新型冠状病毒信息简报

第 52 期（2020 年 5 月 13 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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本简报仅作为科研参考之用，不构成医疗建议，如您怀疑自己感染新型冠状病毒，请去正规医院或者咨询医生。

1. 2020 年 12 日疫情

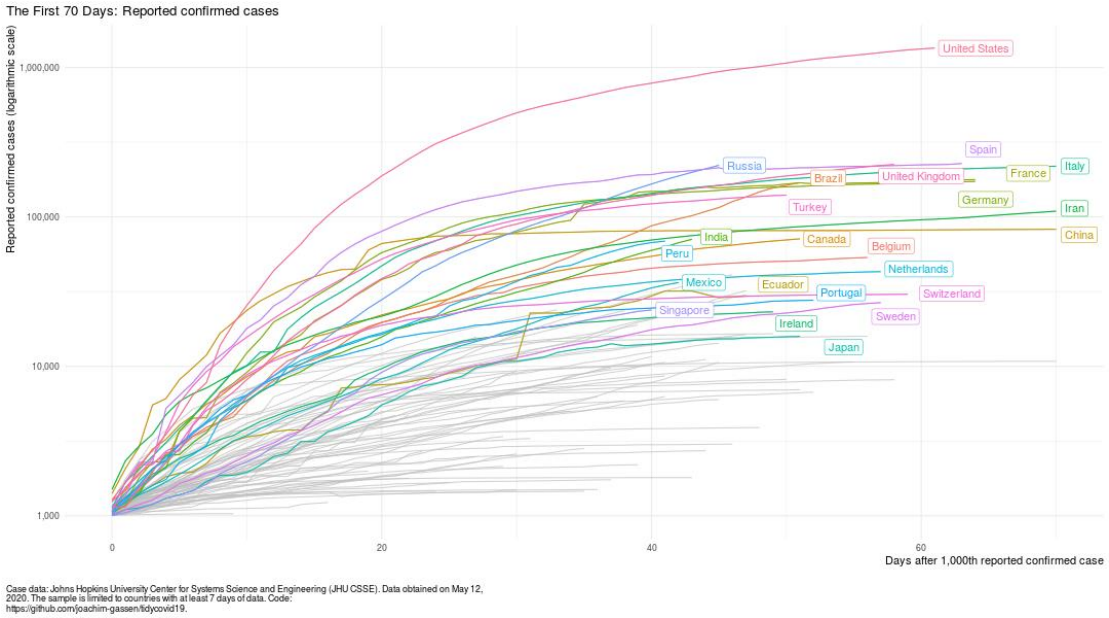
数据来源：WHO

发布时间：2020 年 5 月 12 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 12 日全球累计确诊新型冠状病毒病人 4088848 例，当日新增确诊 82591 例，累计死亡 283153 例，当日新增死亡 4261。

中国累计确诊 84451 例，累计死亡 4644 例，当日新增确诊 1 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 5 月 12 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12日，来源：http://2019ncov.chinacdc.cn/2019-nCoV/）

2. OpenSAFELY：在 1700 万成年 NHS 患者的电子病历中寻找因患 COVID-19 而在住院期间死亡的相关因素

OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients

来源：medRxiv
发布时间：2020-05-07
链接：
https://www.medrxiv.org/content/10.1101/2020.05.06.20092999v1#disqus_thread
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通讯作者单位：The DataLab，Nuffield Dept of Primary Care Health Sciences，University of Oxford，OX2 6GG
DOI 或 PUBMED ID：
编译者：宋珂
中文摘要：

背景：发现谁在新出现能造成快速大量死亡的疾病时处于危险的情况，以及原因，需要对大量且新收集的数据进行全新的流行病学研究。本文中，作者以 England NHS 的身份开展了一项研究工作。在一家为基层医疗系统提供电子病历服务的主要供应商的数据中心上，开发了一个安全且假名化的分析平台，数据包括英格兰大部分病人的详细基层医疗记录，初步的结果如下。

数据来源：电子病历供应商 TPP 管理的基层医疗系统电子病历。在新的 OpenSAFELY 平台上，使用假名与 COVID-19 患者通知系统（CPNS）中已确认在住院期间因 COVID-19 死亡的患者数据进行链接。

人数：17425445 名成年人。

时间段：2020 年 2 月 1 日 至 2020 年 4 月 25 日

主要输出：COVID-19 确诊患者中的死亡病例。

方法：采用 Cox-回归方法进行队列研究分析，生成风险系数：对年龄和性别因素进行校正，并根据临床关注和以往的发现，前瞻性地选择一些协变因素进行多重调整。

结果：COVID-19 造成 5683 人死亡。总而言之，经过全面调整后，因患 COVID-19 而死亡与以下因素密切相关：男性（风险系数 1.99，95%CI 1.88-2.10）；老年人和贫困（两者都有很大的梯度）；无控制的糖尿病（HR 2.36 95%CI 2.18-2.56）；严重哮喘（HR 1.25 CI 1.08-1.44）；以及各种其他前期的医疗状况。与记录为白人的种族相比，黑人的死亡风险更高，完全调整后的模型中的风险系数也仅少量降低（年龄-性别调整后的 HR 2.17 95% CI 1.84-2.57；完全调整的 HR 1.71 95% CI 1.44-2.02）；对于亚洲人也有类似的发现（年龄调整后的 HR 1.95 95% CI 1.73-2.18；完全调整的 HR 1.62 95% CI 1.43-1.82）。

结论：作者对一系列造成 COVID-19 患者死亡的临床危险因素进行了量化研究，其中一些因素在之前的研究中并未被完善的考虑。这是迄今已知的在各国中进行的规模最大的队列研究。亚洲人和黑人群体因 COVID-19 在住院期间死亡的风险显著升高，然而与先前的推测相反，这种情况仅部分归因于已存在的临床风险因素或贫困。因此，迫切需要进一步研究造成这种相关性的驱动因素。贫苦也是主要的危险因素，比合并症或其他危险因素的风险稍高。寻找临床风险因素与英国保护高危人群的政策相一致。作者开发的 OpenSAFELY 平台目前正在快速更新更多 NHS 患者的记录；并将定期更新和扩展现有结果。

Abstract:

Background: Establishing who is at risk from a novel rapidly arising cause of death, and why, requires a new approach to epidemiological research with very large datasets and timely data. Working on behalf of NHS England we therefore set out to deliver a secure and pseudonymised analytics platform inside the data centre of a major primary care electronic health records vendor establishing coverage across detailed primary care records for a substantial proportion of all patients in England. The following results are preliminary.

Data sources: Primary care electronic health records managed by the electronic health record vendor TPP, pseudonymously linked to patient-level data from the COVID-19 Patient Notification System (CPNS) for death of hospital inpatients with confirmed COVID-19, using the new OpenSAFELY platform.

Population: 17,425,445 adults.

Time period: 1st Feb 2020 to 25th April 2020.

Primary outcome: Death in hospital among people with confirmed COVID-19.

Methods: Cohort study analysed by Cox-regression to generate hazard ratios: age and sex adjusted, and multiply adjusted for co-variates selected prospectively on the basis of clinical interest and prior findings.

Results: There were 5683 deaths attributed to COVID-19. In summary after full adjustment, death from COVID-19 was strongly associated with: being male (hazard ratio 1.99, 95%CI 1.88-2.10); older age and deprivation (both with a strong gradient); uncontrolled diabetes (HR 2.36 95% CI 2.18-2.56); severe asthma (HR 1.25 CI 1.08-1.44); and various other prior medical conditions. Compared to people with ethnicity recorded as white, black people were at higher risk of death, with only partial attenuation in hazard ratios from the fully adjusted model (age-sex adjusted HR 2.17 95% CI 1.84-2.57; fully adjusted HR 1.71 95% CI 1.44-2.02); with similar findings for Asian people (age-sex adjusted HR 1.95 95% CI 1.73-2.18; fully adjusted HR 1.62 95% CI 1.43-1.82).

Conclusions: We have quantified a range of clinical risk factors for death from COVID-19, some of which were not previously well characterised, in the largest cohort study conducted by any country to date. People from Asian and black groups are at markedly increased risk of in-hospital death from COVID-19, and contrary to some prior speculation this is only partially attributable to pre-existing clinical risk factors or deprivation; further research into the drivers of this association is therefore urgently required. Deprivation is also a major risk factor with, again, little of the excess risk explained by co-morbidity or other risk factors. The findings for clinical risk factors are concordant with policies in the UK for protecting those at highest risk. Our OpenSAFELY platform is rapidly adding further NHS patients' records; we will update and extend these results regularly.

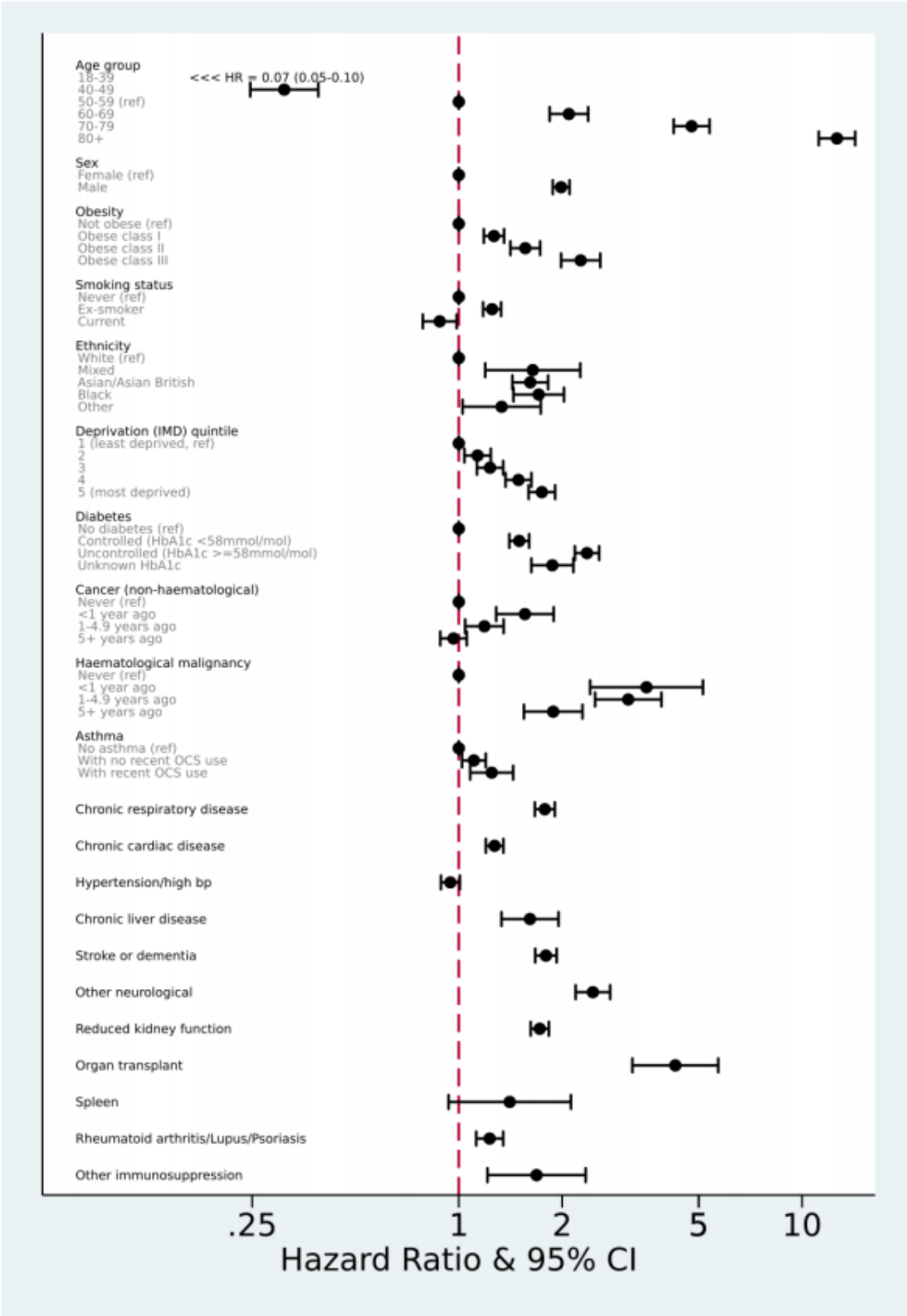

Figure 3. *Estimated Hazard Ratios (shown on a log scale) for each potential risk factor from a multivariable Cox model. Obese class I: 30-34.9kg/m2, class II: 35-39.9kg/m2, class III: >=40kg/m2. OCS = oral corticosteroid. All HRs are adjusted for all other factors listed other than ethnicity. Ethnicity estimates are from a separate model among those with complete ethnicity data, and are fully adjusted for other covariates*

3. 瑞典样本中气味强度估计和 COVID-19 群体预测之间的相关性研究

Relationship between odor intensity estimates and COVID-19 population prediction in a Swedish sample

来源：medRxiv
发布时间：2020-05-11
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DOI 或 PUBMED ID：Preprint

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中文摘要：

为应对 COVID-19 大流行，各国实施了各种战略来减少和减缓该疾病在普通人群中的传播。对于逐步实施人口限制的国家来说，监测 COVID-19 的流行情况对于指导何时实施新的限制或何时取消旧的限制至关重要。研究者评估了气味强度等级是否可以作为 COVID-19 在人群中传播的衡量标准，其总体目标是确定嗅觉系统与 COVID-19 疾病的关系。研究中参与对象包括 2440 名瑞典人，通过一个在线评级工具(www.smelltracker.org)，参与者根据感知的强度和愉悦程度对家居气味进行评级。研究者将平均气味强度等级与瑞典人群中预测的 COVID-19 人群流行率进行比较，发现两者密切相关(r=-0.83)。此外，研究者发现有和没有 COVID-19 症状的个体之间的气味感知强度有很大差异，并且症状的数量与气味强度等级相关。此外还发现从报告无症状到随后报告 COVID-19 症状的个体表现出嗅觉表现的大幅下降。这些数据表明，气味强度的测量，如果在一个大的和有代表性的样本中获得，可以用作普通人群中预测 COVID-19 疾病的指标。重要的是，这一简单的措施可以很容易地在没有广泛获得 COVID-19 测试的国家实施，或者在促进广泛测试之前作为快速的早期患病率预测实施。

Abstract

In response to the COVID-19 pandemic, countries have implemented various strategies to reduce and slow the spread of the disease in the general population. For countries that have implemented restrictions on its population in a step-wise manner, monitoring of COVID-19 prevalence is of importance to guide decision on when to impose new, or when to abolish old, restrictions. We are here determining whether measures of odor intensity in a large sample can serve as one such measure. Online measures of how intense common household odors are perceived and symptoms of COVID-19 were collected from 2440 Swedes. Average odor intensity ratings were then compared to predicted COVID-19 population prevalence over time in the Swedish population and were found to closely track each other (r=-0.83). Moreover, we found that there was a large difference in rated intensity between individuals with and without COVID-19 symptoms and number of symptoms was related to odor intensity ratings. Finally, we found that individuals progressing from reporting no symptoms to subsequently reporting COVID-19 symptoms demonstrated a large drop in olfactory performance. These data suggest that measures of odor intensity, if obtained in a large and representative sample, can be used as an indicator of COVID-19 disease in the general population. Importantly, this simple measure could easily be implemented in countries without

widespread access to COVID-19 testing or implemented as a fast early response before wide-spread testing can be facilitated.

4. 唾液中 SARS-CoV-2 的无提取快速比色 LAMP 法检测

Rapid and extraction-free detection of SARS-CoV-2 from saliva with colorimetric LAMP

来源：medRxiv

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链接：https://www.medrxiv.org/content/10.1101/2020.05.07.20093542v1

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DOI 或 PUBMED ID：Preprint

编译者：张丽双

中文摘要：

需要快速、可靠和广泛的检测来遏制目前的 COVID-19 大流行。目前的金标准诊断分析由于关键试剂（包括鼻拭子、RNA 提取试剂盒、个人防护设备（PPE）、仪器和劳动力）供应短缺而受到阻碍。在这里，研究者提出了一种克服这些挑战的方法，即在不需要 RNA 纯化步骤的情况下，利用环介导逆转录等温扩增（RT-LAMP）对人类唾液样本进行优化，开发一种快速比色分析方法。研究者描述了对 LAMP 反应和唾液预处理方案的优化，该方案能够在人工唾液对照中快速、灵敏地检测每个反应中<100 个病毒基因组。还观察到，在有限数量的临床唾液样本上，这种分析方法具有很高的性能。虽然在这种分析方法得到广泛应用之前，还需要对额外的临床样本进行彻底的验证，但这些初步结果表明，这是一种有希望的方法，可以克服目前限制广泛测试的瓶颈。

Abstract:

Rapid, reliable, and widespread testing is required to curtail the ongoing COVID-19 pandemic. Current gold standard diagnostic assays are hampered by supply shortages in critical reagents including nasal swabs, RNA extraction kits, personal protective equipment (PPE), instrumentation, and labor. Here we present an approach to overcome these challenges with the development of a rapid colorimetric assay using reverse-transcription loop-mediated isothermal amplification (RT-LAMP) optimized on human saliva samples without an RNA purification step. We describe our optimizations of the LAMP reaction and saliva pre-treatment protocols that enabled rapid and sensitive detection of < 10^2 viral genomes per reaction in contrived saliva controls. We also observed high performance of this assay on a limited number of clinical saliva samples. While thorough validation on additional clinical samples are needed before such an assay can be widely used, these preliminary results demonstrate a promising approach to overcome the current bottlenecks limiting widespread testing.

5. COVID-19 的病理生理学研究——一项柏林前瞻性 COVID-19 患者队列(Pa-COVID-19)的研究协议

Studying the pathophysiology of coronavirus disease 2019 - a protocol for the Berlin prospective COVID-19 patient cohort (Pa-COVID-19)

来源：medRxiv
发布时间：2020-05-11
链接：https://www.medrxiv.org/content/10.1101/2020.05.06.20092833v1
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DOI 或 PUBMED ID：Preprint
编译者：宋张悦

中文摘要：

目的：严重急性呼吸道综合征冠状病毒 2 型(SARS-CoV-2)在全球范围内传播，已经引发了全球卫生危机。Pa-COVID-19 旨在提供关于 COVID-19 的临床病程、病理生理学、免疫学和预后的综合数据，以确定预后生物标志物、临床评分和治疗目标，从而改进临床管理和预防干预措施。

方法：Pa-COVID-19 是一项前瞻性观察队列研究，研究对象为在慈善-柏林医科大学(Charite – Universitaetsmedizin Berlin)接受治疗的确诊 SARS-CoV-2 感染患者。研究人员收集流行病学、人口统计学、病史、症状、临床病程、病原体检测和治疗等方面的资料。系统、连续的血液采样将允许进行深入的分子和免疫表型分析、转录组分析和全面的生物数据库。住院期间的纵向数据和样本收集将通过长期随访得到补充。本研究的样本量不是预先确定的。参与者的招募将取决于疾病在德国柏林的出现和传播，以及在慈善-柏林医科大学就诊的患者人数。随着疫情的发展，将考虑在其他研究中心招募人员，以促进建立一个全面的临床和分子数据库。这项研究没有确定的结束日期。

结果：结局指标包括第 15 天的世卫组织临床顺序量表和出院时和随访期间的临床、功能和健康相关生活质量评估。本研究开发了一个可扩展的数据集，可以(i)符合国家护理标准，(ii)促进不同资源的医疗机构的全面数据收集，(iii)允许在标准化研究设计和数据收集的基础上快速实施干预性试验。本研究提出这个可扩展的研究协议，作为在德国 COVID-19 中统一数据收集和深入表型分析的蓝图。

结论：本研究为 COVID-19 的统一、可扩展的数据收集、病理生理分析和深入表型分析建立了一个基本平台，这为改进医疗和确定候选的治疗和预防策略提供了快速的证据。经介入性试验认可的电子数据库允许对候选治疗药物进行快速试验。

Abstract:

Purpose Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide causing a global health emergency. Pa-COVID-19 aims to provide comprehensive data on clinical course, pathophysiology, immunology and outcome of COVID-19, in order to identify prognostic biomarkers, clinical scores, and therapeutic targets for improved clinical management and preventive interventions.

Methods Pa-COVID-19 is a prospective observational cohort study of patients with confirmed SARS-CoV-2 infection treated at Charite – Universitaetsmedizin Berlin. We collect data on epidemiology, demography, medical history, symptoms, clinical course, pathogen testing and treatment. Systematic, serial blood sampling will allow deep molecular and immunological phenotyping, transcriptomic profiling, and comprehensive biobanking. Longitudinal data and sample collection during hospitalization will be supplemented by long-term follow-up.

Results Outcome measures include the WHO clinical ordinal scale on day 15 and clinical, functional and health-related quality of life assessments at discharge

and during follow-up. We developed a scalable dataset to (i) suit national standards of care (ii) facilitate comprehensive data collection in medical care facilities with varying resources and (iii) allow for rapid implementation of interventional trials based on the standardized study design and data collection. We propose this scalable protocol as blueprint for harmonized data collection and deep phenotyping in COVID-19 in Germany.

Conclusion We established a basic platform for harmonized, scalable data collection, pathophysiological analysis, and deep phenotyping of COVID-19, which enables rapid generation of evidence for improved medical care and identification of candidate therapeutic and preventive strategies. The electronic database accredited for interventional trials allows fast trial implementation for candidate therapeutic agents.

6. SARS-CoV-2 中和抗体的快速分离及其在小动物模型中的防护

Rapid isolation of potent SARS-CoV-2 neutralizing antibodies and protection in a small animal model

来源：bioRxiv

发布时间：2020-05-11

链接：https://www.biorxiv.org/content/10.1101/2020.05.11.088674v1

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DOI 或 PUBMED ID：Preprint

编译者：张鹏伟

中文摘要：

制定预防和/或治疗 COVID-19 的对策是全球卫生优先事项。在不到 7 周的时间里，作者招募了一批 SARS-CoV-2 的恢复参与者，开发了中和分析方法来检测血清和单克隆抗体反应，采用高通量抗体分离、生产和鉴定管道来快速筛选 1000 多种抗原特异性抗体，并建立动物模型进行保护性试验。作者报道了多种高效中和抗体（nAb），并证明了 nAb 的被动转移对叙利亚仓鼠中高剂量 SARS-CoV-2 攻击具有保护作用。这项研究表明 nAbs 在 COVID-19 的预防和潜在治疗中有一定的作用。nAbs 定义的保护性表位可以指导疫苗设计。

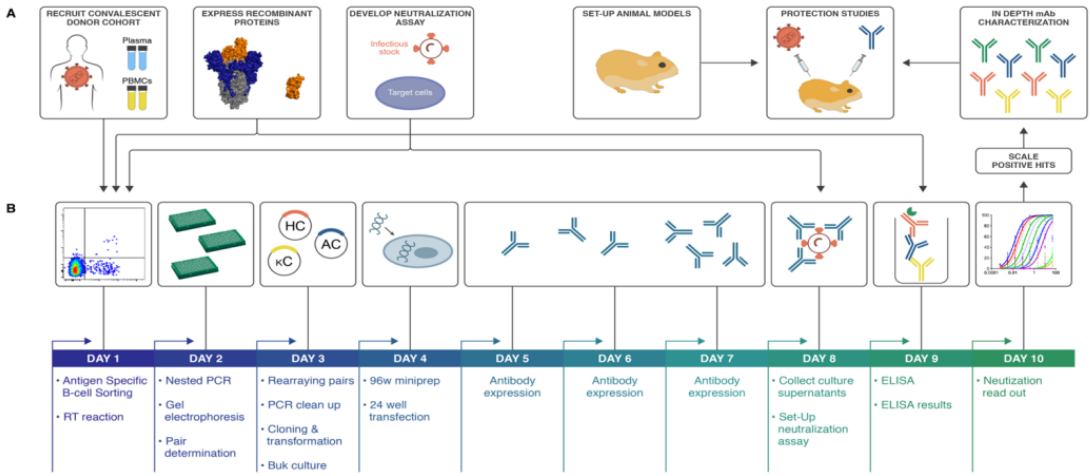

Figure 1. SARS-CoV-2 neutralizing antibody isolation strategy. (A) A natural infection cohort was established to collect plasma and PBMCs samples from individuals who recovered from COVID-19. In parallel, functional assays were developed to rapidly screen all plasma samples for SARS-CoV-2neutralizing activity. SARS-CoV-2 recombinant surface proteins were also produced to use as baits in single memory B-cell sorting and downstream functional characterization of isolated mAbs. Finally, a hamster animal model was set-up to evaluate mAb passive transfer protection. (B) The standard mAb isolation pipeline was optimized to allow high-throughput amplification, cloning, expression and functional screening of hundreds of unpurified Ab heavy and light chain pairs isolated from each of several selected neutralizers in only 10 days. Selected pairs were scaled-up to purify IgG for validation and characterization experiments. The most potent neutralizing mAb was selected to evaluate protection in the Syrian hamster model.

Abstract:
The development of countermeasures to prevent and/or treat COVID-19 is a global health priority. In under 7 weeks, we enrolled a cohort of SARS-CoV-2-recovered participants, developed neutralization assays to interrogate serum and monoclonal antibody responses, adapted our high throughput antibody isolation, production and characterization pipeline to rapidly screen over 1000 antigen-specific antibodies, and established an animal model to test protection. We report multiple highly potent neutralizing antibodies (nAbs) and show that passive transfer of a nAb provides protection against high-dose SARS-CoV-2 challenge in Syrian hamsters. The study suggests a role for nAbs in prophylaxis, and potentially therapy, of COVID-19. The nAbs define protective epitopes to guide vaccine design.

7. SARS-CoV-2 ORF3b 是一种强效干扰素拮抗剂，其活性可通过一种自然发生的延伸变异进一步增强

SARS-CoV-2 ORF3b is a potent interferon antagonist whose activity is further increased by a naturally occurring elongation variant

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中文摘要：

SARS-CoV-2 与更具致病性的 SARS-CoV 的区别之一是其 ORF3b 基因中存在过早终止密码子。文中作者通过体外实验证明了 SARS-CoV-2 ORF3b 是一种有效的干扰素拮抗剂，它比 SARS-CoV 更有效地抑制 I 型干扰素的诱导。系统分析和功能分析显示，来自蝙蝠和穿山甲的 SARS-CoV-2 相关病毒也编码具有很强的抗干扰素活性的截断的 ORF3b 基因产物。此外，对 15,000 多个 SARS-CoV-2 序列的分析确定了一个自然变异，在该变异中重新构建了一个更长的 ORF3b 阅读框。该突变体从 2 例重症患者中分离得到，进一步增强了 ORF3b 抑制干扰素诱导的能力。因此，我们的研究结果不仅有助于解释 COVID-19 患者干扰素应答较差的原因，而且还说明了一种可能性，即具有扩展 ORF3b 的天然 SARS-CoV-2 准种的出现可能会加重 COVID-19 症状。

Abstract

One of the features distinguishing SARS-CoV-2 from its more pathogenic

counterpart SARS-CoV is the presence of premature stop codons in its ORF3b gene. Here, we show that SARS-CoV-2 ORF3b is a potent interferon antagonist, suppressing the induction of type I interferon more efficiently than its SARS-CoV ortholog. Phylogenetic analyses and functional assays revealed that SARS-CoV-2-related viruses from bats and pangolins also encode truncated ORF3b gene products with strong anti-interferon activity. Furthermore, analyses of more than 15,000 SARS-CoV-2 sequences identified a natural variant, in which a longer ORF3b reading frame was reconstituted. This variant was isolated from two patients with severe disease and further increased the ability of ORF3b to suppress interferon induction. Thus, our findings not only help to explain the poor interferon response in COVID-19 patients, but also describe a possibility of the emergence of natural SARS-CoV-2 quasispecies with extended ORF3b that may exacerbate COVID-19 symptoms.

8. 细胞因子通过 pan-JAK-STAT 增强剂激活 SARS-CoV-2 受体 Ace2

Activation of the SARS-CoV-2 receptor Ace2 by cytokines through pan JAK-STAT enhancers

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DOI 或 PUBMED ID：Preprint

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中文摘要：

ACE2 与 SARS-CoV-2 结合，在蛋白酶 TMPRSS2 的协同作用下，促进 SARS-CoV-2 进入细胞。*ACE2* 基因在 SARS-CoV-2 靶细胞（包括 II 型肺细胞）中表达，并被干扰素激活。在母乳中也检测到病毒 RNA，显示 *ACE2* 的表达可能受 JAK-STAT 途径中细胞因子的控制，作者发现在乳腺组织中 *Ace2* 的表达是在孕期和哺乳期诱导的。催乳素激活的转录因子 STAT5 和串联位点结合，与激活组蛋白增强子标记和其他转录成分相吻合。乳腺肺泡细胞和 II 型肺泡细胞中 pan-JAKSTAT 成分的存在，结合 STAT1 和 STAT5 的自动调节，提示细胞因子信号通路在 SARS-CoV-2 靶向细胞中的重要作用。

Abstract:

ACE2, in concert with the protease TMPRSS2, binds the novel coronavirus SARS-CoV-2 and facilitates its cellular entry. The *ACE2* gene is expressed in SARS-CoV-2 target cells, including Type II Pneumocytes, and is activated by interferons. Viral RNA was also detected in breast milk, raising the possibility that *ACE2* expression is under the control of cytokines through the JAK-STAT pathway. Here we show that *Ace2* expression in mammary tissue is induced during pregnancy and lactation. The prolactin-activated transcription factor STAT5 binds to tandem sites that coincide with activating histone enhancer marks and additional transcription components. The presence of pan JAKSTAT components in mammary alveolar cells and in Type II Pneumocytes combined with the

autoregulation of both STAT1 and STAT5 suggests a prominent role of cytokine signaling pathways in cells targeted by SARS-CoV-2.

9. 宿主病毒感染图谱显示严重 COVID-19 患者的特征

Host-viral infection maps reveal signatures of severe COVID-19 patients

来源：Cell

发布时间：2020-05-08

链接：https://www.sciencedirect.com/science/article/pii/S0092867420305687

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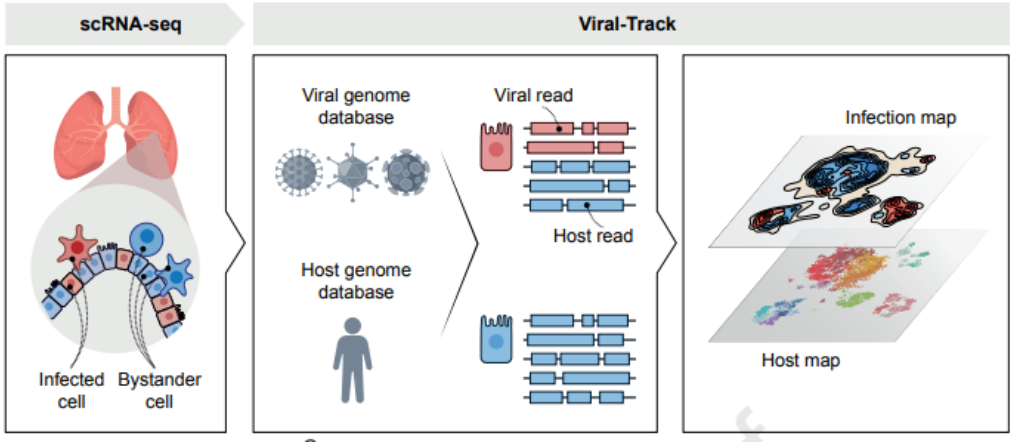
中文摘要：

当前的 COVID-19 大流行是对全球健康的持续威胁。目前，缺乏有关人类宿主如何与病毒（包括 SARS-CoV-2 病毒）相互作用的数据，限制了有效的治疗干预。该研究介绍了 Viral-Track，一种计算方法，它可以全局扫描未比对的 scRNA 序列数据，以确定病毒 RNA 的存在，从而实现对受感染细胞和旁观者细胞的排序。该研究验证了 Viral-Track 的敏感性和特异性，可以系统地从多种感染模型中检测病毒，包括以无监督的方式检测乙型肝炎病毒。将 Viral-Track 应用于重度和轻度 COVID-19 患者的支气管肺泡灌洗样本，发现与轻度患者相比，病毒对重度患者免疫系统的影响显著。Viral-Track 检测到一种人类偏肺病毒（MetaPneumoVirus）的联合感染，主要存在于 I 型干扰素信号转导紊乱的单核细胞中。Viral-Track 为剖析病毒感染和病理机制提供了强有力的技术。

Figure 1 Journal Pre-proof



Abstract:

Viruses are a constant threat to global health as highlighted by the current COVID-19 pandemic. Currently, lack of data underlying how the human host interacts with viruses, including the SARS-CoV-2 virus, limits effective therapeutic intervention. We introduce Viral-Track, a computational method that globally scans unmapped scRNA-seq data for the presence of viral RNA, enabling transcriptional cell sorting of infected versus bystander cells. We demonstrate the sensitivity and specificity of Viral-Track to systematically detect viruses

from multiple models of infection, including hepatitis B virus in an unsupervised manner. Applying Viral-Track to Bronchoalveloar-Lavage samples from severe and mild COVID-19 patients reveals a dramatic impact of the virus on the immune system of severe patients compared to mild cases. Viral-Track detects an unexpected co-infection of the human MetaPneumoVirus, present mainly in monocytes perturbed in type-I IFN-signaling. Viral-Track provides a robust technology for dissecting the mechanisms of viral-infection and pathology.

10. SARS-CoV-2 基因组内 CpG 二核苷酸组成的差异性

Intra-genome variability in the dinucleotide composition of SARS-CoV-2

来源：medRxiv

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中文摘要：

CpG 二核苷酸在单链的 RNA 病毒中 UNDER-REPSENT, 冠状病毒包括 SARS-CoV-2 也不例外。人为改变 CpG 的频率可能是开发减活疫苗得一种合理的方法。为了将这个方法应用于 SARS-CoV-2,我们必需首先理解 CpG 在调控 SARS-CoV-2 复制中的作用。对新的 SARS-CoV-2 的基因组的里 CpG 的组成必需放在其他冠状病毒的背景里一起来看。在病毒属类，冠状病毒类，CpG 的缺乏情况并不会有显著差异，但是可能会依赖宿主不同以及在宿主中主要复制部位（组织嗜性）不同而有所不同。这支持病毒 CpG 二核苷酸含量可能影响跨物种传播。虽然 SARS-CoV-2 呈现处总体强的 CpG 缺乏，在基因组里不同区段有所不同，比如在衣壳蛋白 E，ORF10 就没有 CpG 的缺乏。虽然 ORF10 只在一部分冠状病毒基因组中出现，衣壳蛋白 E 对病毒的复制是必需的。在冠状病毒科，衣壳蛋白 E 中 CpG 的比例呈现处很高的差异性。SARS 和 SARS-CoV-2 相比其他从人体里分离得到的冠状病毒有更高的 CpG 含量。系统发育显示这是一个祖先病毒来源的特征,反映它们起源于蝙蝠,而不是经过动物传播经过进化筛选得到的。CpG 在这些区域的保守性提示他们可能有一个比需要缺乏 CpG 更重要的功能。这些观察可能和未来理性设计减活 SARS-CoV-2 疫苗的策略相关。

Abstract：

CpG dinucleotides are under-represented in the genomes of single stranded RNA viruses, and coronaviruses, including SARS-CoV-2, are no exception to this. Artificial modification of CpG frequency is a valid approach for live attenuated vaccine development, and if this is to be applied to SARS-CoV-2, we must first understand the role CpG motifs play in regulating SARS-CoV-2 replication. Accordingly, the CpG composition of the newly emerged SARS-CoV-2 genome was characterised in the context of other coronaviruses. CpG suppression amongst coronaviruses does not significantly differ according to genera of virus, but does vary according to host species and primary replication site (a proxy for tissue tropism), supporting the hypothesis that viral CpG content may influence cross-species transmission. Although SARS-CoV-2 exhibits overall strong CpG suppression, this varies considerably across the genome, and the Envelope (E)

open reading frame (ORF) and ORF10 demonstrate an absence of CpG suppression. While ORF10 is only present in the genomes of a subset of coronaviruses, E is essential for virus replication. Across the Coronaviridae, E genes display remarkably high variation in CpG composition, with those of SARS and SARS-CoV-2 having much higher CpG content than other coronaviruses isolated from humans. Phylogeny indicates that this is an ancestrally-derived trait reflecting their origin in bats, rather than something selected for after zoonotic transfer. Conservation of CpG motifs in these regions suggests that they have a functionality which over-rides the need to suppress CpG; an observation relevant to future strategies towards a rationally attenuated SARS-CoV-2 vaccine.

11. SARS-CoV-2 中的突变对于 T/U 的强烈偏好和负向选择：给减活疫苗设计的提示

SARS-CoV-2 中的突变对于 T/U 的强烈偏好和负向选择：给减活疫苗设计的提示

Evidence for strong mutation bias towards, and selection against, T/U content in SARS-CoV2: implications for attenuated vaccine design.

来源：medRxiv

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通过反向工程大规模的产生同义突变是一个很有潜力的产生减毒病毒疫苗的策略。对病毒的减毒常常依赖于编码对的去优化以及最大化 CpG 二核酸频率。为了从病毒的进化来了解对病毒进行减毒的策略，从而能反其道而行之强行将病毒往和病毒进化选择相反的方向进行改造，研究者们对所有 SARS-CoV-2 的全基因组序列进行了研究，推测了其中的突变以及对同义位点的选择。对病毒的突变谱分析表明突变有对 T 有很强的偏好，同时伴随的突变负向选择 T（很少出现 TT 二核苷酸）。计算二核苷酸加强了这个结论，观察到的 TT 是基于中性平衡假设预期的 1/4. 在非 4 倍简并位点（编者注 1）的编码区的突变谱明显不同，也和研究者们假定的选择会广泛的负向选择向 T 的突变一致。虽然负向选择 CpG 二核苷酸可能会导致同义突变区的 GC 含量低于突变平衡，观察到的 GC 含量仍然稍微高于平衡，可能的原因是选择了更高表达量（作者之前的研究表明没有内含子的人基因表达量和 GC 含量正相关）。与基因特异性的负向选择 CpG 二核苷酸相一致，研究者们观察到在 SARS-CoV-2 的基因组中存在系统性的 CpG 含量差异。作者们建议一个从进化中得出的基因定制方法来制作减活病毒疫苗，不同往常的，策略是要增加已经最常用的同义编码子（增加同义密码子 T 的使用）。将 SARS-CoV-2 和 H1N1 以及 Ebola 进行比较，发现偏离中性平衡的 GC3（编者注 2）不是一个普遍的特征，作者提醒大家不能将这个结果一般化。

		Derived allele			
Reference allele		**A**	**T**	**C**	**G**
	A	-	**0.05041** 0.02043	**0.01707** 0.01504	**0.09350** 0.07771
	T	**0.02269** 0.01668	-	**0.09398** 0.07340	**0.01343** 0.01126
	C	**0.05842** 0.03265	**0.45704** 0.35280	-	**0.01375** 0.00970
	G	**0.20652** 0.10434	**0.43841** 0.15373	**0.02536** 0.01867	-

Table 1 The 4 x 4 mutational matrix for 972 mutations at four-fold synonymous sites (in bold) and from 5644 mutations observed anywhere in codons (not bold). Rates are defined as the number of observed changes per incidence of the nucleotide in the reference genome at four-fold third sites (bold) or in codons. Note that because of different normalizations, the two sets of numbers are not directly comparable in absolute terms.

编者注 1：编码同一种氨基酸的密码子第三位是可以是 A\T\C\G4 种不同的碱基，这个密码子的第三位就叫做 4 倍简并位点。如果一个氨基酸密码子的某一位是两种不同碱基，那么该位点就是 2 倍简并位点。http://en.wikipedia.org/wiki/Genetic_code

编者注 2：本文中 N4* 指核酸 N 的核酸含量在 4 倍简并位点。GC3 是指 GC 在 3 倍简并位点的含量。

Abstract:

Large-scale re-engineering of synonymous sites is a promising strategy to generate attenuated viruses for vaccines. Attenuation typically relies on de-optimisation of codon pairs and maximization of CpG dinculeotide frequencies.

So as to formulate evolutionarily-informed attenuation strategies, that aim to force nucleotide usage against the estimated direction favoured by selection, here we examine available whole-genome sequences of SARS-CoV2 to infer patterns of mutation and selection on synonymous sites.

Analysis of mutational profiles indicates a strong mutation bias towards T with concomitant selection against T. Accounting for dinucleotide effects reinforces this conclusion, observed TT content being a quarter of that expected under neutrality. A significantly different mutational profile at CDS sites that are not 4-fold degenerate is consistent with contemporaneous selection against T mutations more widely.

Although selection against CpG dinucleotides is expected to drive synonymous site G+C content below mutational equilibrium, observed G+C content is slightly above equilibrium, possibly because of selection for higher expression.

Consistent with gene-specific selection against CpG dinucleotides, we observe systematic differences of CpG content between SARS-CoV2 genes. We propose an evolutionarily informed gene-bespoke approach to attenuation that, unusually, seeks to increase usage of the already most common synonymous codons. Comparable analysis of H1N1 and Ebola finds that GC3 deviated from neutral equilibrium is not a universal feature, cautioning against generalization of results.