

Compassionate Use of Remdesivir for Patients with Severe Covid-19

J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R.P. Myers, D.M. Brainard, R. Childs, and T. Flanigan

Patients

- RT-PCR: positive
- SpO₂ <94% while room air or using O₂
- Creatinine clearance > 30ml/min
- AST, ALT < 5* upper limit
- Not to use other investigational agents for Covid-19.

Method

- Redesivir: 10 days course
 - 200mg IV on day 1
 - 100mg IV QD for 9 days
- Follow up 28 days or until discharge/death
- Open label

Patients

- 53 patients
 - 40 (53 %) received 10-days course or remdesivir
 - 10 (19%): 5-9 days
 - 3 (6%): < 5 days
- Mean Age: 64
- Male:40 (75%)
- Region: US, Japan, Europe, Canada

Patients

- O2 supply:
 - MV:30(57%) ECMO:4(8%) NIV:36%
- Patient with MV support: older, male, higher ALT/Cre, more HTN, DM, Dyslipidemia, asthma
- Duration of MV before initiation of remdesivir: 2 days
- Duration of symptoms before medications: 12 days

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Invasive Ventilation (N = 34)	Noninvasive Oxygen Support (N = 19)	Total (N = 53)
Median age (IQR) — yr	67 (56–72)	53 (41–68)	64 (48–71)
Age category — no. (%)			
<50 yr	6 (18)	8 (42)	14 (26)
50 to <70 yr	14 (41)	7 (37)	21 (40)
≥70 yr	14 (41)	4 (21)	18 (34)
Male sex — no. (%)	27 (79)	13 (68)	40 (75)
Region — no. (%)			
United States	14 (41)	8 (42)	22 (42)
Japan	8 (24)	1 (5)	9 (17)
Europe or Canada	12 (35)	10 (53)	22 (42)
Oxygen-support category — no. (%)			
Invasive ventilation	34 (100)	—	34 (64)
Invasive mechanical ventilation	30 (88)	—	30 (57)
Extracorporeal membrane oxygenation	4 (12)	—	4 (8)
Noninvasive oxygen support	—	19 (100)	19 (36)
Noninvasive positive-pressure ventilation	—	2 (11)	2 (4)
High-flow oxygen	—	5 (26)	5 (9)
Low-flow oxygen	—	10 (53)	10 (19)
Ambient air	—	2 (11)	2 (4)
Median duration of symptoms before remdesivir therapy (IQR) — days	11 (8–15)	13 (10–14)	12 (9–15)
Coexisting conditions — no. (%)			
Any condition	25 (74)	11 (58)	36 (68)
Hypertension	9 (26)	4 (21)	13 (25)
Diabetes	8 (24)	1 (5)	9 (17)
Hyperlipidemia	6 (18)	0	6 (11)
Asthma	5 (15)	1 (5)	6 (11)
Median laboratory values (IQR)			
ALT — IU per liter	48 (31–79)	27 (20–45)	37 (25–61)
AST — IU per liter	39 (30–76)	35 (28–46)	36 (29–67)
Creatinine — mg per deciliter	0.90 (0.66–1.17)	0.79 (0.63–1.00)	0.89 (0.64–1.08)

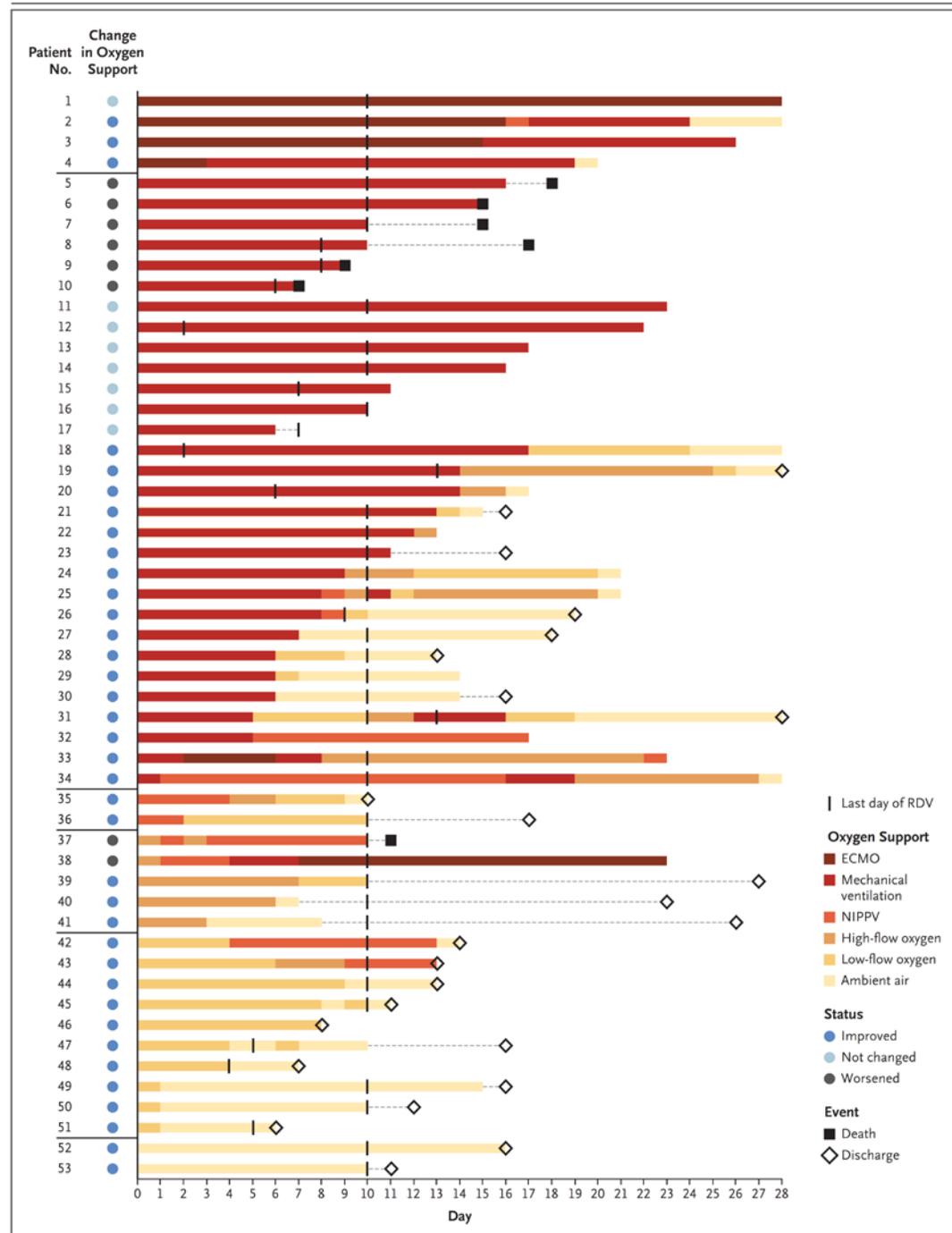
		No. of Patients in Oxygen-Support Group at Baseline (%)			
		Invasive (N=34)	Noninvasive (N=7)	Low-flow oxygen (N=10)	Ambient air (N=2)
Category on ordinal scale →		5	4	3	2
No. of Patients in Oxygen-Support Group after Treatment (%)	Death	6	6 (18)	1 (14)	0
	Invasive	5	9 (26)	1 (14)	0
	Noninvasive	4	3 (9)	0	0
	Low-flow oxygen	3	0	0	0
	Ambient air	2	8 (24)	0	0
	Discharged	1	8 (24)	5 (71)	10 (100)
	Improvement		19 (56)	5 (71)	10 (100)
		↑ Category on ordinal scale			

- 68% showed an improvement
- 15% showed worsening

Safety

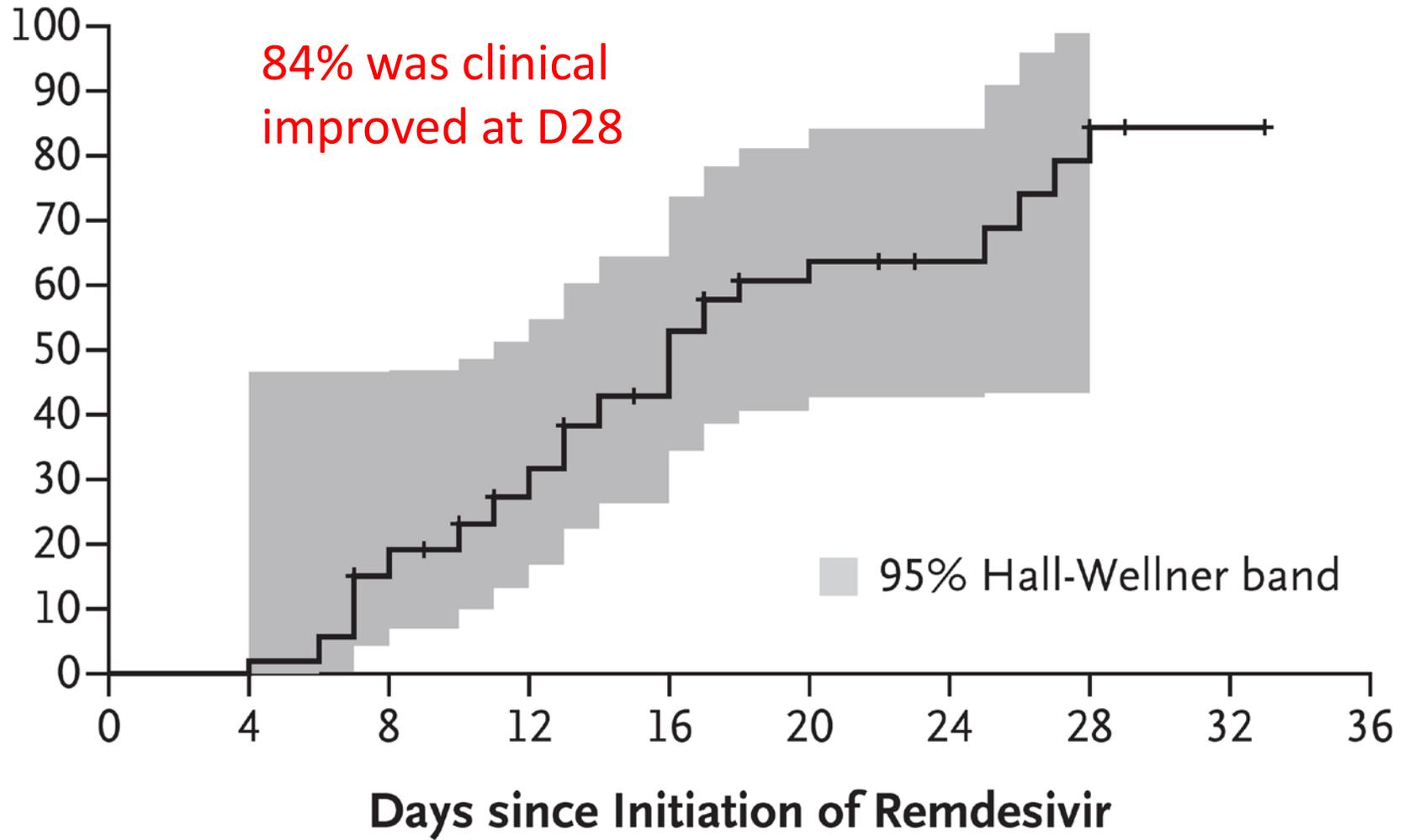
- 32 patients reported AEs
 - Increased hepatic enzymes
 - Diarrhea
 - Skin rash
 - Renal impairment
 - Hypotension
- 12 patients had serious AEs
 - Multiple organ dysfunction syndrome
 - Septic shock
 - AKI
 - hypotension
- 4 (8%) patients discontinued
 - AKI: 1
 - MODS: 1
 - Elevated liver enzyme: 2

- 4 ECMO: all survive
 - 3 of 4 weaning ECMO
- 30 MV:
 - 17/30 extubation
- Mortality: 7/53 (13%)
 - 6 MV, 1 NIPPV
 - Median duration: 15 days



A Overall

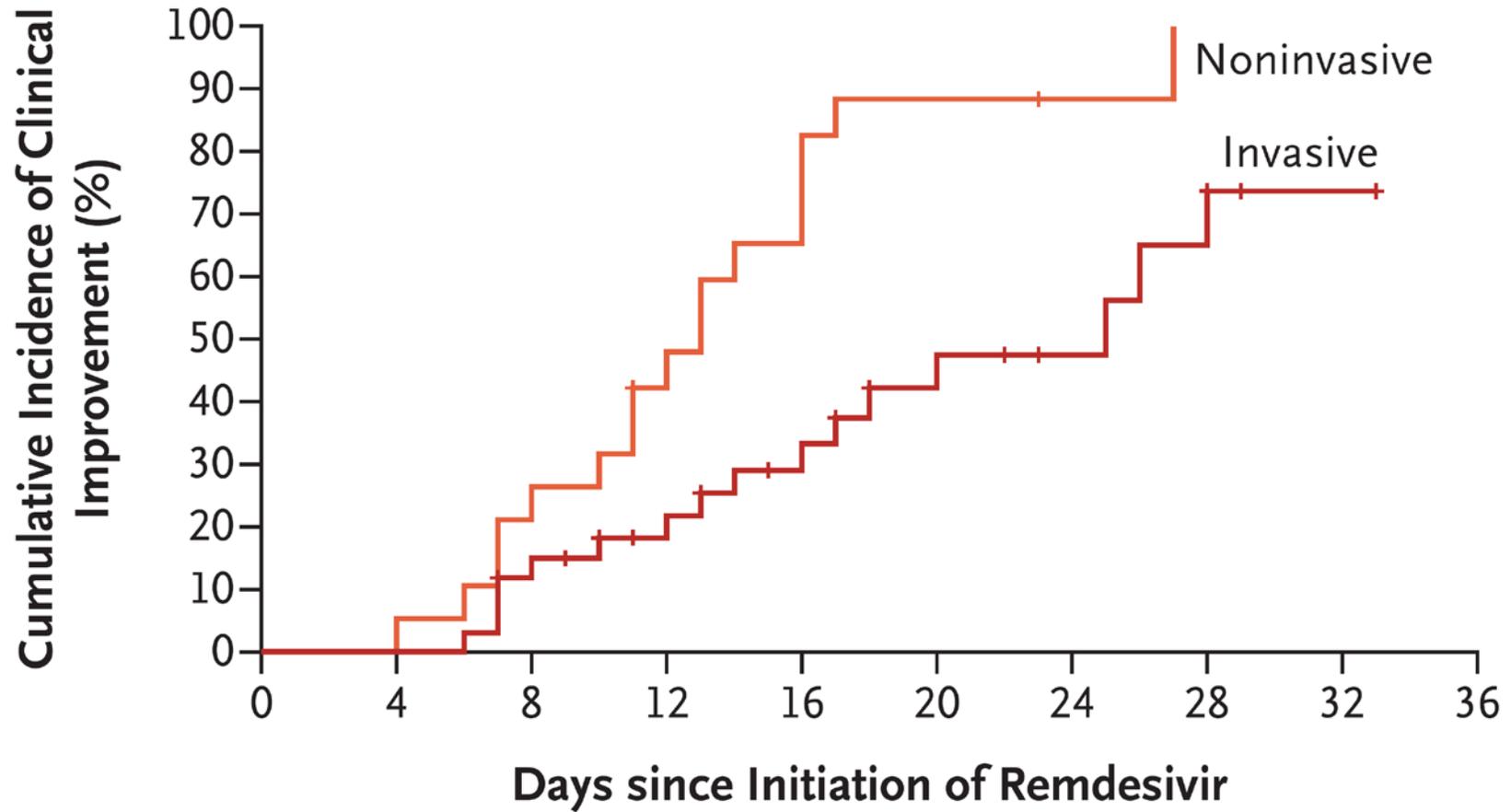
Cumulative Incidence of Clinical Improvement (%)



No. at Risk

53 53 43 33 23 13 7 4 1 0

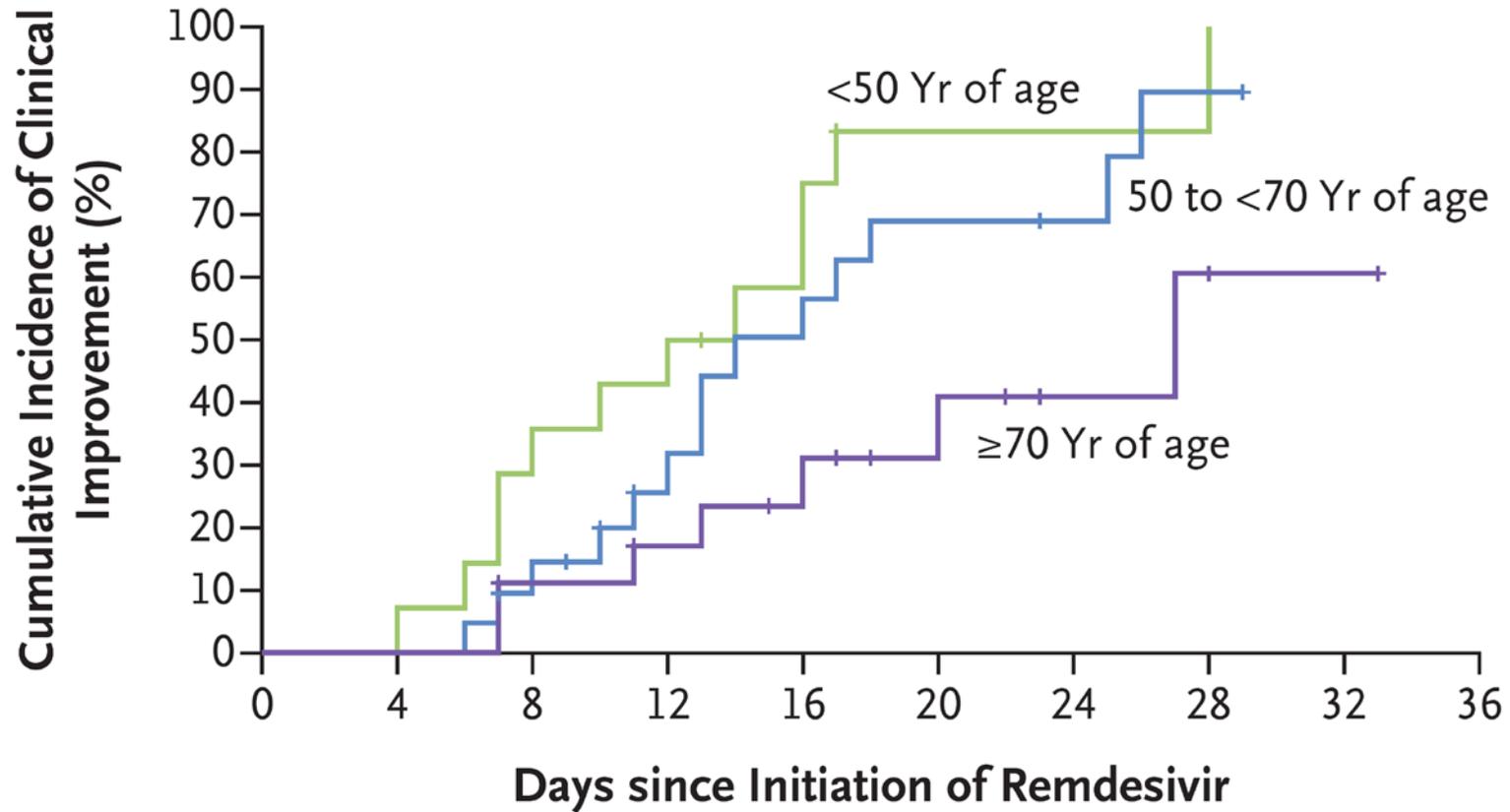
B Baseline Oxygen Support



No. at Risk

Noninvasive	19	19	15	10	6	2	1	0		
Invasive	34	34	28	23	17	11	6	4	1	0

C Age



No. at Risk

<50 Yr of age	14	14	10	8	5	1	1	1	
50 to <70 Yr of age	21	21	18	12	8	5	3	1	0
≥70 Yr of age	18	18	15	13	10	7	3	2	1

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Invasive Ventilation (N=34)	Noninvasive Oxygen Support (N=19)	Total (N=53)
Median age (IQR) — yr	67 (56–72)	53 (41–68)	64 (48–71)
Age category — no. (%)			
<50 yr	6 (18)	8 (42)	14 (26)
50 to <70 yr	14 (41)	7 (37)	21 (40)
≥70 yr	14 (41)	4 (21)	18 (34)
Male sex — no. (%)	27 (79)	13 (68)	40 (75)
Region — no. (%)			
United States	14 (41)	8 (42)	22 (42)
Japan	8 (24)	1 (5)	9 (17)
Europe or Canada	12 (35)	10 (53)	22 (42)
Oxygen-support category — no. (%)			
Invasive ventilation	34 (100)	—	34 (64)
Invasive mechanical ventilation	30 (88)	—	30 (57)
Extracorporeal membrane oxygenation	4 (12)	—	4 (8)
Noninvasive oxygen support	—	19 (100)	19 (36)
Noninvasive positive-pressure ventilation	—	2 (11)	2 (4)
High-flow oxygen	—	5 (26)	5 (9)
Low-flow oxygen	—	10 (53)	10 (19)
Ambient air	—	2 (11)	2 (4)
Median duration of symptoms before remdesivir therapy (IQR) — days	11 (8–15)	13 (10–14)	12 (9–15)
Coexisting conditions — no. (%)			
Any condition	25 (74)	11 (58)	36 (68)
Hypertension	9 (26)	4 (21)	13 (25)
Diabetes	8 (24)	1 (5)	9 (17)
Hyperlipidemia	6 (18)	0	6 (11)
Asthma	5 (15)	1 (5)	6 (11)
Median laboratory values (IQR)			
ALT — IU per liter	48 (31–79)	27 (20–45)	37 (25–61)
AST — IU per liter	39 (30–76)	35 (28–46)	36 (29–67)
Creatinine — mg per deciliter	0.90 (0.66–1.17)	0.79 (0.63–1.00)	0.89 (0.64–1.08)

Table 1. Demographic and Clinical Characte

	Patients by age, All
No. (%)	1591 (100)
Age, median (IQR), y	63 (56–70)
Males	1304 (82)
Females	287 (18)
Comorbidities, No. with data	1043
None	334 (32)
Hypertension	509 (49)
Cardiovascular disease ^a	223 (21)
Hypercholesterolemia	188 (18)
Diabetes, type 2	180 (17)
Malignancy ^b	81 (8)
COPD	42 (4)
Chronic kidney disease	36 (3)
Chronic liver disease	28 (3)
Other ^c	205 (20)
Respiratory support, No.	1300
Invasive mechanical ventilation	1150 (88)
Noninvasive ventilation	137 (11)
Oxygen mask	13 (1)
PEEP, cm H ₂ O	
No.	1017
Median (IQR)	14 (12–16)
FiO ₂ , %	
No.	999
Median (IQR)	70 (50–80)
PaO ₂ /FiO ₂ ratio	
No.	781
Median (IQR)	160 (114–220)
Prone position, No./total (%)	240/875 (27)
ECMO, No./total (%)	5/498 (1)

Abbreviations: COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; IU, international unit; IQR, interquartile range; N/A, not applicable; PEEP, positive end-expiratory pressure.

^a Cardiovascular disease includes cardiomyopathy.

Compare to Italy

- NEJM
 - MV: 64%
 - Lesser Male
 - No mentioned P/F
 - Mortality: 13%
- Italy, Lombardy
 - MV: 88%
 - ICU mortality was 26%

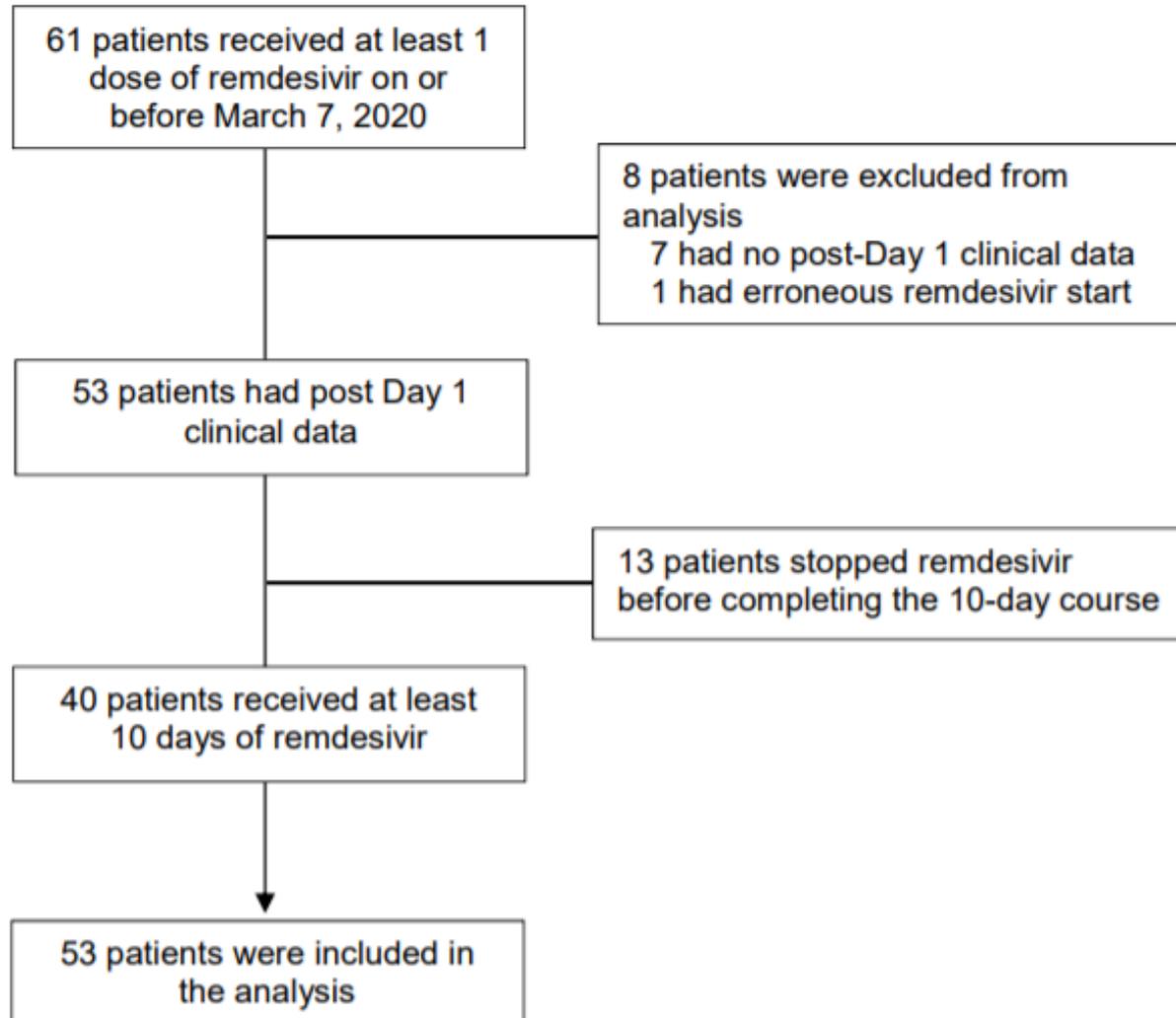
Discussion and Conclusion

- 68% improved in oxygen support
- Overall mortality was 13% (median follow up 18 days)
 - Kaletra trial: 28 –day mortality :22% (MV: 1/199)
 - Cohort report from Wuhan: 17-78% in ICU
- Did not collect viral load
- Duration of Redesivir : 5 days or 10 days
- Small size, short duration, potential missing data
- Need RCT

Summary

- Redesivir 200mg IV once and 100mg IV QD for 9 days
- 68% improvement in oxygenation support
13% mortality
- Side effects:
 - Liver dysfunction
 - AKI
- Pending RCT

Figure S1. Patient Disposition



- The six-point scale consists of the following categories:
- 1, not hospitalized
- 2, hospitalized, not requiring supplemental oxygen;
- 3, hospitalized, requiring supplemental oxygen;
- 4, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both
- 5, hospitalized, requiring invasive mechanical ventilation, ECMO, or both
- 6, death.