臺北市立聯合醫院
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THE LANCET

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

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THE LANCET

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

本篇重點結論

- 在針對237位病患進行Remdesivir治療的隨機雙盲、安慰劑對照的多中心試驗，結果顯示: (實驗組158人；對照組97人，其中1人退出而未納入ITT)
  - ➢**使用Remdesivir與臨床改善時間的差異無關(HR 1.23 [95%CI 0.87-1.75])**
  - ➢在症狀持續時間為10天或更短的患者中，**接受Remdesivir治療者其臨床改善的時間，要比接受安慰劑治療者快 (HR 1.52 [0.95–2.43])，雖然此差異未達統計顯著**
  - ➢不良事件：
    - ✓ Remdesivir組：155位中有102位(66%)，18位(12%)因此提早停藥
    - ✓ 安慰劑組：78位中有50位(64%)，4位 (5%)因此提早停藥

→對於重度COVID-19的住院成年患者，Remdesivir與臨床受益無統計顯著相關

→較早接受Remdesivir治療者其臨床改善時間的減少需要更大型的研究來證實

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前言

- 雖然大多數SARS-CoV-2感染是自限性的，但約**15%受感染的成年人發展為嚴重肺炎**，需要氧氣治療；另外**5%進展為危急重症**，如：低氧性呼吸衰竭、急性呼吸窘迫症候群、多重器官衰竭而需要呼吸器支持，這些情形通常持續數週
- **在需要mechanical ventilation的COVID-19患者中，至少一半在醫院死亡**，對於幾個受影響的國家來說，其醫療體系尤其是ICU已不堪負荷
- **目前尚無特殊抗的病毒藥物被證實可以有效治療重度COVID-19的患者**

前言

Remdesivir

- 是一種adenosine analogue的monophosphoramidate prodrug
- 具廣泛抗病毒譜： filoviruses, paramyxoviruses, pneumoviruses, coronaviruses
- 在體外可抑制所有至今測得的人類和動物冠狀病毒，包括SARS-CoV-2
- 對SARS-CoV-1和MERS-CoV：感染動物試驗中有抗病毒和臨床作用
- **對SARS-CoV-2：**
  - **在人類的鼻腔和支氣管呼吸道上皮細胞中是病毒複製的有效抑製劑**
  - **在SARS-CoV-2感染的非致死獼猴試驗中，早期給藥發現顯著的抗病毒和臨床作用** (減少肺部浸潤和支氣管肺泡灌洗液中的病毒含量)
  - 雖然一些個案報告顯示可使重症患者受益，但對COVID-19的臨床和抗病毒療效仍有待確定

研究方法

研究設計

- 在中國湖北省10家醫院進行隨機雙盲、安慰劑對照的多中心試驗，評估靜脈注射Remdesivir在重度COVID-19住院成人病患的效用和安全性

受試者

- **納入條件：**
  - 18歲以上COVID-19住院病患(女性未懷孕)
  - SARS-CoV-2 RT-PCR檢測為陽性
  - 胸部影像學檢查確定為肺炎
  - 從症狀發作至加入試驗的時間在12天以內
  - 在一般室內空氣，或動脈血氧分壓與吸入氧氣分率的比值(PaO2/FiO2) ≤ 300 mmHg時，其血氧飽和度≤94%

研究方法

受試者

- **排除條件：**
  - 懷孕或哺乳
  - 肝硬化
  - AST或ALT ≥ 正常上限值5倍
  - 已知嚴重腎功能不全 (eGFR < 30 mL / min per 1.73 m^2)，或接受持續性的腎臟替代治療、血液透析或腹膜透析
  - 有可能在72小時內轉到非試驗醫院
  - 在篩選個案前30天內加入COVID-19的研究性治療試驗
- **使用其他藥物，包括lopinavir–ritonavir, interferons, 和corticosteroids是被允許的**

研究方法

隨機分配

- 受試者以2:1方式隨機分配至Remdesivir組或安慰劑組
- 隨機分配依據呼吸支持的程度分層進行，包括：
  - (1)不需氧氣支持，或需鼻導管或面罩的氧氣支持
  - (2)需高流量氧氣，非侵襲性呼吸器，侵襲性呼吸器或ECMO

試驗步驟

- 受試者接受靜脈注射Remdesivir (第1天200 mg，第2-10天每日一次100 mg)，或相同劑量的安慰劑，共10天
- 由受訓護理師使用日記卡對病患每日進行一次評估，收集第0到28天或死亡時的**six-point ordinal scale** 以及安全性的數據
- 收集其他臨床數據以及安全性評估數據

研究方法

Six-point ordinal scale

- 6=死亡
- 5=住院，需要ECMO或侵襲性呼吸器
- 4=住院，需要高流量氧氣(high-flow nasal canula)或非侵襲性呼吸器
- 3=住院，需要氧氣支持(但不需要高流量氧氣或非侵襲性呼吸器)
- 2=住院，不需要氧氣支持
- 1=出院，或達到出院標準
- 出院標準定義為臨床狀況恢復，包括：**退燒，呼吸速率<24 breaths/min，周邊血氧濃度在一般室內空氣下>94%，以及咳嗽緩解；所有條件均維持至少72小時**

研究方法

結果指標

- **Primary endpoint: 在隨機分配後的28天內達到臨床改善的時間**
  - **臨床改善的定義:** (以先達到者為準)

    (1)在six-point ordinal scale的臨床狀況上減少2 points，或

    (2)能存活並出院

- **Secondary outcomes**:
  - 隨機分配後第7、14和28天，six-point ordinal scale每個類別中患者的比例
  - 第28天的全因死亡率
  - 使用侵襲性呼吸器的頻率
  - 需氧氣治療的時間
  - 住院的時間
  - 院內感染的比例

研究方法

安全性指標

- **Safety outcomes:**
  - 治療後出現的不良事件 (treatment-emergent adverse event, TEAE)
  - 嚴重的不良事件
  - 提早停用試驗藥物

分析方法

- 主要療效分析: 對所有隨機分配的患者，以intention-to-treat為基礎進行分析
- 安全性分析: 對所有開始接受指定治療的患者進行

研究結果

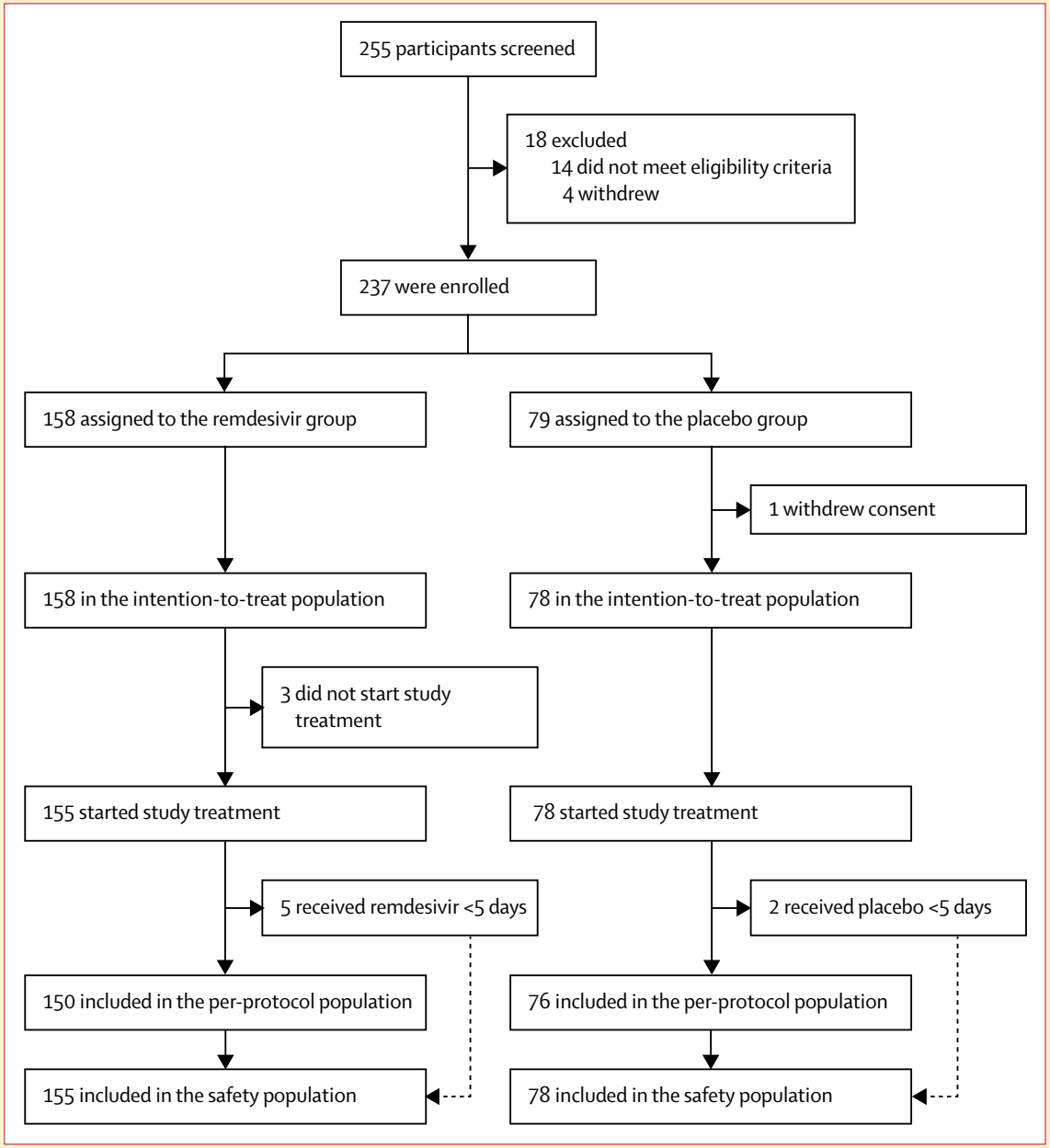


Figure 1: **Trial profile**

- 2020/2/6-3/12間篩選255位患者，其中237位符合納入條件，經隨機分配後
  - Remdesivir組：158位
  - 安慰劑組：79位，其中一名患者在隨機分配後撤回同意書
  - **ITT population包括：Remdesivir組158位，安慰劑組78位**
- Remdesivir組中有3名患者未接受治療，因此未納入安全性分析

研究結果

	Remdesivir group (n=158)	Placebo group (n=78)
Age, years	66·0 (57·0–73·0)	64·0 (53·0–70·0)
Sex		
Men	89 (56%)	51 (65%)
Women	69 (44%)	27 (35%)
Any comorbidities	112 (71%)	55 (71%)
Hypertension	72 (46%)	30 (38%)
Diabetes	40 (25%)	16 (21%)
Coronary heart disease	15 (9%)	2 (3%)
Body temperature, °C	36·8 (36·5–37·2)	36·8 (36·5–37·2)
Fever	56 (35%)	31 (40%)
Respiratory rate >24 breaths per min	36 (23%)	11 (14%)
White blood cell count, ×10⁹ per L		
Median	6·2 (4·4–8·3)	6·4 (4·5–8·3)
4–10	108/155 (70%)	58 (74%)
<4	27/155 (17%)	12 (15%)
>10	20/155 (13%)	8 (10%)
Lymphocyte count, ×10⁹ per L	0·8 (0·6–1·1)	0·7 (0·6–1·2)
≥1·0	49/155 (32%)	23 (29%)
<1·0	106/155 (68%)	55 (71%)
Platelet count, ×10⁹ per L	183·0 (144·0–235·0)	194·5 (141·0–266·0)
≥100	148/155 (95%)	75 (96%)
<100	7/155 (5%)	3 (4%)
Serum creatinine, μmol/L	68·0 (56·0–82·0)	71·3 (56·0–88·7)
≤133	151/154 (98%)	76 (97%)
>133	3/154 (2%)	2 (3%)
Aspartate aminotransferase, U/L	31·0 (22·0–44·0)	33·0 (24·0–48·0)
≤40	109/155 (70%)	49 (63%)
>40	46/155 (30%)	29 (37%)
Alanine aminotransferase, U/L	26·0 (18·0–42·0)	26·0 (20·0–43·0)
≤50	130/155 (84%)	66 (85%)
>50	25/155 (16%)	12 (15%)

Table 1: Baseline patient characteristics

- 年齡中位數：65 (IQR 65-71)
- 性別分布男性：女性
  - 實驗組89(56%):69(44%)
  - 對照組51 (65%):27(35%)
- 最常見合併症：

  (1) HTN (2) DM (3) CAD
- **實驗組比對照組：**
  - **有HTN, DM, CAD的患者較多**
  - **呼吸速>24 breaths/min的患者較多**

研究結果

	Remdesivir group (n=158)	Placebo group (n=78)
Lactate dehydrogenase, U/L	339·0 (247·0–441·5)	329·0 (249·0–411·0)
≤245	36/148 (24%)	17/75 (23%)
>245	112/148 (76%)	58/75 (77%)
Creatine kinase, U/L	75·9 (47·0–131·1)	75·0 (47·0–158·0)
≤185	118/141 (84%)	54/67 (81%)
>185	23/141 (16%)	13/67 (19%)
National Early Warning Score 2 level at day 1	5·0 (3·0–7·0)	4·0 (3·0–6·0)
Six-category scale at day 1		
2—hospital admission, not requiring supplemental oxygen	0	3 (4%)
3—hospital admission, requiring supplemental oxygen	129 (82%)	65 (83%)
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	28 (18%)	9 (12%)
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	0	1 (1%)
6—death	1 (1%)	0
Baseline viral load of nasopharyngeal and oropharyngeal swabs, log_{10} copies per mL	4·7 (0·3)	4·7 (0·4)
Receiving interferon alfa-2b at baseline	29 (18%)	15 (19%)
Receiving lopinavir–ritonavir at baseline	27 (17%)	15 (19%)
Antibiotic treatment at baseline	121 (77%)	63 (81%)
Corticosteroids therapy at baseline	60 (38%)	31 (40%)

Data are median (IQR), n (%), n/N (%), or mean (SE).

Table 1: **Baseline patient characteristics**

- 多數患者在納入研究時，其臨床狀況處於Six-point ordinal scale的3 point
- 在納入研究時，有42位(18%)患者同時使用lopinavir–ritonavir，91位(39%) 患者使用corticosteroids

研究結果

	Remdesivir group (n=158)	Placebo group (n=78)
Time from symptom onset to starting study treatment, days*	11 (9–12)	10 (9–12)
Early (≤10 days from symptom onset)	71/155 (46%)	47 (60%)
Late (>10 days from symptom onset)	84/155 (54%)	31 (40%)
Receiving injection of interferon alfa-2b	46 (29%)	30 (38%)
Receiving lopinavir–ritonavir	44 (28%)	23 (29%)
Vasopressors	25 (16%)	13 (17%)
Renal replacement therapy	3 (2%)	3 (4%)
Highest oxygen therapy support		
Non-invasive mechanical ventilation	14 (9%)	3 (4%)
Invasive mechanical ventilation	11 (7%)	10 (13%)
Extracorporeal membrane oxygenation or mechanical ventilation	2 (1%)	0
Antibiotic	142 (90%)	73 (94%)
Corticosteroids therapy	102 (65%)	53 (68%)
Time from symptom onset to corticosteroids therapy, days	9 (7–11)	8 (6–10)
Duration of corticosteroids therapy, days	9 (5–15)	10 (6–16)

Data are median (IQR) or n (%). *Three patients did not start treatment so are not included in time from symptom onset to start of study treatment subgroup analyses.

Table 2: **Treatments received before and after enrolment**

- 從症狀發作到開始接受治療試驗的中位時間為10天(IQR 9-12)
- 在住院期間，有155名患者(66%)接受corticosteroids治療，從症狀發作到接受corticosteroids治療的中位時間為8.0天(6.0-11.0)
- **從症狀發作到開始接受試驗治療的時間在10天以內者，以對照組的患者較多**

研究結果

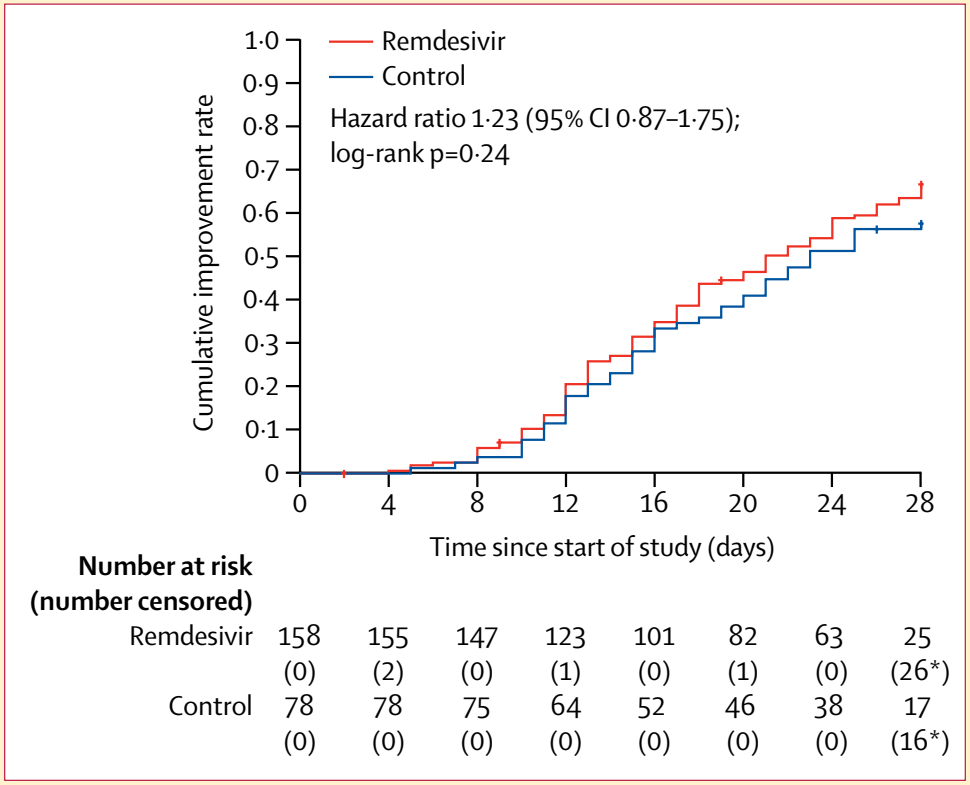


Figure 2: **Time to clinical improvement in the intention-to-treat population**
Adjusted hazard ratio for randomisation stratification was 1·25 (95% CI 0·88–1·78). *Including deaths before day 28 as right censored at day 28, the number of patients without clinical improvement was still included in the number at risk.

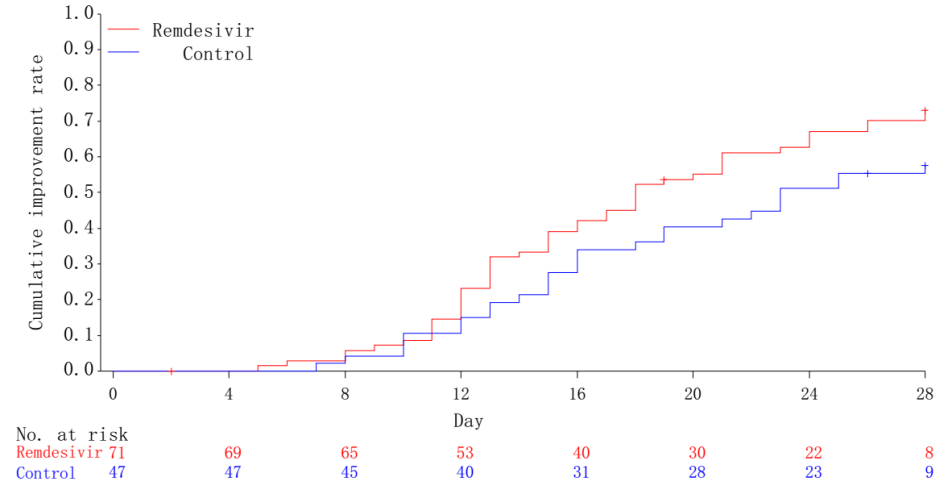
- 最後追蹤日期為2020/4/10
- 在ITT population中:

Remdesivir組的臨床改善時間與對照組無明顯差異

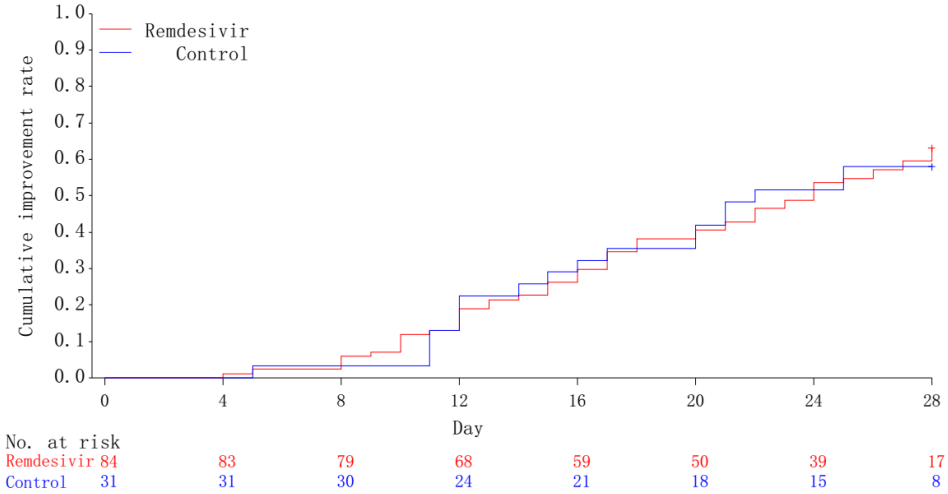
- Remdesivir組中位數: 21.0天[IQR 13.0–28.0]
- 對照組中位數: 23.0天[15.0–28.0]
- HR 1.23 [95%CI 0.87-1.75]

Figure S2. Kaplan Meier plot of time-to-clinical improvement by duration of illness (≤ 10 days [Panel A] vs > 10 days [Panel B]) in the intention-to-treat population.

A



B



Note. (A) In early treatment group (≤ 10 days), median TTCI 18.0 days (remdesivir) vs. 23 days (control); hazard ratio (HR) for clinical improvement, 1.52; 95% confidence interval [CI], 0.95 to 2.43; and (B) in late treatment group (>10 days), median TTCI 23.0 days (remdesivir) vs. 24 days (control); HR for clinical improvement, 1.07; 95% CI, 0.63 to 1.83.

- 在ITT population中，**從症狀發作到開始接受試驗治療的時間在10天以內者，接受Remdesivir治療的患者，其臨床改善的時間較接受安慰劑治療者快，**儘管未達統計顯著(Panel A)
  - ➢Remdesivir組中位數: 18.0天[IQR 12.0–28.0]
  - ➢對照組中位數: 23.0天[15.0–28.0]
  - ➢HR 1.52 [0.95-2.43]

	Remdesivir group (n=158)	Placebo group (n=78)	Difference*
Time to clinical improvement	21·0 (13·0 to 28·0)	23·0 (15·0 to 28·0)	1·23 (0·87 to 1·75)†
Day 28 mortality	22 (14%)	10 (13%)	1·1% (–8·1 to 10·3)
Early (≤10 days of symptom onset)	8/71 (11%)	7/47 (15%)	–3·6% (–16·2 to 8·9)
Late (>10 days of symptom onset)	12/84 (14%)	3/31 (10%)	4·6% (–8·2 to 17·4)
Clinical improvement rates			
Day 7	4 (3%)	2 (3%)	0·0% (–4·3 to 4·2)
Day 14	42 (27%)	18 (23%)	3·5% (–8·1 to 15·1)
Day 28	103 (65%)	45 (58%)	7·5% (–5·7 to 20·7)
Duration of invasive mechanical ventilation, days	7·0 (4·0 to 16·0)	15·5 (6·0 to 21·0)	–4·0 (–14·0 to 2·0)
Duration of invasive mechanical ventilation in survivors, days‡	19·0 (5·0 to 42·0)	42·0 (17·0 to 46·0)	–12·0 (–41·0 to 25·0)
Duration of invasive mechanical ventilation in non-survivors, days‡	7·0 (2·0 to 11·0)	8·0 (5·0 to 16·0)	–2·5 (–11·0 to 3·0)
Duration of oxygen support, days	19·0 (11·0 to 30·0)	21·0 (14·0 to 30·5)	–2·0 (–6·0 to 1·0)
Duration of hospital stay, days	25·0 (16·0 to 38·0)	24·0 (18·0 to 36·0)	0·0 (–4·0 to 4·0)
Time from random group assignment to discharge, days	21·0 (12·0 to 31·0)	21·0 (13·5 to 28·5)	0·0 (–3·0 to 3·0)
Time from random group assignment to death, days	9·5 (6·0 to 18·5)	11·0 (7·0 to 18·0)	–1·0 (–7·0 to 5·0)
Six-category scale at day 7			
1—discharge (alive)	4/154 (3%)	2/77 (3%)	OR 0·69 (0·41 to 1·17)§
2—hospital admission, not requiring supplemental oxygen	21/154 (14%)	16/77 (21%)	..
3—hospital admission, requiring supplemental oxygen	87/154 (56%)	43/77 (56%)	..
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	26/154 (17%)	8/77 (10%)	..
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	6/154 (4%)	4/77 (5%)	..
6—death	10/154 (6%)	4/77 (5%)	..
Six-category scale at day 14			
1—discharge (alive)	39/153 (25%)	18/78 (23%)	OR 1·25 (0·76 to 2·04)§
2—hospital admission, not requiring supplemental oxygen	21/153 (14%)	10/78 (13%)	..
3—hospital admission, requiring supplemental oxygen	61/153 (40%)	28/78 (36%)	..
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	13/153 (8%)	8/78 (10%)	..
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	4/153 (3%)	7/78 (9%)	..
6—death	15/153 (10%)	7/78 (9%)	..
Six-category scale at day 28			
1—discharge (alive)	92/150 (61%)	45/77 (58%)	OR 1·15 (0·67 to 1·96)§
2—hospital admission, not requiring supplemental oxygen	14/150 (9%)	4/77 (5%)	..
3—hospital admission, requiring supplemental oxygen	18/150 (12%)	13/77 (17%)	..
4—hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation	2/150 (1%)	2/77 (3%)	..
5—hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation	2/150 (1%)	3/77 (4%)	..
6—death	22/150 (15%)	10/77 (13%)	..

Data are median (IQR), n (%), or n/N (%). Clinical improvement (the event) was defined as a decline of two categories on the modified seven-category ordinal scale of clinical status, or hospital discharge. OR=odds ratio. *Differences are expressed as rate differences or Hodges-Lehmann estimator and 95% CI. †Hazard ratio and 95% CI estimated by Cox proportional risk model. ‡Three patients in each group were survivors and ten patients in the remdesivir group and seven patients in the placebo group were non-survivors. §Calculated by ordinal logistic regression model.

***Table 3*: Outcomes in the intention-to-treat population**

- **28天死亡率：**
  - 兩組相似
    - 實驗組: 22例[14%]
    - 對照組: 10例[13%]
    - 相差1.1%[95%CI –8.1-至10.3]
  - 以症狀發作到開始接受治療的時間分為
    - **早期治療(≤10天): 對照組較高(15%)**
    - 晚期治療(>10天): 實驗組較高(14%)

- **第14和28天臨床改善率：**
  - 實驗組較對照組高

- **使用侵襲性呼吸器的時間：**
  - 實驗組較對照組短 (但使用侵襲性呼吸器的患者數少，見table 2)

→以上皆未達統計顯著差異

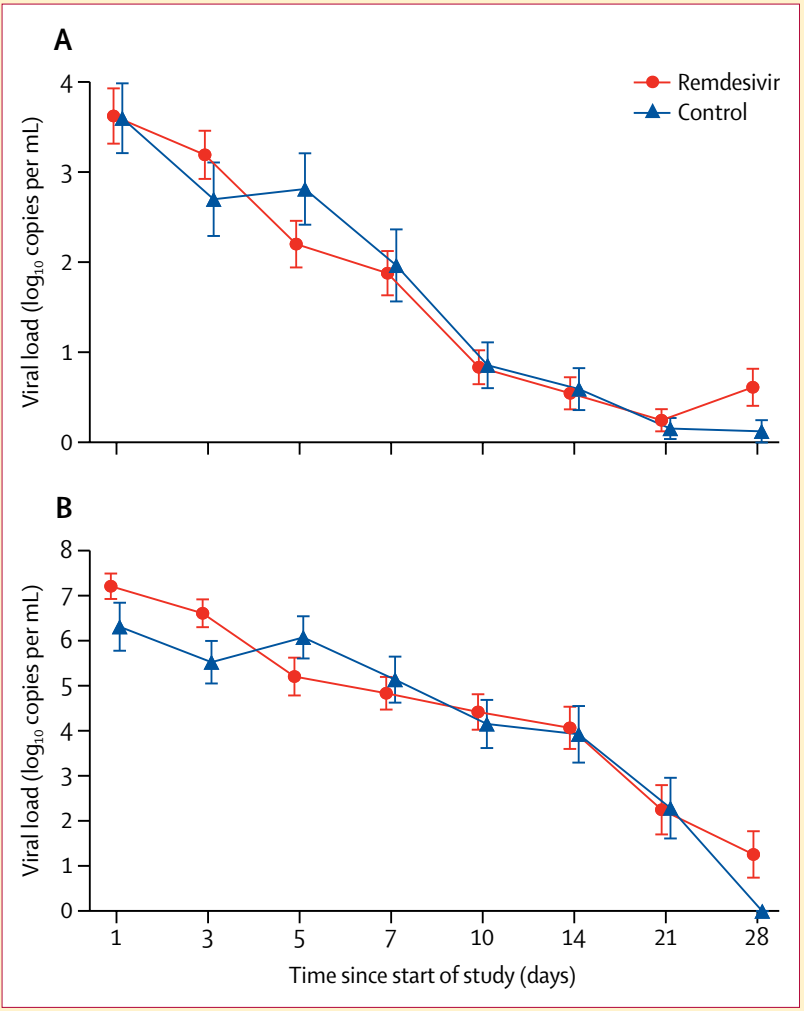


Figure 3: **Viral load by quantitative PCR on the upper respiratory tract specimens (A) and lower respiratory tract specimens (B)**
Data are mean (SE). Results less than the lower limit of quantification of the PCR assay and greater than the limit of qualitative detection are imputed with half of actual value; results of patients with viral-negative RNA are imputed with 0 log_{10} copies per mL.

●Baseline Viral load:

- 236位RT-PCR陽性的受試者中，196位有可得的數據，其中有37位(19%)在納入研究時其鼻咽和口咽拭子檢測不到病毒RNA
- 鼻咽和口咽拭子檢測的平均病毒量(table 1):
  - 實驗組: 4.7 log_{10} copies/mL(SE 0.3)
  - 對照組: 4.7 log_{10} copies/mL(SE 0.4)

●病毒量定量PCR檢測:

- **上呼吸道檢體(Fig 3A):** 病毒量隨時間下降的趨勢兩組相似
- **下呼吸道檢體(Fig 3B):**
  - 103位可得痰液檢體的患者中納入研究時的平均病毒量，實驗組較對照組高將近1-log
  - 在以納入研究時的痰液病毒量進行調整後，實驗組在第5天的病毒量和對照組無顯著差異，但病毒量下降較對照組略快(p=0.0672)

	Remdesivir group (n=155)		Placebo group (n=78)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Adverse events (in ≥2% of patients in any treatment group)				
Any	102 (66%)	13 (8%)	50 (64%)	11 (14%)
Hypoalbuminaemia	20 (13%)	0	12 (15%)	1 (1%)
Hypokalaemia	18 (12%)	2 (1%)	11 (14%)	1 (1%)
Increased blood glucose	11 (7%)	0	6 (8%)	0
Anaemia	18 (12%)	1 (1%)	12 (15%)	2 (3%)
Rash	11 (7%)	0	2 (3%)	0
Thrombocytopenia	16 (10%)	4 (3%)	5 (6%)	3 (4%)
Increased total bilirubin	15 (10%)	1 (1%)	7 (9%)	0
Increased blood lipids	10 (6%)	0	8 (10%)	0
Increased white blood cell count	11 (7%)	0	6 (8%)	0
Hyperlipidaemia	10 (6%)	0	8 (10%)	0
Increased blood urea nitrogen	10 (6%)	0	5 (6%)	0
Increased neutrophil	10 (6%)	0	4 (5%)	0
Aspartate aminotransferase increased	7 (5%)	0	9 (12%)	0
Constipation	21 (14%)	0	12 (15%)	0
Nausea	8 (5%)	0	2 (3%)	0
Diarrhoea	5 (3%)	0	2 (3%)	0
Vomiting	4 (3%)	0	2 (3%)	0
Reduced serum sodium	4 (3%)	0	2 (3%)	0
Increased serum potassium	4 (3%)	2 (1%)	1 (1%)	0
Serious adverse events				
Any	28 (18%)	9 (6%)	20 (26%)	10 (13%)
Respiratory failure or acute respiratory distress syndrome	16 (10%)	4 (3%)	6 (8%)	4 (5%)
Cardiopulmonary failure	8 (5%)	0	7 (9%)	1 (1%)
Pulmonary embolism	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Recurrence of COVID-19	1 (1%)	0	0	0
Cardiac arrest	1 (1%)	0	0	0
Acute coronary syndrome	0	0	1 (1%)	1 (1%)
Tachycardia	0	0	1 (1%)	0
Septic shock	1 (1%)	0	1 (1%)	1 (1%)

(Table 4 continues in next column)

	Remdesivir group (n=155)		Placebo group (n=78)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
(Continued from previous column)				
Lung abscess	0	0	1 (1%)	1 (1%)
Sepsis	0	0	1 (1%)	1 (1%)
Bronchitis	0	0	1 (1%)	1 (1%)
Thrombocytopenia	1 (1%)	1 (1%)	0	0
Increased D-dimer	0	0	1 (1%)	1 (1%)
Haemorrhage of lower digestive tract	1 (1%)	1 (1%)	0	0
Ileus	0	0	1 (1%)	0
Deep vein thrombosis	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Acute kidney injury	1 (1%)	0	0	0
Diabetic ketoacidosis	0	0	1 (1%)	1 (1%)
Multiple organ dysfunction syndrome	1 (1%)	0	2 (3%)	0
Events leading to drug discontinuation				
Any	18 (12%)	3 (2%)	4 (5%)	1 (1%)
Respiratory failure or acute respiratory distress syndrome	7 (5%)	1 (1%)	1 (1%)	0
Secondary infection	4 (3%)	0	7 (9%)	2 (3%)
Cardiopulmonary failure	3 (2%)	0	1 (1%)	0
Nausea	1 (1%)	0	0	0
Vomiting	1 (1%)	0	0	0
Ileus	0	0	1 (1%)	0
Increased alanine aminotransferase	2 (1%)	1 (1%)	0	0
Rash	2 (1%)	0	0	0
Poor appetite	1 (1%)	0	0	0
Increased total bilirubin	1 (1%)	0	0	0
Acute kidney injury	1 (1%)	1 (1%)	0	0
Seizure	0	0	1 (1%)	0
Aggravated schizophrenia	0	0	1 (1%)	1 (1%)
Aggravated depression	0	0	1 (1%)	1 (1%)

Data are n (%) and include all events reported after antiviral treatment. Some patients had more than one adverse event. 36 patients discontinued the drug, 22 because of adverse events and 14 patients for other reasons (eg, hospital discharge or early death). COVID-19=coronavirus disease 2019.

Table 4: **Summary of adverse events in safety population that occurred in more than one participant**

- 不良事件
  - ➢實驗組: 102/155 (66%)
  - ➢對照組: 50/78 (64%)
- **嚴重不良事件:**
  - **➢實驗組: 28/155 (18%)**
  - **➢對照組: 20/78 (26%)**
- **因不良事件或嚴重不良事件而終止使用研究藥物者在實驗組較多**
  - ➢實驗組: 18/155 (12%)
  - →其中有7位(5%)是因呼吸衰竭或急性呼吸窘迫症候群
  - ➢對照組: 4/78 (5%)

討論

- **此研究顯示，在重度COVID-19患者，使用靜脈注射Remdesivir與安慰劑相比，無法顯著改善臨床改善時間、死亡率或清除病毒的時間**
  - 可能原因：
    - ✓ 由於武漢採用嚴格的公共衛生措施，導致在3月中的新病例顯著減少，使得**此研究未能達到目標收案人數**
    - ✓ 由於病床供應受到限制，導致**大多數患者在疾病後期才得以納入**
  - **然而，在症狀發作後10天內開始接受治療的患者中，Remdesivir與臨床改善時間的中位數減少5天相關，雖然未達統計顯著**

討論

- 此研究中，**Remdesivir並未顯著降低SARS-CoV-2在上呼吸道或痰液檢體的RNA loads或可檢測性**，儘管Remdesivir在冠狀病毒感染的臨床前模型中顯示其具有強大的抗病毒作用
- **Remdesivir藥物劑量:**
  - 在健康成年人中，可耐受150 mg /天的劑量持續14天；在一名伊波拉腦膜腦炎患者，可耐受150 mg/天持續3天，隨後225mg/天持續11天的處方劑量
  - 但Remdesivir在COVID-19重症患者中的藥物動力學仍未明，特別是所治療患者的呼吸道細胞中的活性核苷酸代謝產物三磷酸酯(active nucleotide metabolite (GS-441524) triphosphate)的濃度
  - 在有安全性數據的情形下，**對於重度COVID-19以更高劑量(例如: 每日劑量150–200 mg)的Remdesivir進行研究值得考慮**
  - 此研究中受試者對藥物具有足夠的耐受性，未發現新的安全性問題

討論

- **藥物安全性**
  - **接受Remdesivir治療的患者，發生嚴重不良事件的比例較接受安慰劑者為低**
  - 但**接受Remdisivire治療的患者，由於不良事件而提前終止使用研究藥物的比例，較接受安慰劑者為高**，不良事件包括：腸胃道症狀(厭食、噁心和嘔吐)，轉胺酶或膽紅素增加，以及心肺狀況惡化

討論

- **研究限制**
  - 研究**檢定力不足**以檢測臨床結果的假設差異
  - 在 COVID-19的**相當晚期才開始治療**
  - 缺乏有關**感染性病毒恢復**的數據或可能出現**對Remdesivir感受性降低**的數據

討論

- 值得注意的是，在非人類靈長類動物中，Remdesivir對支氣管肺泡灌洗液中SARS-CoV-2感染性恢復的抑製作用比對照大得多；但**與對照組相比在上和下呼吸道檢體中病毒RNA的檢測並沒有呈現一致的下降**
- 在連續的體外傳代後，**Coronaviruses對於Remdesivir的抑制作用已具有部分抗性，但仍然易受較高濃度Remdesivir的影響**，使其適應性受損
- 在此研究的患者中，**頻繁使用corticosteroids可能促進了病毒的複製**，正如在SARS和MERS中所觀察到的，儘管在這些研究中僅報導了病毒RNA的檢測時間延長，而非具傳染性的病毒
- **對於重度COVID-19的患者，使用更長療程和更高劑量的Remdesivir是否有益，目前尚無答案**

總結

- **此研究的靜脈注射Remdesivir處方劑量可以充分耐受，但在重度COVID-19患者中並未提供顯著的臨床或抗病毒效用**
- 我們**無法排除具有臨床意義的差異**，且在此研究中顯示某些臨床參數的數值減少
- 持續進行**更大樣本數的研究**將可以讓我們更加了解Remdesivir對COVID-19的效用
- 關於**增強Remdesivir的抗病毒效力**(例如: 更高劑量的處方，與其他抗病毒藥組合，或SARS-CoV-2中和抗體)，以及**減輕造成COVID-19嚴重度增加的免疫病理宿主反應**(例如: IL-6，IL-1或TNFα的抑製劑) 的策略，需要對重度COVID-19患者進行嚴格的研究