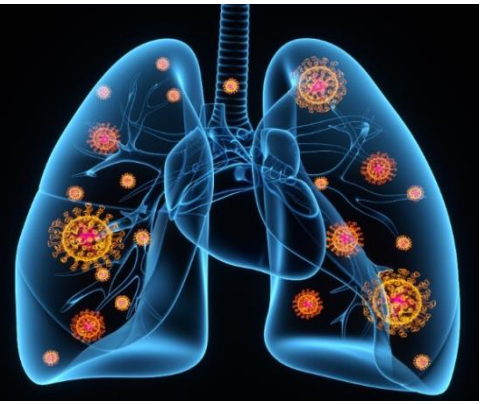

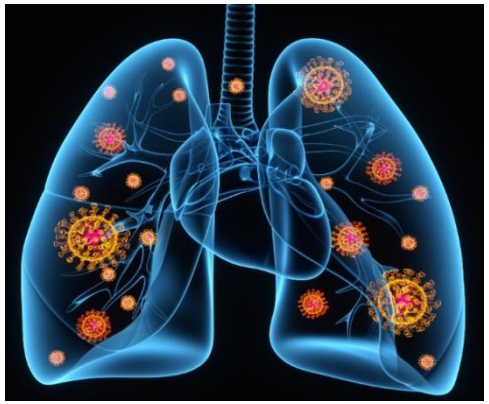

隱形缺氧

(臨床表現, 致病機轉, 預後, 預防與處置)

高國晉 醫師

林口長庚醫院內科部胸腔內科

2021/6/12 AM 9:05-9:45

內容

- 前言
- 定義
- 臨床表現
- 致病機轉
- 預後
- 預防與處置
- 總結

內容

- 前言
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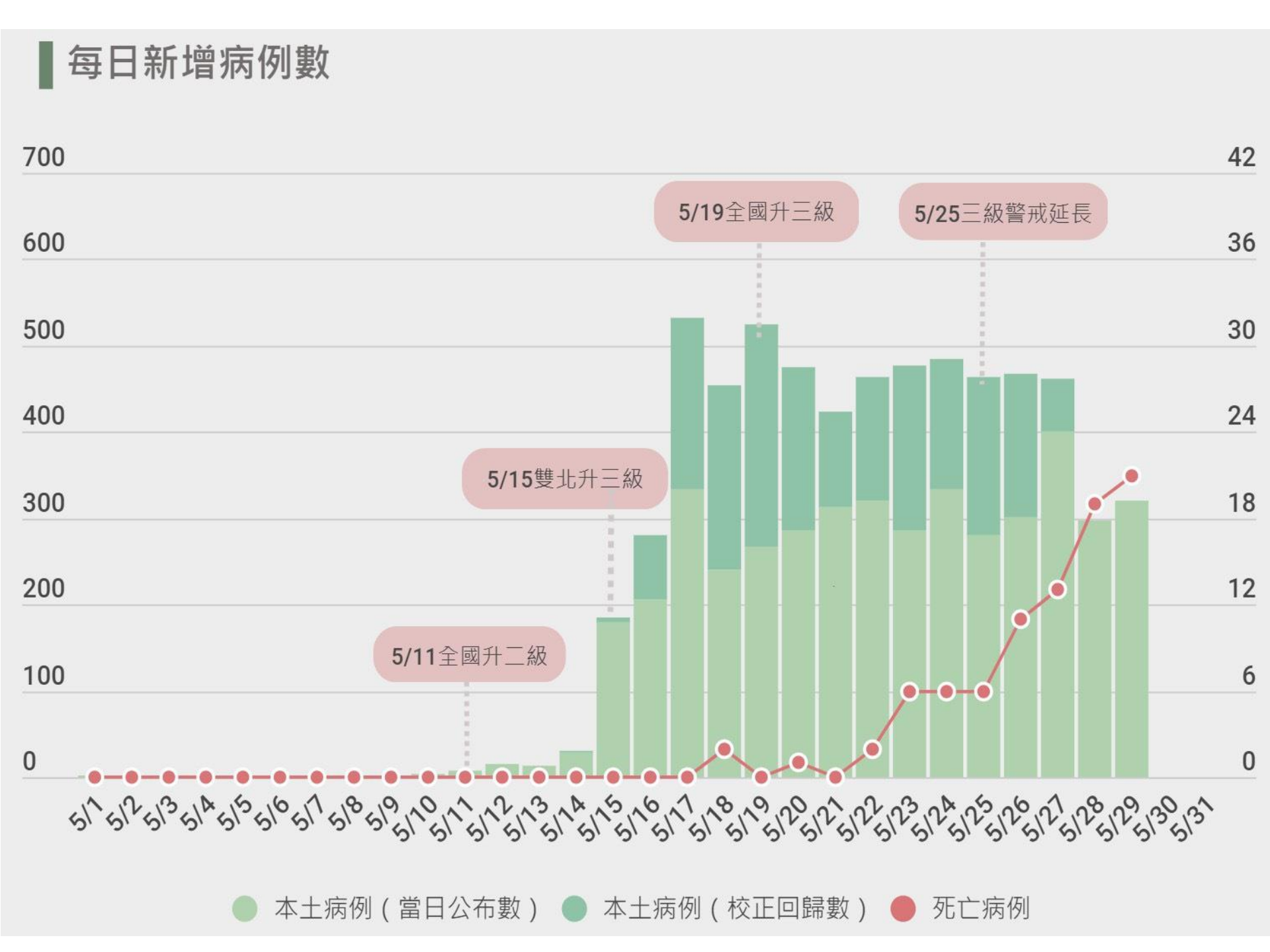
- 預後
- 預防與處置
- 總結

每日新增病例數


700
600
500
400
300
200
100
0
42
36
30
24
18
12
6
0
5/19全國升三級
5/25三級警戒延長
5/15雙北升三級
5/11全國升二級
5/1
5/2
5/3
5/4
5/5
5/6
5/7
5/8
5/9
5/10
5/11
5/12
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5/26
5/27
5/28
5/29
5/30
5/31
本土病例（當日公布數）
本土病例（校正回歸數）
死亡病例

國內新冠肺炎疫情嚴峻，截至今（9）日全台染疫身亡人數已達333人，近日更出現多起猝死個案。對此，中央流行疫情指揮中心醫療應變組副組長羅一鈞今日表示，新冠肺炎的病程變化得很快速，尤其「隱形缺氧」最有可能導致年輕人或年長者在家中缺氧身亡，這種缺氧較沒有明顯前兆，且發病時再緊急送醫也時間已晚。

針對近日多起猝死案例都是無症狀迅速病逝，其病程是否有相似處？羅一鈞指出，目前統計5月11日到6月7日有公佈296例，其中35例為到院前死亡，占11.8%，這個病程可以變化得很快速，也有「隱形缺氧」的情形，到院前死亡的個案，由於是在家中猝死，無法調查個案在死亡前或病程開始出現何種症狀，不過就專家與國外研究探討，都顯示隱形缺氧最有可能導致不管年輕人或年長者，在家中缺氧身亡，這種缺氧「比較沒有明顯前兆」，且通常氧氣濃度很低、症狀嚴重時，再緊急送醫也時間已晚，

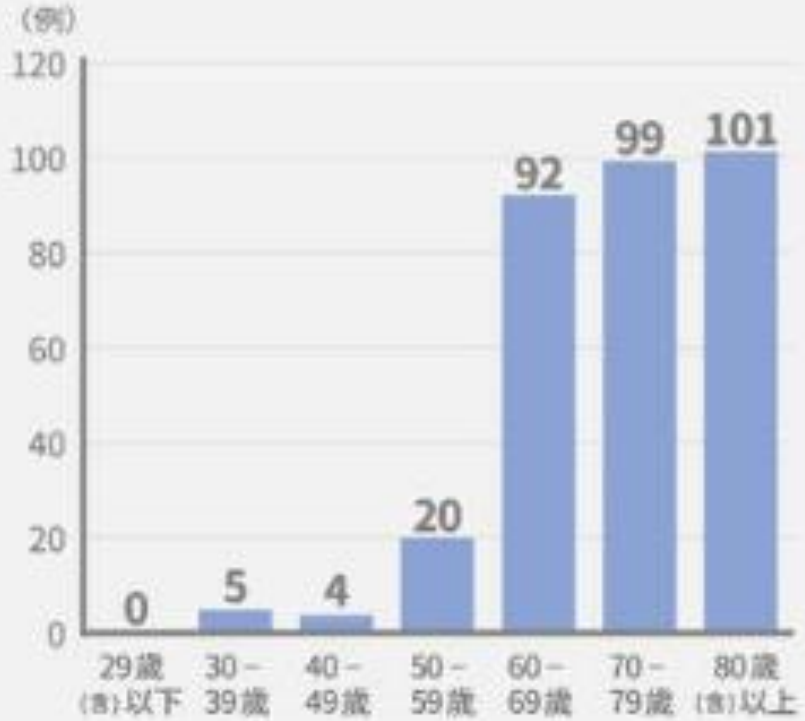
羅一鈞表示，家戶感染是指揮中心調查匡列跟處理的本週重點，希望確診個案都能從家中移出到安置場所或醫院，減少在家中突然病況惡化的狀況。就今日統計來講，前天確診病例當中，雙北的確診病患都沒有在居家隔離，已全都設法安置到檢疫所或醫院。

2021/6/9 指揮中心 CDC 記者會

台灣新冠疫情累積死亡案例

2021/6/9

死亡案例年齡及死亡地點分布



死亡地點分布
5/18 累積至 5/31(人)

家中／到院前死亡	13人
集中檢疫所／防疫旅館	8人
醫院／有住院紀錄	288人
地點不明／調查中	12人

備註：2021年5月18日前
已累計有12例死亡，不另計死亡年齡及死亡地點

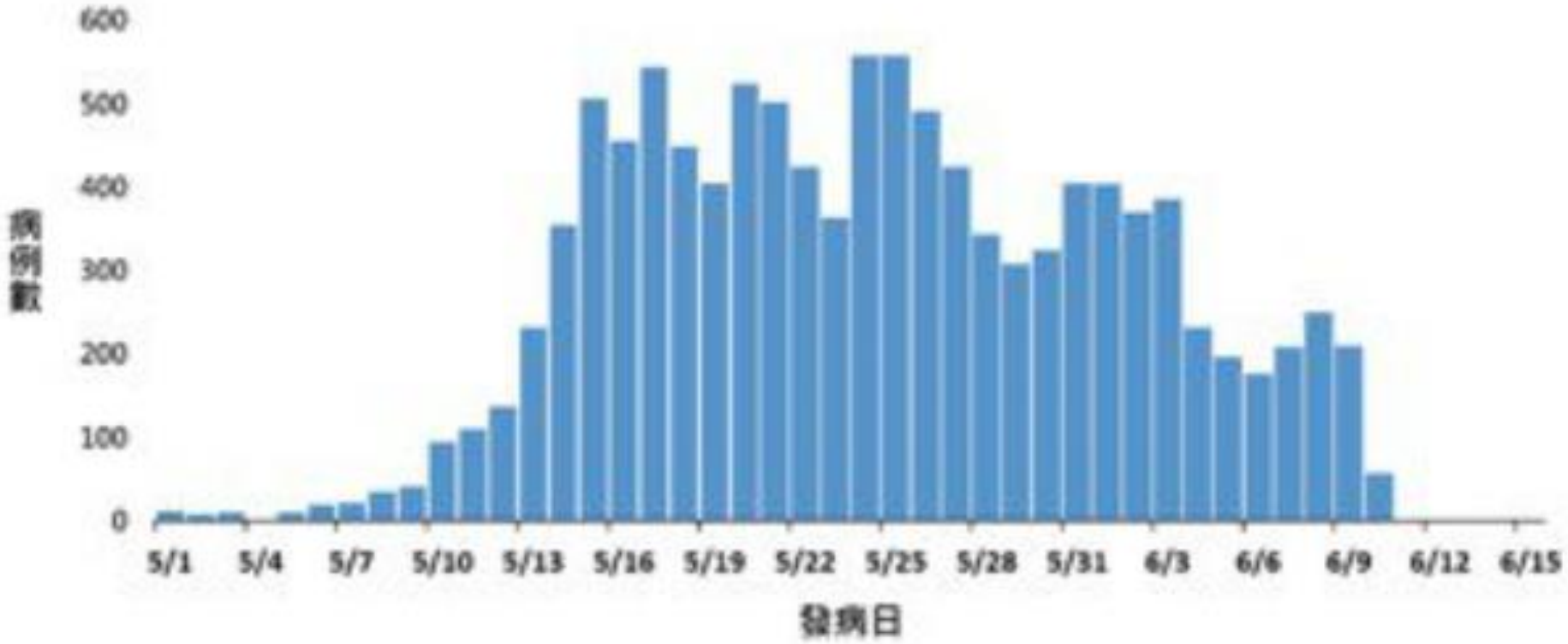
資料來源／中央流行疫情指揮中心　整理／葉懿德　製圖／盧亞屏

(台灣新冠疫情死亡案例之相關數據。整理／葉懿德 製圖／盧亞萍)

2021/6/9

指揮中心指出，依據國際研究顯示，新冠病毒感染患者輕症比率大約佔8成左右，但其中約9%的患者可能惡化為重症，主要的重症危險因子有高齡、肥胖、慢性腎病、心血管疾病/高血壓、慢性肺病、免疫抑制疾病/免疫抑制治療等影響免疫功能之疾病，以及懷孕等，且其病程演化迅速，甚至導致死亡。截至本(110)年6月10日監測資料，國內輕中度COVID-19確診病例約佔所有確診個案84%，死亡病例數佔確診病例2.7%。

5/1起COVID-19本土確定病例發病趨勢

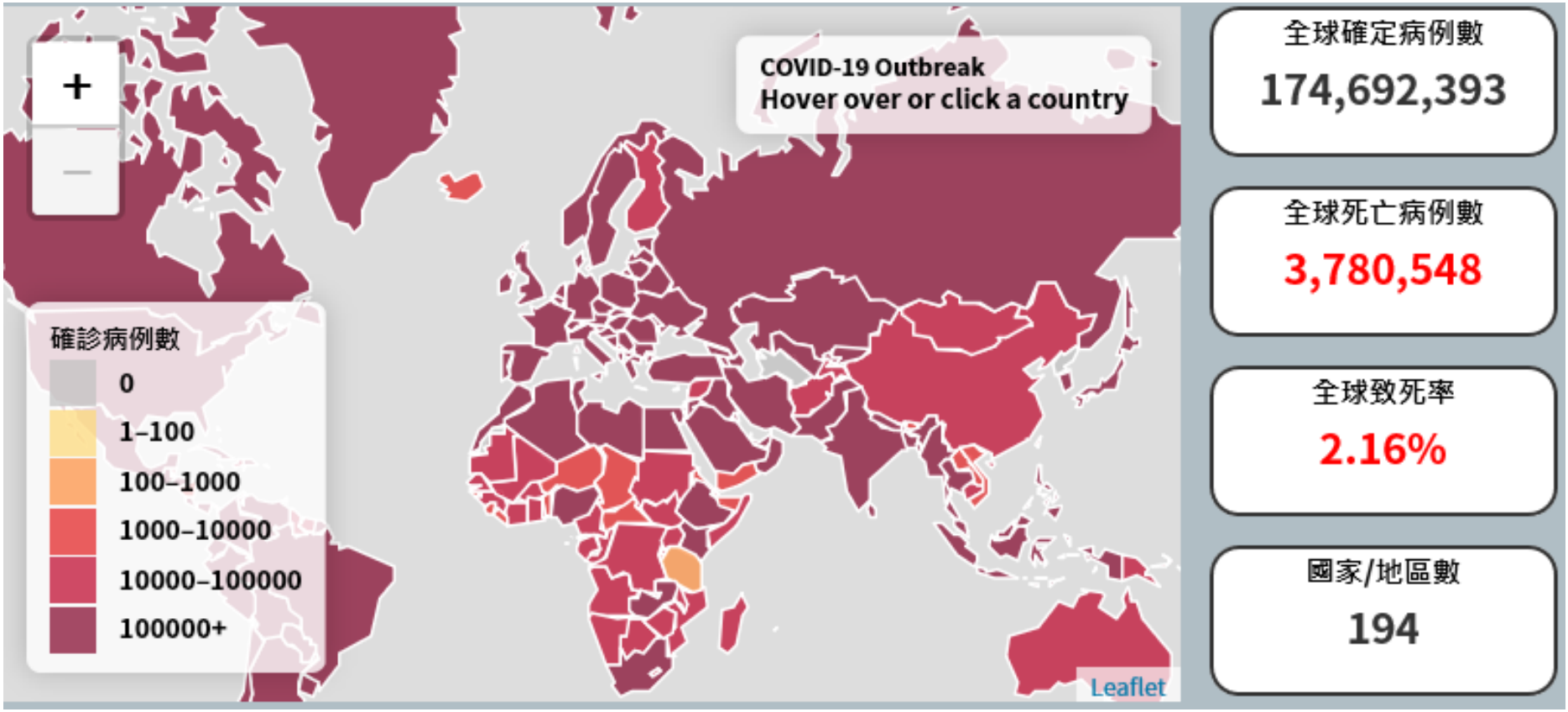


資料更新：2021/6/11

至2021/6/11

中央流行疫情指揮中心

COVID-19: Global



更新時間：2021-06-11 09:20

COVID-19: Taiwan

致死率: **3.08%**

	通報數	排除	確診	死亡
國內通報總計	804,931	781,334	12,500	385
昨日新增	35,017	34,517	266	

國內檢驗總計	累計件數
	1,367,353

更新時間：2021-06-11 09:20

死亡案例分析與分類

- 死亡後才確診: 在社區內
  - 確診者還沒被確診就已死亡
- 確診後迅速死亡，未接受治療: 在自家/檢疫所/防疫旅館
  - 居家隔離、檢疫所隔離、防疫旅館隔離
- 確診後，接受治療後死亡: 在醫院

從5月18日到6月9日，共有321人死亡。
其中有20.9%是死亡當天或死亡後才確診。
其中有24%是確診後3天內就死亡。

從5月18日到5月31日，每天公佈的新聞稿中明白地顯示著，死亡當天或死亡後確診的比例高達33.9%。確診3天內就死亡的比例高達36.6%。如果把確診後3天內死亡與死亡當天或之後才確診的人數加總一共79人，是這段期間死亡人數112人的70.5%之多。

而從6月1日到6月9日，確診後3天內死亡，死亡當天或成後確診，以及加總占死亡人數比例的三個數字分別是17.2%，13.9%，31.1%。

公佈日	確診3日內死亡	確診3日內占比	死亡後或當日確診	死亡後確診占比	確診4天後死亡人數	確診4天後死亡占比	死亡人數
5月18日	1	50.0%	1	50.0%	0	0.0%	2
5月20日	0	0.0%	1	100.0%	0	0.0%	1
5月22日	0	0.0%	2	100.0%	0	0.0%	2
5月23日	4	66.7%	1	16.7%	1	16.7%	6
5月24日	4	66.7%	2	33.3%	0	0.0%	6
5月25日	4	66.7%	1	16.7%	1	16.7%	6
5月26日	7	63.6%	3	27.3%	1	9.1%	11
5月27日	2	15.4%	4	30.8%	7	53.8%	13
5月28日	3	15.8%	10	52.6%	6	31.6%	19
5月29日	8	38.1%	6	28.6%	7	33.3%	21
5月30日	3	30.0%	2	20.0%	5	50.0%	10
5月31日	5	33.3%	5	33.3%	5	33.3%	15
6月1日	4	30.8%	1	7.7%	8	61.5%	13
6月2日	3	25.0%	1	8.3%	8	66.7%	12
6月3日	1	5.9%	0	0.0%	16	94.1%	17
6月4日	10	47.6%	2	9.5%	9	42.9%	21
6月5日	4	10.8%	7	18.9%	26	70.3%	37
6月6日	2	5.6%	13	36.1%	21	58.3%	36
6月7日	4	15.4%	4	15.4%	18	69.2%	26
6月8日	5	22.7%	0	0.0%	17	77.3%	22
6月9日	3	12.0%	1	4.0%	21	84.0%	25
合計	77	24.0%	67	20.9%	177	55.1%	321

From 台大王明鉅副院長 FB

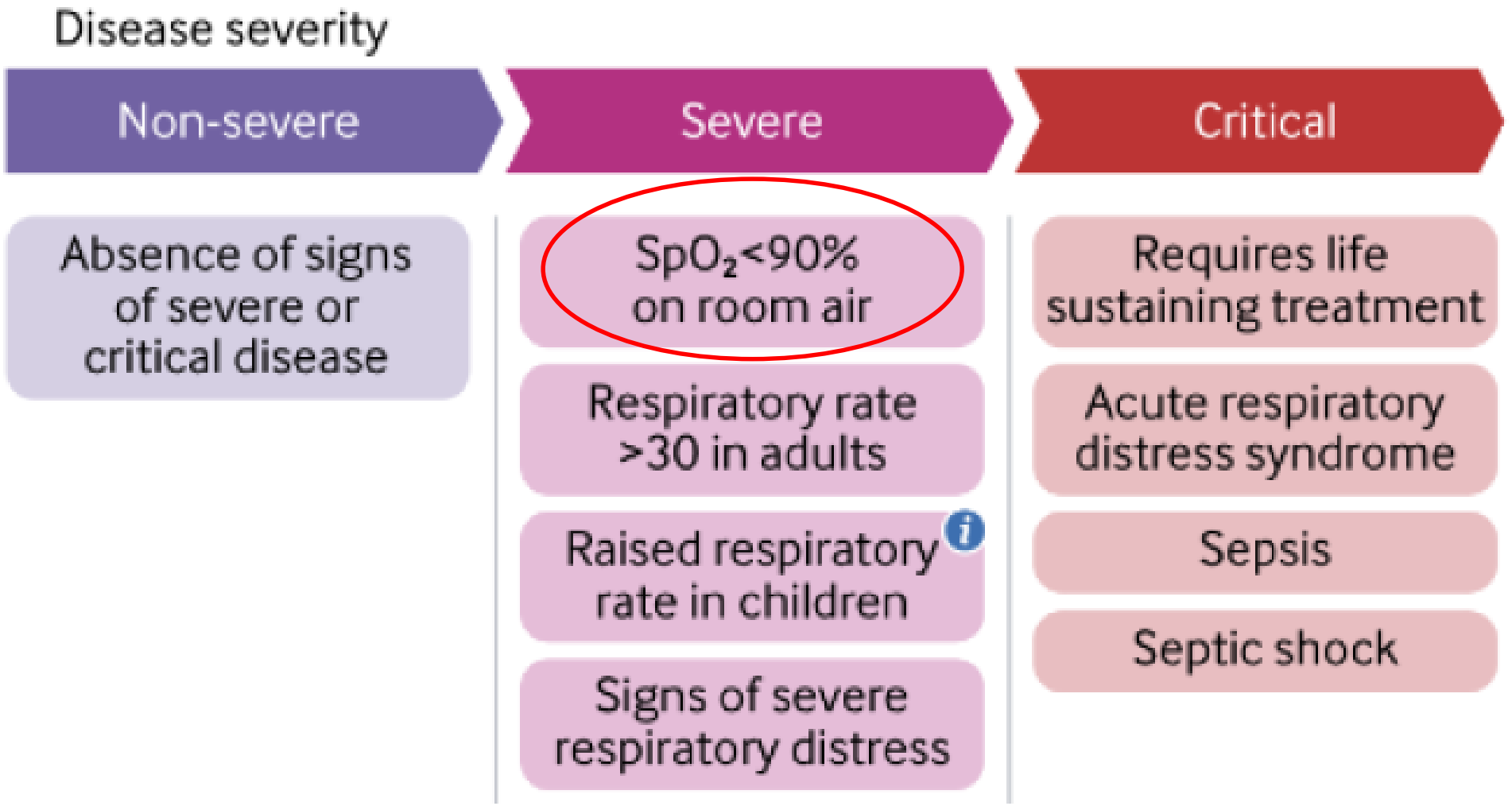
17年沒生病 72歲健身阿公罹武漢肺炎4天後喪命

© 由 TVBS新聞網 提供　湖北1名72歲的健身阿公邱鈞，在大陸十分出名。(圖 / 翻攝自騰訊網)

武漢肺炎至今在大陸已經超過4萬例確診病例，更有超過900人死亡，全球更是人心惶惶。就連大陸湖北知名的72歲健身達人邱鈞也難以倖免，2日確診罹患武漢肺炎，3日住進醫院，院方證實他已經在6日過世。

2020年2月11日

疾病嚴重度分類: 重度、危急症



Infographic co-produced by BMJ and MAGIC; designer Will Stahl-Timmins (see BMJ Rapid Recommendations).

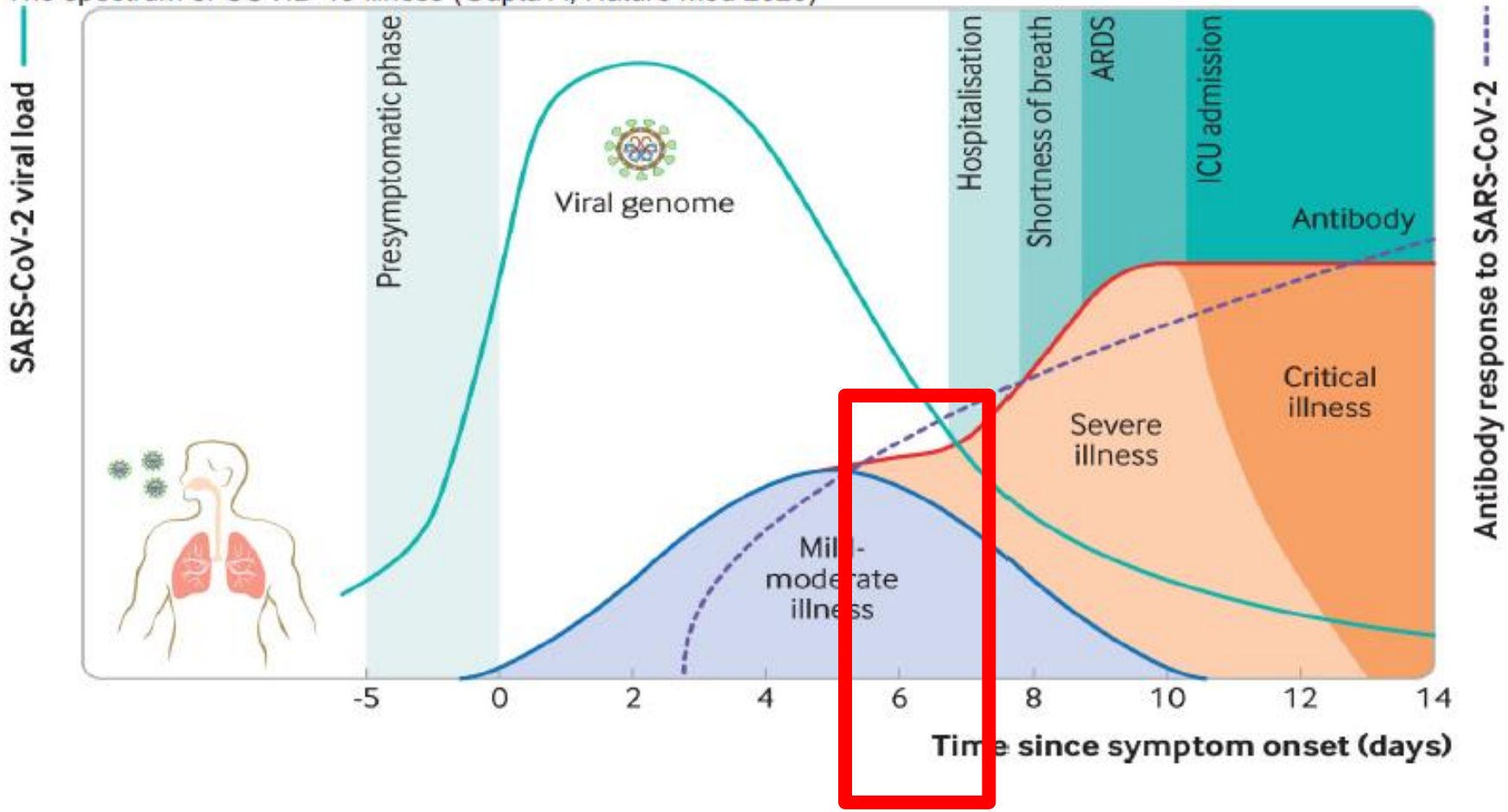
疾病嚴重度分類: 輕度、中度

Mild disease		Symptomatic patients (Table 6.1) meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. See the WHO website for most up-to-date case definitions *(1)*.
Moderate disease	**Pneumonia**	**Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥ 90% on room air *(86)*. **Child** with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 *(87)*. While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications. **Caution:** The oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously. For example, clinicians must use their judgment to determine whether a low oxygen

COVID 19 Clinical management, Living guidance 25 January 2021, WHO

病程進展

1. The spectrum of COVID-19 illness (Gupta A, Nature Med 2020)



The NEW ENGLAND JOURNAL of MEDICINE

Severe Covid-19

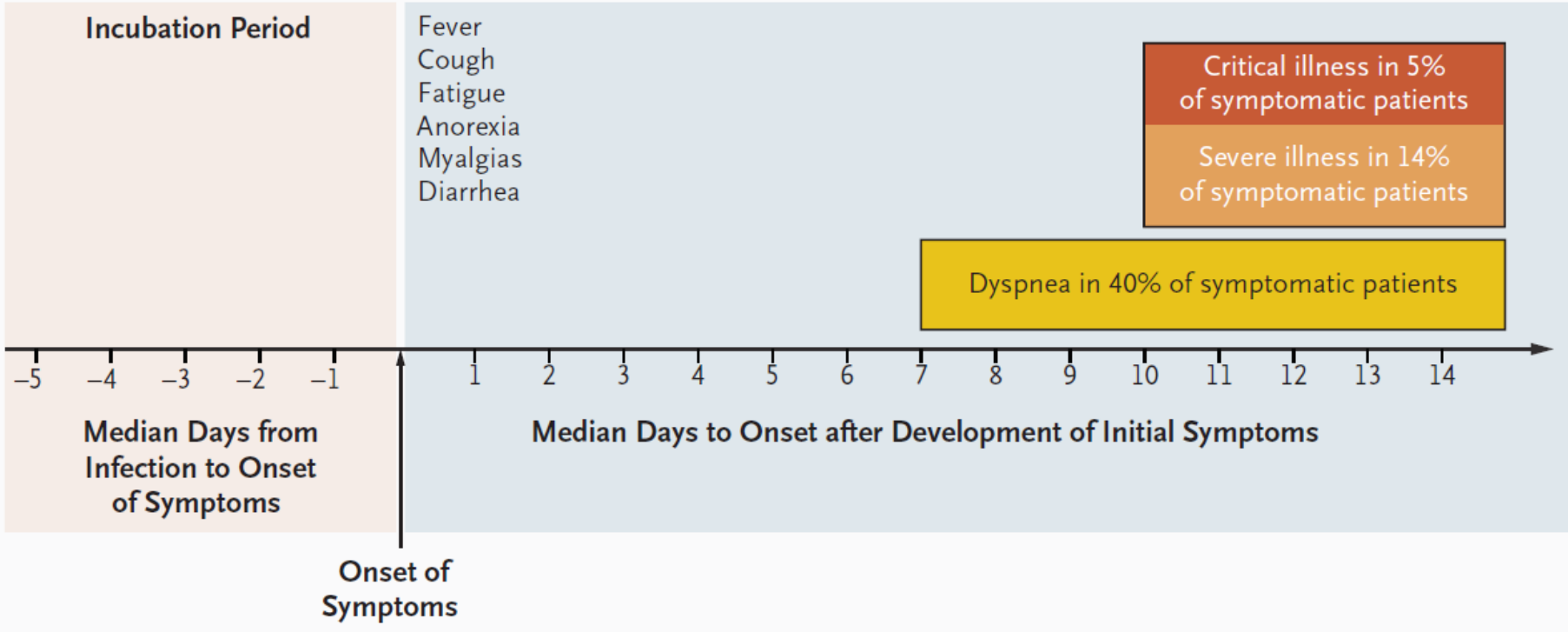


Figure 1. Timeline of Symptoms of Severe Coronavirus Disease 2019 (Covid-19).

The left border of the colored boxes shows the median time to onset of symptoms and complications. There is wide variation in the duration of symptoms and complications. Adapted from Zhou et al.[2] and the Centers for Disease Control and Prevention.[1]

JAMA. 2020;324(8):782-793.

內容

- 前言
- 定義
- 臨床表現
- 致病機轉
- 預後
- 預防與處置
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定義 (1)

- **隱形缺氧 (Silent hypoxia)**
- 快樂缺氧 (Happy hypoxia)
- 隱形低血氧症 (Silent hypoxemia)
- 快樂低血氧症 (Happy hypoxemia)

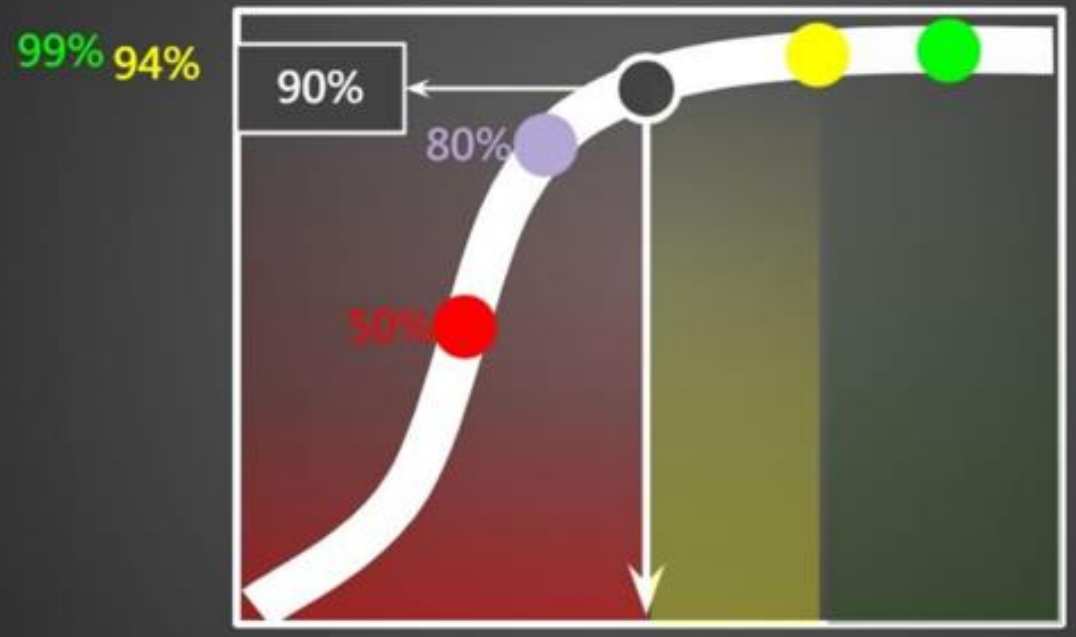
定義 (2)

- 缺氧(Hypoxia)是身體組織含氧量少的情形，是由低血氧症(Hypoxemia)引起的，也就是血液中的氧氣濃度，低於正常水平。
  - 正常的動脈血氧濃度大約是75~100毫米汞柱(mmHg)，若數值低於60 mmHg，就代表缺氧並需給予氧氣治療
- 這兩者也可能是其他疾病導致呼吸和循環困難的症狀。

正常人的動脈血氧飽和度

正常	偏低	危險

血氧飽和度




A
SPO2: 79%
HR:82

內容

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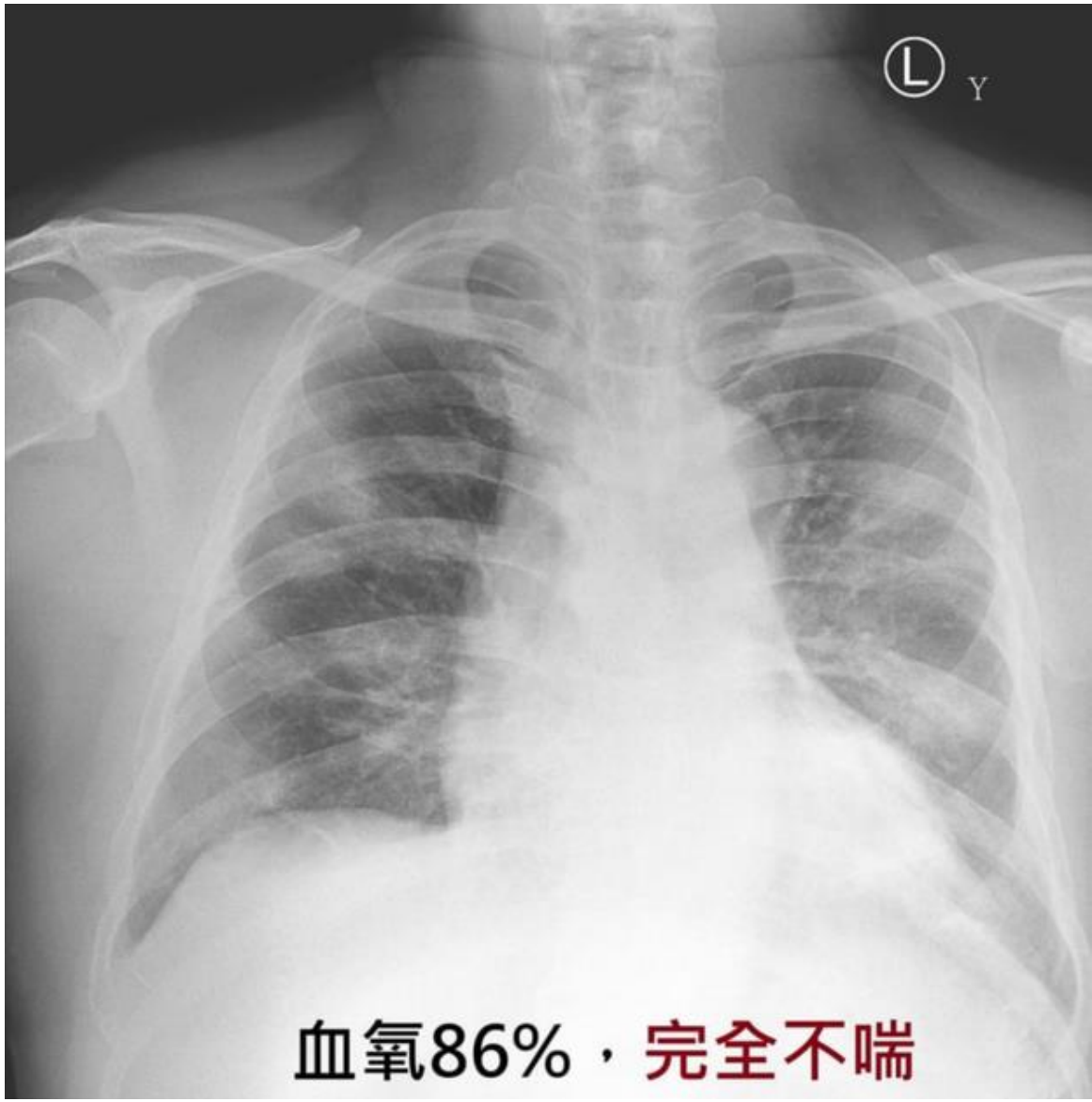
臨床表現

- **隱形**: 無症狀 (asymptomatic)、不自覺、或快速惡化
- **缺氧**的症狀:
  - 呼吸道問題: 呼吸困難、呼吸急促、咳嗽及哮喘
  - 心血管問題: 心跳加快
  - 腦部及精神問題: 頭痛及意識混亂
  - 皮膚: 顏色從櫻桃色轉至藍色
  - 其他: 坐立不安及出汗

😨60歲男性，發燒來就醫（無接觸史）

💥快篩採檢陽性，血氧低卻一點也不喘

#快樂低血氧其實真的還不少



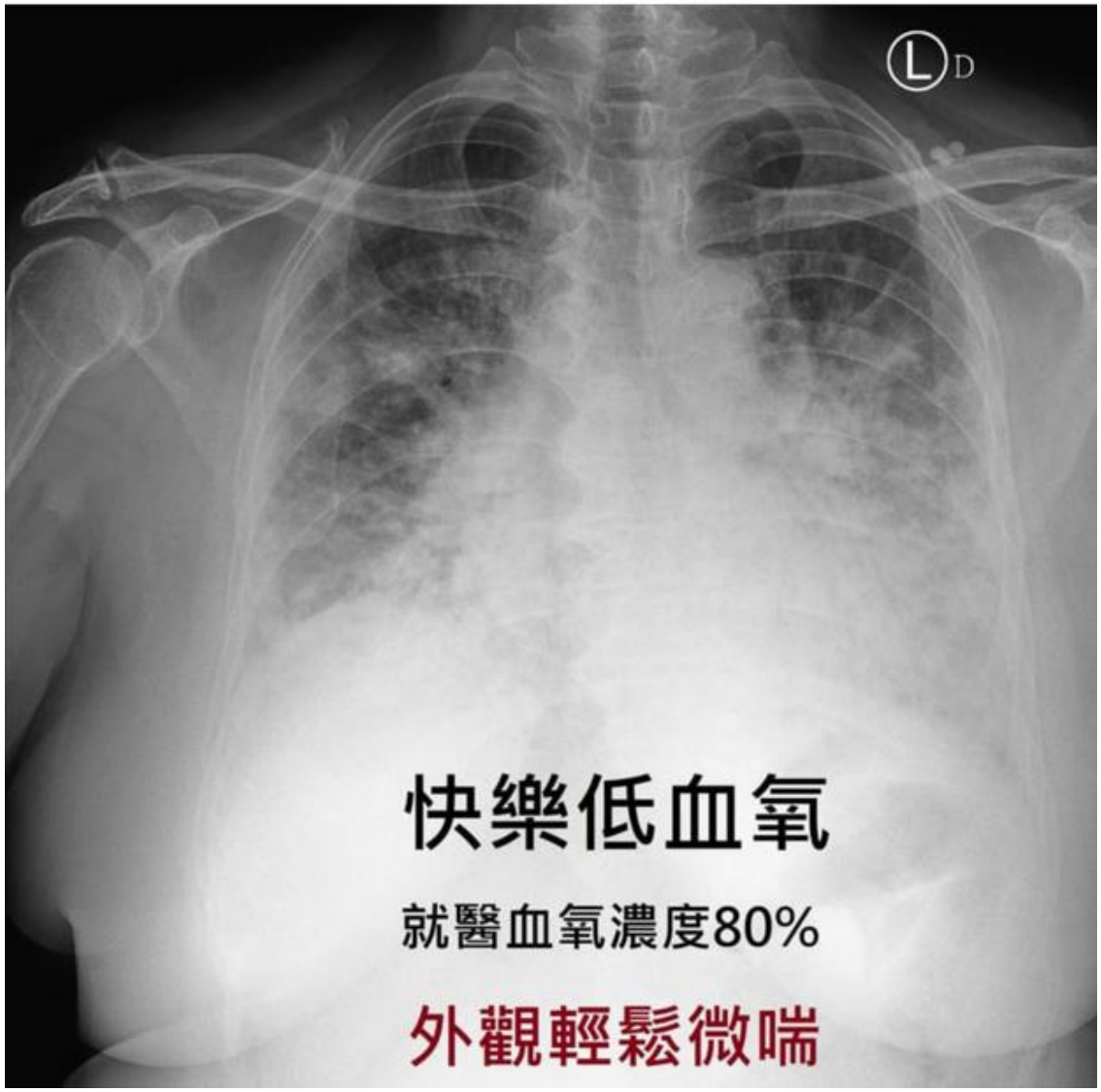
From 蘇一峰 醫師 FB

😥60歲女性，先生已經確診，病人前天確診但是醫院無床進入檢疫所，今天在檢疫所發現有缺氧情形.....

😨到急診血氧飽和度只有80，病人自己覺得還好一點點喘.....

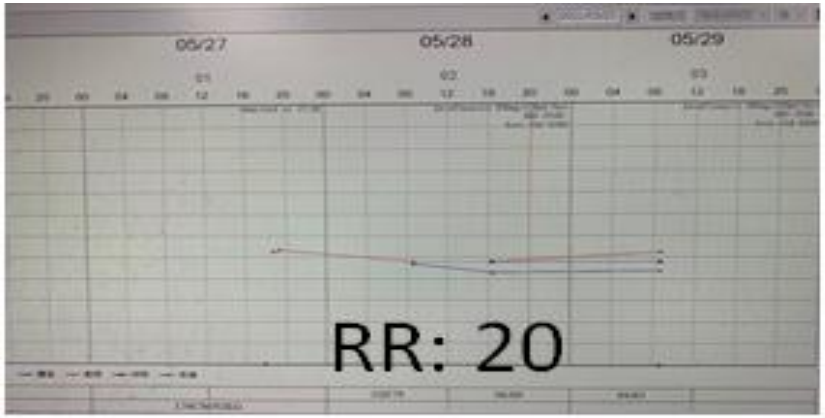
#插管進加護病房

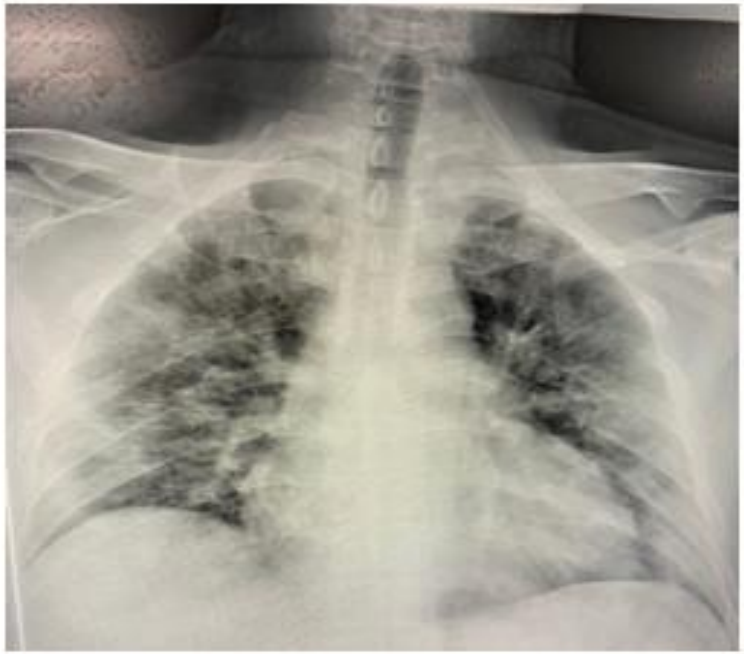
💥認識快樂低血氧症 (Happy Hypoxia)！
https://tvgh-suvy.blogspot.com/2021/05/happy-hypoxia.html



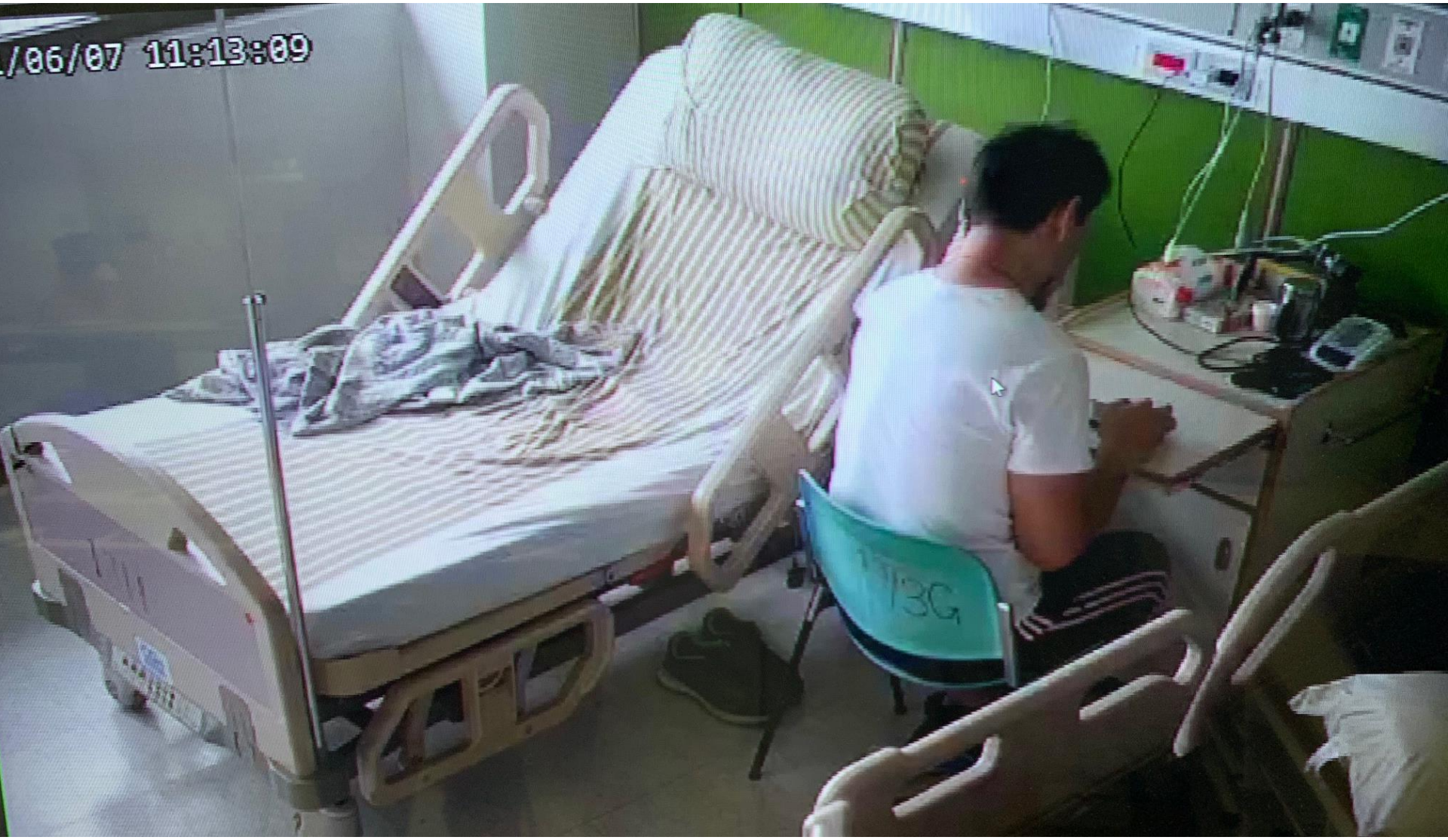
From 蘇一峰 醫師 FB

Case 1: 45 y/o male





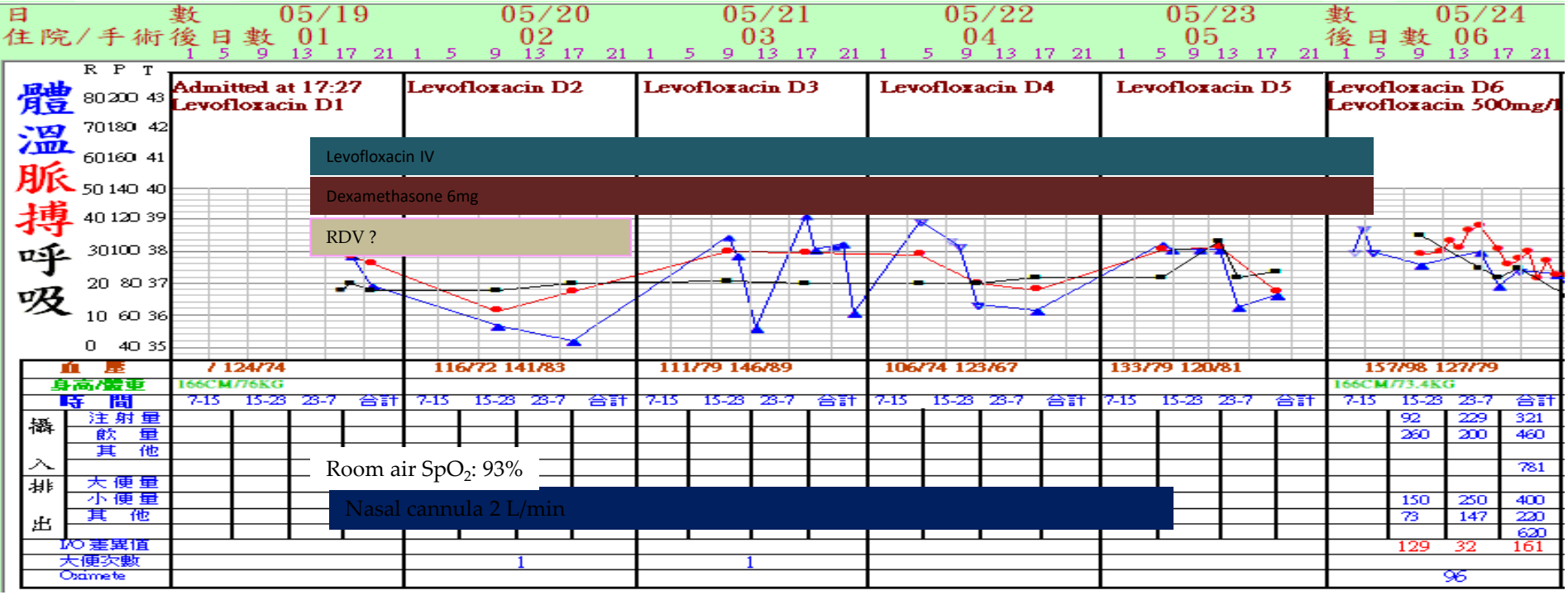
Simple mask 6 L/min

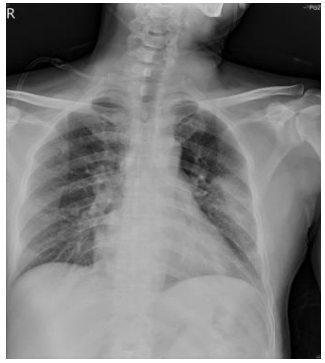

/06/07 11:13:09

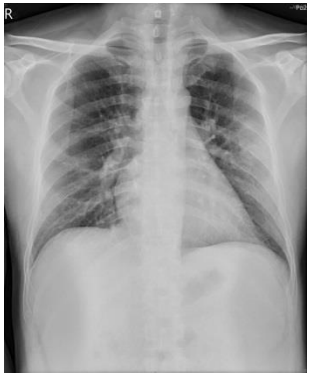
Case 2: 38 y/o male

- Nationality: Vietnam; Occupation: worker
  - TOCC history: colleagues usually went to 萬華
- Present illness
  - PCR (+) on 5/14
  - After then, symptoms began; sent to our hospital (5/19)
    - Fever, chills
    - Muscle soreness
    - Loss of smell and taste
    - No dyspnea

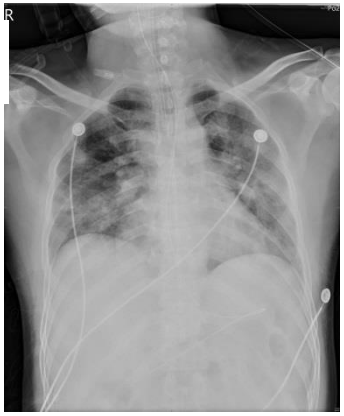
Course and Treatment (1)





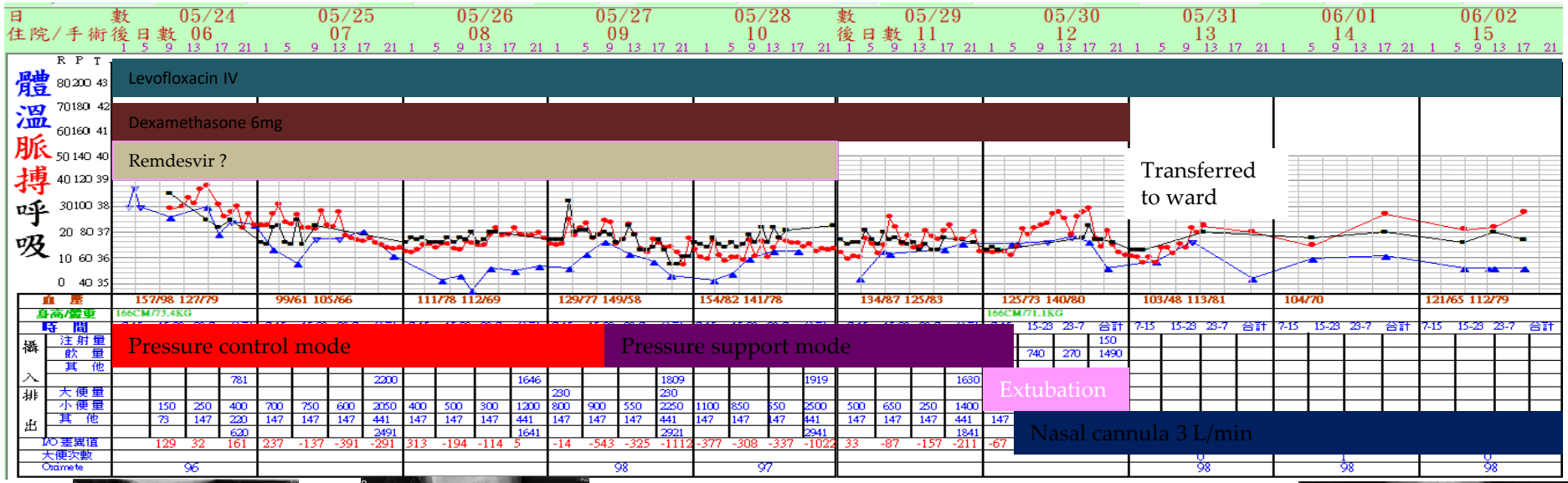


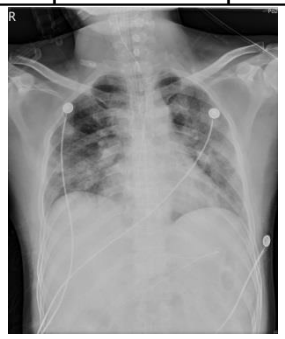
general malaise
severe dry cough

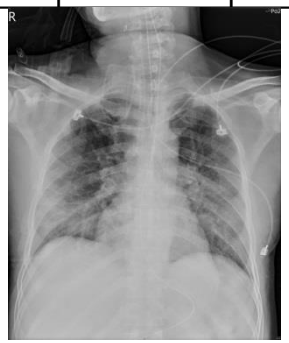


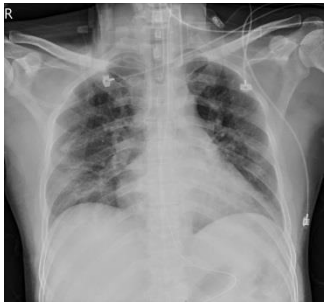
~8:00 SpO_2: 88% (NC 2L/min)
→ NC 5L/min
~09:00 SpO_2: 91-93%
→ non-rebreathing mask
~11:00 SpO_2: 96%, PaO_2: 73.8
→ Elective intubation

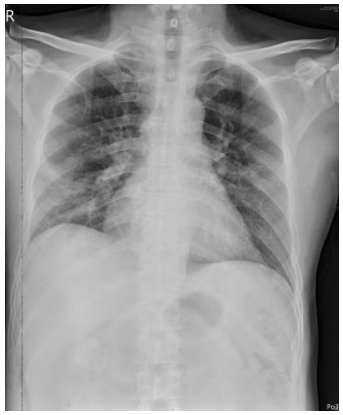
Course and Treatment (2)







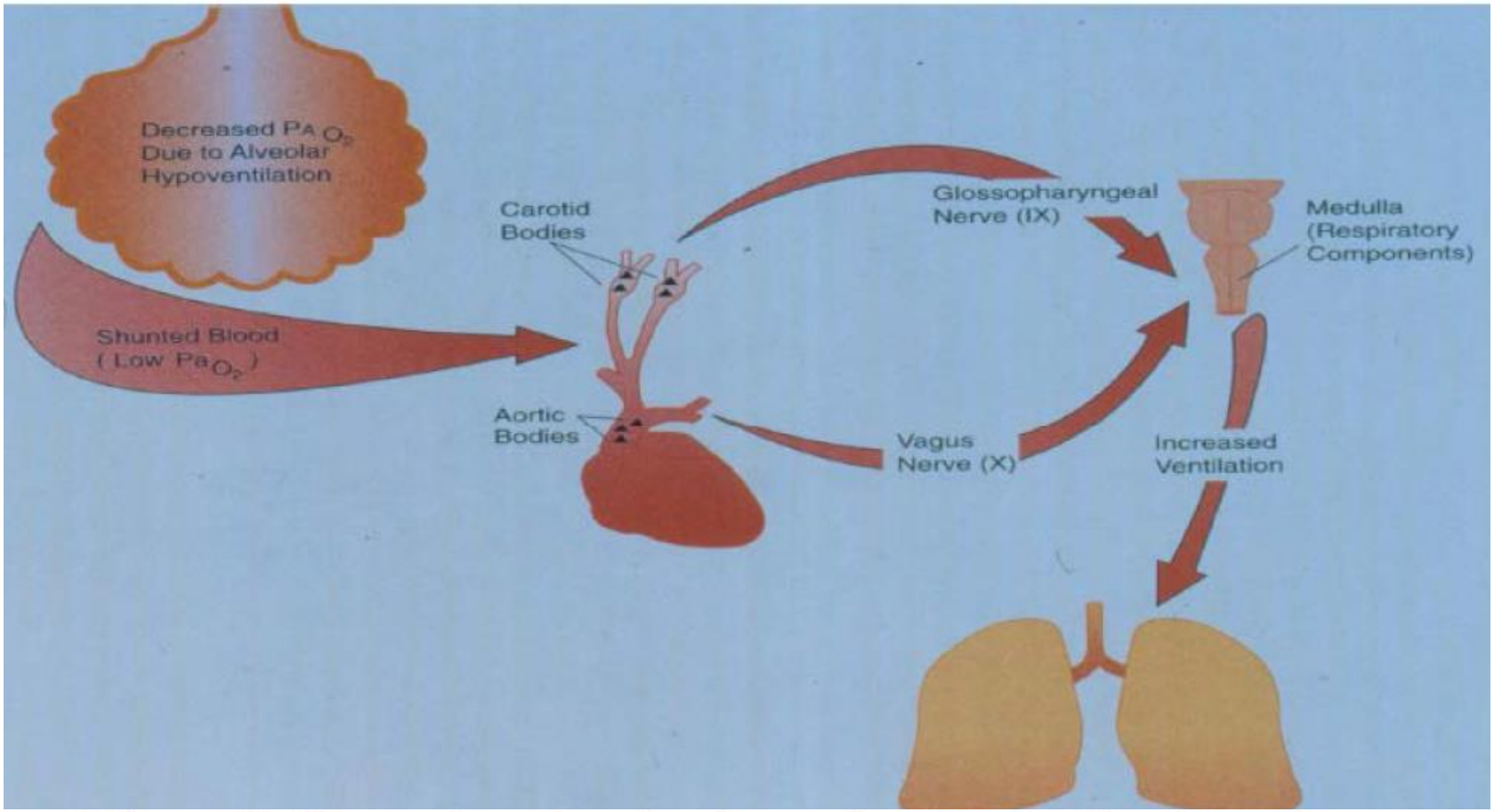




內容

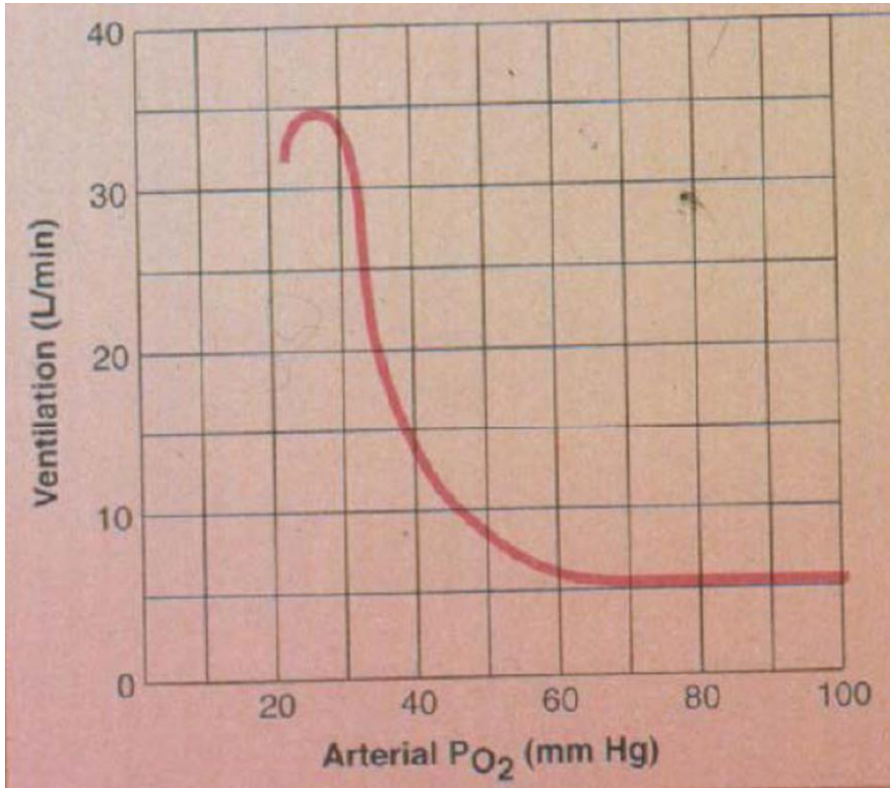
- 定義
- 臨床表現
- 致病機轉
- 預後
- 預防與處置
- 總結

Low PaO2 stimulate medulla to increase ventilation

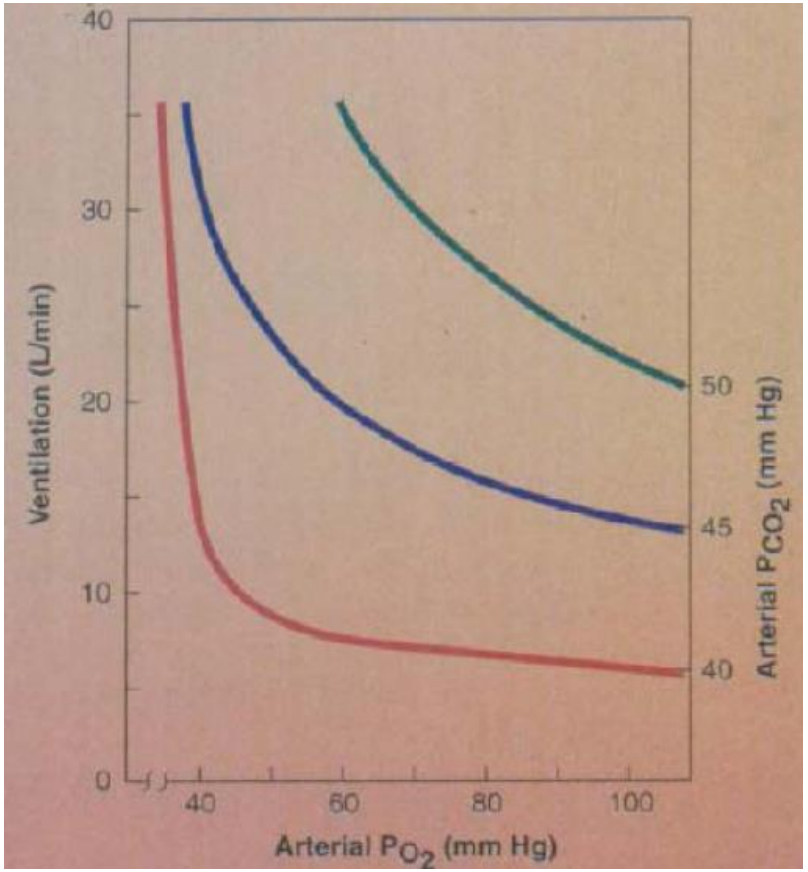


Schematic illustration showing how a low PaO_2 stimulates the respiratory components of the medulla to increase alveolar ventilation.

PaO2 and PaCO2



The effect of low Pao_2 level on ventilation



The effect of Pao_2 on ventilation at three different Pao_2 values. Note that as the Pao_2 value increases, the sensitivity of the peripher chemoreceptors increases

Silent hypoxia (1)

- Clinical screening and management based on 3 symptoms: Fever, Cough and Dyspnea
- Dyspnea:
  - 1/3 of patients without dyspnea
  - Dyspnea reported in 18.7% of 1099 hospitalized with COVID, many of whom showed abnormal CT scan (86%) and need O2 therapy (41%)
  - In patients with abnormal radiologic finding consistent with COVID pneumonia, only 50% report dyspnea

Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382(April (18)):1708–20.
Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(February (10223)):497–506.

Silent hypoxia (2)

- Some patients deteriorate rapidly and without warning
  - More than 2/3 patients hospitalized in ICU come directly from home to ICU or admit to ICU after less than 3 days of stand ward hospitalization
- Many patients who later develop respiratory failure experienced hypoxemia and hypocapnia without sign of respiratory distress, particularly elderly patients

Xie J, Tong Z, Guan X, Du B, Qiu H. Clinical characteristics of patients who died of coronavirus disease 2019 in China. JAMA Netw Open 2020;3(April (4))e205619.

Silent hypoxia (3)

- Mechanism: not yet clear
  - Anosmia-hyposmia is a frequent clinical sign in COVID; Whether the virus has access to the brain and contribute to the association between dyspnea and anosmia-hyposmia remain to be determinated
  - Thrombi within the pulmonary vasculature

Anosmia: 嗅覺喪失

Boudjema S, Finance J, Coulibaly F, Meddeb L, Tissot-Dupont H, Michel M, et al. Olfactory and gustative disorders for the diagnosis of COVID-19. Travel Med Infect Dis 2020;(September):101875.

Tobin MJ, Laghi F, Jubran A. Why COVID-19 silent hypoxemia is baffling to physicians. Am J Respir Crit Care Med 2020;202(August (3)):356–60.

Couzin-Frankel J. The mystery of the pandemic's 'happy hypoxia'. Science 2020;368 (May (6490)):455–6.

Why COVID-19 Silent Hypoxemia Is Baffling to Physicians

Martin J. Tobin, Franco Laghi, and Amal Jubran

Division of Pulmonary and Critical Care Medicine, Hines Veterans Affairs Hospital and Loyola University of Chicago Stritch School of Medicine, Hines, Illinois

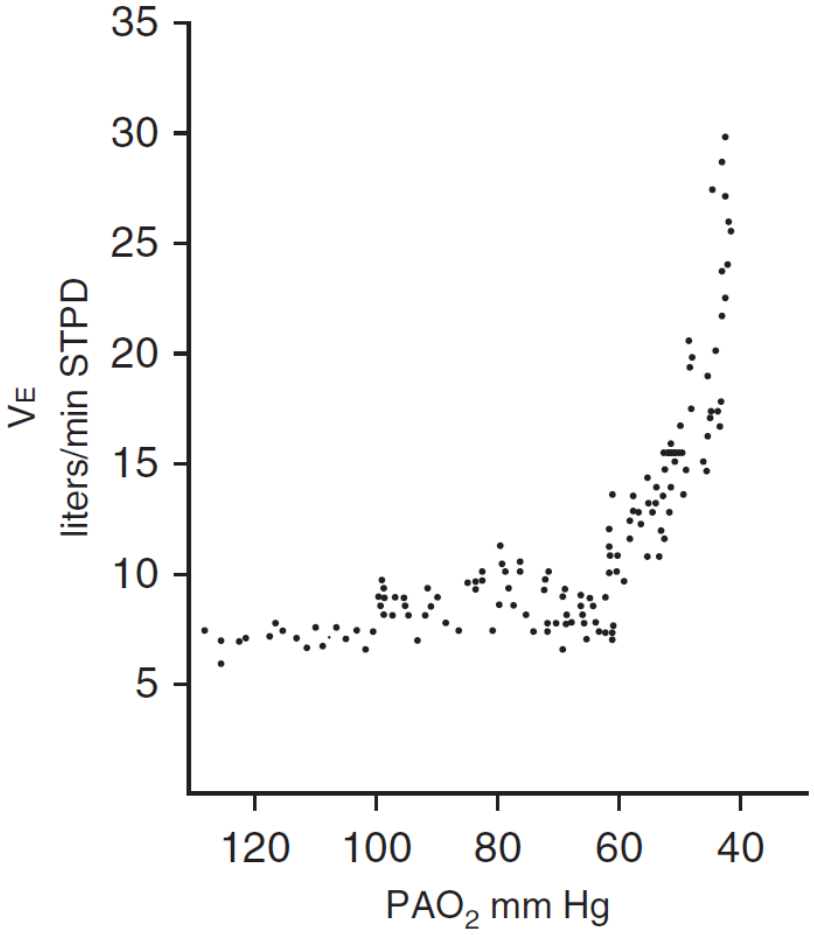


Figure 1. The ventilatory response to progressive isocapnic hypoxia in a healthy subject. Little change in $\dot{V}_E$ is noted until alveolar oxygen tension ($P_{A_{O_2}}$) falls to 60 mm Hg, and thereafter the response is very steep. Each data point represents the mean value for $P_{A_{O_2}}$ and $\dot{V}_E$ for three successive breaths. Adapted by permission from Reference 11. STPD = standard temperature and pressure dry.

Am J Respir Crit Care Med Vol 202, Iss 3, pp 356–360, Aug 1, 2020

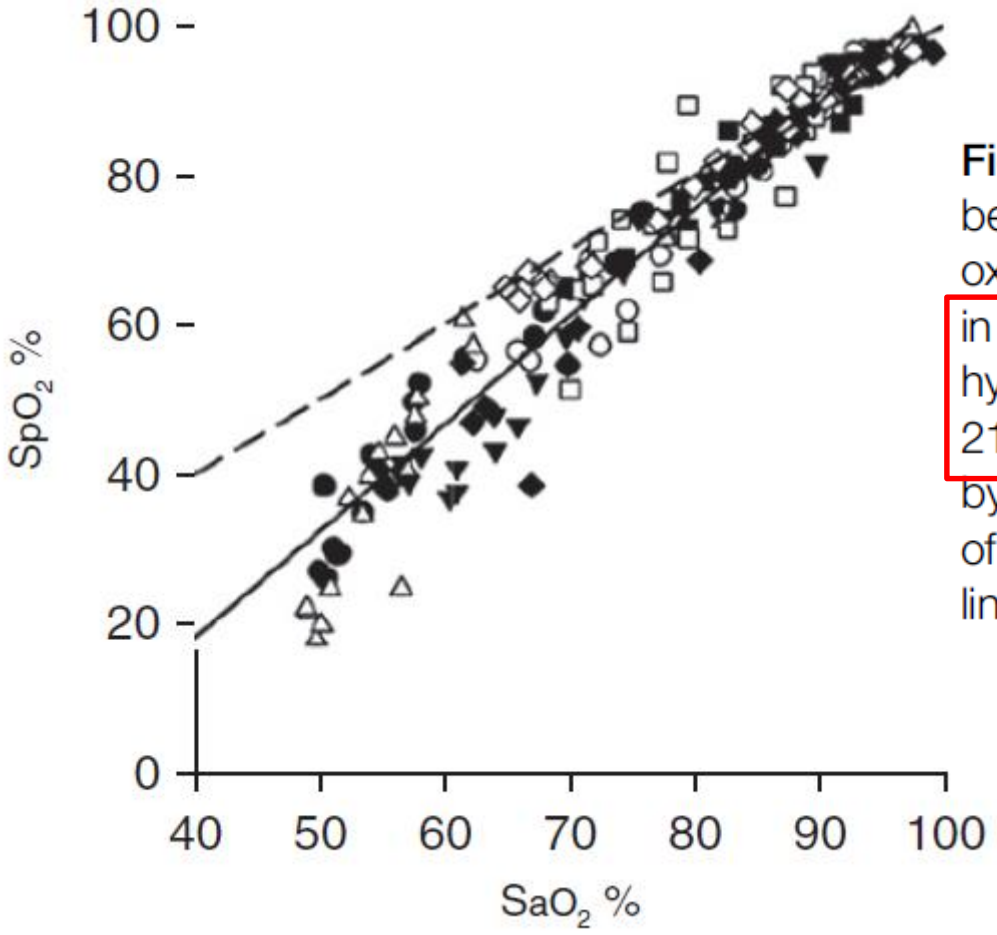


Figure 2. Scatterplot of the relationship between estimated oxygen saturation from pulse oximetry (Sp_{O_2}) and Sa_{O_2} from blood gas analysis in healthy subjects exposed to profound hypoxemia in a hypobaric chamber (Pa_{O_2}, 21.6–27.8 mm Hg). Each subject is represented by a different symbol. The dashed line is the line of identity, and the solid line is the regression line. Adapted by permission from Reference 28.

Am J Respir Crit Care Med Vol 202, Iss 3, pp 356–360, Aug 1, 2020

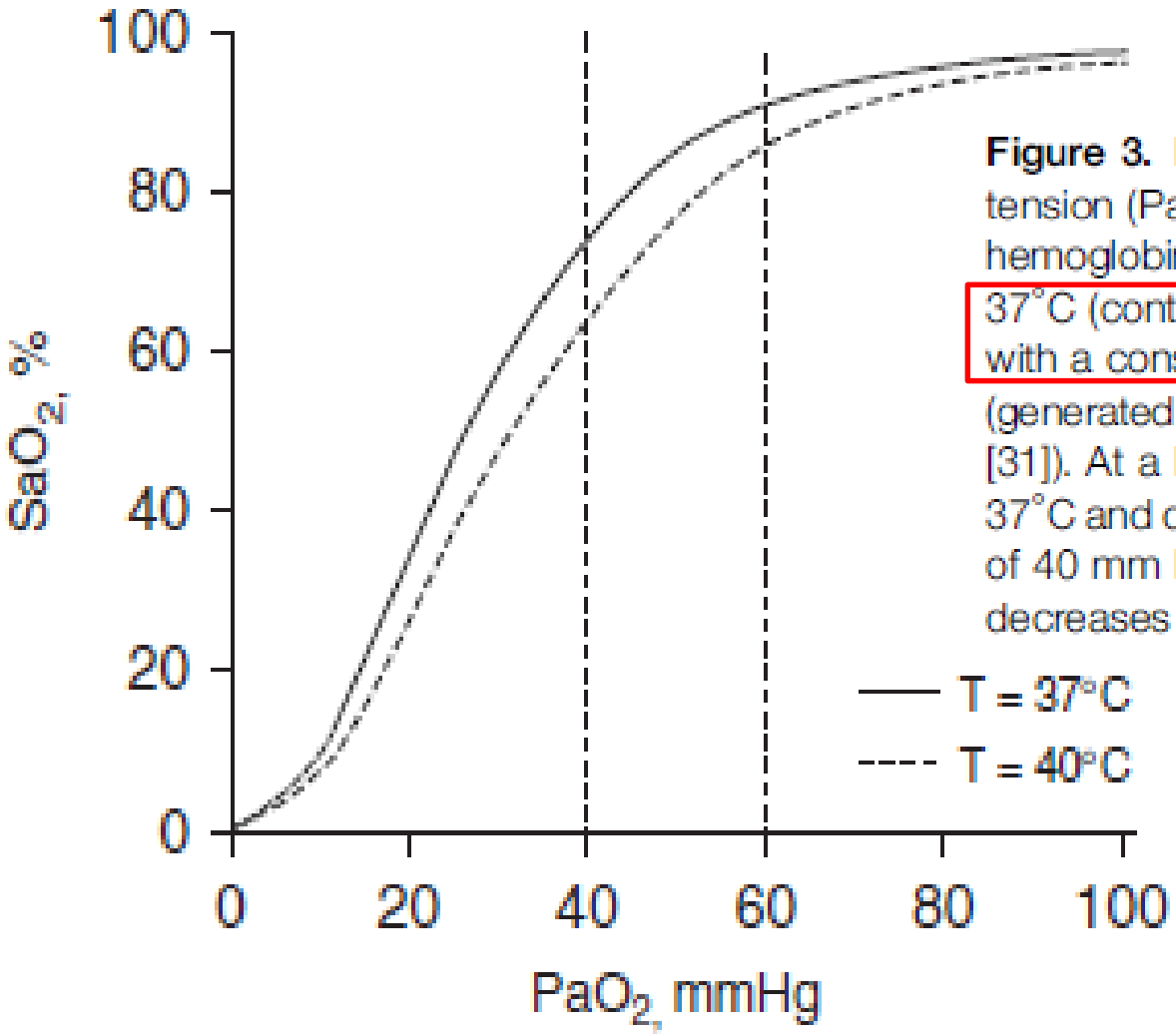


Figure 3. Relationship between arterial oxygen tension (Pa_{O_2}) and percentage saturation of hemoglobin with oxygen (Sa_{O_2}) at temperature 37°C (continuous line) and 40°C (dashed line), with a constant pH 7.40 and Pco_2 of 40 mm Hg (generated with digital subroutine of Kelman [31]). At a Pa_{O_2} of 60 mm Hg, Sa_{O_2} is 91.1% at 37°C and decreases to 85.8% at 40°C. At a Pa_{O_2} of 40 mm Hg, Sa_{O_2} is 74.1% at 37°C and decreases to 64.2% at 40°C.

Am J Respir Crit Care Med Vol 202, Iss 3, pp 356–360, Aug 1, 2020

First ultrastructural autoptic findings of SARS-Cov-2 in olfactory pathways and brainstem

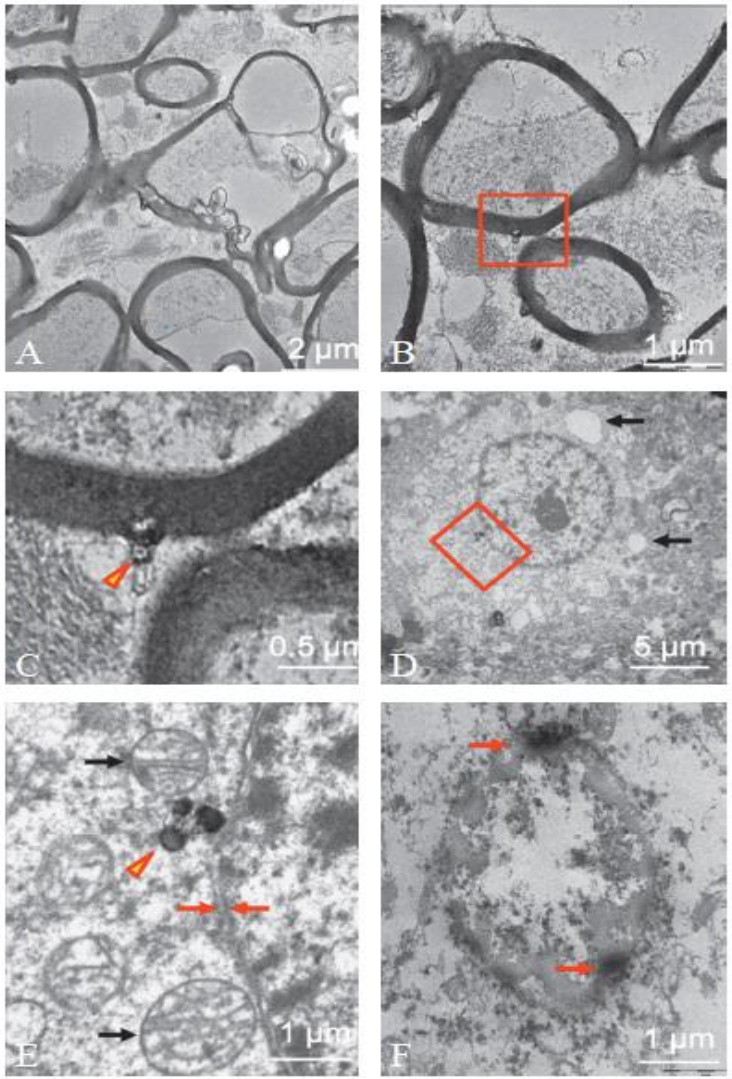


Figure 1.—Neurologic damage in SARS-CoV-2 infection. Ultrastructure of the: medulla oblongata (A-C); gyrus rectus (D, E); olfactory nerve (F). A) Marked axonal damage at the medulla oblongata, with irregular axonal swelling and disarrangement of the myelin sheath. The damage appears to be widespread. B) A spherical particle with size suspicious for a viral particle (box) is observed in the periaxonal matrix near the outer surface of a myelin sheath. C) Magnification of the box area in B: the spherical particle (~98 nm) has a crown shape with a dense inner core and electron-dense periphery with small external projections. A small roundish electron-dense structure is detected in the center of the particle. This morphology is compatible to that of SARS-CoV-2. D) The image shows a neuron of the gyrus rectus, as demonstrated also by the presence of a nucleolus at the center of the euchromatic nucleus; numerous phenomena of autophagy in the cytoplasm (arrows) suggest cell damage. E) Magnification of the box area in D, showing a viral-like particle of 160 nm (arrowhead). Black arrows indicate two well preserved mitochondria; arrows show the typical double nuclear envelope of the neuron. The good ultrastructural preservation of these organelles demonstrates adequate methods of collection and fixation, and suggests that the tissue damage is related to the viral infection. F) Severe tissue damage in the olfactory nerve: the oval structure is difficult to identify, and is characterized by extensive phenomena of autophagy with markedly electron-dense peripheral aggregates (arrows). Images by Unitech NO LIMITS.

Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019 A Review

嗅覺喪失　　味覺喪失

Anosmia and Ageusia

The prevalence of anosmia and ageusia ranges widely in the literature. In a study of patients hospitalized in Wuhan, the prevalence of hypogeusia and hyposmia was 5.6% and 5.1%, respectively,[59] while 19.4% of patients in Italy had some form of chemosensory dysfunction.[66] Approximately 88.5% and 88.0% of patients in Germany reported olfactory and gustatory dysfunction, respectively.[67] Of patients without nasal congestion, 79.7% were hyposmic.[67] Anosmia has also been noted in other respiratory infections, such as influenza.[66,68] In COVID-19, anosmia is typically not accompanied by nasal swelling or rhinitis. Given the reports of anosmia presenting as an early symptom of COVID-19, dedicated testing for anosmia may offer the potential for early detection of COVID-19 infection.

JAMA Neurol. 2020 August 01; 77(8): 1018–1027.

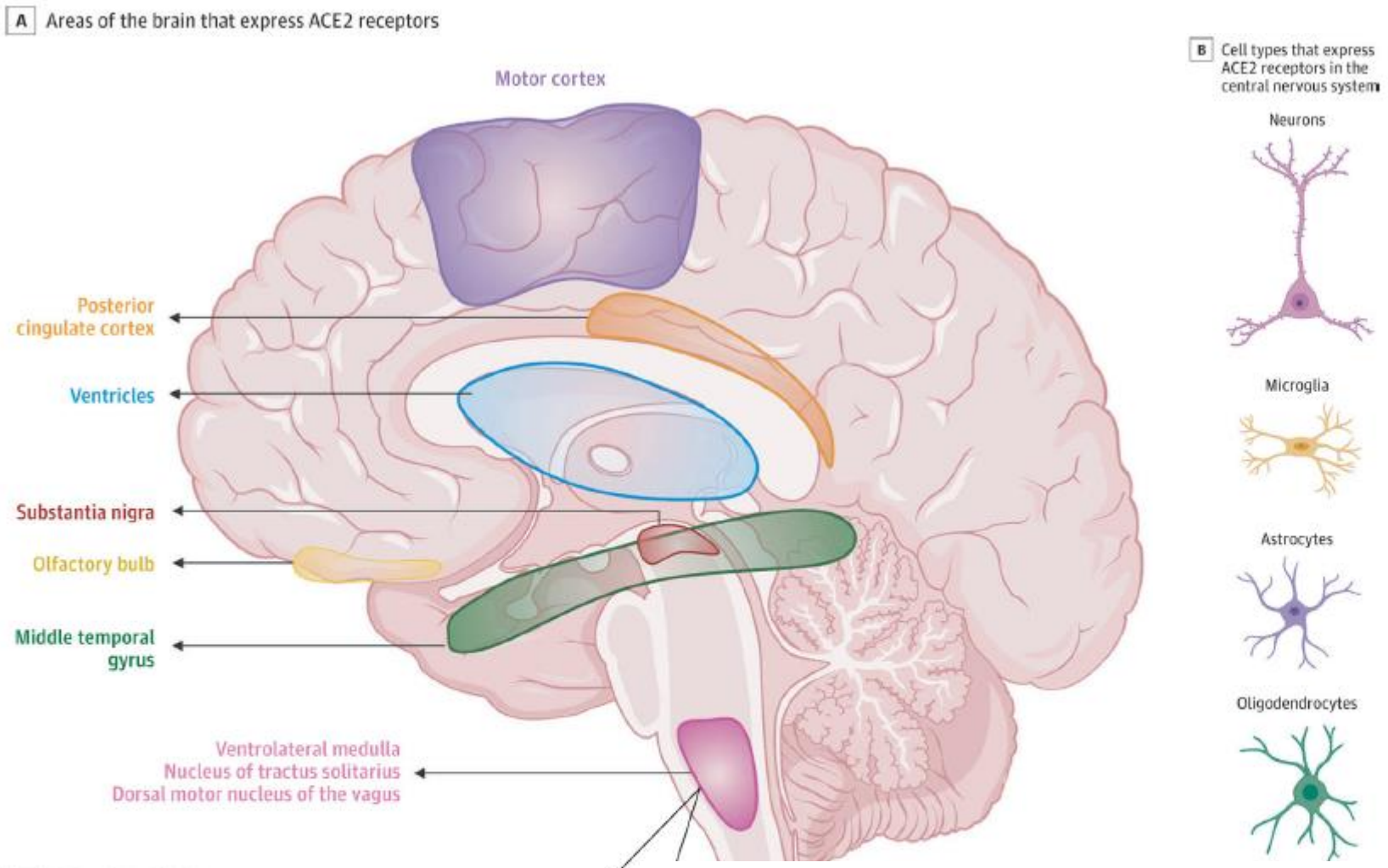


Figure 1. Angiotensin-Converting Enzyme 2 (ACE2) Expression in the Brain

Emerging data suggest that ACE2 receptors are expressed in multiple regions of the human and mouse brain, including the motor cortex, posterior cingulate cortex, ventricles, substantia nigra, olfactory bulb, middle temporal gyrus, ventrolateral medulla, nucleus of tractus solitarius, and dorsal motor nucleus of the vagus nerve (A) and on several key cell types that make up the central nervous system, including neurons, microglia, astrocytes, and oligodendrocytes (B).[35–37] C, ACE2 receptors on a medullary neuron binding to the SPIKE protein on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

JAMA Neurol. 2020 August 01; 77(8): 1018–1027.

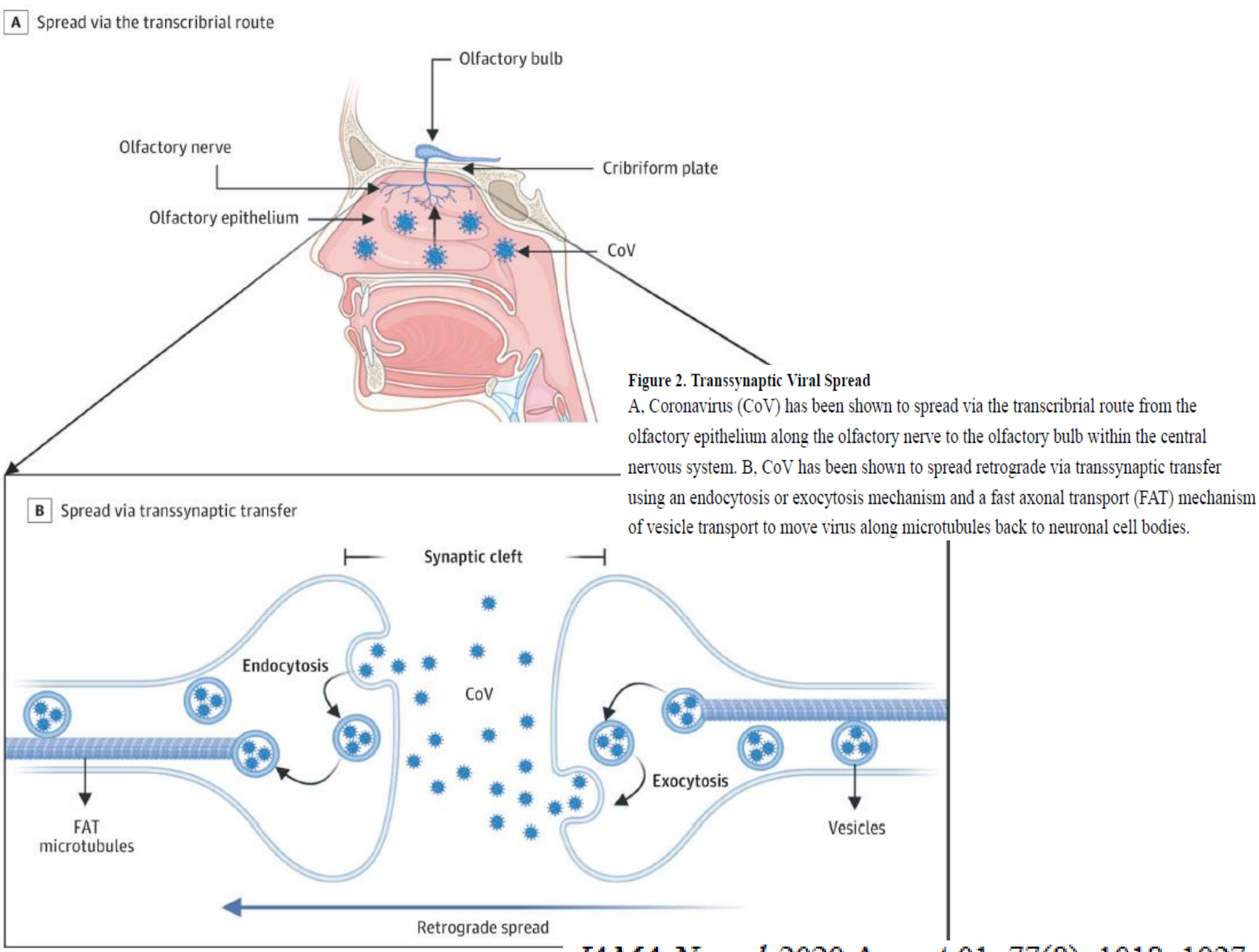


Figure 2. Transsynaptic Viral Spread

A, Coronavirus (CoV) has been shown to spread via the transcribrial route from the olfactory epithelium along the olfactory nerve to the olfactory bulb within the central nervous system. B, CoV has been shown to spread retrograde via transsynaptic transfer using an endocytosis or exocytosis mechanism and a fast axonal transport (FAT) mechanism of vesicle transport to move virus along microtubules back to neuronal cell bodies.

JAMA Neurol. 2020 August 01; 77(8): 1018–1027.

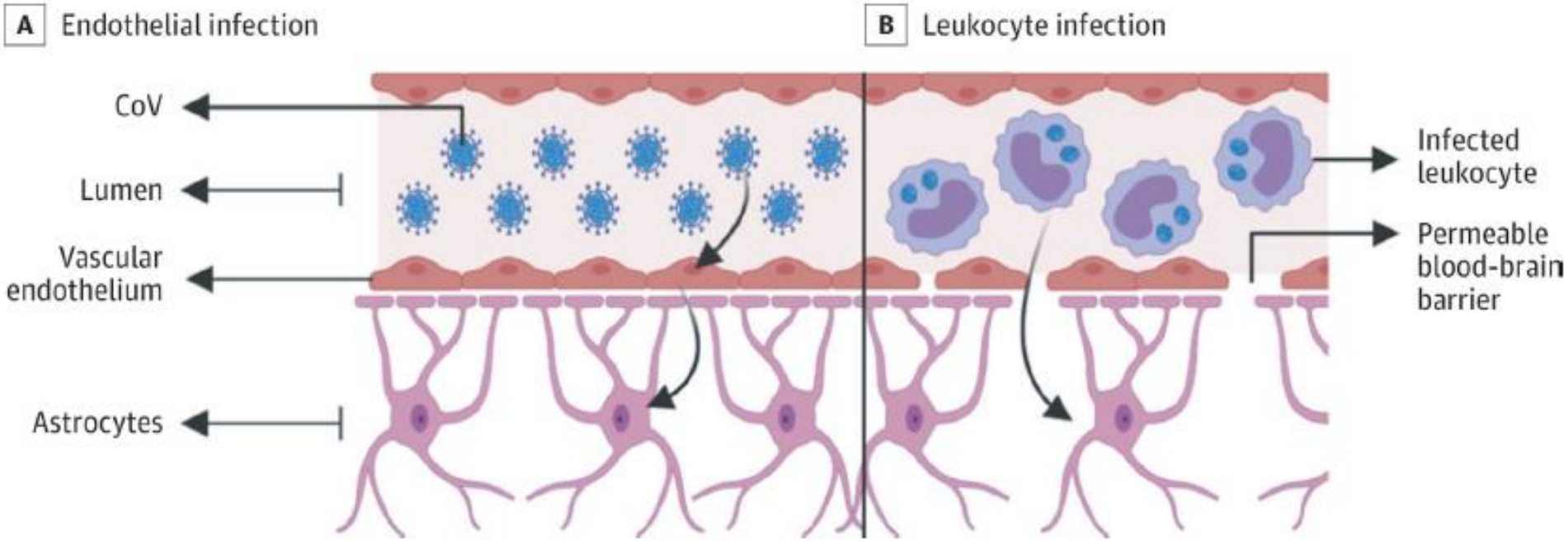


Figure 3. Mechanisms of Spread Across the Blood-Brain Barrier

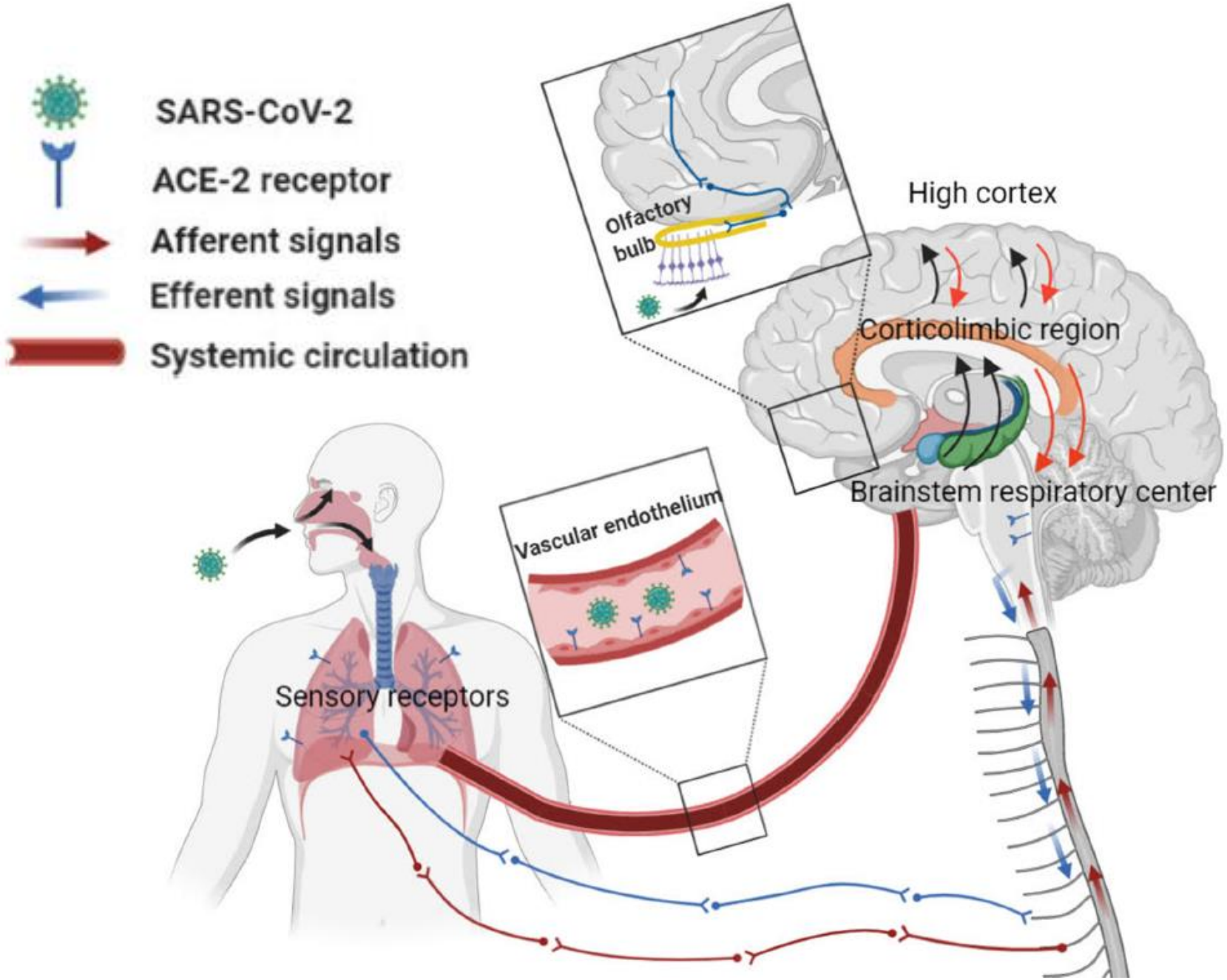
A, Infected vascular endothelial cells have been shown to spread severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to glial cells in the central nervous system. B, Known as the *Trojan horse mechanism*, infected leukocytes can cross the blood-brain barrier to infect the central nervous system. CoV indicates coronavirus.

JAMA Neurol. 2020 August 01; 77(8): 1018–1027.

Dyspneic and non-dyspneic (silent) hypoxemia in COVID-19: Possible neurological mechanism

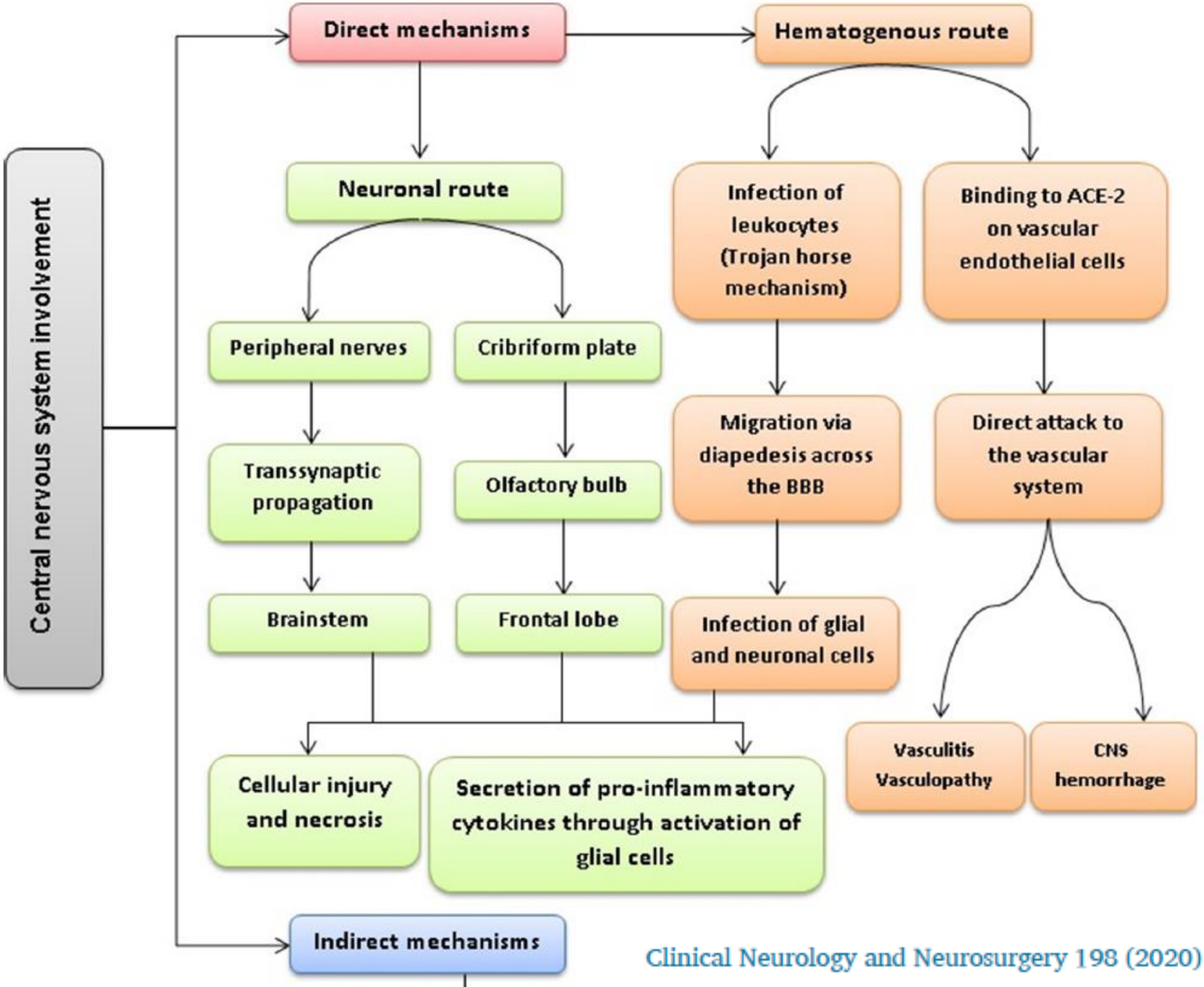
A B S T R A C T

SARS-CoV-2 mainly invades respiratory epithelial cells by adhesion to angiotensin-converting enzyme 2 (ACE-2) and thus, infected patients may develop mild to severe inflammatory responses and acute lung injury. Afferent impulses that result from the stimulation of pulmonary mechano-chemoreceptors, peripheral and central chemoreceptors by inflammatory cytokines are conducted to the brainstem. Integration and processing of these input signals occur within the central nervous system, especially in the limbic system and sensorimotor cortex, and importantly feedback regulation exists between O_2, CO_2, and blood pH. Despite the intensity of hypoxemia in COVID-19, the intensity of dyspnea sensation is inappropriate to the degree of hypoxemia in some patients (silent hypoxemia). We hypothesize that SARS-CoV-2 may cause neuronal damage in the corticolimbic network and subsequently alter the perception of dyspnea and the control of respiration. SARS-CoV-2 neuronal infection may change the secretion of numerous endogenous neuropeptides or neurotransmitters that distribute through large areas of the nervous system to produce cellular and perceptual effects. SARS-CoV-2 mainly enter to CNS via direct (neuronal and hematologic route) and indirect route. We theorize that SARS-CoV-2 infection-induced neuronal cell damage and may change the balance of endogenous neuropeptides or neurotransmitters that distribute through large areas of the nervous system to produce cellular and perceptual effects. Thus, SARS-CoV-2-associated neuronal damage may influence the control of respiration by interacting in neuromodulation. This would open up possible lines of study for the progress in the central mechanism of COVID-19-induced hypoxia. Future research is desirable to confirm or disprove such a hypothesis.



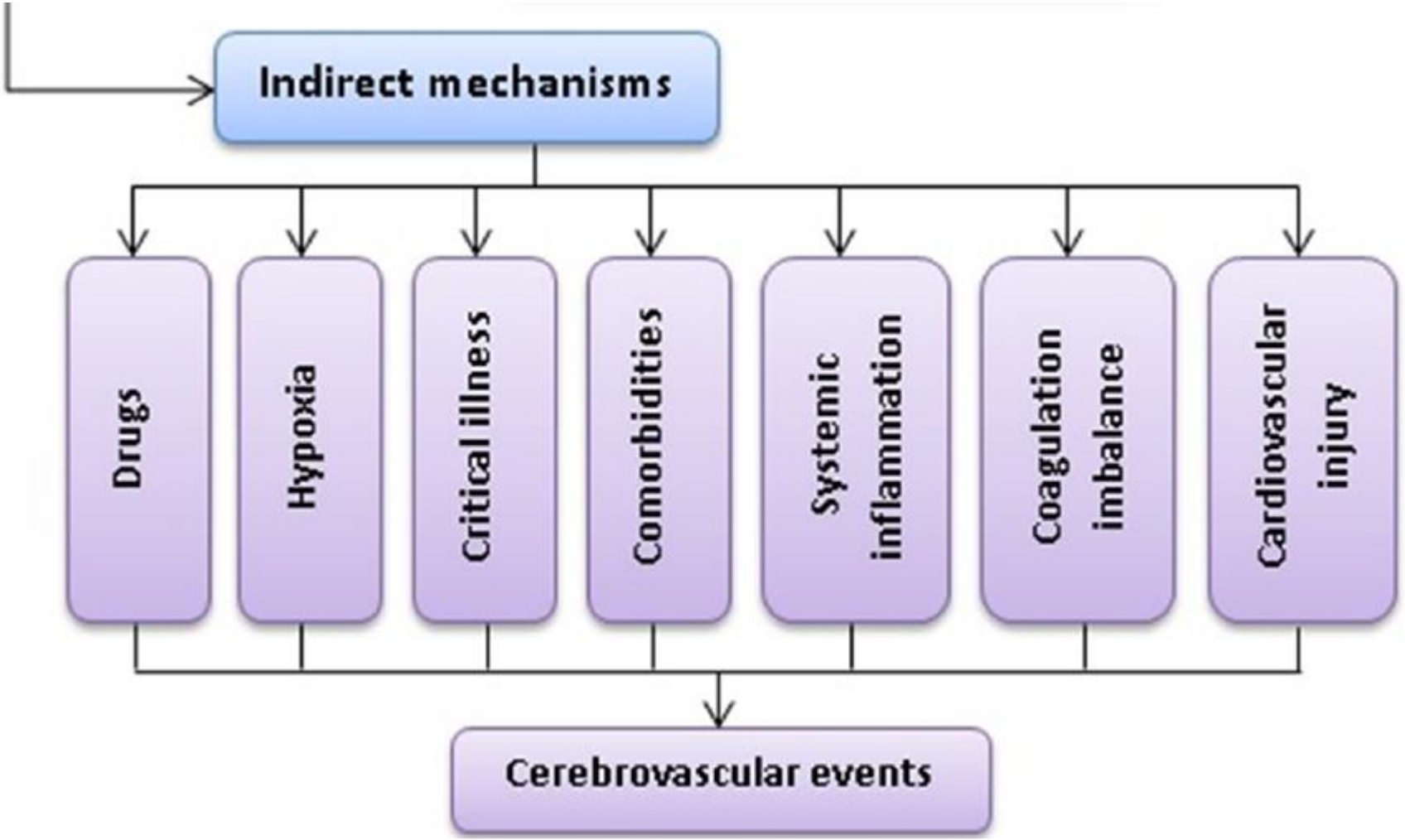
Clinical Neurology and Neurosurgery 198 (2020) 106217

Fig. 2. Potential mechanisms of central nervous system involvement by SARS-CoV-2.

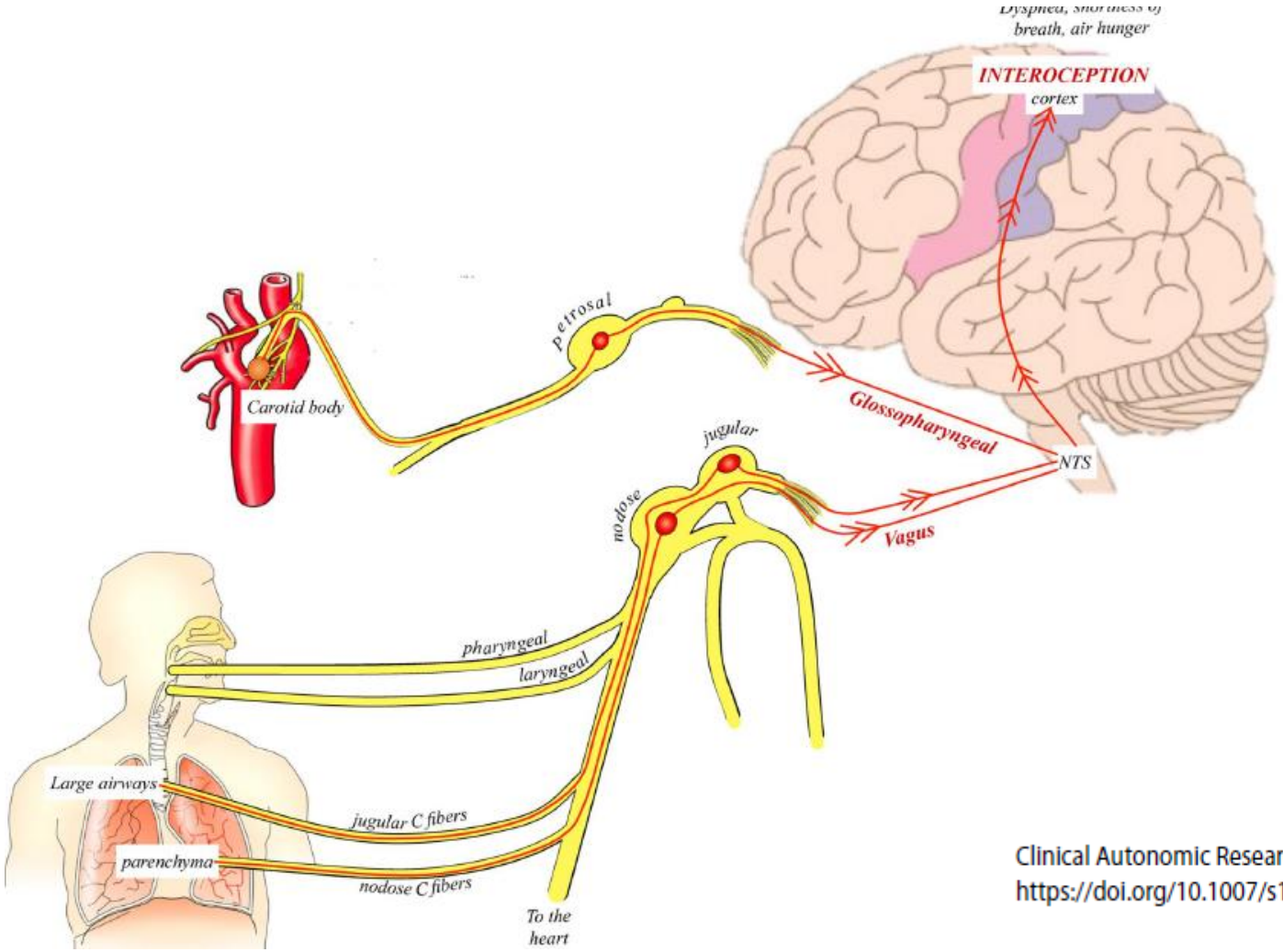


Clinical Neurology and Neurosurgery 198 (2020) 106217

Fig. 2. Potential mechanisms of central nervous system involvement by SARS-CoV-2.



Is 'happy hypoxia' in COVID-19 a disorder of autonomic interoception? A hypothesis



Clinical Autonomic Research
https://doi.org/10.1007/s10286-020-00715-z

Fig. 1 Neurophysiology of dyspnea. Main afferent (sensory) homeostatic information arising from areas of the vasculature and lungs give rise to the sensation of dyspnea. When stimulated, the chemoreceptive and mechanoreceptive signals are transmitted to the brainstem via the glossopharyngeal and vagus nerves, converging at the nucleus of the tractus solitarus (*NTS*). Subsequent projections continue to the somatosensory cortex and other higher brain regions, which provide the interoceptive sense of the internal environment of the body. The processing of these signals within the cortex gives rise to sensations such as air hunger, dyspnea, or shortness of breath. This interceptive processing appears to be abnormally blunted in patients with coronavirus disease 2019

Relevance of carotid bodies in COVID-19: A hypothetical viewpoint

A B S T R A C T

We have considered some of the available evidence to account for the impact of SARS-CoV on the regulatory control of the autonomic nervous and respiratory systems. Apart from stimulating general interest in the subject, our hope was to provide putative explanations for some of the patients' symptoms based on described physiological and pathophysiological mechanisms seen in other diseases. Herein, we have focused on the carotid bodies. In this hypothetical viewpoint, we have discussed the plasticity of the carotid body chemoreflex and made a comparison between acute and chronic exposures to high altitude with COVID-19. From these discussions, we have postulated that the sensitivity of the hypoxic ventilatory response may well determine the outcome of disease severity and those that live at high altitude may be more resistant. We have provided insight into silent hypoxia and attempted to explain an absence of ventilatory drive and anxiety yet maintenance of consciousness. In an attempt to discover more about the mysteries of COVID-19, we conclude with questions and some hypothetical studies that may answer them.

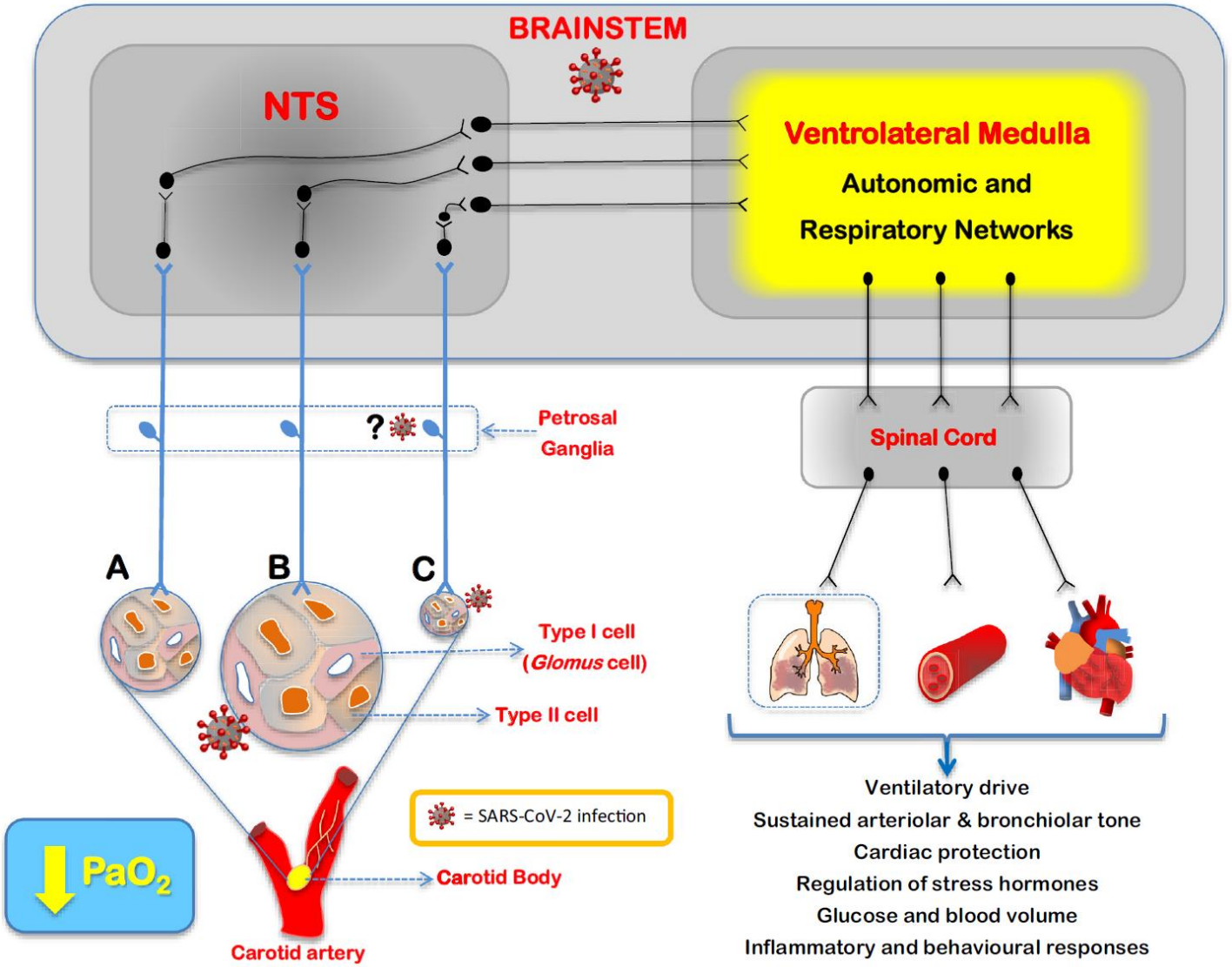


Fig. 1. Schematic drawing of the peripheral chemoreflex pathways in the brainstem and representing the different profile of carotid body in COVID-19 patients: Carotid Body A) in the majority of patients the carotid body reflex responds very well to the hypoxic challenge and the glomus cells are not infected by SARS-CoV-2; Carotid Body B) in a small percentage of patients the carotid bodies may be overactive even before the SARS-CoV-2 infection or became overactive as consequence of the acute phase of the infection; and Carotid Body C) in a smaller percentage of the population the carotid bodies are de-sensitised or non functional even before the SARS-CoV-2 infection or glomus cells were killed after the infection (Villadiego et al., 2021). We also acknowledge infection of SARS-CoV-2 in the brainstem (Bulfamante et al., 2020) and because of the loss of taste (ageusia), we cannot rule out within the petrosal ganglion (e.g. Gautier and Ravussin, 2020); both these loci could affect chemoreflex function.

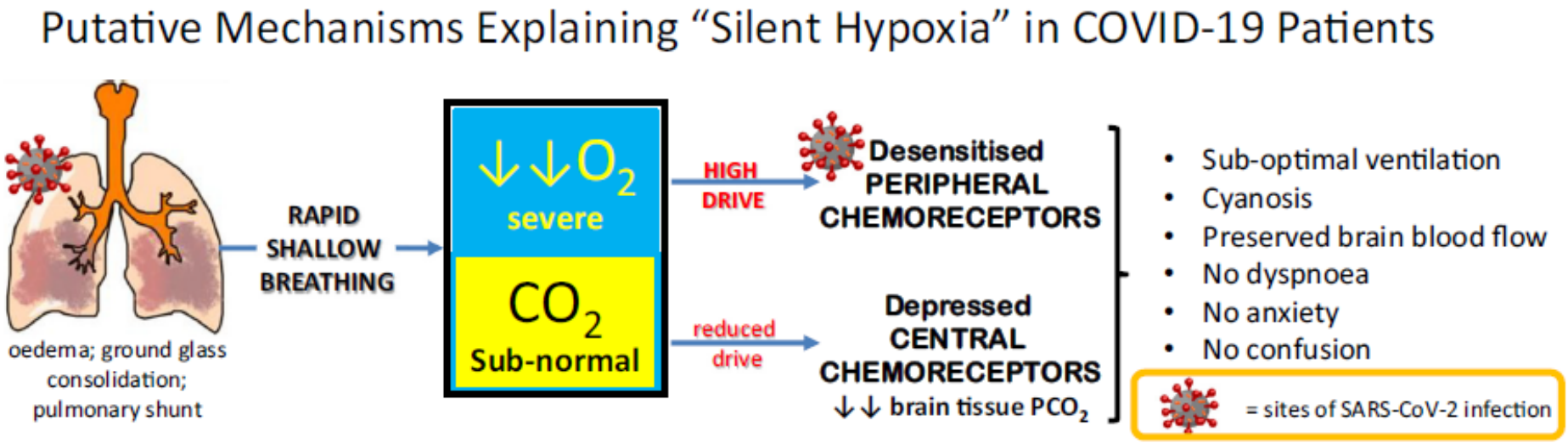


Fig. 2. Schematic to summarise the interactions of respiratory blood gases and chemoreceptor (peripheral and central) ventilatory drive in the condition of COVID-19 induced silent hypoxia. For details see text. Note, the recent finding of Lambermont et al. (2021) is consistent with infection of the carotid body itself via ACE2, which expression is high in the carotid body of humans (Villadiego et al., 2021).

"Acute Vascular Distress Syndrome, AVDS" in COVID-19

- Hypocapnic hypoxia without dyspnea: **R-to-L intrapulmonary shunt**
  - SARS-CoV-2 induce vascular proliferation in the lungs in anatomic and radiologic studies
  - R-to-L shunt by contrast echo without CXR lesions
- R-to-L shunt will induce hypoxia >> a normal increase in ventilation. However, in face of a shunt, hyperventilation will not increase PaO2 but will decrease PaCO2, with CO2 being more diffusible than O2.
  - Hypocapnia develop and abolish increasing ventilation and explaining the absence of respiratory efforts and dyspnea.
- When lungs show GGO/consolidations, hypoxia could worsen but hypocapnia would lessen, with the consequent normalization of PaCO2 and the appearance of feelings of dyspnea

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The Pathophysiology and Dangers of Silent Hypoxemia in COVID-19 Lung Injury

Table 1. Purported mechanistic explanations for silent hypoxemia and associated reported findings in COVID-19 lung injury and non-COVID-19 ARDS.

	COVID-19 Lung Injury	Non-COVID-19 ARDS
Vascular regulation		
Proposed	Vasoplegia and HPV impaired	Intact vascular responsiveness
Observed	• Vascular imaging demonstrates vascular engorgement and increased perfusion in areas of diseased lung [21, 26] • Lung vasculature expresses ACE-2 [52] • Benefit from almitrine and inhaled pulmonary vasodilators argues against global vasoplegia [59, 77] • Mildly elevated PA pressure, by echocardiography and PA catheterization [44-46] • No direct evidence of HPV impairment	• Hypoxemia in ARDS is responsive to almitrine, inhaled pulmonary vasodilators; worsened by systemic vasodilators [57, 58] • Mildly elevated PA pressure and PVR, by PA catheterization [47, 48] • Direct evidence of HPV responsiveness [54]
Conclusion	Very limited data, with need for more investigation due to ACE-2 expression in the pulmonary endothelium and arterial smooth muscle.	
Lung compliance		
Proposed	Compliance minimally reduced	Compliance greatly reduced
Observed	• C_{ST} range: 20-90 ml/cmH_2O in newly intubated patients [2, 4, 23, 24]	• C_{ST} range: 10-78 ml/cmH_2O [32, 33]
Conclusion	Minimal and clinically non-significant differences in observed values, especially given wide range of compliance seen in non-COVID-19 ARDS.	

ANNALSATS Articles in Press. Published February 23, 2021 as 10.1513/AnnalsATS.202011-1376CME

Neural oxygen sensing and dyspnea perception		
Proposed	Impaired central and peripheral O_2 sensing and dyspnea perception secondary to direct viral effects	Preserved O_2 sensing at both peripheral and central chemoreceptors and intact dyspnea perception
Observed	• Viral access in brainstem and cortex in humans [68] • Viral brainstem access in animals [67] • Carotid body & brain express ACE-2 [65, 66] • 9-34% patients with no reported dyspnea [1, 2, 4]	• 0-27% patients with no reported dyspnea in SARS and H1N1 influenza ARDS [11-14] • No direct HVR testing performed
Conclusion	Very limited data, with need for more investigation due to ACE-2 expression in the brain and chemoreceptors and documented viral presence in these sites.	

ARDS: acute respiratory distress syndrome, HPV: hypoxic pulmonary vasoconstriction, ACE-2: angiotensin-converting enzyme 2, PA: pulmonary artery, PVR: pulmonary vascular resistance, C_{ST}: static compliance, HVR: hypoxic ventilatory response, ALI: acute lung injury, SARS; severe acute respiratory syndrome.

The olfactory nerve is not a likely route to brain infection in COVID-19: a critical review of data from humans and animal models

Abstract

One of the most frequent symptoms of COVID-19 is the loss of smell and taste. Based on the lack of expression of the virus entry proteins in olfactory receptor neurons, it was originally assumed that the new coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) does not infect olfactory neurons. Recent studies have reported otherwise, opening the possibility that the virus can directly infect the brain by traveling along the olfactory nerve. Multiple animal models have been employed to assess mechanisms and routes of brain infection of SARS-CoV-2, often with conflicting results. We here review the current evidence for an olfactory route to brain infection and conclude that the case for infection of olfactory neurons is weak, based on animal and human studies. Consistent brain infection after SARS-CoV-2 inoculation in mouse models is only seen when the virus entry proteins are expressed abnormally, and the timeline and progression of rare neuro-invasion in these and in other animal models points to alternative routes to the brain, other than along the olfactory projections. COVID-19 patients can be assured that loss of smell does not necessarily mean that the SARS-CoV-2 virus has gained access to and has infected their brains.

Acta Neuropathologica (2021) 141:809–822

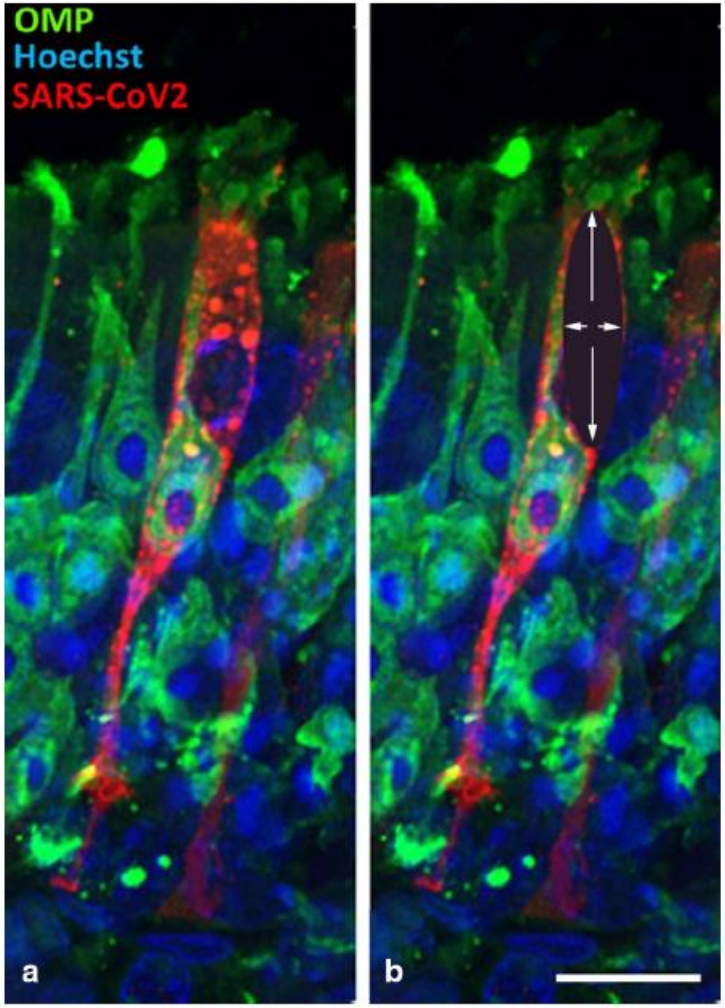


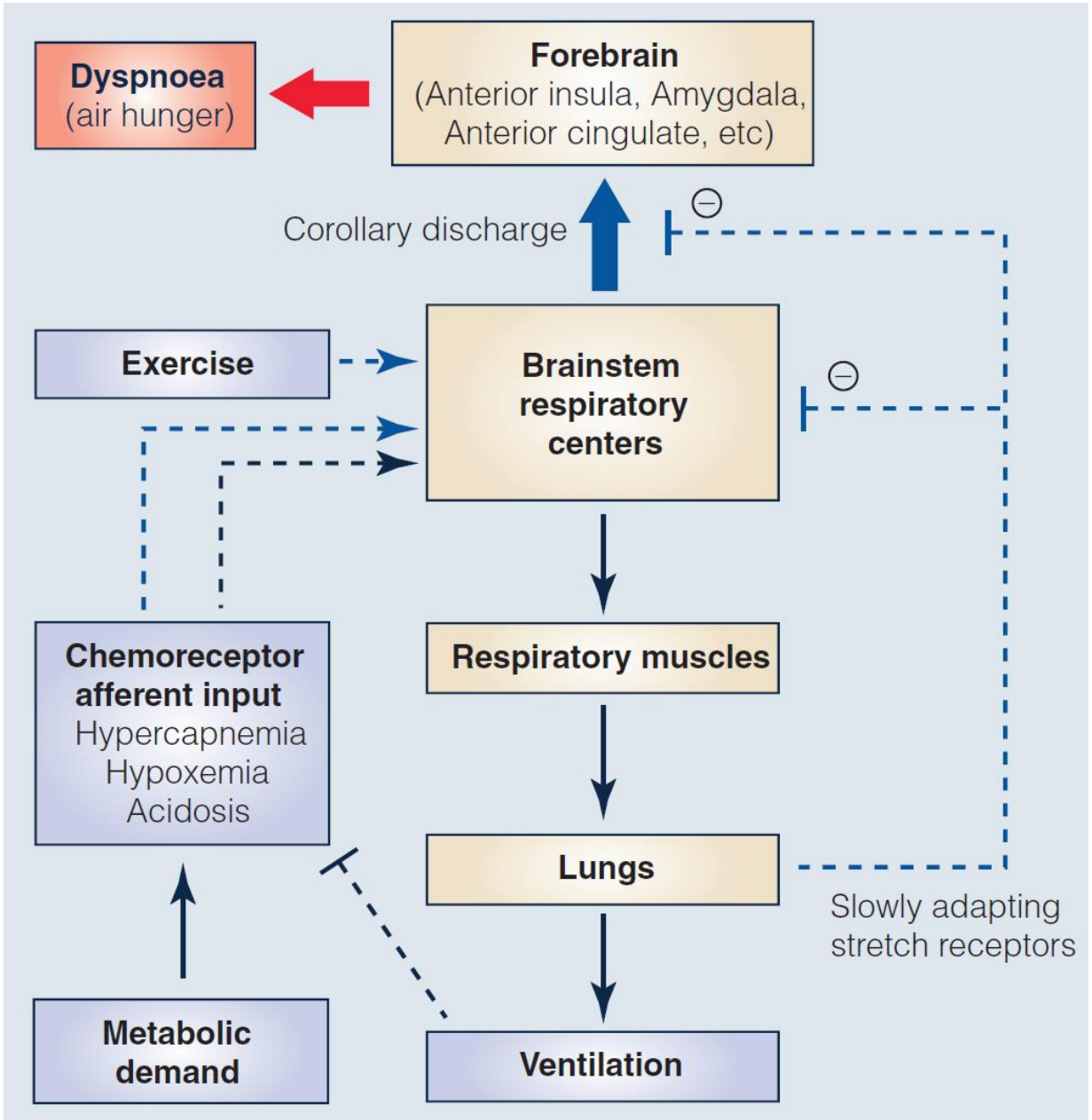
Fig. 1 SARS-CoV-2 nucleocapsid protein (red) immunolabeled in the olfactory epithelium, double-labeled for olfactory marker protein (OMP, green) and stained with Hoechst nuclear stain (blue). **a** The SARS-CoV-2 (red) is present in a sustentacular cell that partially overlaps with an OMP-labeled olfactory receptor neuron. **b** When in the same image the sustentacular cell body is invisible (black ellipsoid shadow with white arrows), as it would be when the plane of section is not entirely perpendicular to the epithelium, then the SARS-CoV-2 protein would be erroneously interpreted to be co-localized within the OMP-expressing olfactory receptor neuron. Scale bar = 10 µm. Image is adapted from Bryche et al. [15]

Animal Models and Humans: Nasal Infection with SARS-CoV-2	Probability of Brain Infection
"older" hACE2 mouse models	VERY HIGH
"newer" hACE2 mouse models	LOW
non-transgenic animal models	VERY LOW
human patients	VERY LOW – LOW (?)

Fig. 2 Probability of brain infection after nasal inoculation in animal models or in SARS-CoV-2 infected patients. Note that the probability of brain infection in humans resembles that in non-transgenic animal models and in the newer human ACE2 (hACE2) mouse models, but not the infection probability in the older transgenic mouse models that use the K18 cytokeratin promoter

Acta Neuropathologica (2021) 141:809–822

Silent hypoxaemia in COVID-19 patients



J Physiol 599.4 (2021) pp 1057–1065

Why COVID-19 Silent Hypoxemia Is Baffling to Physicians

Martin J. Tobin, Franco Laghi, and Amal Jubran

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- **Silent hypoxemia: Idiosyncratic action on receptors involved in chemosensitivity to oxygen**
- These mechanisms include:
  - **The way dyspnea and the respiratory centers respond to low levels of oxygen**
  - **The way the prevailing PaCO2 blunts the brain's response to hypoxia**
  - **Effects of Disease and Age on control of breathing**
  - **Inaccuracy of pulse oximetry at low oxygen saturations**
  - **Temperature-induced shifts in the oxygen dissociation curve**

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- 臨床表現
- 致病機轉
- 預後
- 預防與處置
- 總結

Asymptomatic hypoxia in COVID-19 is associated with poor outcome

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Objectives: Describe and evaluate the outcome of a coronavirus disease-2019 (COVID-19) patient without shortness of breath.
Design and methods: We retrospectively collected data from COVID-19 patients diagnosed and cared for in Marseille, France. We selected data from patients who at admission, had a low dose CT scanner, dyspnea status, and oxygen saturation available. Blood gas was analyzed in a sample subset of patients.
Results: Among 1712 patients with COVID-19, we report that 1107 (64.7%) do not complain of shortness of breath at admission. The low-dose computed tomography (LDCT) scan showed signs compatible with pneumonia in 757/1,107 (68.4%) of patients without dyspnea. In a subset of patients who had underwent at least one blood gas analysis (n = 161) and presented without dyspnea at admission, 28.1% (27/96) presented with a hypoxemia/hypocapnia syndrome. Asymptomatic hypoxia was associated with a very poor outcome (33.3% were transferred to the ICU and 25.9% died).
Conclusion: The absence of shortness of breath in an old patient with comorbidity merit medical attention and should not be considered as a good sign of well-being. The poor prognosis of asymptomatic hypoxia, highlight the severity of this mild clinical presentation. In these patients, pulse oximetry is an important mean to predict the outcome along with news score and LDCT scanner.

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Table 1
Clinical characteristics of patients according to dyspnea status (n = 1,712).

	No dyspnea[a] (n = 1107, 65%)		Dyspnea[a] (n = 605, 35%)		p-value[b]	All (n = 1712)	
	n	%	n	%		n	%
Sex							
Men	529	47.8	257	42.5	0.035	786	45.9
Age at inclusion							
<45 y.o	361	32.6	203	33.6	0.314	564	32.9
45–54 y.o	273	24.7	157	26.0		430	25.1
55–64 y.o	239	21.6	143	23.6		382	22.3
65–74 y.o	122	11.0	53	8.8		175	10.2
≥75 y.o	112	10.1	49	8.1		161	9.4
Time from symptom onset to admission							
<3 days (or no symptom)	234	21.1	59	9.8	<0.001	293	17.1
3–5 days	324	29.3	177	29.3		501	29.3
>5 days	549	49.6	369	61.0		918	53.6
Risk factors							
Hypertension	248	22.4	135	22.3	0.966	383	22.4
Diabetes mellitus	152	13.7	73	12.1	0.330	225	13.1
Cancer	66	6.0	30	5.0	0.388	96	5.6
Chronic respiratory disease	116	10.5	93	15.4	0.003	209	12.2
Chronic heart diseases	109	9.8	37	6.1	0.008	146	8.5
Obesity	164	14.8	112	18.5	0.047	276	16.1
Clinical symptoms							
Fever	179	16.2	126	20.8	0.016	305	17.8
Cough	553	50.0	400	66.1	<0.001	953	55.7
Anosmia	350	31.6	258	42.6	<0.001	608	35.5
Ageusia	354	32.0	265	43.8	<0.001	619	36.2
NEWS score							
0–4	991	89.5	502	83.0	<0.001	1493	87.2
5–6	76	6.9	43	7.1		119	7.0
>6	40	3.6	60	9.9		100	5.8
Clinical outcomes							
Death	11	1.0	16	2.6	0.009	27	1.6
Transfer to intensive care unit	16	1.4	31	5.1	<0.001	47	2.7
Transfer to intensive care unit and/or death	23	2.1	44	7.3	<0.001	67	3.9

No dyspnea

Table 4
Clinical characteristics of patients according to hypoxemia/hypocapnia syndrome (n = 161).

	Hypoxemia/ hypocapnia (n = 49, 30%)		Hypoxemia/ hypercapnia (n = 53, 33%)		Hyperxemia/ hypocapnia (n = 35, 22%)		Hyperxemia/ hypercapnia (n = 24, 15%)		All (n = 161)	
	n	%	n	%	n	%	n	%	n	%
Sex										
Men	39	79.6*	27	50.9	13	37.1*	11	45.8	90	55.9
Age at inclusion										
<45 y.o	2	4.1*	24	45.3*	12	34.3*	7	29.2	45	28.0
45–54 y.o	3	6.1	5	9.4	6	17.1	6	25	20	12.4
55–64 y.o	13	26.5	8	15.1	11	31.4	3	12.5	35	21.7
65–74 y.o	9	18.4	5	9.4	4	11.4	4	16.7	22	13.7
≥75 y.o	22	44.9	11	20.8	2	5.7	4	16.7	39	24.2
Time from symptom onset to admission										
<3 days (or no symptom)										
3–5 days										
>5 days										
Risk factors										
Hypertension										
Clinical outcomes										
Death	10	20.4*	3	5.7	2	5.7	2	8.3	17	10.6
Transfer to intensive care unit	21	42.9*	6	11.3*	7	20.0	4	16.7	38	23.6
Transfer to intensive care unit and/or death	26	53.1*	9	17.0*	8	22.9	6	25	49	30.4
Fever	13	26.5	11	20.8	10	28.6	7	29.2	41	25.5
Cough	28	57.1	27	50.9	24	68.6	14	58.3	93	57.8
Dyspnea	22	44.9	19	35.8	18	51.4	6	25.0	65	40.4
Anosmia	8	16.3	14	26.4	13	37.1	5	20.8	40	24.8
Aguesia	12	24.5	11	20.8	13	37.1	5	20.8	41	25.5
NEWS score										
0–4	8	16.3	39	73.6	22	62.9	14	58.3	83	51.6
5–6	14	28.6	6	11.3	7	20.0	3	12.5	30	18.6
>6	27	55.1	8	15.1	6	17.1	7	29.2	48	29.8
Clinical outcomes										
Death	10	20.4*	3	5.7	2	5.7	2	8.3	17	10.6
Transfer to intensive care unit	21	42.9*	6	11.3*	7	20.0	4	16.7	38	23.6
Transfer to intensive care unit and/or death	26	53.1*	9	17.0*	8	22.9	6	25	49	30.4

* $p < 0.05$ Fisher's exact test (

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Prevalence and outcome of silent hypoxemia in COVID-19

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BACKGROUND: In the early stages of COVID-19 pneumonia, hypoxemia has been described in absence of dyspnea ("silent" or "happy" hypoxemia). Our aim was to report its prevalence and outcome in a series of hypoxemic patients upon Emergency Department admission.

METHODS: In this retrospective observational cohort study we enrolled a study population consisting of 213 COVID-19 patients with PaO_2/FiO_2 ratio <300 mmHg at hospital admission. Two groups (silent and dyspneic hypoxemia) were defined. Symptoms, blood gas analysis, chest X-ray (CXR) severity, need for intensive care and outcome were recorded.

RESULTS: Silent hypoxemic patients (68-31.9%) compared to the dyspneic hypoxemic patients (145-68.1%) showed greater frequency of extra respiratory symptoms (myalgia, diarrhea and nausea) and lower plasmatic LDH. PaO_2/FiO_2 ratio was 225±68 mmHg and 192±78 mmHg in silent and dyspneic hypoxemia respectively (P=0.002). Eighteen percent of the patients with PaO_2/FiO_2 from 50 to 150 mmHg presented silent hypoxemia. Silent and dyspneic hypoxemic patients had similar $PaCO_2$ (34.2±6.8 mmHg *vs.* 33.5±5.7 mmHg, P=0.47) but different respiratory rates (24.6±5.9 bpm *vs.* 28.6±11.3 bpm respectively, P=0.002). Even when CXR was severely abnormal, 25% of the population was silent hypoxemic. Twenty-six point five percent and 38.6% of silent and dyspneic patients were admitted to the ICU respectively (P=0.082). Mortality rate was 17.6% and 29.7% (log-rank P=0.083) in silent and dyspneic patients.

CONCLUSIONS: Silent hypoxemia is remarkably present in COVID-19. The presence of dyspnea is associated with a more severe clinical condition.

Minerva Anestesiologica 2021 March;87(3):325-33

TABLE II.—*Gas exchange variables upon admission.*

Gas exchange	Overall (N.=213)	Silent hypoxemia (N.=68)	Dyspneic hypoxemia (N.=145)	P value
FiO_2	0.24 [0.21-0.60]	0.21 [0.21-0.41]	0.28 [0.21-0.60]	0.003*
PaO_2 (mmHg)	68.9±29.4	65.9±23.0	70.4±31.9	0.24
PaO_2/FiO_2 (mmHg)	202±76	225±68	192±78	0.002*
A-aO2	183±167	137±141	206±174	0.003*
$SatO_2$ (%)	91.8±7.3	91.9±6.4	91.8±7.68	0.97
$PaCO_2$ (mmHg)	34.0±6.5	34.2±6.8	33.5±5.7	0.47
Respiratory rate (bpm)	27.3±10.1	24.6±5.9	28.6±11.3	0.002*
pH	7.46±0.06	7.46±0.05	7.46±0.06	0.76
CXR severity	3 [2-5]	3 [2-4]	3 [2-5]	0.11
ROX Index	11.7 [6.1-17.7]	15.7 [9.4-19.5]	9.0 [5.0-15.7]	<0.001

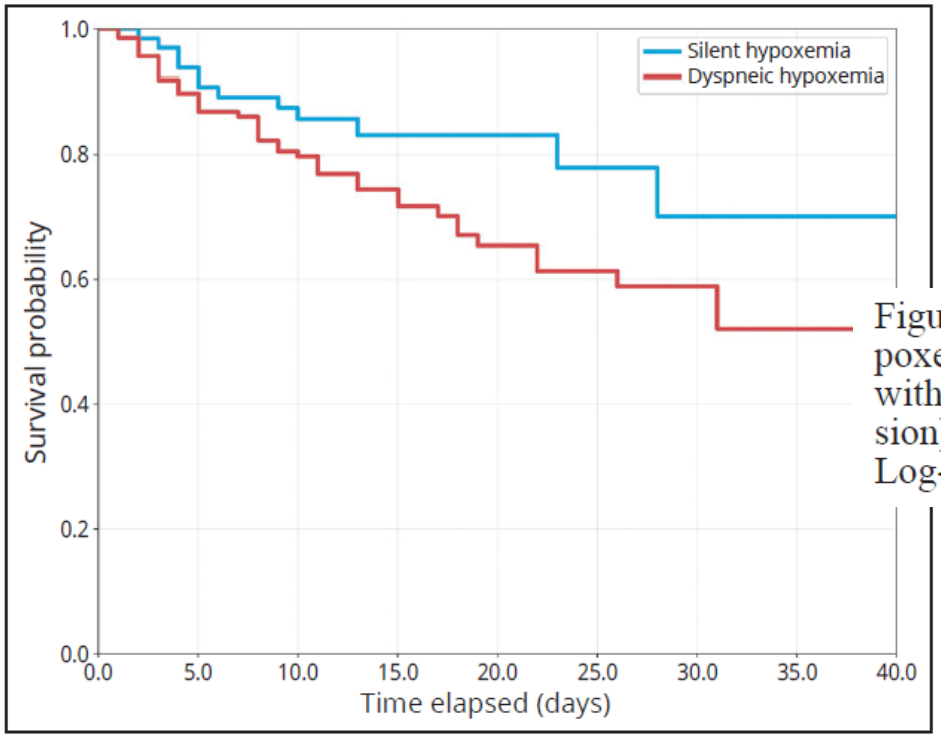

Figure 3.—Survival probability of patients with silent hypoxemia (light grey; blue in the online version) and patients with dyspneic hypoxemia (dark grey; red in the online version).
Log-rank test P value =0.083.

Conclusions

- Around 30% of the hypoxic patients (P/F <300) coming to ER due to COVID infection did not complain dyspnea
- The silent hypoxemic patients were characterized by a higher incidence of extra-pulmonary symptoms (mainly nausea and diarrhea) and , they were less severe than the dyspneic patients
- We speculate that the presence of dyspnea reflects the incipient development of edema within the lung and should be considered an unfavorable symptom that could trigger the decision to escalate the respiratory support in COVID

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(1) 英國虛擬病房

- 英國虛擬病房研究計劃「CO@h」（COVID Oximetry @home，新冠肺炎在家監測）
- 「虛擬病房」就是將輕症患者分流在家隔離，並搭配血氧儀監測其血氧濃度，病況惡化才即時送院。
- 「CO@h」計劃只要求患者每天使用脈搏血氧儀測量血氧飽和度3次，無論是用專門的智慧型手機應用程式、網站，或是紙筆，都可以記錄結果。
- 當血氧下降到93%或94%，病患就應該通知醫師。如果監測到低於92%的結果，應該立即叫救護車，在一小時內到院治療。

Pulse Oximeter (脈衝式血氧機)

- 夾在手指上，透過指甲床內紅血球對於紅外線及紅光的吸收差異來計算血氧濃度，只要指甲乾淨、沒有塗指甲油、指尖溫暖，是數值滿準確的非侵入性檢查，還可連續性偵測血氧。

血氧濃度監測建議

血氧濃度	5天內死亡率	建議
95%~100%	1.67%	正常
93%~94%	2.24%	尋求支援
92%以下	14.33%	1小時內就醫

資料來源：NHS England covid safety netting guidance

「虛擬病房」計劃，讓死亡率、住院時間大降

	無實施虛擬病房	有實施虛擬病房
平均住院天數	13.2天	6.9天
30天內死亡率	20.5%	5.8%
加護病房入住率	8.2%	3.6%
30天內再入院率	8.7%	0%

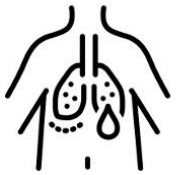
註：2020年11月至2021年3月間，英國有無實施「虛擬病房」計劃之地區比較

資料來源：〈COVID Oximetry @home: evaluation of patient outcomes〉

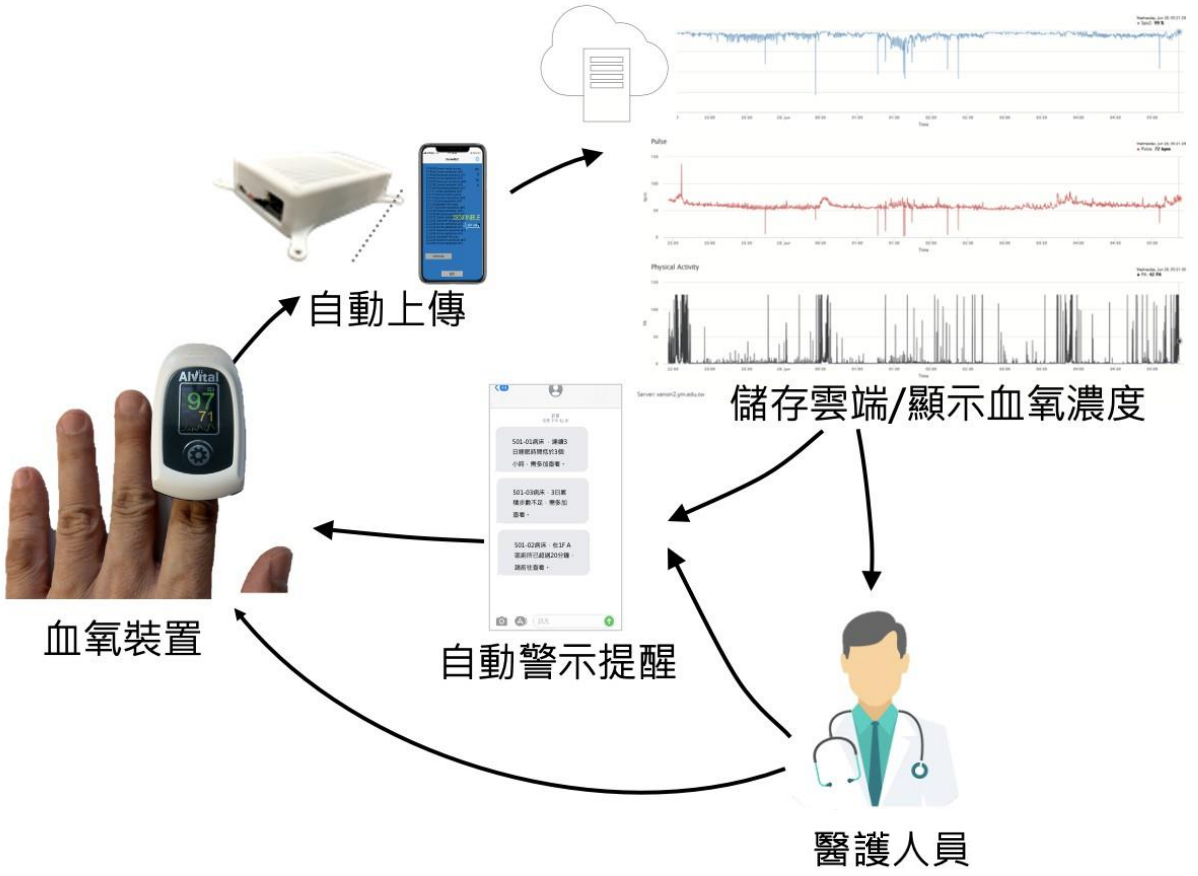
血氧濃度
自動連續監測系統

解決未滿足需求

預警生命危險



預警無症狀缺氧

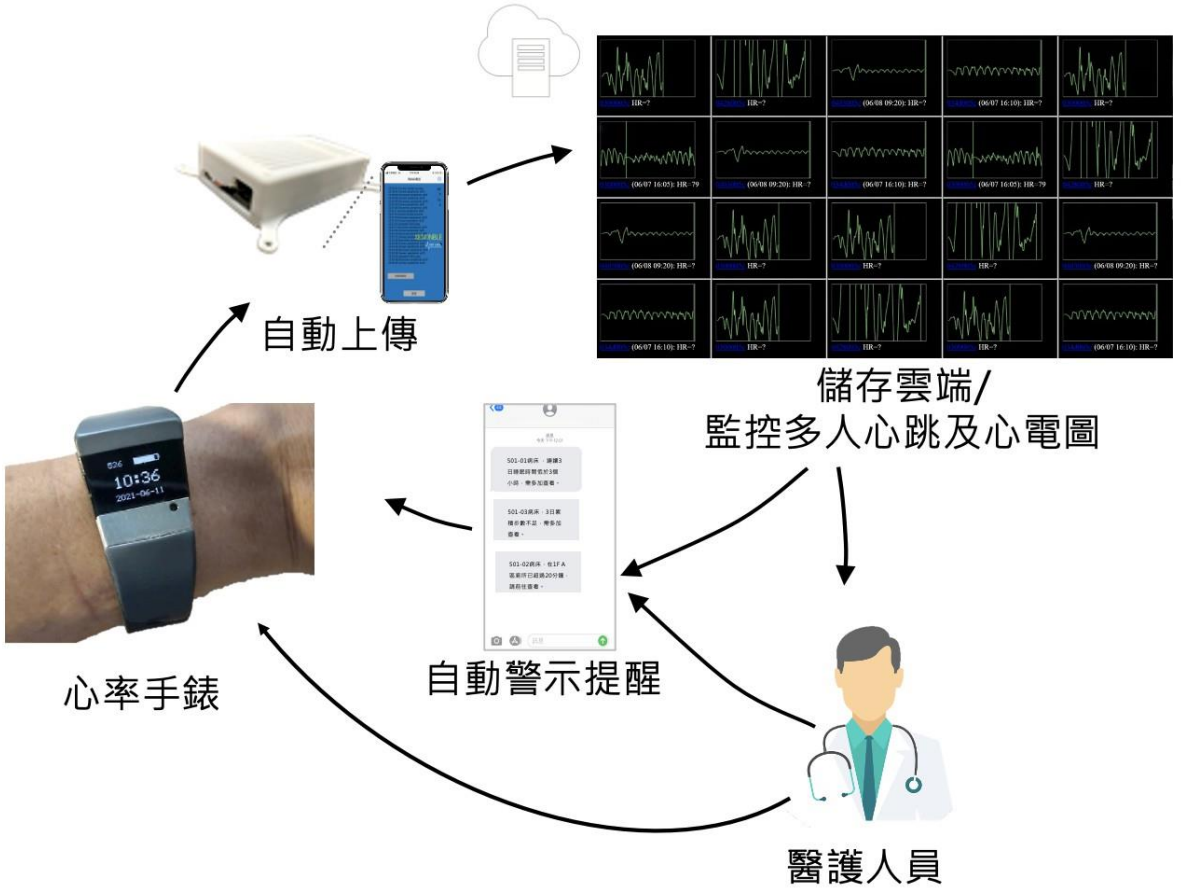


生命跡象
自動連續監測系統

解決未滿足需求

預警生命危險

24小時監控



(2) 現在的台灣

- 於社區，找出潛在的已被感染者
  - 廣設篩檢站
- 於檢疫所/檢疫旅館，及早發現隱形缺氧與及時偵測惡化
  - 轉送至醫院治療
- 於醫院，中重度及危急症接受適當的治療
  - 專責病房、負壓隔離病房
  - 專責ICU、ICU負壓隔離病房

Dilemma of countering happy hypoxaemia COVID-19 patients

Keigo Kobayashi , Hatsuyo Takaoka, Toshiyuki Hirano, Takashi Inoue

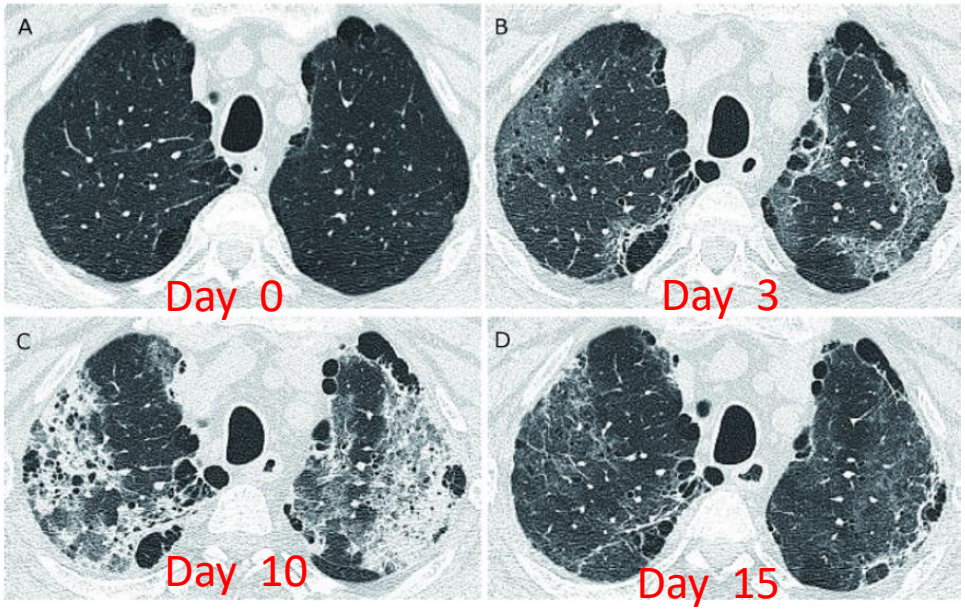


Figure 1 Chest CT images of the upper lobes of the lungs (A) day 0: there is no pneumonitis in upper lobes on admission. (B) day 3: Ground glass opacities have emerged. (C) day 10: the ground grass opacities have progressed to organising pneumonia. (D) day 15: the organising pneumonia has regressed but some ground grass opacities remain.

Learning points

- Happy hypoxaemia is not uncommon among COVID-19 patients.
- Patients with happy hypoxaemia can worsen and recover within a short period.
- It is preferable for some patients with happy hypoxaemia to remain in hospital for monitoring of their response to medication and to ensure the optimal use of oxygen therapy.

The large number of COVID-19 patients is overwhelming hospitals and causing bed shortages. Patients with happy hypoxaemia may request early discharge. However, physicians should be cautious about early discharge of patients with happy hypoxaemia because remaining in hospital enables their therapy to be monitored, and they may make a more rapid recovery.

Kobayashi K, *et al*. *BMJ Case Rep* 2021;**14**:e241588.

(3) Modified 6 minute walking test (Exercise test)

Silent hypoxia in patients with SARS CoV-2 infection before hospital discharge

Objective: To assess the degree of hypoxia and subjective dyspnea elicited by a 6-minute walking test (6MWT) in COVID-19 patients prior to discharge.

Methods: A 6MWT was performed in 26 discharge-ready COVID-19 patients without chronic pulmonary disease or cardiac failure. Heart rate, oxyhemoglobin saturation (SpO_2), respiratory rate, and subjective dyspnea measured on the Borg CR-10 scale were measured before and immediately after the 6MWT, with continuous monitoring of SpO_2 and heart rate during the 6MWT. The 6MWT was terminated if SpO_2 dropped below 90%. A historical cohort of 204 patients with idiopathic pulmonary fibrosis (IPF) was used for comparison.

Results: 13 (50%) of the COVID-19 patients developed exercise-induced hypoxia ($SpO_2 < 90\%$) during the 6MWT, of which one third had pulmonary embolism. COVID-19 patients experienced less hypoxia-related dyspnea during the 6MWT compared with patients with IPF.

Conclusion: The 6MWT is a potential tool in the diagnosis of asymptomatic exercise-induced hypoxia in hospitalized COVID-19 patients prior to discharge. Due to important methodological limitations, further studies are needed to confirm our findings and to investigate their clinical consequences.

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Proposed Modifications in the 6-Minute Walk Test for Potential Application in Patients With Mild COVID-19: A Step to Optimize Triage Guidelines

Table. Proposed Modifications in the 6-Min Walk Test for Potential Application in Patients With Mild COVID-19

Item	Existing[10]	Suggested Modification
Timing	Not applicable	Fourth or fifth day of clinical illness
Additional contraindication specific to the present context	Not applicable	Patients aged ≥70 y or pregnant women
Wearing a surgical mask	Not applicable	Mandatory
Definition of abnormality	Distance walked compared with reference standards[a]	Single cutoff point for distance walked <0.26 mile (<1400 feet)[12b] or Spo_2 falling below 90%
Contraindication	Room air Spo_2 at rest ≤85%	Room air Spo_2 at rest ≤93%
The presence of a physician	Not mandatory	Mandatory[c]
Evaluation of dyspnea and fatigue[d]	Optional	Mandatory
Stoppage of test	Saturation falling below 80%	Saturation falling below 90%
Resumption of test	When saturation improves	Abandon the test and recommend higher level of care

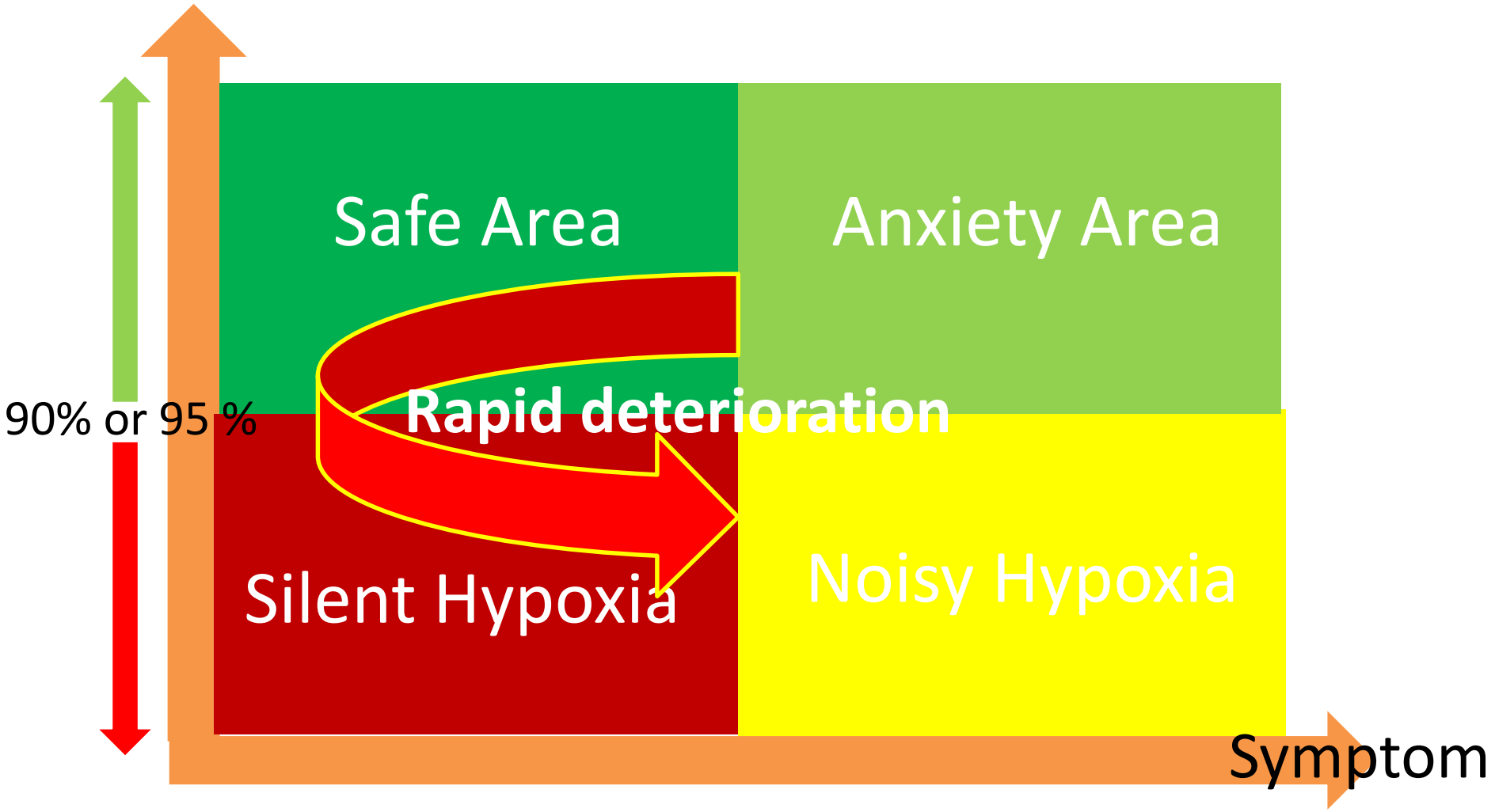
2020 ANESTHESIA & ANALGESIA

總結

Pulse Oximeter（脈衝式血氧機)

- 要準確
  - 尤其在低血氧時

Clinical Spectrum

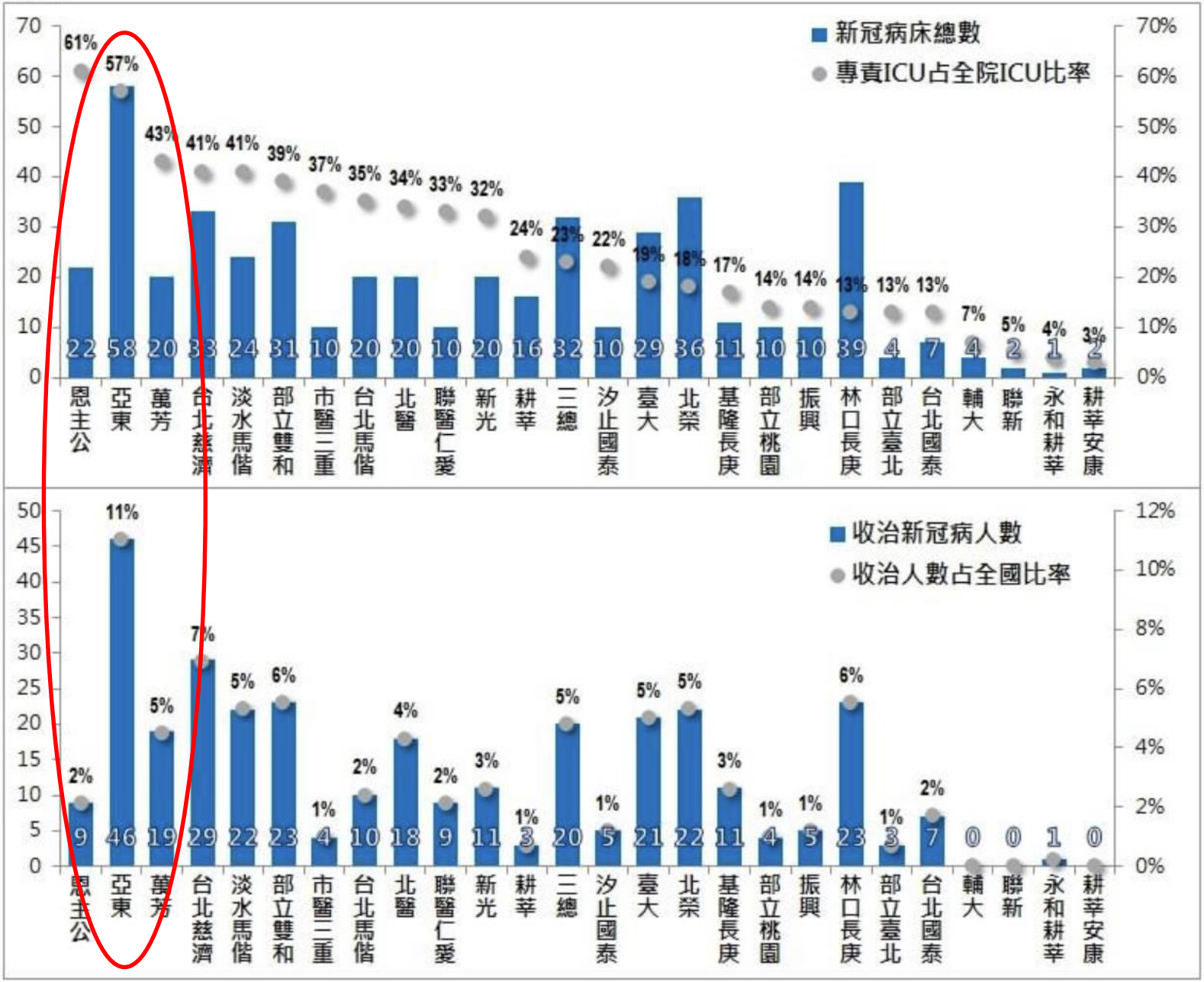


By 高國晉

北北基桃COVID-19 專責ICU統計分析表

截至2021/6/8 18:00

資料來源：緊急醫療管理系統



台灣抗COVID-19第一戰神:
亞東 張厚台醫師

Thank you for your attention !

Q and A