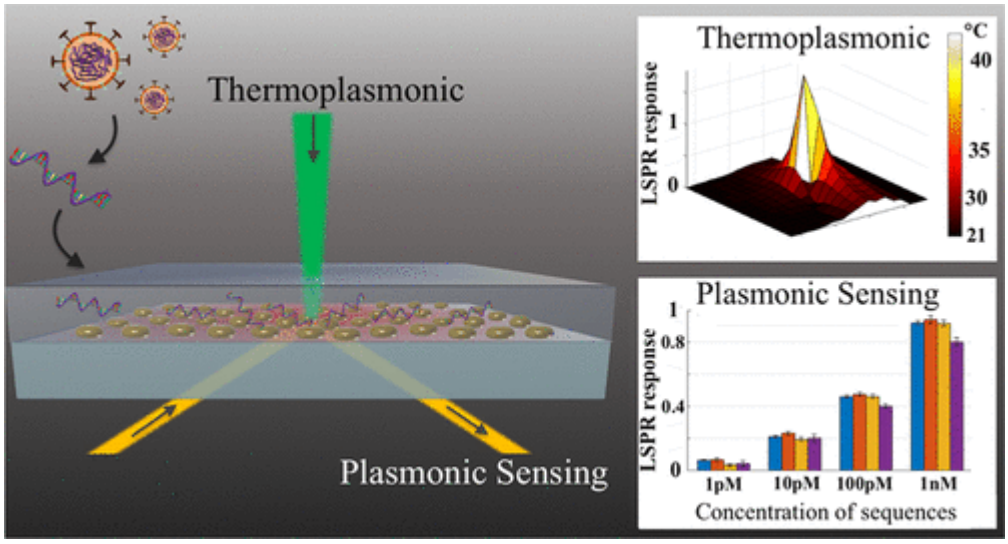
DOI：10.1021/acsnano.0c02439

编译者：刘焕珍

中文摘要：

可靠的疾病实验室诊断一直是促进公共卫生干预的首要优先事项之一。常规使用的逆转录聚合酶链反应(RT-PCR)是目前 COVID-19 诊断的参考方法。然而，在病毒爆发的早期阶段，PCR 诊断的假阴性或假阳性错误屡见报道，严重影响 COVID-19 的快速诊断及后续治疗。作者合作开发出双功能等离子体生物传感器，该传感器结合等离子体光热效应(PPT)和局部表面等离子体共振(LSPR)感应传导，可对 COVID-19 的临床诊断提供可选择且有前途的解决方案。携带互补 DNA 目的探针的纳米金颗粒(AuNIs)可以通过核酸杂交对 SARS-CoV-2 冠状病毒序列进行敏感检测。为了获得更好的传感性能，当以等离子体共振频率照明时，在同一 AuNIs 芯片上产生等离子体热效应(PPT)。定位的 PPT 可以提高原位杂交温度，便于对两个相似的基因序列进行准确的鉴别。双功能 LSPR 生物传感器对选定的 SARS-CoV-2 序列表现出很高的灵敏度，最低检测限值为 0.22 pM，并允许在多基因混合物中精确检测特定的目标。本研究开发的双功能等离子体系统已经成功地证明了对 SARS-Cov-2 病毒检测的高灵敏度、快速和可靠的诊断能力，有望提供可靠且易于实现的诊断平台，提高临床试验的诊断准确性，缓解 PCR 检测的压力。

注：作者提到估计最低的检测灵敏度在 10,000 拷贝数量级，参考之前 FDA 和中国药监局批准的基于 RT-PCR 的检测 LOD，这个灵敏度较差（相对绝大部分试剂 LOD 为 1000copy/ml 以下）。有待仔细查证。



Abstract:

The ongoing outbreak of the novel coronavirus disease (COVID-19) has spread globally and poses a threat to public health in more than 200 countries. Reliable

laboratory diagnosis of the disease has been one of the foremost priorities for promoting public health interventions. The routinely used reverse transcription polymerase chain reaction (RT-PCR) is currently the reference method for COVID-19 diagnosis. However, it also reported a number of false-positive or -negative cases, especially in the early stages of the novel virus outbreak. In this work, a dual-functional plasmonic biosensor combining the plasmonic photothermal (PPT) effect and localized surface plasmon resonance (LSPR) sensing transduction provides an alternative and promising solution for the clinical COVID-19 diagnosis. The two-dimensional gold nanoislands (AuNIs) functionalized with complementary DNA receptors can perform a sensitive detection of the selected sequences from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) through nucleic acid hybridization. For better sensing performance, the thermoplasmonic heat is generated on the same AuNIs chip when illuminated at their plasmonic resonance frequency. The localized PPT heat is capable to elevate the in situ hybridization temperature and facilitate the accurate discrimination of two similar gene sequences. Our dual-functional LSPR biosensor exhibits a high sensitivity toward the selected SARS-CoV-2 sequences with a lower detection limit down to the concentration of 0.22 pM and allows precise detection of the specific target in a multigene mixture. This study gains insight into the thermoplasmonic enhancement and its applicability in the nucleic acid tests and viral disease diagnosis.

4. 纽约市地区 5700 名 COVID-19 住院患者的特征、合并基础疾病和结局

Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area

来源：JAMA

发布时间：2020-04-22

链接：https://jamanetwork.com/journals/jama/fullarticle/2765184?resultClick=1

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通讯作者：Karina W. Davidson

通讯作者单位：Northwell Health, New York

DOI：10.1001/jama.2020.6775

编译者：宋张悦

中文摘要：

重要性：目前关于美国 COVID-19 需要住院治疗的患者的特征和结局的信息还很有限。

目的：描述在美国医疗系统住院的 COVID-19 患者的临床特征和结局。

设计、设置和参与者：纽约州的纽约市、长岛和韦斯特切斯特县的 12 家医院收治了大量 COVID-19 患者，这些病例都收录在 Northwell 卫生系统内。本研究纳入了 2020 年 3 月 1 日至 2020 年 4 月 4 日期间（包括这些日期）的所有按顺序入住医院的患者病例。

暴露：需要入院的患者经过鼻咽样本聚合酶链反应检测结果均为阳性，确诊为严重急性呼吸系统综合征冠状病毒 2 型(SARS-CoV-2)感染。

主要结局和措施：住院期间的临床结局，如有创机械通气、肾脏替代治疗和死亡。本研究还收集了统计资料、基线共病、生命体征和检测结果。

结果：本研究共纳入 5700 例患者（中位年龄：63 岁[四分位间距{IQR}：52-75；范围：0-

107 岁]；39.7%的女性）。最常见的共病是高血压（3026 例，56.6%）、肥胖（1737 例，41.7%）和糖尿病(1808 例，33.8%)。在临床分诊时，30.7%的患者发热，17.3%的患者呼吸频率大于 24 次/分钟，27.8%的患者需要供氧。呼吸道病毒共感染率为 2.1%。对 2634 例在研究结束时出院或死亡的患者进行了结局评估。住院期间，373 例患者（14.2%）（中位年龄：68 岁[IQR：56-78]，33.5%是女性）在重症监护病房接受治疗，320 人（12.2%）接受有创机械通气，81 人（3.2%）接受肾脏替代治疗，553 人（21%）死亡。需要机械通气的死亡率为 88.1%。出院后中位随访时间为 4.4 天(IQR：2.2-9.3)。研究期间共有 45 名患者(2.2%)再次入院。再入院患者的中位时间为 3 天(IQR:1.0-4.5)。3066 例患者在最终研究随访时仍住院(中位年龄：65 岁[IQR：54-75 岁])，截尾时中位随访时间为 4.5 天(IQR：2.4-8.1)。小于 20 岁的男性和女性患者的死亡率为 0%(0/20)。

结论和相关性：本病例系列提供了纽约市地区按顺序住院的 COVID-19 确诊患者的特征和早期结局。

Abstract:

Importance There is limited information describing the presenting characteristics and outcomes of US patients requiring hospitalization for coronavirus disease 2019 (COVID-19).

Objective To describe the clinical characteristics and outcomes of patients with COVID-19 hospitalized in a US health care system.

Design, Setting, and Participants Case series of patients with COVID-19 admitted to 12 hospitals in New York City, Long Island, and Westchester County, New York, within the Northwell Health system. The study included all sequentially hospitalized patients between March 1, 2020, and April 4, 2020, inclusive of these dates.

Exposures Confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by positive result on polymerase chain reaction testing of a nasopharyngeal sample among patients requiring admission.

Main Outcomes and Measures Clinical outcomes during hospitalization, such as invasive mechanical ventilation, kidney replacement therapy, and death. Demographics, baseline comorbidities, presenting vital signs, and test results were also collected.

Results A total of 5700 patients were included (median age, 63 years [interquartile range {IQR}, 52-75; range, 0-107 years]; 39.7% female). The most common comorbidities were hypertension (3026; 56.6%), obesity (1737; 41.7%), and diabetes (1808; 33.8%). At triage, 30.7% of patients were febrile, 17.3% had a respiratory rate greater than 24 breaths/minute, and 27.8% received supplemental oxygen. The rate of respiratory virus co-infection was 2.1%. Outcomes were assessed for 2634 patients who were discharged or had died at the study end point. During hospitalization, 373 patients (14.2%) (median age, 68 years [IQR, 56-78]; 33.5% female) were treated in the intensive care unit care, 320 (12.2%) received invasive mechanical ventilation, 81 (3.2%) were treated with kidney replacement therapy, and 553 (21%) died. Mortality for those requiring mechanical ventilation was 88.1%. The median postdischarge follow-up time was 4.4 days (IQR, 2.2-9.3). A total of 45 patients (2.2%) were readmitted during the study period. The median time to readmission was 3 days (IQR, 1.0-4.5) for readmitted patients.

Among the 3066 patients who remained hospitalized at the final study follow-up date (median age, 65 years [IQR, 54-75]), the median follow-up at time of censoring was 4.5 days (IQR, 2.4-8.1).
Conclusions and Relevance This case series provides characteristics and early outcomes of sequentially hospitalized patients with confirmed COVID-19 in the New York City area.

5. I 型干扰素活性受损与重症 Covid-19 患者炎症反应加重相关

Impaired type I interferon activity and exacerbated inflammatory responses in severe Covid-19 patients
来源：medRxiv
发布时间：2020-04-23
链接：https://www.medrxiv.org/content/10.1101/2020.04.19.20068015v1
第一作者：Jérôme Hadjadj, Nader Yatim,
通讯作者：Benjamin Terrier
通讯作者单位：法国巴黎科什（Cochin）医院内科
DOI 或 PUBMED ID：Preprint
编译者：雷颖
中文摘要：
背景：2019 年冠状病毒病(Covid-19)是一个重大的全球威胁，已经在世界各地造成了 10 万多人的死亡。它的特点是不同的疾病进展模式意味着不同的宿主免疫反应。然而，Covid-19 严重程度所涉及的免疫学特征和分子机制迄今尚不清楚。
方法：作者对一个有 50 名 Covid-19 患者、疾病严重程度不同的队列进行了一项综合免疫分析，包括免疫细胞的深入表型分析、全血转录组和细胞因子定量分析等。所有患者在第一次症状后 8 至 12 天进行测试，并且没有抗炎治疗。
结果：在重症和危重患者中发现了一种独特的表型。它表现为严重受损的 I 型干扰素(IFN)反应，其特征是干扰素的产生和活性较低，导致受干扰素刺激基因的下调。这与持续的血液病毒负荷和加重的炎症反应有关，而这部分是由转录因子 NFκB 驱动的。它还表现为肿瘤坏死因子(TNF)-α 和白细胞介素(IL)-6 的产生和信号增加，以及天然免疫趋化因子的增加。
结论：作者认为在血液中 I 型 IFN 的缺乏是重症 Covid-19 的标志，可以识别和定义高危人群。作者的研究为测试 IFN 给药和针对 IL-6 或 TNF-α 的适应抗炎治疗提供了一个理论依据。这些数据也引起了对干扰 IFN 通路的药物使用的关注。
注：
参考 4 月 20 日简报第 10 条，4 月 21 日简报第 5 条，关于 SARS-CoV-2 引起的宿主免疫反应中 I 型以及 II 型干扰素的缺失。目前看来，体内、离体以及体外都支持该假设。对干扰素通路在 COVID-19 病理过程中的作用要开展进一步研究以确定相关药物的使用。

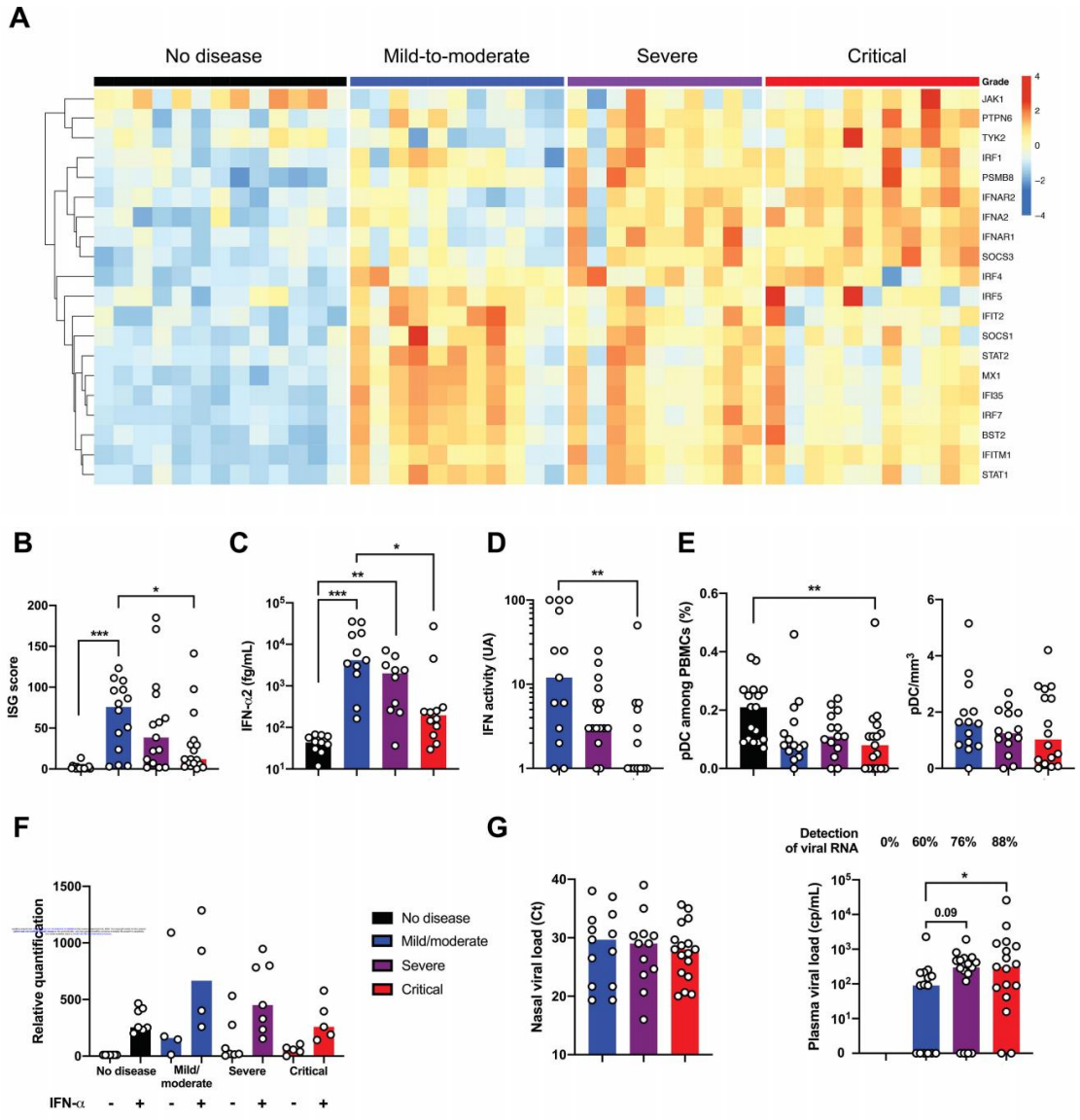

Figure 3. Impaired type I IFN response in severe patients with SARS-CoV2 infection. (A) Heatmap showing expression of type 1 IFN-related gene using the reverse transcription- and PCR-free Nanostring nCounter technology in patients with mild-tomoderate (n=11), severe (n=10) and critical (n=11) patients with SARS-CoV2 infection, and 13 healthy controls (no disease). Up-regulated genes are shown in red and down-regulated genes in blue. (B) IFN stimulated gene (ISG) score based on expression of 6 genes (IFI44L, IFI27, RSAD2, SIGLEC1, IFIT1 and IS15) measured by q-RT-PCR in whole blood cells from mild-to-moderate (n=14), severe (n=15) and critical (n=17) patients, and 18 healthy controls. (C) IFN-α2 (fg/mL) concentration evaluated by SIMOA and (D) IFN activity in plasma according to clinical severity. (E) Quantification of plasmacytoid dendritic cells (pDC) as a percentage of PBMCs and as cells/ml according to severity group. (F) ISG score before and after stimulation of whole blood cells by IFN-α (103 UI/mL for 3 hours). (G) Viral loads in nasal swab estimated by RT-PCR and expressed in Ct and blood viral load evaluated by digital PCR (B-F) Results represent the fold-increased expression compared to the mean of unstimulated controls and are

normalized to GAPDH. P values were determined by the Kruskal-Wallis test, followed by Dunn's post-test for multiple group comparisons with median reported; *P < 0.05; **P < 0.01; ***P < 0.001.

Abstract

Background: Coronavirus disease 2019 (Covid-19) is a major global threat that has already caused more than 100,000 deaths worldwide. It is characterized by distinct patterns of disease progression implying a diverse host immune response. However, the immunological features and molecular mechanisms involved in Covid-19 severity remain so far poorly known.

Methods: We performed an integrated immune analysis that included in-depth phenotypical profiling of immune cells, whole-blood transcriptomic and cytokine quantification on a cohort of fifty Covid19 patients with a spectrum of disease severity. All patient were tested 8 to 12 days following first symptoms and in absence of anti-inflammatory therapy.

Results: A unique phenotype in severe and critically ill patients was identified. It consists in a profoundly impaired interferon (IFN) type I response characterized by a low interferon production and activity, with consequent downregulation of interferon-stimulated genes. This was associated with a persistent blood virus load and an exacerbated inflammatory response that was partially driven by the transcriptional factor NFκB. It was also characterized by increased tumor necrosis factor (TNF)-α and interleukin (IL)-6 production and signaling as well as increased innate immune chemokines.

Conclusion: We propose that type-I IFN deficiency in the blood is a hallmark of severe Covid-19 and could identify and define a high-risk population. Our study provides a rationale for testing IFN administration combined with adapted anti-inflammatory therapy targeting IL-6 or TNF-α in most severe patients. These data also raise concern for utilization of drugs that interfere with the IFN pathway.

6. COVID-19 重症患者外周血免疫应答的单细胞图谱

A single-cell atlas of the peripheral immune response to severe COVID-19

来源：medrxiv

发布时间：2020-04-23

链接：https://www.medrxiv.org/content/10.1101/2020.04.17.20069930v1

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中文摘要：

SARS-CoV-2 已造成全球大流行，因此迫切需要更好地了解 COVID-19 的病理生理学。该研究对 7 例确诊 COVID-19 患者和 6 例健康对照者的外周血单个核细胞（PBMCs）进行了单细胞 RNA 测序（scRNA-seq）。7 名 COVID-19 患者均为男性，年龄在 20 至 80 岁之间，在症状出现后 2-16 天搜集样本。其中一名患者（C1）被取样两次。4 份 COVID-19 样本中，患者诊断为

急性呼吸窘迫综合征（ARDS）；其余四个样本来自病情较轻的患者（表一）。

鉴定了 COVID-19 外周血免疫细胞表型的重组，COVID-19 病例与对照组之间存在显著的表型差异，主要存在于单核细胞、T 细胞和自然杀伤（NK）细胞（图 1a,b）。CD14+单核细胞，T 细胞和 NK 细胞中多种干扰素刺激基因（ISG）标记上调，CD14+单核细胞 HLA II 家族基因下调。该文章鉴定出新的 B 细胞衍生粒细胞群（Activated Granulocytes），仅在 ARDS 患者中显著增加(图 1d)。这些细胞表达几种基因，这些基因编码了中性粒细胞颗粒蛋白(如 ELANE、LTF 和 MMP8)。重要的是，外周血单核细胞和淋巴细胞不表达大量的促炎细胞因子，这表明循环白细胞对潜在的 COVID-19 细胞因子风暴没有显著贡献。总之，该研究提供了迄今为止对 COVID-19 重症患者外周血免疫应答最彻底的细胞图谱。

编者注：

第 1 期（ 2020 年 3 月 19 日报） 编录了题为：血液单细胞免疫图谱显示干扰素-MAPK 通路介导 COVID -19 适应性应答 的文章。

第 23 期（2020 年 4 月 10 日报）编录了题为：通过单细胞分析托珠单抗在重症 COVID-19 患者治疗中减轻由单核细胞中心免疫相互作用引起的炎症风暴 的文章。

Donor	Age	Sex	Days from reported symptom onset	Days from closest reported or measured fever	Admission level	Ventilated/ ARDS?	Days intubated	Days paralyzed	PaO_2/FIO_2 on ICU admission	Clinical outcome
C1	60-69	M	9	9	ICU	No				Now extubated, on room air, expect discharge home
			11	11		Yes	17	2	91	
C2	40-49	M	16	16	ICU	No	-	-	-	Discharged home
C3	30-39	M	9	9	ICU	Yes	25	4	100	Tracheostomy, prolonged ICU course
C4	30-39	M	9	9	ICU	Yes	16	3	71	Now extubated, on supplemental oxygen, expect discharge home
C5	50-59	M	15	1	ICU	No	-	-	-	Discharged home
C6	>80	M	2	No fever	ICU	Yes	11	0	126	Deceased
C7	20-29	M	12	No fever	Floor	No	-	-	-	Discharged home

Table 1: Demographics, sample characteristics, and disease course of COVID-19 patients

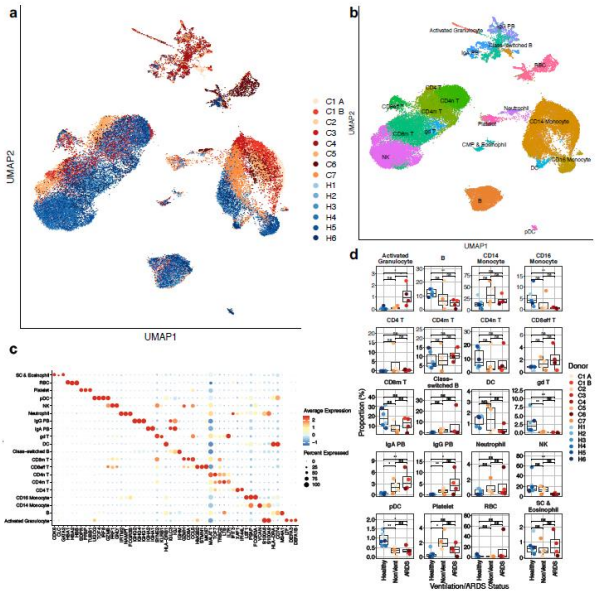

Figure 1 | Expansion of plasmablasts and depletion of multiple innate immune cell subsets in the periphery of patients with COVID-19.

Abstract:
There is an urgent need to better understand the pathophysiology of Coronavirus disease 2019 (COVID-19), the global pandemic caused by SARS-CoV-2. Here, we apply single-cell RNA sequencing (scRNA-seq) to peripheral blood mononuclear cells (PBMCs) of 7 patients hospitalized with confirmed COVID-19 and 6 healthy controls. We identify substantial reconfiguration of peripheral immune cell phenotype in COVID-19, including a heterogeneous interferon-stimulated gene (ISG) signature, HLA class II downregulation, and a novel B cell-derived granulocyte population appearing in patients with acute respiratory failure requiring mechanical ventilation. Importantly, peripheral monocytes and lymphocytes do not express substantial amounts of pro-inflammatory cytokines, suggesting that circulating leukocytes do not significantly contribute to the potential COVID-19 cytokine storm. Collectively, we provide the most thorough cell atlas to date of the peripheral immune response to severe COVID-19.

7. 重组 SARS-CoV-2 spike S1-Fc 融合蛋白在非人灵长类动物中诱导高水平的中和反应

Recombinant SARS-CoV-2 spike S1-Fc fusion protein induced high levels of neutralizing responses in nonhuman primates

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DOI 或 PUBMED ID：Preprint
编译者：张鹏伟

中文摘要：
COVID-19 的爆发已经成为一种全球性的流行病，在全球范围内造成超过 200 万例确诊病例和超过 12.6 万人死亡。在这项研究中，我们检测了 CHO 表达的重组 SARS-CoV-2 S1-Fc 融合蛋白作为 COVID-19 疫苗的潜在候选蛋白在小鼠、兔子和猴子中的免疫原性。我们证明，S1-Fc 融合蛋白具有极强的免疫原性，正如第 7 天观察到的强抗体滴度所证明。用假病毒中和试验观察了 S1-Fc 融合蛋白免疫家兔后第 14 天的强病毒中和活性。最重要的是，在不到 20 天三次注射 S1-Fc 融合蛋白后，在活 SARS-CoV-2 感染试验中，两只猴子的病毒中和滴度比一名恢复的 COVID-19 患者高。我们的数据有力地表明， CHO 表达的 SARS-CoV-2s1-Fc 重组蛋白可能是研制抗 COVID-19 疫苗的有力候选者。

亮点：
CHO 表达的 S1-Fc 蛋白在多种动物中具有很强的免疫原性，能迅速诱导产生强的抗体
S1-Fc 蛋白对活病毒有较强的中和作用
稳定的 CHO 细胞系表达 50mg/L 的 S1-Fc 和一个 3000L 的生物反应器，每 10 天可生产 300 万剂人 COVID-19 疫苗，使之成为一种可获得和负担得起的全球疫苗接种选择

Abstract:
The COVID-19 outbreak has become a global pandemic responsible for over 2,000,000 confirmed cases and over 126,000 deaths worldwide. In this study, we examined

the immunogenicity of CHO-expressed recombinant SARS-CoV-2 S1-Fc fusion protein in mice, rabbits, and monkeys as a potential candidate for a COVID-19 vaccine. We demonstrate that the S1-Fc fusion protein is extremely immunogenic, as evidenced by strong antibody titers observed by day 7. Strong virus neutralizing activity was observed on day 14 in rabbits immunized with the S1-Fc fusion protein using a pseudovirus neutralization assay. Most importantly, in less than 20 days and three injections of the S1-Fc fusion protein, two monkeys developed higher virus neutralizing titers than a recovered COVID-19 patient in a live SARS-CoV-2 infection assay. Our data strongly suggests that the CHO-expressed SARS-CoV-2 S1-Fc recombinant protein could be a strong candidate for vaccine development against COVID-19.

Highlights:

1. CHO-expressed S1-Fc protein is very immunogenic in various animals and can rapidly induce strong antibody production
2. S1-Fc protein solicits strong neutralizing activities against live virus
3. Stable CHO cell line expressing 50 mg/L of S1-Fc and a 3,000 L Bioreactor can produce 3 million doses of human COVID-19 vaccine every 10 days, making it an accessible and affordable option for worldwide vaccination

8. Moderna 的 COVID-19 疫苗 Mrna-1273 一期临床试验开始第二轮的疫苗接种

根 据 https://www.biospace.com/article/moderna-vaccine-clinical-trial-moves-into-2nd-round-of-dosing/4 月 23 日新闻，该一期临床试验的第二轮接种已经开始。

https://clinicaltrials.gov/ct2/show/NCT04283461 里的临床注册信息显示，该一期临床试验是一个开放式 3 臂试验,每试验臂 15 个受试者,疫苗接种分别为 25mcg, 100mcg 以及 250mcg 三个剂量，每个剂量分别在第 1 天和第 29 天接种两针。

该试验的受试者将会接受为期 12 个月的随访。一期临床试验主要可以告诉我们疫苗的安全性，疫苗的有效性要进一步通过二期以及三期试验来进行研究。我们可以看到临床注册信息里是否产生抗体等参数被放入了试验的次要临床试验终点,有望从一期试验里获得一些关于有效性的消息。

9. 细胞疗法能否阻止严重 COVID-19 患者的细胞因子风暴？

Can cell therapies halt cytokine storm in severe COVID-19 patients?

来源：Science Translational Medicine

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链接：https://stm.sciencemag.org/content/12/540/eabb5673

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DOI 或 PUBMED ID：10.1126/scitranslmed.abb5673

编译者：张丽双

中文摘要：

COVID-19 患者接受间充质干细胞(MSC)治疗的初步研究显示其安全性。

利用 MSC 治疗炎症的方法现在被试图用来对抗 COVID-19 诱导的细胞因子风暴。COVID-19 的严重程度可能部分归因于患者对感染的反应。在一些患者中，病毒会导致炎症介质的大量分

泌，导致肺泡肿胀、炎症浸润和气体交换减少。为了对抗这场细胞因子风暴，已有 20 多个旨在用 MSC 治疗 COVID-19 的临床试验在 ClinicalTrials.gov.注册。

冷子宽等人最近在中国进行了 10 例 MSC 移植的初步研究。所有患者经 PCR 检测 SARS-CoV-2 阳性，发热、呼吸短促、咳嗽、休息时血氧饱和度<95%。其中 7 名患者接受同种异体 MSC 静脉注射，3 名患者接受生理盐水作为安慰剂对照。7 名 MSC 治疗的患者症状均得到缓解，而安慰剂治疗的患者中有一名出现 ARDS，另一名死亡。在整个康复过程中，监测 MSC 治疗最严重患者的应答。值得注意的是，MSC 治疗后 C-反应蛋白水平下降了 10 倍，表明全身炎症有所下降。对治疗前后细胞因子水平的分析显示，与安慰剂比较，MSC 治疗后 TNF-α 降低而抗炎 IL-10 升高。

尽管这项研究并不能明确地阐明 MSC 治疗 COVID-19 的疗效或 MSC 预防或治疗细胞因子风暴的作用机制，但它确实提供了重要的安全性数据和有效性提示，推动了 MSC 治疗 COVID-19 的进一步探索。特别值得注意的是，在美国 NIH 资助的一项随机、多中心、安慰剂对照的 2/3 期试验中，对 240 名患者进行了研究。随着多个临床试验在世界各地展开，我们不必等待太长时间来确定 MSC 是否是治疗严重 COVID-19 的可行和有效的治疗方案。

Abstract:

A pilot study of COVID-19 patients treated with mesenchymal stem cells demonstrates safety.

Mesenchymal stromal cell (MSC) therapies, which have been explored for decades as a treatment for inflammatory diseases, are now being called into action to combat the cytokine storm induced by COVID-19. The severity of COVID-19 may be due in part to the patient’s response to the infection. In some patients, the virus induces an outpouring of inflammatory mediators that leads to swelling, inflammatory infiltration, and reduced gas exchange in the alveoli of the lungs. To combat this cytokine storm, over 20 clinical trials aiming to treat COVID-19 with MSCs have been registered with ClinicalTrials.gov.

Leng et al. recently conducted a pilot study of MSC transplantation in 10 patients in China. All patients tested positive for SARS-CoV-2 by polymerase chain reaction and had fever, shortness of breath, cough, and oxygen saturation at rest <95%. Seven of the patients received intravenous infusions of allogeneic MSCs while three received saline as a placebo control. All seven MSC treated patients experienced resolution of symptoms while one of the placebo-treated patients went on to develop ARDS and another died. The response of the most severely ill patient treated with MSCs was monitored throughout recovery. Of note, C-reactive protein levels dropped 10-fold after MSC treatment, suggesting a drop in systemic inflammation. Analysis of cytokine levels before and after treatment revealed that MSC treatment, but not placebo, was associated with a halt in the increase of serum tumor necrosis factor－α and an increase in anti-inflammatory interleukin-10 concentrations in the serum.

Although this study is not designed to make definitive claims regarding the efficacy of MSC therapy for COVID-19 or the mechanisms by which MSCs may function to prevent or treat cytokine storm, it does provide important safety data and hints of efficacy that have motivated further exploration of MSCs as a treatment for COVID-19. Of particular note is a randomized, multicenter, placebo-controlled, Phase 2/3 trial enrolling 240 patients being conducted through a public-private

partnership between the U.S. National Institutes of Health–funded Cardiothoracic Surgical Trials Network and Mesoblast. As multiple clinical trials are launched around the world, we should not have to wait long to determine if MSCs are a viable and effective treatment option for severe COVID-19.

10. TMPRSS2 和 TMPRSS4 介导 SARS-CoV-2 病毒感染人小肠上皮细胞

TMPRSS2 and TMPRSS4 mediate SARS-CoV-2 infection of human small intestinal enterocytes

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DOI：

编译者：宋珂

中文摘要：在 COVID-19 患者中，经常发现胃肠道症状，或在粪便中检测到 SARS-CoV-2 病毒 RNA。然而，目前人们尚不明确 SARS-CoV-2 能否在人的肠道中复制，以及其与可能的粪口传播途径的临床相关性。本文中，作者证明 SARS-CoV-2 能够有效地感染人小肠中的 ACE2+成熟肠上皮细胞。除 TMPRSS2 外，另一种粘膜特异性丝氨酸蛋白酶-TMPRSS4，也可以增强 SARS-CoV-2 病毒 Spike 蛋白的融膜活性，介导病毒侵入宿主细胞。但是，当新合成的病毒被释放入肠腔后，就被人结肠液迅速灭活。并且从 COVID-19 患者的粪便样本中，未发现恢复感染能力的病毒。结果表明，肠道是潜在的 SARS-CoV-2 病毒复制的场所，可能会导致局部和全身性疾病，影响整个疾病进展。

注：这篇文章中体外实验均采用和口腔炎病毒嵌合病毒进行相关测试，应该是方便接入荧光报告基因，另外猜测可能和实验室安全级别要求限制的使用有关系。

Abstract: Both gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA have been frequently observed in COVID-19 patients. However, whether SARS-CoV-2 replicate in the human intestine and its clinical relevance to potential fecal-oral transmission remain unclear. Here, we demonstrate productive infection of SARS-CoV-2 in ACE2+ mature enterocytes in human small intestinal enteroids. In addition to TMPRSS2, another mucosa-specific serine protease, TMPRSS4, also enhanced SARS-CoV-2 spike fusogenic activity and mediated viral entry into host cells. However, newly synthesized viruses released into the intestinal lumen were rapidly inactivated by human colonic fluids and no infectious virus was recovered from the stool specimens of COVID-19 patients. Our results highlight the intestine as a potential site of SARS-CoV-2 replication, which may contribute to local and systemic illness and overall disease progression.

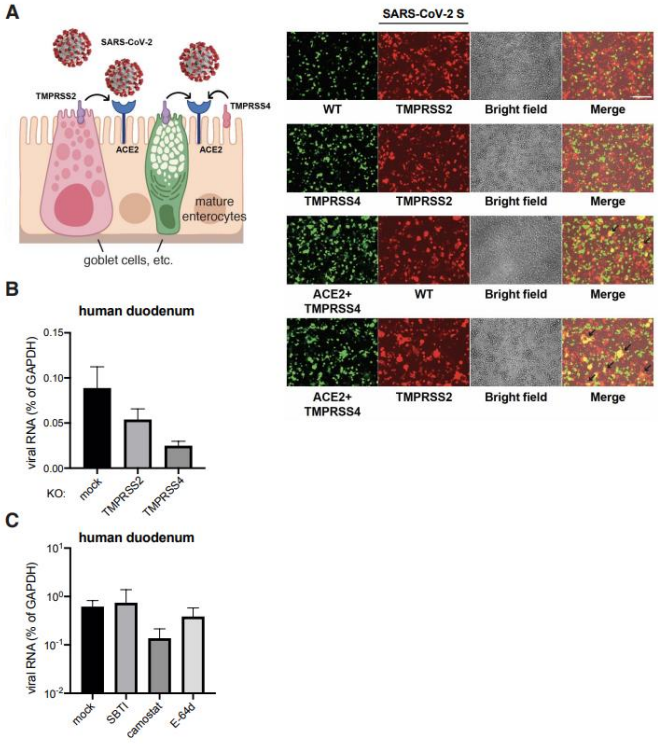

Fig. 4. TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection in enteroids

(A) Schematic diagram of SARS-CoV-2 infection of human mature enterocytes (left panel). An HEK293 stable cell line expressing ACE2 and TMPRSS4 were transfected with GFP and an HEK293 stable cell line expressing TMPRSS2 were transfected with SARS-CoV-2 S and TdTomato for 24 hours. These two cell lines were then mixed at 1:1 ratio and cultured for another 24 hours. Note the formation of cell-cell fusion (yellow), highlighted by black arrows.

(B) Human duodenum enteroids in 3D Matrigel were transduced with lentiviruses encoding Cas9 and sgRNA against TMPRSS2 or TMPRSS4 (oligonucleotide information in Table S1). Gene knockout enteroids were seeded into monolayers and infected with $1.5X10^5$ PFUs of SARS-CoV-2 chimera virus for 24 hours. The expression of VSV-N was measured by RT-qPCR and normalized to that of GAPDH.

(C) Human duodenum enteroids seeded into collagen-coated 96-well plates were differentiated for 3 days, pre-treated with 50 μg/ml of soybean trypsin inhibitor (SBTI), 10 μM of camostat mesylate, or 10 μM of E-64d for 30 minutes, and infected with $1.5X10^5$ PFUs of SARS-CoV-2 chimera virus for 24 hours. The expression of VSV-N was measured by RT-qPCR and normalized to that of GAPDH.

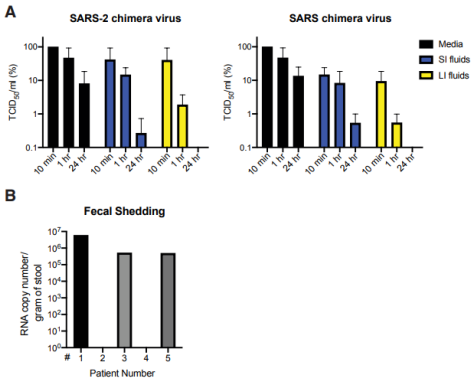

Fig. 5. SARS-CoV-2 rapidly lose infectivity in the human GI tract

(A) 2.9X10^5 PFUs of SARS-CoV-2 and SARS-CoV chimera viruses were incubated with M199 media, human small intestinal (SI) fluids, or human large intestinal (LI) fluids for indicated time points at 37 ºC. The infectivity of viruses was subsequently determined by a standard TCID50 cell culture based assay.

(B) Stool specimens from five COVID-19 patients were collected and subjected to QPCR experiments to quantify the absolute levels of SARS-CoV-2 N gene.